Pergamon

Bioorganic & Medicinal Chemistry, Vol. 3, No. 4, pp. 403–410, 1995

0968-0896/95 $9.50 + .00

0968-0896(95)00027-5

Hydroxylamine Analogs of 2,6 Di-*t*-butylphenols: Dual Inhibitors of Cyclooxygenase and 5-Lipoxygenase or Selective 5-Lipoxygenase Inhibitors

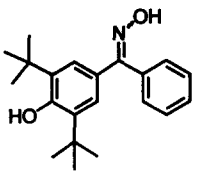
James B. Kramer,[a] Thomas Capiris,[a] Jagadish C. Sircar,[a] David T. Connor,[a] Dirk A. Bornemeier,[b] Richard D. Dyer,[b] Paul J. Kuipers,[c] John A. Kennedy,[c] Clifford D. Wright,[c] Godwin C. N. Okonkwo,[c] Mark E. Lesch,[c] Denis J. Schrier[c] and Diane H. Boschelli[a]*

Departments of [a]Chemistry, [b]Immunopathology and [c]Biochemistry
Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company
2800 Plymouth Rd., Ann Arbor, MI 48105, U.S.A.

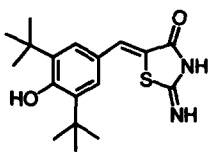
Abstract—The preparation of hydroxylamine analogs of 2,6-di-*tert*-butylphenols (DTBP) and the inhibition of cyclooxygenase (CO) and 5-lipoxygenase (5-LO) by these compounds is discussed.

Introduction

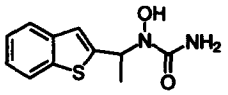
Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the treatment of inflammatory diseases such as arthritis.[1] These agents reduce the pain and swelling associated with inflammation by blocking the cyclooxygenase (CO) catalyzed metabolism of arachidonic acid (AA) to proinflammatory prostaglandins. Since prostaglandins are also cytoprotective, decreasing their levels results in a high incidence of gastric ulcers in patients who are chronically treated with NSAIDs.[2] This adverse event may be attenuated in the presence of an inhibitor of 5-lipoxygenase (5-LO), the enzyme responsible for the conversion of AA to leukotrienes. Leukotrienes are also implicated in inflammatory processes, and in contrast to prostaglandins, the leukotrienes promote mucosal damage.[3] Dual inhibitors of CO and 5-LO might, therefore, be anti-inflammatory agents with improved efficacy and reduced side effects.[4]



TZI 41078
1



CI-1004
2

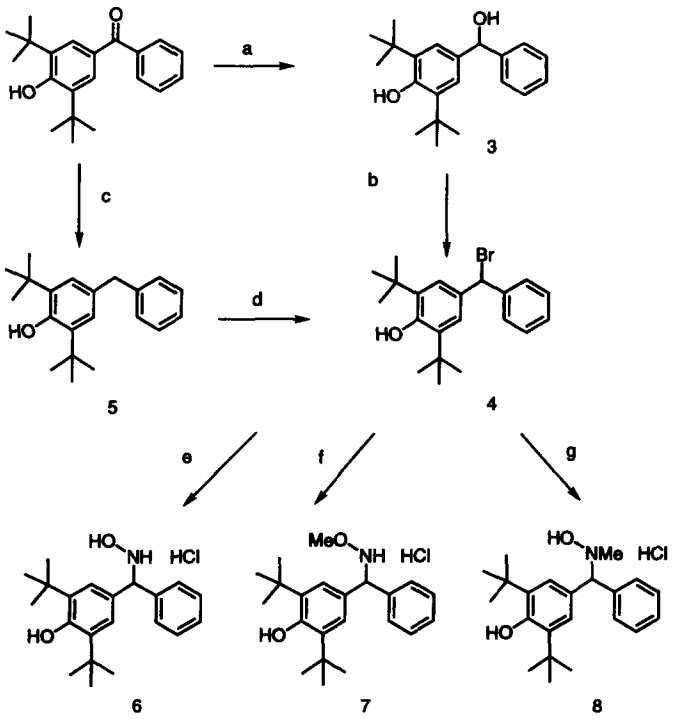


zileuton
9

One of the first reported inhibitors of both CO and 5-LO was TZI 41078 (1) 3,5-di-*tert*-butyl-4-hydroxybenzophenone oxime.[5] A wide range of di-*tert*-butylphenol (DTBP) containing compounds were subsequently found to be dual inhibitors[6,7] including CI-1004 (2) (*Z*)-5-[[3,5-di-*tert*-butyl-4-hydroxyphenyl]methylene]-2-imino-4-thiazolidinone, which is currently in preclinical development at Parke-Davis.[8] As part of our continuing studies in this area, we have prepared a series of DTBP analogs wherein the oxime functionality of TZI 41078 was replaced by various substituted hydroxylamines.

Results and Discussion

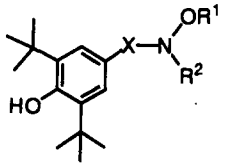
The reduction of [3,5-di-*tert*-butyl-4-hydroxyphenyl] phenylmethanone[9] with sodium borohydride to provide the corresponding alcohol **3** is depicted in Scheme 1. Treatment of **3** with bromotrimethylsilane gave bromide **4**, which was used directly. This compound was also prepared by an alternate route involving reduction of [3,5-di-*tert*-butyl-4-hydroxyphenyl]phenylmethanone to the methylene derivative **5**.[10] Bromination of **5** with *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide provided **4**. Reaction of **4** with hydroxylamine tetrahydropyran ether followed by acid hydrolysis resulted in formation of the unsubstituted hydroxylamine **6**. The substituted derivatives **7** and **8** were prepared by reaction of **4** with *O*-methylhydroxylamine and *N*-methylhydroxylamine respectively. The unsubstituted hydroxylamine **6** and the N-Me hydroxylamine analog **8** effectively blocked the production of $PGF_{2\alpha}$ and LTB_4 from rat basophilic leukemia cells (data shown in Table 1).[11] Conversely blocking the OH group with a methyl group as in **7**, provided a selective inhibitor of 5-LO.



a) $NaBH_4$, EtOH, rt (93%); b) CCl_4, TMSBr; c) $NaBH_4$, EtOH, 60 °C (18%); d) NBS, CCl_4, benzoyl peroxide; e) 1) H_2NOTHP, THF 2) conc. HCl (24%); f) H_2NOMe–HCl, 2,6-lutidine, THF (57%); g) MeNHOH–HCl, 2,6-lutidine, THF (42%).

Scheme 1.

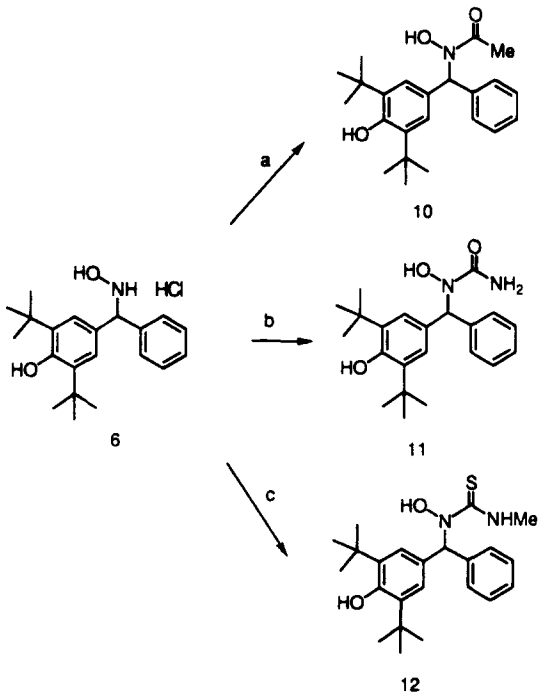
Table 1. Inhibition of 5-LO and CO



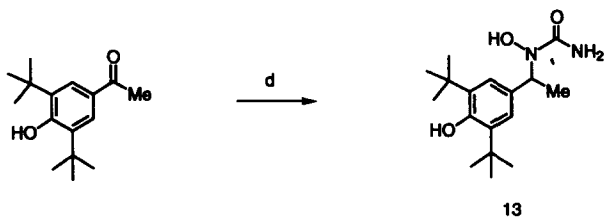
Compound	X	R^1	R^2	5-LO[a]	CO[a]
1	TZI 41078			1.0	21
2	CI 1004			0.77	0.39
9	zileuton			1.2	>10
6	CHPh	H	H	2.3	4.1
7	CHPh	Me	H	93%@16	N[b]@16
8	CHPh	H	Me	1.2	4.3
10	CHPh	H	COMe	4.8	59%@16
11	CHPh	H	$CONH_2$	97%@10	N@10
12	CHPh	H	CSNHMe	98%@16	N@16
13	CHMe	H	$CONH_2$	79%@16	N@16
15a	SCH_2CHMe		E-oxime	0.76	0.54
15b	SCH_2CHMe		Z-oxime	0.50	0.65
16	SCH_2CHMe	H	H	0.52	0.51
17	SCH_2CHMe	H	$CONH_2$	100%@10	N@10
18	SCH_2CHMe	H	COMe	100%@10	N@10
19	SCH_2CHMe	H	CSNHMe	100%@10	N@10

[a]Data reported as IC_{50} (μM) or the per cent inhibition at the stated concentration—10 or 16 μM. IC_{50} calculated as the concentration of test compound causing 50% inhibition of LTB_4 (5-LO) or $PGF_{2\alpha}$ (CO) formation. Standard errors for replicate determinations in these assays average 11% of the values shown for 5-LO and 8% of the values shown for CO.
[b]*N* = less than 40% inhibition at the screening concentration.

There are several reports of selective 5-LO inhibitors that contain N-substituted acetohydroxamic acids and/or hydroxyureas.[12] One example is zilueton (**9**) *N*-1-[benzo[*b*]thien-2-ylethyl]-*N*-hydroxyurea, which is currently in clinical trials.[13] In an attempt to maximize inhibition of 5-LO we prepared the N- substituted analogs of **6**, as shown in Scheme 2. Independent treatment of **6** with acetyl chloride and trimethylsilyl isocyanate provided **10** and **11** respectively. As shown in Table 1, both **10** and **11** showed activity against 5-LO, with **10** also showing weak activity against CO. The *N*-hydroxy-*N*-methylthiourea analog **12**, obtained by reaction of **6** with methylisothiocyanate, was a selective 5-LO inhibitor.



a) CH_3COCl, NaOAc, dioxane (60%); b) TMSOCN, THF (47%); c) CH_3NCS, toluene (88%).



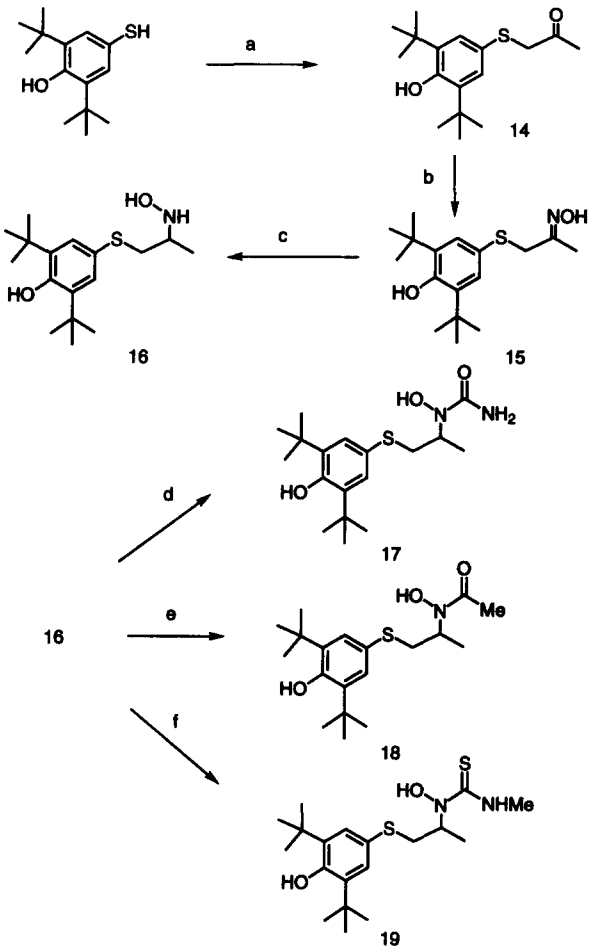
d) 1) H_2NOH–HCl, NaOAc, MeOH (87%); 2) $NaCNBH_3$, AcOH (32%); 3) TMSOCN, THF (60 %).

Scheme 2.

To evaluate the contribution of the phenyl group of **11** to 5-LO inhibition, the corresponding methyl analog, **13**, was prepared as depicted in Scheme 2. 3,5-Bis(1,1-dimethylethyl)-4-hydroxyacetophenone was converted to its oxime,[14] reduced and treated with trimethylsilyl isocyanate followed by acid to provide **13**. This compound was also a selective 5-LO inhibitor but less potent than **9**. It appeared that both a DTBP and an N-acyl or N-urea substitiuted hydroxylamine group were the structural requirements for a compound to possess selective *in vitro* activity against 5-LO. By employing a thiomethylene spacer between these two groups, the resulting compounds, exemplified by **17**, would retain the relationship of the aromatic ring to the N-hydroxyurea group present in zileuton.

The conversion of 2,6-bis(1,1-dimethylethyl)-4-mercaptophenol to the ketone derivative **14**, via direct alkylation with chloroacetone or via a two step protocol of initial reaction with propylene oxide [15] with subsequent oxidation of the resultant alcohol with sulfur trioxide–pyridine is depicted in Scheme 3. Ketone **14** was converted to oxime **15** by treatment with hydroxylamine hydrochloride. Reduction of **15** with borane–pyridine complex provided the key hydroxylamine **16**. This sequence was used to convert **14** to **16** since the route that provided **6** from the corresponding ketone could not be applied to this series.

The substituted hydroxamates **17–19** were prepared by reaction of **16** with sodium cyanate, acetyl chloride and methyl isothiocyanate, respectively. All three were selective 5-LO inhibitors, showing no detectable activity against CO unlike the unsubstituted hydroxylamine derivative **16**, which was a dual inhibitor. The intermediate oxime **15** was separated by chromatography into its *E* and *Z* isomers, **15a** and **b**. While these compounds were also potent *in vitro* inhibitors of 5-LO and CO, they were inactive when administered orally in carageenin-induced footpad edema (CFE), a model of acute inflammation. From the initial series of compounds, **6** was active in both CFE (ID_{40} = 13.2 mg kg^{-1}) and mycobacterium footpad edema (MFE), a 3-day subacute model of inflammation (ID_{40} = 3.8 mg kg^{-1}). In a rat model of gastrointestinal irritation, **6** was nonulcerogenic at doses up to 200 mg kg^{-1}, while indomethacin and naproxen resulted in the formation of ulcers after single doses of 5.4 and 9.5 mg kg^{-1} respectively.[16]



a) $ClCH_2COMe$, pyr, CH_2Cl_2 (75%) or 1) propylene oxide, K_2CO_3, EtOH (84%); 2) SO_3-pyr, Et_3N, DMSO, CH_2Cl_2 (90%); b) NH_2OH–HCl, pyr, EtOH (97%); c) BH_3-pyr, 6N HCl, MeOH (84%); d) NaOCN, 6N HCl, THF; e) CH_3COCl, pyr, CH_2Cl_2 (41%); f) CH_3NCS, THF (87%)

Scheme 3.

In summary, the *N*-acyl or *N*-urea substituted hydroxylamine derivatives of DTBP were selective 5-LO inhibitors while the precursor hydroxylamines were inhibitors of both CO and 5-LO. One dual inhibitor, **6**, was nonulcerogenic and is undergoing additional evaluation.

Experimental

Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a Bruker AM 250 spectrometer, with chemical shifts reported in δ units relative to TMS. IR spectra were recorded on a Nicolet MX-1 FTIR or a Mattson Cygnus 100 FT-IR spectrometer. Mass spectra were recorded on a Fisons TRIO-2A, a Finnigan 4500 or a VG Analytical 7070E/HF mass spectrometer. All new compounds yielded satisfactory NMR, IR and MS data. Elemental analyses were performed by the Parke-Davis Analytical Chemistry staff and were within ±0.4% of the theoretical values. Reactions were run under an atmosphere of nitrogen or argon. Flash chromatography was performed with E. Merck silica gel 60, 230–400 mesh.

3,5-Bis(1,1-dimethylethyl)-4-hydroxy-α-phenylbenzenemethanol (3). To a 10–15°C solution of 3.1 g (10.0 mmol) of [3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-phenylmethanone in 50 mL of absolute EtOH was added 1.89 g (50.0 mmol) of $NaBH_4$ over a period of 25 min. The reaction mixture was kept at room temperature for 1.5 h, then cooled to 0°C and 4 N HCl (12 mL) was slowly added. The white precipitate was collected and washed with H_2O, then dissolved in Et_2O and washed with saturated sodium bicarbonate. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 2.9 g (93%) of **3**, mp 117–119°C; ^1H NMR ($CDCl_3$): δ 1.3 (*s*, 18H), 2.1 (*d*, *J* = 3.0 Hz, 1H), 5.1 (*s*, 1H), 5.7 (*d*, *J* = 3.0 Hz, 1H), 7.1 (*s*, 2H), 7.1–7.4 (*m*, 5H); Anal. calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03; found: C, 80.86; H, 9.02.

3,5-Bis(1,1-dimethylethyl)-4-hydroxy-α–phenylbenzylbromide (4). To a solution of 31.2 g (100 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxy-α–phenylbenzenemethanol in 350 mL of CCl_4 was added 34.8 g (227 mmol) of bromotrimethylsilane. After stirring for 40 min at room temperature the reaction mixture was concentrated to dryness. The resulting brown oil was

used directly without purification; ^{1}H NMR (CCl_4); δ 1.3 (*s*, 18H), 4.9 (*s*, 1H), 6.0 (*s*, 1H), 7.0–7.3 (*m*, 7H).

Alternate preparation of 4

4-Benzyl-2,6-bis(1,1-dimethylethyl)phenol (5). To a 10°C suspension of 15.52 g (50.0 mmol) of [3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]phenylmethanone in 200 mL of absolute EtOH was added 760 mg (20.0 mmol) of $NaBH_4$. The reaction mixture was kept at room temperature for 3 days. Additional portions of $NaBH_4$ (1.0 g, 26.0 mmol) were added and the mixture was heated at 60°C for 1 h. The reaction mixture was diluted with 100 mL of H_2O, then cooled to 0°C and acidified to pH 2 with 6 N H_2SO_4. The mixture was concentrated to one-third the original volume and extracted with three portions of Et_2O. The Et_2O extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography eluting with CH_2Cl_2 hexane (1:2) to give 2.7 g (18%) of **5**, mp 55–58°C; IR (film) 3643, 2958, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.4 (*s*, 18H), 3.9 (*s*, 2H), 5.1 (*s*, 1H), 7.0 (*s*, 2H), 7.1–7.3 (*m*, 5H); MS (EI) m/z 296; Anal. calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52; found: C, 84.99; H, 9.86.

N-Bromosuccinimide (1.00 g, 5.6 mmol) was added to a suspension of 1.27 g (4.00 mmol) of 4-benzyl-2,6-bis(1,1-dimethylethyl)phenol in 25 mL CCl_4. A catalytic amount of benzoylperoxide was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to dryness to afford 3,5-bis(1,1-dimethylethyl)-4-hydroxy-α-phenylbenzylbromide (**4**) as an orange oil.

2,6-Bis(1,1-dimethylethyl)-4[(hydroxyamino)phenylmethyl]phenol, hydrochloride (6). To a solution of 14.81 g (47.0 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxy-α-phenylbenzenemethanol in 200 mL of CCl_4 was added 17.40 g (113.6 mmol) of bromotrimethylsilane. After 30 min the reaction mixture was evaporated to dryness. The residue was dissolved in 100 mL of tetrahydrofuran and added dropwise to a solution of 18.00 g (153.6 mmol) of hydroxylamine tetrahydropyranyl ether in 200 mL of tetrahydrofuran. The mixture was heated at reflux for 1.5 h then kept at room temperature for 16 h. Concentrated HCl (32 mL) was added and the mixture heated at reflux for 30 min. The reaction mixture was evaporated to dryness, dissolved in Et_2O and washed with H_2O, saturated sodium bicarbonate, and brine, followed by drying over Na_2SO_4. After solvent evaporation the crude product was recrystallized from Et_2O:hexane to provide 9.30 g of white crystals. A 7.27 g portion was dissolved in Et_2O and treated with 10 mL of 20% HCl in Et_2O. The resultant white crystalline precipitate was removed by filtration to provide 5.75 g of **6** (24%), mp 197–200°C; IR (KBr) 3635, 1437 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.4 (*s*, 18H), 5.6 (*s*, 1H), 7.2 (*s*, 1H), 7.3–7.7 (*m*, 7H), 11.0 (*br s*, 1H), 12.1 (*br s*, 2H); MS (EI) m/z -OH 310, m/z -NHOH 295; Anal. calcd for $C_{21}H_{29}NO_2$–HCl: C, 69.31; H, 8.31; N, 3.85; Cl, 9.74; found: C, 68.94; H, 8.17; N, 3.74; Cl, 10.05.

2,6-Bis(1,1-dimethylethyl)-4[(methoxyamino)phenylmethyl]phenol, hydrochloride (7). A solution of 6.23 g (16.6 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxy-α-phenylbenzylbromide in 100 mL of tetrahydrofuran was added over 20 min to a mixture of 4.18 g (50.0 mmol) of methoxylamine hydrochloride and 5.62 g (52.4 mmol) of 2,6-lutidine in 175 mL of tetrahydrofuran. After heating at reflux for 16 h, additional 5.62 g (52.4 mmol) of 2,6-lutidine and 2.0 g (23.9 mmol) of methoxylamine hydrochloride were added and heating was continued for 24 h. The reaction mixture was evaporated and the residue was dissolved in Et_2O, washed with H_2O, 1 N HCl, saturated sodium bicarbonate, and brine, followed by drying over Na_2SO_4. Removal of solvents and treatment of the residue with 5 mL of 20% HCl in Et_2O followed by recrystallization from EtOAc:Et_2O gave 3.6 g (57%) of **7**, mp 183–185°C; IR (KBr) 3600, 1573, 1437 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.3 (*s*, 18H), 3.9 (*s*, 3H), 5.7 (*s*, 1H), 7.2–7.5 (*m*, 7H), 7.7 (*d*, *J* = 7.4 Hz, 2H); MS (CI) m+1/z 342; Anal. calcd for $C_{22}H_{31}NO_2$–HCl: C, 69.91; H, 8.53; N, 3.71; Cl, 9.38; found: C, 69.71; H, 8.53; N, 3.43; Cl, 9.50.

2,6-Bis(1,1-dimethylethyl)-4[(hydroxymethylamino)phenylmethyl]phenol, hydrochloride (8). Sustitution of *N*-methylhydroxylamine hydrochloride for methoxylamine hydrochloride in the above reaction provided (42%) of **8** after recrystallization from EtOH:Et_2O, mp 166–169°C; IR (KBr) 3630, 1437 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.4 (*s*, 18H), 2.9 (*s*, 3H), 5.6 (*s*, 1H), 7.1–7.5 (*m*, 7H), 7.8 (*d*, *J* = 7.5 Hz, 2H), 11.5 (*br s*, 1H); MS (CI) m+1/z 342; Anal. calcd for $C_{22}H_{31}NO_2$–HCl: C, 69.91; H, 8.53; N, 3.71; Cl, 9.38; found: C, 69.78; H, 8.67; N, 3.50; Cl, 9.07.

N-*[[3,5-bis(1,1-dimethylethyl)-4[(hydroxyphenyl]phenylmethyl]*-N-*hydroxyacetamide (10).* A solution of 386 mg (4.70 mmol) of NaOAc in 5 mL of H_2O was added to a solution of 610 mg (1.85 mmol) of 2,6-bis(1,1-dimethylethyl)-4[(hydroxyamino)phenylmethyl]phenol in 25 mL of 1,4-dioxane. Acetyl chloride (276 mg, 3.5 mmol) was added over 2 min and the reaction mixture was stirred at room temperature for 2 h. Following the addition of 50 mL of H_2O, the volume was reduced by approximately 50% and extracted with two portions of Et_2O. The combined Et_2O layers were washed with saturated sodium bicarbonate and brine then dried over Na_2SO_4. Concentration *in vacuo* gave a white foam that was recrystallized from hexane to provide 410 mg (60%) of **10**, mp 163.5–166°C; IR (KBr) 3613, 1635 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.3 (*s*, 18H), 2.1 (*s*, 3H), 6.6 (*s*, 1H), 6.9 (*s*, 1H), 7.0 (*s*, 2H), 7.2–7.4 (*m*, 5H), 9.6 (*s*, 1H); MS (EI) m+1/z 370, m/z -OH 352; Anal. calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79; found: C, 74.56; H, 8.69; N, 3.58:

N-*[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]phenylmethyl]*-N-*hydroxyurea (11).* Trimethylsilyl isocyanate (580 mg, 5.0 mmol) was added to a solution of 980 mg (3.0 mmol) of 2,6-bis(1,1-dimethylethyl)-4[(hydroxyamino)phenylmethyl]phenol in 15 mL of tetrahydro-

furan. The reaction mixture was heated at reflux for 30 min then stirred at room temperature for 17 h. The reaction mixture was poured into saturated NH_4Cl and partially concentrated *in vacuo* to remove the tetrahydrofuran. Water was added and the mixture extracted with EtOAc. The extracts were washed with brine and dried over Na_2SO_4. Concentration *in vacuo* gave a residue that was recrystallized from Et_2O:hexane to provide 530 mg (47%) of **11**, mp 188–189°C; IR (KBr) 3600, 1680, 1550 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.3 (*s*, 18H), 6.3 (*s*, 1H), 6.4 (*s*, 2H), 6.8 (*s*, 1H), 7.0 (*s*, 2H), 7.2–7.4 (*m*, 5H), 9.1 (*s*, 1H); MS (EI) m/z -OH 353; Anal. calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56; found: C, 71.17; H, 8.30; N, 7.41.

N-*[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]phenylmethyl]*-N-*hydroxy*-N'-*methylthiourea (12).* Methyl isothiocyanate (257 mg, 3.5 mmol) was added to a solution of 980 mg (3.0 mmol) of 2,6-bis(1,1-dimethylethyl)-4[(hydroxyamino)phenylmethyl] phenol in 25 mL of toluene. The reaction mixture was stirred at room temperature for 2 h then poured into 25 mL of hexane and the resultant solid collected by filtration to provide 1.05 g (88%) of **12**, mp 158–159.5°C; IR (KBr) 3638, 3386,1540 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.3 (*s*, 18H), 2.9 (*d*, *J* = 4.4 Hz, 3H), 6.9 (*s*, 1H), 7.1 (*s*, 2H), 7.2–7.5 (*m*, 5H), 7.7 (*s*, 1H), 8.3 (*m*, 1H), 9.5 (*s*, 1H); MS (EI) m+1/z 401; Anal. calcd for $C_{23}H_{32}N_2O_2S$: C, 68.96; H, 8.05; N, 6.99; S, 8.00; found: C, 68.93; H, 8.12; N, 6.77; S, 7.73.

N-*[1-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl]*--N-*hydroxyurea (13).* A mixture of 37.3 g (150 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxyacetophenone, 45.0 g (550 mmol) of NaOAc and 34.7 g (500 mmol) of hydroxylamine hydrochloride in 350 mL of MeOH was stirred at room temperature for 20 h. The reaction mixture was evaporated to dryness and washed with H_2O and the resultant solid was recrystallized from MeOH:tetrahydrofuran:hexane to provide 34.4 g (87%) of 3,5-bis(1,1-dimethylethyl)-4-hydroxyacetophenone oxime, mp 212–215°C.

To an ice-water cooled solution of 26.3 g (100 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxyacetophenone oxime in 500 mL of HOAc was added 31.4 g (500 mmol) of sodium cyanoborohydride over 18 min. The mixture was stirred for 45 min at room temperature then evaporated to dryness. The residue was treated with 500 mL of ice cold 2 N NaOH and the solution was brought to room temperature, then acidified to pH 5 with 100 mL of HOAc. The precipitate was collected and washed with H_2O followed by Et_2O. The crude product was recrystallized from HOAc: Et_2O to provide 8.45 g (32%) of 2,6-bis(1,1-dimethylethyl)4-[1-(hydroxyamino)ethyl] phenol acetate, mp 150.5–152°C.

To a solution of 814 mg (2.5 mmol) of 2,6-bis(1,1-dimethylethyl)4-[1-(hydroxyamino)ethyl]phenol acetate in 10 mL of tetrahydrofuran was added 868 mg (7.5 mmol) of 85% trimethylsilyl isocyanate. The reaction mixture was heated at reflux for 45 min then allowed to stand at room temperature for 16 h. The mixture was poured into a saturated aqueous NH_4Cl solution then partially concentrated to remove the tetrahydrofuran. The product was extracted into EtOAc and dried over Na_2SO_4. Recrystallization of the residue from Et_2O:hexane gave 460 mg (60%) of **13**, mp 162–163.5°C; IR (KBr) 1648, 1559, 1436 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4 (*s*, 18H), 1.5 (*d*, *J* = 7.0 Hz, 3H), 5.1 (*br s*, 2H), 5.2 (*s*, 1H), 5.5 (*q*, *J* = 7.0 Hz, 1H), 5.9 (*s*, 1H), 7.2 (*s*, 2H); MS (EI) m+1/z 309. Anal. calcd for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15; N, 9.08; found: C, 66.16; H, 9.17; N, 8.90

1-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-2-propanone (14). To a 0°C solution of 3.0 g (12.6 mmol) of 2,6-bis(1,1-dimethylethyl)-4-mercaptophenol and 2.0 mL (25.2 mmol) of pyridine in 100 mL of CH_2Cl_2 was added 2.0 mL (25.2 mmol) of chloroacetone. The reaction was allowed to warm to room temperature. After 3 h the reaction was cooled to 0°C, and the addition of pyridine and chloroacetone was repeated. The reaction was warmed at room temperature for 4 h then partitioned between EtOAc and a dilute aqueous HCl solution. The organic layer was washed four times with H_2O, followed by brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was crystallized from EtOAc:hexane to yield 2.8 g (75%) of **14**, mp 105–106°C; IR (KBr) 2967, 1699, 1424, 1238 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4 (*s*, 18H), 2.3 (*s*, 3H), 3.6 (*s*, 2H), 5.3 (*s*, 1H), 7.2 (*s*, 2H); MS (EI) m/z 294; Anal. calcd for $C_{17}H_{26}O_2S$: C, 69.34; H, 8.90; S, 10.89; found: C, 69.35; H, 8.92; S, 10.97

1-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-2-propanone (14) via 2,6-bis(1,1-dimethylethyl)-4-[2-(hydroxypropyl)thio]phenol

To a room temperature solution of 4.0 g (16.8 mmol) of 2,6-bis(1,1-dimethylethyl)-4-mercaptophenol and 2.0 mL (28.5 mmol) of propylene oxide in 100 mL of degassed EtOH was added 2.3 g (16.8 mmol) of K_2CO_3. After 2 h, the reaction was diluted with EtOAc and washed with a dilute aqueous HCl solution, then H_2O, followed by brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography, eluting with EtOAc:hexane yielding 4.2 g (84%) of 2,6-bis(1,1-dimethylethyl)-4-[2-(hydroxypropyl)thio] phenol as a heavy oil which slowly crystallized, mp 81–83°C; IR (KBr) 2971, 1422, 1233 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3 (*d*, *J* = 6.0 Hz, 3H), 1.4 (*s*, 18H), 2.6 (*d*, *J* = 2.7 Hz, 1H), 2.7–3.0 (*m*, 2H), 3.8 (*m*, 1H), 5.3 (*s*, 1H), 7.3 (*s*, 2H); MS (EI) m/z 296; Anal. calcd for $C_{17}H_{28}O_2S$: C, 68.87; H, 9.44; Found: C, 68.61; H, 9.44

To a –10°C solution of 2.4 g (8.1 mmol) of 2,6-bis(1,1-dimethylethyl)-4-[2-(hydroxypropyl)thio] phenol and 3.4 mL (24.8 mmol) of triethylamine in 80 mL of CH_2Cl_2 was added a room temperature solution of 3.9 g (24.3 mmol) of SO_3–pyridine complex in 80 mL of

dimethylsulfoxide. After 4.5 h the reaction was diluted with Et_2O. The solution was washed twice with aqueous citric acid, three times with H_2O, then once with saturated aqueous sodium bicarbonate, followed by brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 2.3 g (80%) of **14** as a pale yellow solid; ^1H NMR ($CDCl_3$): δ 1.4 (*s*, 18H), 2.3 (*s*, 3H), 3.6 (*s*, 2H), 5.3 (*s*, 1H), 7.2 (*s*, 2H).

1-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-2-propanone oxime (15). A room temperature solution of 1.0 g (3.4 mmol) of **14**, 300 mg (3.7 mmol) of hydroxylamine hydrochloride, and 0.3 mL (3.7 mmol) of pyridine in 34 mL of EtOH was stirred for 30 min. The reaction was diluted with EtOAc and washed four times with H_2O and once with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography, eluting with EtOAc:hexane to give a total of 1.0 g (97%) of **15**. Most of the material eluted as a mixture of both *E* and *Z* isomers. Those fractions containing only one isomer were concentrated and NOE experiments were used to confirm the sterochemistry. **15a** = *E* isomer: mp 118–122°C; IR (KBr) 3637, 2960, 1424, 1235, cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4 (*s*, 18H), 2.0 (*s*, 3H), 3.5 (*s*, 2H), 5.2 (*s*, 1H), 7.2 (*s*, 2H), 7.9 (*s*, 1H); MS (EI) m/z 309; Anal. calcd for $C_{17}H_{27}NO_2S$: C, 65.98; H, 8.79; N, 4.53; S, 10.36; found: C, 65.96; H, 8.54; N, 4.16; S, 10.41

15b = *Z* isomer: mp 121–123°C; IR (KBr) 3635, 2958, 1425 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4 (*s*, 18H), 1.9 (*s*, 3H), 3.7 (*s*, 2H), 5.2 (*s*, 1H), 7.3 (*s*, 2H), 8.1 (*s*, 1H); MS (EI) m/z 309; Anal. calcd for $C_{17}H_{27}NO_2S$: C, 65.98; H, 8.79; N, 4.53; S, 10.36; found: C, 66.27; H, 8.80; N, 4.26; S, 9.98.

2,6-Bis(1,1-dimethylethyl)-4-[[2-(hydroxyamino)propyl]thio] phenol (16). A room temperature solution of 1.0 g (3.2 mmol) of **15** and 1.6 mL (16.2 mmol) of borane–pyridine complex in 32 mL of MeOH was stirred for 10 min followed by the addition of 2.7 mL (16.2 mmol) of 6 N HCl. The reaction was stirred for 2 h, then partitioned between Et_2O and H_2O. The organic phase was washed three times with H_2O, twice with saturated aqueous sodium bicarbonate, and once with brine, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 500 mL of MeOH:$CHCl_3$ (1:99) followed by MeOH:$CHCl_3$ (2:98) to yield 0.85 g (84%) of **16**, mp 149–153°C (dec); IR (KBr) 3583, 2941, 1422, 1236, 1115 cm^{-1}; ^1H NMR (DMSO- d_6): δ 1.0 (*d*, *J* = 6.5 Hz, 3H), 1.4 (*s*, 18H), 2.6–2.7 (*m*, 1H), 2.9 (*m*, 1H), 3.1–3.2 (*m*, 1H), 5.6 (*s*, 1H), 7.0 (*s*, 1H), 7.1 (*s*, 2H), 7.3 (*s*, 1H); MS (EI) m/z 311; Anal. calcd for $C_{17}H_{29}NO_2S$: C, 65.55; H, 9.38; N, 4.50; S, 10.29; found: C, 65.43; H, 9.48; N, 4.36; S, 10.44.

N-*[2-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-1-methylethyl]*-N-*hydroxy urea (17).* To a 0°C solution of 0.20 g (0.64 mmol) of **16** and 0.21 g (3.2 mmol) of sodium cyanate in 6 mL of tetrahydrofuran was added 0.53 mL (3.2 mmol) of 6 N HCl. The reaction was stirred at 0°C for 30 min and at room temperature for 1 h, then diluted with Et_2O and washed once with a dilute aqueous sodium bicarbonate solution, three times with H_2O, then once with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography, eluting with EtOAc:CH_2Cl_2 (3:7). Co-evaporation with Et_2O:hexane gave **17** as an amorphous solid; IR (KBr) 2960, 1653, 1647, 1426, cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.1 (*d*, *J* = 6.9 Hz, 3H), 1.4 (*s*, 18H), 2.6–2.8 (*m*, 1H), 2.9–3.1 (*m*, 1H), 4.2 (*m*, 1H), 6.3 (*s*, 2H) 7.0 (*s*, 1H), 7.1 (*s*, 2H), 9.0 (*s*, 1H); MS (EI) m/z 354; Anal. calcd for $C_{18}H_{30}N_2O_2S$: C, 60.98; H, 8.53; N, 7.90; S, 9.04; found: C, 61.18; H, 8.66; N, 7.50; S, 9.14.

N-*[2-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-1-methylethyl]*-N-*hydroxy acetamide (18).* To a 0°C solution of 0.20 g (0.64 mmol) of **16** and 0.62 mL (0.77 mmol) of pyridine in 6.5 mL of CH_2Cl_2 was added 0.46 mL (0.64 mmol) of acetyl chloride. After 5 min the reaction was diluted with Et_2O and washed twice with H_2O and once with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified twice by chromatography, eluting with Et_2O:hexane (8:2) yielding 0.95 g (41%) of **18** as an amorphous solid; IR (KBr) 2957, 1616, 1425, 1234 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.1 (*d*, *J* = 6.7 Hz, 3H), 1.4 (*s*, 18H), 2.0 (*s*, 3H), 2.7–2.9 (*m*, 1H), 2.9–3.1 (*m*, 1H), 4.5 (*m*, 1H), 7.1 (*s*, 1H), 7.2 (*s*, 2H), 9.5 (*s*, 1H); MS (EI) m/z 353; Anal. calcd for $C_{19}H_{31}NO_3S{\cdot}2H_2O$: C, 63.90; H, 8.86; N, 3.92; Found: C, 63.90; H, 8.78; N, 3.64.

N-*[2-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-1-methylethyl]*-N-*hydroxy*-N'-*methyl thiourea (19).* To a 0°C solution of 200 mg (0.64 mmol) of **16** in 6 mL of tetrahydrofuran was added a room temperature solution of 60 mg (0.83 mmol) of methyl isothiocyanate in 6 mL of tetrahydrofuran. The reaction was stirred for 1 h at 0°C then 1 h at room temperature then diluted with Et_2O and washed three times with H_2O and once with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography eluting with EtOAc:CH_2Cl_2 (12:88) followed by recrystallization from MeOH:H_2O to yield 200 mg (87%) of **19**, mp 152–153°C; IR (KBr) 3376, 2957, 1540, 1425 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.1 (*d*, *J* = 6.7 Hz, 3H), 1.4 (*s*, 18H), 2.7–2.8 (*m*, 1H), 2.9 (*d*, *J* = 4.4 Hz , 3H), 3.0–3.1 (*m*, 1H), 5.3 (*m*, 1H), 7.1 (*s*, 1H), 7.2 (*s*, 2H), 8.2 (*q*, *J* = 4.4 Hz, 1H), 9.5 (*s*, 1H); MS (EI) m/z 384; Anal. calcd for $C_{19}H_{32}N_2O_2S_2$: C, 59.34; H, 8.38; N, 7.28; Found: C, 59.29; H, 8.36; N, 7.12.

Acknowledgement

We thank the Parke-Davis Analytical Chemistry Department for obtaining the spectral data and elemental analyses.

References and Notes

1. Lombardino, G. *Nonsteroidal Antiinflammatory Drugs*; Wiley Interscience, John Wiley and Sons; New York, 1985; Baum, C; Kennedy, D. L.; Forbes, M. B. *Arthritis Rheum.* **1985**, *28*, 686.

2. Gabriel, S. E.; Bombardier, C. *J. Rheumatol.* **1990**, *17*, 1; Soll, A. H. *Ann. Int. Med.* **1991**, *114*, 307; Allison, M. C.; Howatson, M. B.; Torrance, M. B.; Lee, F. D.; Russell, R. L. *N. Engl. J. Med.* **1992**, *327*, 749.

3. Belch, J. J. F. *Prost. Leuk. Essent. Fatty Acids* **1989**, *36*, 219; Vaananen, P. M.; Keenan, C. M.; Grisham, M. B.; Wallace, J. L. *Inflammation* **1992**, *18*, 227.

4. For a review on dual inhibitors see: Carty, T. J.; Marfat, A.; Masamune, H. *Ann. Rep. Med. Chem.* **1988**, *23*, 181.

5. Mikami, T.; Miyazawa, K.; Miyasaki, K.; Susuki, Y. *Jap. J. Pharm.* **1988**, *46(suppl.)*, 89; Kobayashi, M.; Nozaki, M.; Tsurumi, K.; Mikami, T.; Miyasaki, K. *Jap. J. Pharm.* **1988**, *46(suppl.)*, 296.

6. Serradell, M. N.; Castaner, J.; Castaner, R. M., *Drugs Fut.* **1989**, *14*, 307.

7. Kramer, J. B.; Boschelli, D. H.; Connor, D. T.; Kostlan, C. R.; Kuipers, P. J.; Kennedy, J. A.; Wright, C. D.; Bornemeier, D. A.; Dyer, R. D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2827.; Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090; Flynn, D. L.; Capiris, T.; Cetenko, W. J.; Connor, D. T.; Dyer, R. D.; Kostlan, C. R.; Nies, D. E.; Schrier, D. J.; Sircar, J. C. *J. Med. Chem.* **1990**, *33*, 2070.

8. Unangst, P. C.; Connor, D. T.; Cetenko, W.A.; Sorenson, R. J.; Kostlan, C. R.; Sircar, J. C.; Wright, C. D.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1994**, *37*, 322.

9. Cook, C. D.; Gilmour, N. D. *J. Org. Chem.* **1960**, *25*, 1429.

10. For examples of alternate preparations of **5** see: Krull, I. S.; Schuster, D. I. *Tetrahedron Lett.* **1968**, *2* 135; Nishinaga, A.; Nakamura, K; Matsuura, T.; Rieker, A.; Koch, D.; Griesshammer, R. *Tetrahedron* **1979**, *35*, 2493.

11. The whole cell assays used to determine the inhibition of 5-LO and of CO and the protocols for the CFE and MFE assays were described previously, see Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. *J. Med. Chem.* **1993**, *36*, 1802.

12. Batt, D. G. *Prog. Med. Chem.* **1992**, *29*, 1.

13. Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J.; Dyer, R.; Bell, R. L.; Summers, J. B.; Brooks, D. W. *J. Pharmacol. Exp. Ther.* **1991**, *256*, 929.

14. 3,5-Bis(1,1-dimethylethyl)-4-hydroxyacetophenone oxime is known but its preparation was not reported, see: Ivakhnenko, E. P.; Prokofev, A. I.; Shif, A. I.; Kompan, O. E.; Yufit, D. S.; Struchkov, Yu. T.; Kletskii, M. E.; Olekhnovich, L. P.; Minkin, V. I. *Zh. Org. Khim.* **1987**, *23*, 2273.

15. Muller, R. A.; Partis R. A. Deason, J. R. *US Patent* 4,711,903 (1987).

16. Schrier, D. J.; Baragi, V. M.; Connor, D. T.; Dyer, R. D.; Jordan, J. H.; Imre, K. M.; Lesch, M. E.; Mullican, M. D.; Okonkwo, G. C. N.; Conroy, M. C. *Prostaglandins* **1994**, *47*, 17.

(*Received in U.S.A.* 20 *November* 1994; *accepted* 17 *January* 1995)