Dibenzoxepinone Hydroxylamines and Hydroxamic Acids: Dual Inhibitors of Cyclooxygenase and 5-Lipoxygenase with Potent Topical Antiinflammatory Activity

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Hydroxylamine and hydroxamic acid derivatives of a known nonsteroidal antiinflammatory dibenzoxepine series display both cyclooxygenase (CO) and 5-lipoxygenase (5-LO) inhibitory properties. Many of these new dual CO/5-LO inhibitors also exhibit potent topical antiinflammatory activity in the arachidonic acid-induced murine ear edema model. On the basis of their promising profile of *in vitro* and *in vivo* activities, hydroxamic acids **24h**, 3-(6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)-*N*-hydroxy-*N*-methylpropanamide (HP 977), and **25**, 3-(6,11-dihydrodibenz[*b*,*e*]oxepin-2-yl)-*N*-hydroxy-*N*-methylpropanamide (P10294), were selected as developmental candidates for the topical treatment of inflammatory skin disorders.

Introduction

Eicosanoids have been implicated as mediators in numerous inflammatory processes, and the role of these 20-carbon unsaturated fatty acids in the pathogenesis of inflammatory skin disorders has received considerable attention in recent dermatological research. Cutaneous inflammatory disorders, such as atopic dermatitis, eczema, and psoriasis,[1] display elevated epidermal levels of eicosanoids.[2] Elevations in both prostaglandins[3] ($PGE_2/PGF_{2\alpha}$) and leukotrienes[4,5] (LTB_4) have been reported in psoriatic skin. Topical corticosteroids impart potent antiinflammatory effects in a variety of skin disorders, albeit with significant side effect liability especially on chronic administration. Topical steroids have been shown to attenuate arachidonate and LTB_4 release[6] and inhibit phospholipase A_2.[7] Classical nonsteroidal antiinflammatory (NSAID) agents, such as ibuprofen, have been found to impart physiological action primarily via inhibition of the cyclooxygenase (CO) pathway. The potent CO inhibitor indomethacin, however, was found to exacerbate rather than ameliorate psoriasis, implying the importance of the lipoxygenase pathways.[8] With this in mind, we chose to explore the concurrent blockade of the two major metabolic pathways of the cascade, i.e., dual inhibition of the CO and 5-lipoxygenase (5-LO) enzymes, as a potentially viable approach to antipsoriatic therapy.

Corey's early discovery that arachidonate hydroxamic acid inhibits 5-LO *in vitro*[9] sparked a flurry of medicinal research toward specific 5-LO inhibitors with antiinflammatory activity.[10] We and others[11] saw the potential of generating dual CO/5-LO inhibitors by incorporating a hydroxamate moiety into a known CO inhibitory NSAID nucleus such as isoxepac[12] (Figure 1). In addition, since aralkylhydroxylamines such as QA-208,199 have been reported to be potent lipoxygenase inhibitors,[13] we also replaced the carboxylate with substituted hydroxylamines to further explore structure−activity relationships (SAR). Other published reports[14] led us to explore several reverse hydroxamate derivatives.

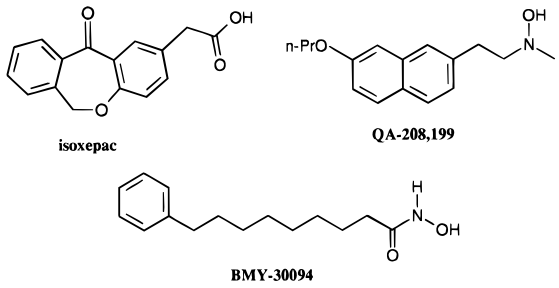

Figure 1. Reference antiinflammatory agents.

Herein are described the synthesis and SAR of this new series of *N*-hydroxy-(6,11-dihydro-11-oxodibenz[*b*,*e*]-oxepin-2-yl)alkanamines and -alkanamides and related reverse amide derivatives as topically effective dual CO/5-LO inhibitors. Compounds **24h** and **25** were selected for toxicological assessment.

Chemistry

The synthetic sequence utilized in the preparation of the required dibenzoxepine intermediates is outlined in Scheme 1. The construction of the dibenzoxepine nucleus utilized methodology developed for the related thieno[3,2-*c*][1]benzoxepinone alkanols.[15] α-(Bromomethyl)benzoates **1a,b** were condensed with (4-hydroxyphenyl)propanol (**2**), 4-salicylaldehyde (**3**), or ethyl (4-hydroxyphenyl)alkanoates **4** with K_2CO_3 in 2-butanone to afford ethyl 2-[(aryloxy)methyl]benzoates which were directly saponified to the corresponding acids **5** and **6** and diacid **7**. Cyclodehydration of **5**, **6**, or **7** with trifluoroacetic anhydride provided dibenz[*b*,*e*]oxepin-2-alkanol **8a**, 2-carboxaldehyde **9**, and 2-alkanoic acids **10a**−**d**. Reduction of 2-acetic acid **10a** with borane−THF provided a separable mixture of 2-ethanol **8b** and desoxo-2-ethanol **11**. Zinc in refluxing acetic acid selectively reduced dibenzoxepinonepropanoic acid **10c** to the dibenzoxepinepropanoic acid **12**.

The *N*-hydroxydibenz[*b*,*e*]oxepin-2-alkanamines were prepared as shown in Scheme 2. Conversion of alkanols **8a**,**b** and **11** to their methanesulfonates **13a**,**b** and **14** followed by nucleophilic displacement with secondary hydroxylamines yielded the desired aralkylhydroxylamines **15a**−**d** and the desoxo analog **17**, respectively.

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

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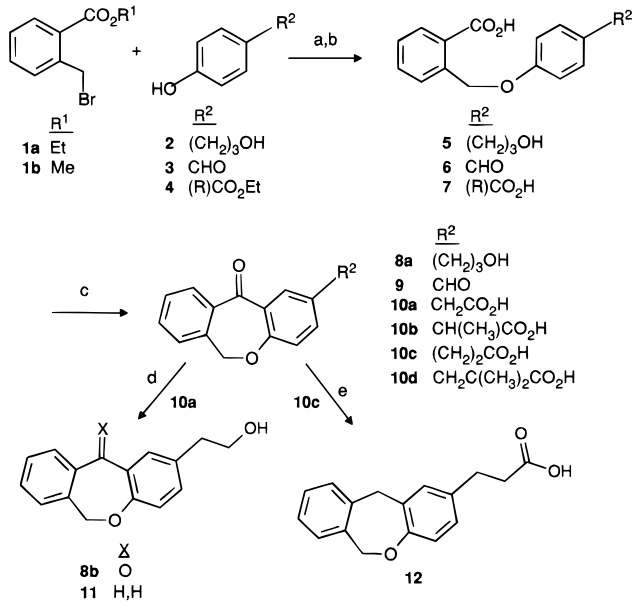
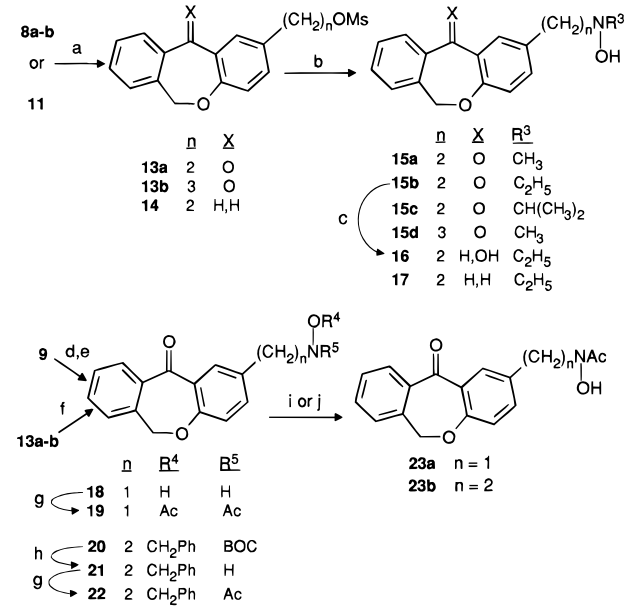
Scheme 1. Dibenzoxepin Intermediates[a]



[a] (a) K_2CO_3, 2-butanone; (b) KOH, aqueous EtOH; (c) trifluoroacetic anhydride, CH_2Cl_2; (d) borane−THF; (e) Zn, HOAc.

Scheme 2. Hydroxylamine Derivatives[a]



[a] (a) CH_3SO_3Cl, Et_3N; (b) R_3NHOH-HCl, KOtBu; (c) $NaBH_4$; (d) NH_2OH-HCl, pyridine; (e) borane−pyridine; (f) Boc-NHOBn, NaH, DMF; (g) AcCl, Et_3N; (h) HCl(g), EtOAc; (i) LiOH; (j) 5% Pd/C, HCO_2NH_4.

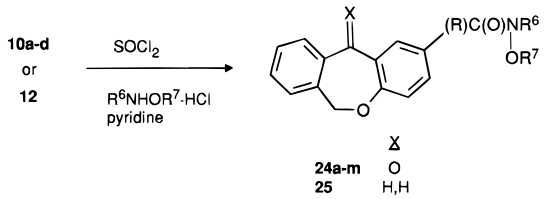
Borohydride reduction of ethylhydroxylamine **15b** provided the diarylmethanol analog **16**.

The one- and two-carbon-linked reverse *N*-acetyl-*N*-hydroxydibenz[*b*,*e*]oxepin-2-alkanamines **23a,b** were prepared as illustrated in Scheme 2. Conversion of aldehyde **9** to its oxime followed by borane−pyridine reduction yielded hydroxylamine **18**. N,O-Diacetylated derivative **19** was subjected to selective hydrolysis with LiOH[14] to provide (arylmethyl)-*N*-hydroxyacetamide **23a**.

An alternate route was used in the preparation of the two-carbon-linked derivative due to difficulties in the preparation of the corresponding acetaldehyde needed for the above methodology. Methanesulfonate **13a** was condensed with *N*-Boc-*O*-benzylhydroxylamine[16] to give compound **20**. Boc-deprotection and acetylation provided *N*-(benzyloxy)amine **21** and *N*-(benzyloxy)acetamide **22** successively. Ammonium formate hydrogenolysis of **22** resulted in (arylethyl)-*N*-hydroxyacetamide **23b**.

Physiochemical data for (hydroxylamino)alkyl compounds **15a**−**d**, **16**, and **17** and for the reversed *N*-hydroxyamides **23a,b** are summarized in Table 1. Treatment of the acid chlorides of compounds **10a**−**d** and **12** with various hydroxylamines yielded hydroxamic acids **24a**−**m** and **25**, respectively. Physiochemical data for hydroxamic acids **24a**−**m** and **25** are summarized in Table 2.

Scheme 3. Hydroxamic Acids



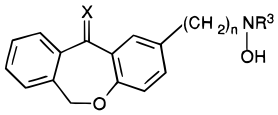
Biological Results and Discussion

Biological assay results for (hydroxylamino)alkyl compounds **15a**−**d**, **16**, and **17** and for the reversed *N*-hydroxyamides **23a,b** are summarized in Table 3. Table 4 contains similar data for hydroxamic acids **24a**−**m** and **25**. The 5-LO inhibitory activity of these compounds was assessed by measurement of 5-HETE levels utilizing the method of Cochran and Finch-Arietta[17] with RBL-1 cell-free supernatant prepared according to the method of Jakschik and Kuo.[18] The CO inhibitory potency was evaluated by attenuation of PGE_2 levels in cultured 3T3 fibroblasts by the method of Lindgren.[19] Topical antiinflammatory activity was determined via the arachidonic acid-induced mouse ear edema model of Young[20] using a 3:7 propylene glycol: ethanol vehicle. This vehicle was utilized due to its reduced volatility, improved reproducibility, and relevancy to known topical vehicles versus the reported vehicle acetone.

The (hydroxylamino)alkyl compounds **15a**−**d**, **16**, and **17** and the reversed *N*-hydroxyamides **23a,b** in Table 3 all displayed potent *in vitro* 5-LO and CO inhibition and *in vivo* topical antiinflammatory activity. Primary differences occurred in their relative CO inhibitory potencies. Methyl- and ethylhydroxylamines **15a,b** were nearly 1 order of magnitude more potent than the corresponding isopropylhydroxylamine **15c**. Reduction of the diaryl ketone unit of **15b** to the diarylmethanol **16** had no effect on *in vitro* potency; however, further reduction to the diarylmethane **17** caused a 5-fold reduction in CO inhibitory activity. Extending the methylene linker in *N*-acetyl derivative **23a** to the two-carbon homolog **23b** had no effect on *in vitro* activity but produced a modest improvement in topical activity.

A more diverse SAR was observed with hydroxamic acids **24a**−**m** and **25** in Table 4. Among the aryl acetamides **24a**−**e**, *N*-alkylation appears important for both 5-LO inhibition and topical antiinflammatory activity. As seen in other studies, unsubstituted **24a** was almost 10-fold weaker against 5-LO[21] and nearly devoid of *in vivo* activity in the arachidonic acid ear edema model. Alkyl analogs **24b**−**e** all have micromolar 5-LO potency. Increasing steric bulk in *N*-cyclohexyl

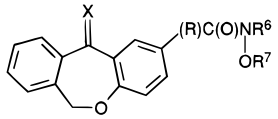
Table 1. Physicochemical Data of (Hydroxylamino)alkyl Analogs[a]



no.	*n*	X	R^3	starting material	method	mp[b] (°C)	yield[c] (%)	recrystn solvent[d]	formula	anal.[e]
15a	2	O	CH_3	**8b**	A	101−102	19	A	$C_{17}H_{17}NO_3$	C,H,N
15b	2	O	C_2H_5	**8b**	A	86−88[f]	42		$C_{18}H_{19}NO_3$	C,H,N
15c	2	O	$CH(CH_3)_2$	**8b**	A	122−124	32	B	$C_{19}H_{21}NO_3$	C,H,N
15d	3	O	CH_3	**8a**	A	113−114.5	52	B	$C_{18}H_{19}NO_3$	C,H,N
16	2	H, OH	C_2H_5	**15b**	B	116−118	65	C	$C_{18}H_{21}NO_3$	C,H,N
17	2	H, H	C_2H_5	**11**	A	102−103	23	C/D	$C_{18}H_{21}NO_2$	C,H,N
23a	1	O	$C(O)CH_3$	**19**	C	129−130	52	E/F	$C_{17}H_{15}NO_4$	C,H,N
23b	2	O	$C(O)CH_3$	**22**	D	113−115	71	E/F	$C_{18}H_{17}NO_4$	C,H,N

[a] All compounds exhibited IR, ^{1}H NMR, and MS spectra consistent with the assigned structure. [b] Melting points are uncorrected. [c] Yields were calculated from the indicated starting material unless otherwise noted and are not optimized. [d] A = methanol; B = acetonitrile; C = ethyl ether; D = cyclohexane; E = ethyl acetate; F = hexane; G = ethanol; H = acetone. [e] Analytical results are within ±0.4% of theoretical values unless otherwise noted. [f] Chromatographed, unrecrystallized.

Table 2. Physicochemical Data of Hydroxamic Acid Analogs[a]



no.	X	R	R^6	R^7	starting material	mp[b] (°C)	yield[c,g] (%)	recrystn solvent[d]	formula	anal.[e]
24a	O	CH_2	H	H	**10a**	152−155	34	G	$C_{16}H_{13}NO_4$	H,N,C[h]
24b	O	CH_2	CH_3	H	**10a**	118−120	17	H	$C_{17}H_{15}NO_4$	C,H,N
24c	O	CH_2	C_2H_5	H	**10a**	119−121	49	H	$C_{18}H_{17}NO_4$	C,H,N
24d	O	CH_2	iC_3H_7	H	**10a**	144−145	40	H	$C_{19}H_{19}NO_4$	C,H,N
24e	O	CH_2	cC_6H_{13}	H	**10a**	130−131	51	H	$C_{22}H_{23}NO_4$	C,H,N
24f	O	$CH(CH_3)$	CH_3	H	**10b**		68	oil	$C_{18}H_{17}NO_4$	C,H,N
24g	O	$CH(CH_3)$	C_2H_5	H	**10b**		30	oil	$C_{19}H_{19}NO_4$	H,N,C[i]
24h	O	$(CH_2)_2$	CH_3	H	**10c**	101−103	64	E	$C_{18}H_{17}NO_4$	C,H,N
24i	O	$(CH_2)_2$	C_2H_5	H	**10c**	120−121	47	E/F	$C_{19}H_{19}NO_4$	C,H,N
24j	O	$(CH_2)_2$	iC_3H_7	H	**10c**	117−118	29	H/D	$C_{20}H_{21}NO_4$	C,H,N
24k	O	$(CH_2)_2$	cC_6H_{13}	H	**10c**	146−147	31	E/F	$C_{23}H_{25}NO_4$	C,H,N
24l	O	$(CH_2)_2$	CH_3	CH_3	**10c**	112−114	60	E	$C_{19}H_{19}NO_4$	C,H,N
24m	O	$CH_2C(CH_3)_2$	CH_3	H	**10d**	192−194	55	E/A	$C_{20}H_{21}NO_4$	C,H,N
25	H, H	$(CH_2)_2$	CH_3	H	**12**	120−122	50	E	$C_{18}H_{19}NO_3$	C,H,N

[a−e] See Table 1. [g] Method E. [h] Anal. ($C_{16}H_{13}NO_4$) H, N; C: calcd, 67.84; found, 67.11. [i] Anal. ($C_{19}H_{19}NO_4$) H, N; C: calcd, 70.14; found, 69.64.

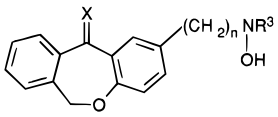
24e significantly decreased topical effectiveness relative to *N*-methyl-, -ethyl-, and -isopropylacetamides **24b**−**d**. α-Methylation (**24f,g**) also diminished *in vivo* potency. Lengthening the acetamide chain of *N*-methyl **24b** by a methylene unit to **24h** produced a marked 120-fold enhancement in 5-LO inhibitory potency. The related *N*-alkylpropanamides **24i**−**k** displayed a more modest 2−4 fold improvement in 5-LO potency. O-Methylation of the hydroxamide moiety (**24l**) negated 5-LO activity as has been previously observed.[21] The SAR trend for ear edema activity of **24i**−**k** followed that seen with the corresponding acetamides. α,α-Dimethylation (**24m**) caused a 10-fold reduction in 5-LO potency versus **24h** and surprisingly produced a proinflammatory response in the arachidonic acid ear edema assay. Finally, diarylmethane analog **25** retained the potent antiinflammatory profile of **24h**.

In vivo dose-ranging studies led to the selection of *N*-methylhydroxamic acids **24h** and **25** as the most promising candidates for further study. The bioprofile of these compounds relative to standards is highlighted in Table 5. Compounds **24h** and **25** are among the most potent 5-LO inhibitors known. They are nearly 10-fold more potent at inhibiting cell-free 5-LO than the antioxidant nordihydroguaiaretic acid (NDGA)[21] and more than 25-fold more potent than the topical dual 5-LO/CO inhibitor BMY-30094.[22] To address cell penetration concerns, compound **24h** was also evaluated in an A-23187-stimulated HL-60 whole cell 5-LO assay and found to possess similar potency to that seen in the cell-free assay. Compounds **24h** and **25** are mild CO inhibitors being slightly weaker than ibuprofen and BMY-30094 but 30−50-fold weaker than indomethacin. Compounds **24h** and **25** displayed potent topical anti-inflammatory activity in the arachidonic acid ear edema model relative to topical agents NDGA and BMY-30094. Isoxepac was inactive in both the *in vitro* 5-LO and *in vivo* ear edema assays. On the basis of this profile, compounds **24h** and **25** were selected for more in depth biological evaluation (to be reported elsewhere) and toxicological assessment.

Experimental Section

Chemistry. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-200 spectrometer using tetramethylsilane as an internal standard. IR

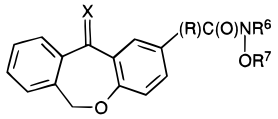
Table 3. Biological Data of (Hydroxylamino)alkyl Analogs **15**−**17** and Reversed Hydroxyamides **23a**,**b**[a]



				IC$_{50}$ (μM)		
no.	*n*	X	R^3	5-HETE[b]	PGE$_2$[c]	AAEE[d] change (%)
15a	2	O	CH_3	0.24 (0.21−0.26)	0.08 (0.02−0.75)	−46**
15b	2	O	C_2H_5	0.48 (0.44−0.52)	0.19 (0.06−1.28)	−50**
15c	2	O	$CH(CH_3)_2$	0.13 (0.09−0.13)	(−47%)*	−47**
15d	3	O	CH_3	0.62 (0.58−0.63)	0.24 (0.21−0.28)	−53**
16	2	H, OH	C_2H_5	0.45 (0.41−0.49)	0.12 (0.01−1.95)	−47**
17	2	H, H	C_2H_5	0.32 (0.32−0.34)	0.46 (0.14−1.05)	−50**
23a	1	O	$C(O)CH_3$	0.21 (0.12−0.34)	0.75 (0.15−10.82)	−47**
23b	2	O	$C(O)CH_3$	0.19 (0.18−0.20)	(−53%)**	−61**

[a] Where indicated, significance was determined by the Students *T*-test: * indicates $p < 0.05$; ** indicates $p < 0.01$. [b] Inhibition of 5-HETE levels in RBL-1 cell-free supernatant. Number in parentheses represents 95% confidence range or percent change at 50 μM. [c] Inhibition of PGE$_2$ levels in murine 3T3 fibroblast culture. Number in parentheses represents 95% confidence range or percent change at 1.0 μM. [d] Percent change in arachidonic acid-induced mouse ear edema versus vehicle (70:30 ethanol:propylene glycol) control at 1.0 mg/ear.

Table 4. Biological Data of Hydroxamic Acid Analogs[a]



					IC$_{50}$ (μM)		
no.	X	R	R^6	R^7	5-HETE[b]	PGE$_2$[c]	AAEE[d] change (%)
24a	O	CH_2	H	H	9.0 (8.35−9.22)	(−86%)**	−19
24b	O	CH_2	CH_3	H	1.19 (1.14−1.25)	>1.0	−63**
24c	O	CH_2	C_2H_5	H	0.58 (0.48−0.60)	(−47%)**	−52**
24d	O	CH_2	iC_3H_7	H	1.23 (1.12−1.36)	>1.0	−52**
24e	O	CH_2	cC_6H_{13}	H	0.67 (0.60−0.74)	>1.0	−29
24f	O	$CH(CH_3)$	CH_3	H	1.3 (1.26−1.53)	0.21 (0.06−0.40)	−44
24g	O	$CH(CH_3)$	C_2H_5	H	(−94%)**	(−62%)**	−38*
24h	O	$(CH_2)_2$	CH_3	H	0.01 (0.006−0.022)	0.53 (0.18−1.28)	−66**
24i	O	$(CH_2)_2$	C_2H_5	H	0.15 (0.14−0.15)	(−73%)**	−55**
24j	O	$(CH_2)_2$	iC_3H_7	H	0.58 (0.52−0.62)	(−45%)**	−63**
24k	O	$(CH_2)_2$	cC_6H_{13}	H	2.0 (1.75−2.12)	>1.0	−14
24l	O	$(CH_2)_2$	CH_3	CH_3	>50	NT	−41**
24m	O	$CH_2C(CH_3)_2$	CH_3	H	0.66 (0.52−0.85)	NT	+29
25	H, H	$(CH_2)_2$	CH_3	H	0.02 (0.019−0.029)	(−60%)**	−67**

[a−d] See Table 3.

Table 5. Comparative Biological Profiles of **24h** and **25** vs Standards[a]

	IC$_{50}$ (μM)		
compd	5-HETE[b]	PGE$_2$[c]	AAEE[d] ED$_{50}$ (mg/ear)
24h	0.01 (0.006−0.022)[e]	0.53 (0.18−1.28)	0.69 (0.60−0.80)
25	0.02 (0.019−0.029)	(−60%)**	0.70 (0.44−0.93)
NDGA[f]	0.12 (0.09−0.16)		3.10 (2.52−4.11)
BMY-30094	0.48 (0.42−0.55)	0.11 (0.02−0.48)	2.56 (2.12−3.53)
indomethacin		0.02 (0.008−0.05)	1.63 (1.22−2.38)
ibuprofen		0.22 (0.21−0.24)	(−11%)
isoxepac	(−1.5%)		(+55%)

[a−c] See Table 3. [d] Effective dose to produce a 50% reduction in arachidonic acid-induced mouse ear edema versus vehicle (70:30 ethanol: propylene glycol) control. Number in parentheses represents 95% confidence range or percent change at 1.0 mg/ear. [e] IC$_{50}$ (HL-60 whole cell 5-LO): 0.014 μM (0.0128−0.0161). Inhibition of 5-HETE levels in A-23187-stimulated HL-60 cell culture. Number in parentheses represents 95% confidence range. [f] NDGA = nordihydroguaiaretic acid.

spectra were recorded on a Perkin Elmer 841 or 1420 spectrometer. Mass spectra (MS) were generated with a Finnigan 4500 GC−MS instrument equipped with an INCOS data system. Elemental analysis (C,H,N) results are within ±0.4% of theoretical values unless indicated otherwise. Microanalyses were performed by Oneida Research Services, Inc., Whitesboro, NY. Reactions were routinely performed under N_2 atmosphere unless otherwise indicated.

2-[[4-(3-Hydroxypropyl)phenoxy]methyl]benzoic Acid (5). A solution of methyl 2-(bromomethyl)benzoate (**1b**; 87.6 g, 0.38 mol) in 2-butanone (500 mL) was added dropwise to a stirred suspension of 3-(4-hydroxyphenyl)propanol (**2**; 57.9 g, 0.38 mol), K_2CO_3 (157 g, 1.14 mol), and a catalytic amount of KI in 2-butanone (500 mL). The resulting mixture was warmed to reflux and maintained there for 24 h. After the mixture had cooled to room temperature, filtration and concentration gave an oil. A solution of the crude product in CH_2Cl_2 (500 mL) was washed with 10% aqueous NaOH (1500 mL) and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed via HPLC (Waters Associates Prep LC/

System 500, silica gel, 60% hexane/EtOAc) to give 68.7 g (60%) of methyl 2-[[4-(3-hydroxypropyl)phenoxy]methyl]benzoate as a solid: mp 50.5−52 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 1H), 1.87 (m, 2H), 2.65 (t, 2H, J = 6.6 Hz), 3.66 (t, 2H, J = 8.0 Hz), 3.9 (s,3H), 5.47 (s, 2H), 6.91 (d, 2H, J = 8.8 Hz), 7.10 (d, 2H, J = 8.6 Hz), 7.40 (t, 1H, J = 6.4 Hz), 7.58 (t, 1H, J = 7.4 Hz), 7.75 (d, 1H, J = 7.4 Hz), 8.0 (d, 1H, J = 7.8 Hz); EIMS 300 ($M^{\bullet+}$). Anal. ($C_{18}H_{20}O_4$) C, H.

A mixture of methyl 2-[[4-(3-hydroxypropyl)phenoxy]methyl]-benzoate (59.4 g, 0.20 mol) and KOH (127.1 g, 2.27 mol) in 95% ethanol (500 mL) was warmed to reflux and maintained there overnight. After cooling and diluting with water (900 mL), the mixture was acidified with concentrated HCl (200 mL) and partitioned with EtOAc (1 L). The organic extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was recrystallized (EtOH/water) to give 49.1 g of **5** as white needles: mp 139−140 °C; ^{1}H NMR (DMSO-d_6) δ 1.67 (m, 2H), 2.54 (t, 2H, J = 7.7 Hz), 3.40 (t, 2H, J = 6.6 Hz), 4.4 (br s, 1H), 5.41 (s, 2H), 6.88 (d, 2H, J = 8.8 Hz), 7.11 (d, 2H, J = 8.6 Hz), 7.43 (t, 1H, J = 7.3 Hz), 7.58 (m, 2H), 7.90 (d, 1H, J = 8.0 Hz), 13.0 (br s, 1H); EIMS 286 ($M^{\bullet+}$). Anal. ($C_{17}H_{18}O_4$) C, H.

Following this procedure, utilizing starting materials **3** and **4a**−**d** provided benzoic acids **6** and **7a**−**d**, respectively.[12,23,24]

3-(6,11-Dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)propanol (8a). Trifluoroacetic anhydride (82.7 g, 0.39 mol) was added dropwise to a suspension of **5** (46.7 g, 0.16 mol) in CH_2Cl_2 (500 mL). The resulting solution was warmed to reflux and maintained there for 4 h. After cooling and washing with water (200 mL), the organic extract was concentrated to give 56.6 g of a solid. A portion of the residue (54 g) was diluted with acetone (300 mL) and 10% aqueous HCl (250 mL), and the resulting solution was warmed to reflux and maintained there for 24 h. After cooling and concentration to remove acetone, the resulting mixture was brought to pH 8 with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (1 L). The organic extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed via HPLC (Waters Associates Prep LC/System 500, silica gel, 1:1 hexane: EtOAc) to give 38.8 g (86%) of **8a** as an oil: ^{1}H NMR (DMSO-d_6) δ 1.73 (m, 2H), 2.65 (t, 2H, J = 7.7 Hz), 3.42 (dd, 2H, J_1 = 6.4 Hz, J_2 = 11.6 Hz), 4.45 (t, 1H, J = 5.0 Hz), 5.27 (s, 2H), 7.03 (d, 1H, J = 8.4 Hz), 7.4−7.7 (m, 4H), 7.80 (d, 1H, J = 7.8 Hz), 7.90 (d, 1H, J = 2.4 Hz); EIMS 268 ($M^{\bullet+}$). Anal. ($C_{17}H_{16}O_3$) C, H.

Following this procedure, utilizing starting materials **6** and **7a**−**d** provided dibenzoxepinones **9** and **10a**−**d**, respectively.[12,23,24,25]

2-(6,11-Dihydrodibenz[*b,e*]oxepin-2-yl)ethanol (11). The preparation of 2-(6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)-ethanol[26] (**8b**) was reported via reduction of known 2-(6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)acetic acid[12] (**10a**) with borane−THF. Extending the reaction time at room temperature from 16 to 72 h, starting with **10a** (100 g, 0.37 mol) and 1.0 M borane−THF (0.37 mol), followed by flash chromatography (silica gel, 5:3 hexane:EtOAc) resulted in isolation of both **8b** (55.6 g, 59%) and **11** (14.8 g, 17%). Compound **11**, an oil, was used directly: ^{1}H NMR ($CDCl_3$) δ 2.74 (t, 2H, J = 6.7 Hz), 2.90 (br s, 1H), 3.80 (t, 2H, J = 6.7 Hz), 4.31 (s, 2H), 5.28 (s, 2H), 6.80 (d, 1H, J = 8.0 Hz), 6.88−7.08 (m, 2H), 7.10−7.33 (m, 4H).

3-(6,11-Dihydrodibenz[*b,e*]oxepin-2-yl)propanoic Acid (12). Zinc dust (18.0 g, 275 mmol) was added portionwise to a solution of **10c** (6.0 g, 21 mmol) in glacial acetic acid (120 mL). The resulting slurry was warmed to reflux and maintained there for 2 h. Filtration and concentration gave a residue that was taken up in EtOAc and washed with 2 N HCl. The organic extract was dried and concentrated and the resulting solid recrystallized (EtOAc) to give 4.3 g (76%) of **12** as white crystals: mp 181−183 °C; ^{1}H NMR (DMSO-d_6) δ 2.40−2.80 (m, 4H), 4.21 (s, 2H), 5.27 (s, 2H), 6.63 (d, 1H, J = 8.2 Hz), 6.89−6.98 (m, 2H), 7.22−7.34 (m, 4H), 12.10 (br s, 1H); EIMS 268 ($M^{\bullet+}$). Anal. ($C_{17}H_{16}O_3$) H; C: calcd, 76.10; found, 75.59.

2-(6,11-Dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)-*N*-ethyl-*N*-hydroxyethylamine (15b). Method A. *N*-Ethylhydroxylamine hydrochloride (3.95 g, 0.04 mol) was added to a solution of potassium *tert*-butoxide (4.48 g, 0.04 mol) in absolute EtOH (500 mL). 2-(6,11-Dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)ethanol methanesulfonate[23] (**13b**; 3.32 g, 0.01 mol) was added to the resulting suspension, and the slurry was warmed to reflux and maintained there for 4.5 h. The cooled mixture was diluted with water (500 mL) and concentrated. The resulting aqueous suspension was diluted with CH_2Cl_2 (500 mL) and washed with water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed via HPLC (Waters Associates Prep LC/System 500, silica gel, 20% hexane/EtOAc) to give 1.24 g (42%) of **15b** as a solid: mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J = 7.0 Hz), 2.77 (q, 2H, J = 7.0 Hz), 2.93 (s, 4H), 5.16 (s, 2H), 6.60 (br s, 1H), 6.98 (d, 1H, J = 8.4 Hz), 7.35−7.55 (m, 4H), 7.9 (d, 1H, J = 7.4 Hz), 8.1 (s, 1H); EIMS 297 ($M^{\bullet+}$). Anal. ($C_{18}H_{19}NO_3$) C, H, N.

The properties of **15a**,**c**,**d** and **17**, prepared in a similar manner from **8a**,**b**[26] and **11**, respectively, are included in Table 1.

2-(6,11-Dihydro-11-hydroxydibenz[*b,e*]oxepin-2-yl)-*N*-ethyl-*N*-hydroxyethylamine (16). Method B. A solution of **15b** (4.1 g, 13.7 mmol) in MeOH (100 mL) at 0 °C was treated with sodium borohydride (1.04 g, 27.5 mmol) in two portions and stirred for 2 h, allowing the mixture to warm to room temperature. The mixture was concentrated, diluted with $CHCl_3$, and washed with saturated $NaHCO_3$. Concentration of the organics gave a residue that was purified by flash chromatography (silica gel, 5% MeOH/$CHCl_3$) and recrystallization (Et_2O) to yield 2.7 g (65%) of **16** as white crystals: mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.2 Hz), 2.68−2.84 (m, 7H), 4.97 (d, 1H, J = 13.0 Hz), 5.57 (s, 1H), 5.75 (d, 1H, J = 13.0 Hz), 6.85 (d, 1H, J = 8.2 Hz), 7.02−7.40 (m, 6H); CIMS 300 ($MH^{\bullet+}$). Anal. ($C_{18}H_{21}NO_3$) C, H, N.

***N*-Acetoxy-*N*-[2-(6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)ethyl]acetamide (19).** A mixture of 6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-carboxaldehyde (**9**; 10.8 g, 45 mmol), hydroxylamine hydrochloride (6.4 g, 91 mmol), pyridine (75 mL), and ethanol (125 mL) was stirred at 50 °C for 3 h. After concentrating, diluting with $CHCl_3$, and washing with 2 N HCl and water, the organic extract was dried (Na_2SO_4). Concentration provided 10.7 g (93%) of 6,11-dihydro-11-oxodibenz-[*b,e*]oxepin-2-carboxaldehyde oxime as an oil that was used directly: ^{1}H NMR ($CDCl_3$) δ 5.25 (s, 2H), 7.10 (d, 1H, J = 9.0 Hz), 7.40 (dd, 1H, J_1 = 2.0 Hz, J_2 = 7.0 Hz), 7.45−7.66 (m, 3H), 7.86 (dd, 1H, J_1 = 3.0 Hz, J_2 = 13.0 Hz), 7.93 (dd, 1H, J_1 = 2.0 Hz, J_2 = 12.0 Hz), 8.20 (s, 1H), 8.33 (d, 1H, J = 2.0 Hz).

A mixture of 6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-carboxaldehyde oxime (8.5 g, 34 mmol), borane−pyridine complex (10.9 g, 117 mmol), and ethanol (100 mL) was stirred at 0 °C as 4 M HCl (65 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1 h and then made basic with saturated K_2CO_3 solution and concentrated to remove ethanol. The resulting aqueous mixture was extracted with CH_2Cl_2, and the organic extract was dried (Na_2SO_4). Concentration and flash chromatography provided 5.9 g (68%) of 1-(6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)-*N*-hydroxymethylamine (**18**) as a yellow solid which was used directly.

Acetyl chloride (4.0 g, 50 mmol) was added dropwise to a solution of **18** (5.9 g, 23 mmol) and Et_3N (7.0 g, 69 mmol) in CH_2Cl_2 at 0 °C. After 1 h at 0 °C, the reaction was quenched into 2 N HCl (100 mL) and the separated aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, 2:1 hexane:EtOAc) and recrystallization (Et_2O/hexane) to yield 2.8 g (36%) of **19** as off-white crystals: mp 107−109 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.15 (s, 3H), 4.85 (s, 2H), 5.20 (s, 2H), 7.05 (d, 1H, J = 8.4 Hz), 7.35−7.60 (m, 4H), 7.9 (d, 1H, J = 7.4 Hz), 8.1 (s, 1H); CIMS 340 ($MH^{\bullet+}$). Anal. ($C_{19}H_{17}NO_5$) C, H, N.

***N*-[(6,11-Dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)methyl]-*N*-hydroxyacetamide (23a). Method C.** A solution of lithium hydroxide monohydrate (2.1 g, 50 mmol) in water (50 mL) was added dropwise to a solution of **19** (2.4 g, 7.1 mmol) in 2-propanol (120 mL) at room temperature. The resulting mixture was stirred for 1 h and concentrated. The residue was diluted with 2 N HCl and extracted with Et_2O. The

organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, 2:1 hexane:EtOAc) and recrystallization (EtOAc/hexane) to yield 1.1 g (52%) of **23a** as white crystals: mp 129−130 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 4.85 (s, 2H), 5.10 (br s, 3H), 7.0 (br s, 1H), 7.35−7.90 (m, 4H), 8.05 (s, 1H), 8.35 (br s, 1H); EIMS 297 ($M^{\bullet+}$). Anal. ($C_{17}H_{15}NO_4$) C, H, N.

***N*-[2-(6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)ethyl]-*N*-(phenylmethoxy)acetamide (22).** A solution of *tert*-butyl *N*-(benzyloxy)carbamate (26.8 g, 0.12 mol) in anhydrous DMF (100 mL) was added dropwise to a slurry of sodium hydride (3.16 g, 0.13 mol) in DMF (50 mL). The resulting solution was added to a solution of 2-(6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)ethanol methanesulfonate[23] (**13b**) (40 g, 0.12 mol) in DMF (150 mL) and warmed at 100 °C overnight. After the mixture was diluted with water, extraction (EtOAc), drying, concentration, and preparative HPLC (silica gel, 2:1 hexane: EtOAc) provided 30 g (54%) of *N*-[2-(6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)ethyl]-*N*-(phenylmethoxy)-1,1-(dimethylethyl)carbamate (**20**) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.90 (t, 2H, J = 8.0Hz), 3.64 (t, 2H, J = 8.0 Hz), 4.83 (s, 2H), 5.17 (s, 2H), 6.96 (d, 1H, J = 8.0 Hz), 7.15−7.60 (m, 9H), 7.90 (dd, 1H, J_1 = 2.0 Hz, J_2 = 6.7 Hz), 8.07 (d, 2H, J = 3.0 Hz).

A solution of **20** (26.0g, 57 mmol) in anhydrous EtOAc (200 mL) was treated with saturated ethereal HCl (90 mL) and stirred for 10 min. The resulting precipitate was collected and dried to give 10.6 g (52%) of 2-(6,11-dihydro-11-oxodibenz[*b*,*e*]-oxepin-2-yl)-*N*-(phenylmethoxy)ethylamine hydrochloride (**21**)- as a powder that was used directly.

A mixture of **21** (10.6 g, 30 mmol) and triethylamine (5.3 g, 52 mmol) in THF (150 mL) was treated with acetyl chloride (2.4 g, 30 mmol) and stirred for 2 h. The resulting mixture was filtered, concentrated, and flashed chromatographed (silica gel, 2:1 hexane:EtOAc) to yield 4.1 g (34%) **22** as a semisolid that was used directly: ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.93 (t, 2H, J = 7.5 Hz), 3.84 (t, 2H, J = 7.5 Hz), 4.80 (s, 2H), 5.17 (s, 2H), 6.97 (d, 1H, J = 8.0 Hz), 7.20−7.63 (m, 9H), 7.88 (dd, 1H, J_1 = 2.0 Hz, J_2 = 6.7 Hz), 8.10 (d, 2H, J = 3.0 Hz).

***N*-[2-(6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)ethyl]-*N*-hydroxyacetamide (23b). Method D.** A solution of **22** (4.0 g, 10 mmol) in EtOH (50 mL) was treated with ammonium formate (3.2 g, 51 mmol) and 5% Pd/C (0.7 g). The mixture was stirred at room temperature for 1.5 h, filtered through a pad of Celite, and concentrated. The residue was purified by flash chromatography (silica gel, 2:1 hexane:EtOAc) and recrystallization (EtOAc/hexane) to yield 1.3 g (42%) of **23b** as white crystals: mp 113−115 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.05 (m, 2H), 3.85 (m, 2H), 5.15 (s, 2H), 7.0 (d, 1H, J = 8.2 Hz), 7.25−7.60 (m, 4H), 9.95 (d, 1H, J = 8.0 Hz), 8.05 (s, 1H), 8.6 (br s, 1H); EIMS 311 ($M^{\bullet+}$). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

3-(6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)-*N*-hydroxy-*N*-methylpropanamide (24h). Method E. A slurry of 3-(6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)propanoic acid[24] (**10c**; 9.9 g, 35 mmol) in CH_2Cl_2 (100 mL) containing DMF (0.3 mL) was treated dropwise with oxalyl chloride (6.1 mL, 70 mmol) at 0 °C. The resulting mixture was warmed to room temperature, stirred for 2 h, and evaporated to give 10.6 g of crude 3-(6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)propanoyl chloride.

A solution of the acid chloride (5.3 g, 17.5 mmol) in THF (50 mL) was added dropwise to a mixture of *N*-methylhydroxylamine hydrochloride (2.2 g, 26.3 mmol) and triethylamine (9.7 mL, 70 mmol) in THF:H_2O (4:1, 125 mL) at 0 °C. After the mixture had stirred for 4 h at room temperature, EtOAc (600 mL) was added and the organics were washed successively with dilute HCl, water, and dilute $NaHCO_3$ and dried. Evaporation gave a foam which solidified on trituration with Et_2O. Recrystallization from ethyl acetate gave 3.5 g (64%) of **24h** as off-white crystals: mp 101−103 °C; ^{1}H NMR (DMSO-d_6) δ 2.67 (t, 2H, J = 7.4 Hz), 2.84 (t, 2H, J = 7.4 Hz), 3.10 (s, 3H), 5.27 (s, 2H), 6.63 (d, 1H, J = 8.2 Hz), 7.44−7.70 (m, 4H), 7.78 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 2.4 Hz), 9.6 (br s, 1H); EIMS 311 ($M^{\bullet+}$). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

The properties of **24a**−**g**,**i**−**m**, and **25**, prepared in a similar manner from **10a**−**d**[12,23,24] and **12**, respectively, are included in Table 2. Representative ^{1}H NMR data are given below.

24a: ^{1}H NMR (DMSO-d_6) δ 3.35 (s, 2H), 5.30 (s, 2H), 7.05 (d, 1H, J = 8.4 Hz), 7.40−7.70 (m, 4H), 7.78 (d, 1H, J = 7.4 Hz), 7.92 (d, 1H, J = 2.4 Hz), 8.90 (br s, 1H), 10.50 (br s, 1H).

24e: ^{1}H NMR (DMSO-d_6) δ 1.00−1.80 (m, 10H), 3.75 (s, 2H), 4.15 (br s, 1H), 5.30 (s, 2H), 7.04 (d, 1H, J = 8.4 Hz), 7.40−7.80 (m, 5H), 7.92 (d, 1H, J = 2.4 Hz), 9.50 (br s, 1H).

24g: ^{1}H NMR (DMSO-d_6) δ 1.05 (t, 3H, J = 7.0 Hz), 1.30 (t, 3H, J = 7.0 Hz), 3.40−3.60 (m, 2H), 4.20−4.40 (m, 1H), 5.30 (s, 2H), 7.05 (d, 1H, J = 8.4 Hz), 7.50−7.70 (m, 4H), 7.78 (d, 1H, J = 7.6 Hz), 7.98 (d, 1H, J = 2.4 Hz), 9.70 (br s, 1H).

24j: ^{1}H NMR (DMSO-d_6) δ 1.05 (t, 6H, J = 6.6 Hz), 2.15 (t, 2H, J = 7.0 Hz), 2.84 (t, 2H, J = 2.0 Hz), 4.40−4.60 (m, 1H), 5.30 (s, 2H), 7.05 (d, 1H, J = 8.4 Hz), 7.45−7.70 (m, 4H), 7.78 (d, 1H, J = 7.6 Hz), 7.92 (d, 1H, J = 2.4 Hz), 9.25 (br s, 1H).

24l: ^{1}H NMR ($CDCl_3$) δ 2.75 (t, 2H, J = 7.0 Hz), 3.00 (t, 2H, J = 2.0 Hz), 3.15 (s, 3H), 3.65 (s, 3H), 5.15 (s, 2H), 7.00 (d, 1H, J = 8.4 Hz), 7.35−7.60 (m, 4H), 7.92 (d, 1H, J = 7.4 Hz), 8.10 (s, 1H).

24m: ^{1}H NMR (DMSO-d_6) δ 1.15 (s, 6H), 3.00 (s, 2H), 3.15 (s, 3H), 5.28 (s, 2H), 7.00 (d, 1H, J = 8.4 Hz), 7.30−7.80 (m, 5H), 7.90 (s, 1H), 9.95 (s, 1H).

25: ^{1}H NMR (DMSO-d_6) δ 2.55−2.75 (m, 4H), 3.10 (s, 3H), 4.21 (s, 2H), 5.27 (s, 2H), 6.65 (d, 1H, J = 8.4 Hz), 6.90−7.00 (m, 2H), 7.20−7.35 (m, 4H), 9.75 (br s, 1H).

Biological Methods. *In Vitro* Cell-Free RBL-1 5-Lipoxygenase Assay. 5-LO inhibition was determined by measurement of the inhibition of (*S*)-5-hydroxy-6-*trans*-8,11,-14-*cis*-eicosatetraenoic acid (5-HETE) levels in a modification of the method reported by Cochran and Finch-Arietta.[17] Test compounds, dissolved in dimethyl sulfoxide (DMSO), were diluted to various concentrations maintaining a final DMSO concentration of 1%. RBL-1 cell-free supernatants were prepared by a modification of the method reported by Jakschik and Kuo.[18] The supernatants were frozen with liquid N_2 and stored at −80 °C in 200 μL aliquots. The supernatants were quick-thawed and kept on ice until assay. Duplicate reaction tubes (10 × 75 mm) containing 35 mM NaH_2PO_4 (pH 7.0), 5 μM ATP, 50 μM $CaCl_2$, test compound or standard, 0.1% DMSO, and 10 μM arachidonic acid were prepared and equilibrated at 37 °C. The reaction was initiated by addition of supernatant protein (150 μg) to each assay tube. The reaction was terminated after 10 min by the addition of 10 μL of citric acid solution (0.3 M) and the mixture diluted with BGGE (pH 8.5) buffer. The diluted sample 5-HETE levels were quantitated by radioimmunoassay (Advanced Magnetics, Bulletin 6010). The samples were incubated for 2 h at 25 °C, and dextran-coated charcoal was used to absorb the unbound ligand. Nonspecific binding (without antiserum), total binding (with nonsample media), and standard curve samples were run concurrently with test samples. Antibody-bound 5-HETE was quantitated by scintillation counting. 5-HETE (ng/10 min at 37 °C) was quantitated from the standard curve. The mean 5-HETE levels were determined, and the percent change from control values was calculated.

***In Vitro* Murine 3T3 Fibroblast Cyclooxygenase Assay.** CO inhibition was determined by measurement of the inhibition of prostaglandin E_2 (PGE_2) levels in a modification of the method reported by Lindgren.[19] Test compounds, dissolved in absolute ethanol, were diluted to various concentrations in Dulbecco's modified Eagle's medium (DMEM) where ethanol concentrations were <0.1%. 3T3 mouse fibroblasts (CCL 92-3T3; American type culture collection) were seeded in 24 mm tissue culture wells (2×10^{-4} cells/well) and cultured for 24 h. Media were removed by aspiration and replaced with complete DMEM (1 mL/well) containing test compound, standard, or vehicle (4 wells/treatment). The cells were incubated for 24 h, media removed, and the media PGE_2 levels quantitated by radioimmunoassay (Advanced Magnetics, Bulletin 6001). The samples were incubated for 2 h at 25 °C, and charcoal was used to absorb the unbound ligand. Nonspecific binding (without antiserum), total binding (with nonsample media), and standard curve samples were run concurrently with test samples. The duplicate determinations

of PGE_2 (pg/well) in each sample was quantitated from the standard curve. The mean PGE_2 level was determined for each treatment group and the percent change from control values quantified.

***In Vivo* Arachidonic Acid-Induced Mouse Ear Edema Assay.** Ear edema determinations were performed by a modification of the method reported by Young.[20] Arachidonic acid (5,8,11,14-eicosatetraenoic acid; Sigma Chemical Co.) was dissolved in 3:7 propylene glycol:ethanol at a final concentration of 4 mg/20 μL, and the test compound was dissolved in 3:7 propylene glycol:ethanol at a concentration of 1 mg/20 μL. Male CFW (Swiss Webster, Charles River) mice ($N = 6$) received vehicle alone or test compound in vehicle on the right ear (10 μL/outer ear and 10 μL/inner ear). After 30 min, the right ear of all groups received arachidonic acid (4 mg/20 μL) and the left ear received vehicle alone (20 μL/ear). After an additional 1 h, mice were sacrificed by cervical dislocation and an ear punch was taken from each ear with a 4 mm trephine. The punch biopsies were weighed on an analytical balance. The difference in right and left ear punch weights was determined, and the mean difference in ear weights was calculated for each group. The percent change in mean ear weights from the vehicle control group was quantitated for each compound treatment group.

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