(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-methyl-*N*-hydroxyureidyl)methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (CMI-392), a Potent Dual 5-Lipoxygenase Inhibitor and Platelet-Activating Factor Receptor Antagonist

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By incorporating an *N*-hydroxyurea functionality onto diaryltetrahydrofurans, a novel series of compounds was investigated as dual 5-lipoxygenese (5-LO) inhibitor and platelet-activating factor (PAF) receptor antagonist. These dual functional compounds were evaluated in vitro for 5-LO inhibition in RBL cell extracts and human whole blood, and PAF receptor antagonism in a receptor binding assay. PAF-induced hemoconcentration and arachidonic acid- and TPA-induced ear edema in mice were used to determine in vivo activities. The structure−activity relationship analysis to define a preclinical lead is presented. (±)-*trans*-2-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-methyl-*N*-hydroxyureidyl)methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (**40**, CMI-392) was selected for further study. In the arachidonic acid-induced mouse ear edema model, **40** was more potent than either zileuton (a 5-LO inhibitor) or BN 50739 (a PAF receptor antagonist), and it demonstrated the same inhibitory effect as a physical combination of the latter two agents. These results suggest that a single compound which both inhibits leukotriene synthesis and blocks PAF receptor binding may provide therapeutic advantages over single-acting agents. The clinical development of compound **40** is in progress.

Introduction

Leukotrienes (LTs) are potent lipid mediators produced by the oxidation of arachidonic acid by 5-lipoxygenase (5-LO).[1] LTB_4, C_4, D_4, and E_4 play major roles in inflammatory and allergic responses.[2,3] For example, LTB_4, a potent chemotactic agent for neutrophils and eosinophils, is an important mediator of inflammation.[4] LTC_4, D_4, and E_4 are potent bronchoconstrictors, as well as the slow-reacting substance of anaphylaxis.[5] Platelet-activating factor (PAF) is a potent inflammatory phospholipid mediator with a wide variety of biological activities.[6,7] It is generated and released by many inflammatory cells, as well as by renal and cardiac tissues under appropriate immunological and nonimmunological stimulation,[8] and it appears to play a pathological role during immune and inflammatory responses in a number of disorders.[9]

As both LTs and PAF are potent proinflammatory mediators induced under similar pathological conditions, the administration of a mixture of 5-LO inhibitor and PAF antagonist may provide an effective antiinflammatory therapeutic.[10] From cost and pharmacodynamic considerations, a single compound which both inhibits LT synthesis and blocks PAF activity, if feasible, could offer therapeutic advantages over a mixture of single acting agents.

A number of monofunctional and dual functional 5-LO inhibitors and PAF receptor antagonists have been reported.[11−13] The introduction of a hydroxyurea functionality onto certain scaffolds has been shown to confer 5-LO inhibitory activity, possibly involving chelation of Fe^{3+} required for catalysis.[13] To optimize dual 5-LO inhibition and PAF receptor antagonist activities in a single compound, we have incorporated an *N*-hydroxyurea functionality onto a well-characterized family of PAF receptor antagonists, the 2,5-diaryltetrahydrofurans (Figure 1). A number of hydroxyureidyl derivatives of diaryltetrahydrofurans have been synthesized in our laboratories previously, which show dual 5-LO inhibitory and PAF receptor antagonistic activities.[14−17] In this paper, we describe the discovery of (±)-*trans*-2-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-methyl-*N*-hydroxyureidyl)methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (**40**, CMI-392) as a potent dual 5-LO inhibitor and PAF receptor antagonist which is currently being evaluated in human clinical trials as a novel antiinflammatory agent.

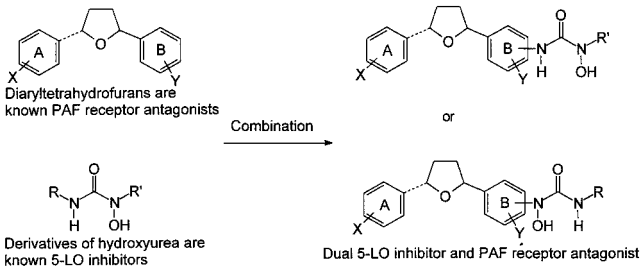

Figure 1. Design of dual 5-lipoxygenase inhibitor and PAF receptor antagonist.

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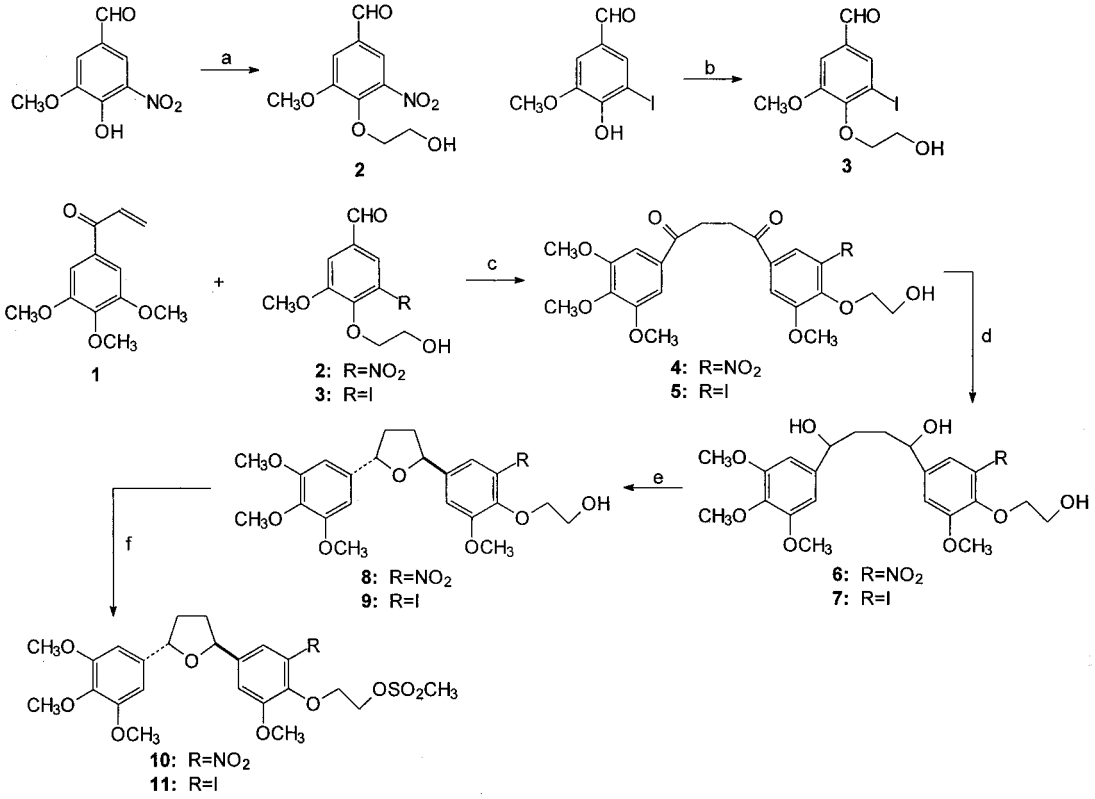
Scheme 1[a]



[a] (a) ICH_2CH_2OH, K_2CO_3, 18-crown-6, DMF, △; (b) ICH_2CH_2OH, NaH, DMF; (c) 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, Et_3N △; (d) $NaBH_4$, THF, CH_3OH, H_2O; (e) CF_3COOH, $CHCl_3$; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2.

Chemistry

The preparation of the key intermediates **10** and **11** is shown in Scheme 1. Compound **1** was obtained in three steps from 3,4,5-trimethoxyacetophenone as previously described.[18] Compounds **2** and **3** were prepared by alkylation of 5-nitrovanillin and 5-iodovanillin with iodoethanol in 23% and 93% yield, respectively. Condensation of **1** and **2** or **1** and **3** in the presence of thiazolium catalyst and triethylamine gave 1,4-diketones **4** (60% yield) and **5** (51% yield), respectively. Reduction of the diketones **4** and **5** with sodium borohydride in methanol and tetrahydrofuran gave the corresponding 1,4-diols **6** (99% yield) and **7** (99% yield). The diols **6** and **7** were then cyclized with 5% trifluoroacetic acid in chloroform at 0 °C to give a mixture of cis and trans isomers of 2,5-diaryltetrahydrofurans which were separated by column chromatography to give the desired trans isomers **8** and **9** in 21% and 41% yield, respectively. The mesylation of **8** and **9** with methanesulfonyl chloride and triethylamine in dichloromethane gave the key intermediates **10** (99% yield) and **11** (77% yield).

The conversion of intermediate **10** to the final substituted hydroxyureidyldiaryltetrahydrofurans is shown in Scheme 2. Heating **10** with a variety of substituted thiophenols, triethylamine, and ethanol gave **12**−**18** in a yield between 82% and 95%. Reduction of these nitro compounds with zinc, calcium chloride, and ethanol gave the corresponding amines **19**−**25** in 69% to 94% yields. Compounds **19**−**25** were then treated with triphosgene followed by *n*-butylhydroxylamine to give compounds **26**−**32** in a yield between 43% and 85%. The sulfones **33**, **34**, and **35** were prepared from the corresponding thioether compounds with magnesium monoperoxyphthalic acid (MMPP) in the yield of 53%, 67%, and 63%, respectively.

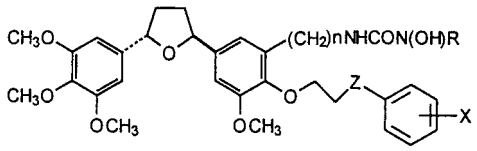
The final substituted hydroxyureidyltetrahydrofurans synthesized from intermediate **11** are shown in Scheme 3. Treatment of **11** with 4-chlorothiophenol yielded **36** in 87% yield. Reaction of **36** with CuCN in DMF gave **37** (90% yield). Reduction of **37** with sodium borohydride and boron trifluoride etherate gave the amine **38** in 21% yield. Treatment of **38** with triphosgene, followed by *n*-butylhydroxylamine gave **39** (32% yield). Similar treatment of **38** with methylhydroxylamine yielded **40** in 80% yield.

Results and Discussion

Compounds described in this paper were evaluated in several in vitro and in vivo assays. The in vitro assays included PAF receptor binding,[18] 5-LO enzyme inhibition using rat basophilic leukemic (RBL) cell extracts, and the inhibition of LTB_4 production in human whole blood (HWB).[19,20] The in vivo assays were PAF-induced hemoconcentration[21] and arachidonic acid-induced ear edema in mice.[22,23] The results are summarized in Tables 1 and 2.

We have previously synthesized CMI-206 (**41**) and its analogues.[16] The biological data indicate that trans isomers are always more potent than the corresponding cis isomers in antagonizing PAF, but there is little difference between the trans and corresponding cis isomers for inhibiting 5-LO. The *n*-butyl chain on the ureidyl group also produces potent overall activity.[16] Accordingly, the essential features of the trans isomers with an *n*-butylhydroxyureidyl chain at C-5 on ring B

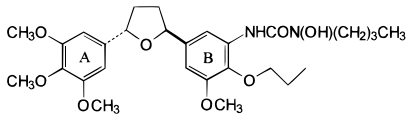
Table 1. In Vitro Activity of Selected Hydroxyurea Compounds



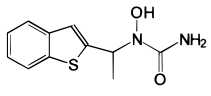
					IC_{50} (nM)		HWB[d]	
compd[a]	*n*	Z	R	X	PAF[b]	5-LO[c]	IC_{50} (μM)	Inh (%)
26	0	S	$CH_3CH_2CH_2CH_2$	4-Cl	20	58	6.5	
27	0	S	$CH_3CH_2CH_2CH_2$	3,4-Cl	45	17		61
28	0	S	$CH_3CH_2CH_2CH_2$	4-Br	21	19	1.2	
29	0	S	$CH_3CH_2CH_2CH_2$	2-Br	23	33		48
30	0	S	$CH_3CH_2CH_2CH_2$	3-Br	22	43	7.5	
31	0	S	$CH_3CH_2CH_2CH_2$	2,3,5,6-F	2	118		3
32	0	S	$CH_3CH_2CH_2CH_2$	4-OMe	39	71		32
33	0	SO_2	$CH_3CH_2CH_2CH_2$	4-Br	38	ND*		72
34	0	SO_2	$CH_3CH_2CH_2CH_2$	2-Br	25	161		19
35	0	SO_2	$CH_3CH_2CH_2CH_2$	2,3,5,6-F	285	520		ND*
39	1	S	$CH_3CH_2CH_2CH_2$	4-Cl	167	ND*		26
40	1	S	CH_3	4-Cl	10	100	7.8	
41					33	424	3.5	
MK 287[e]					6			
WEB 2086[f]					94			
zileuton[g]						804	1.0	
A-78773[g]						298	0.1	

[a] All synthetic compounds (**26**−**40**) had C, H, N or C, H, N, S analyses ±0.4% the theoretical except **33** which has the following: Anal. ($C_{33}H_{41}O_{10}N_2SBr$) C, H, N; C: calcd, 53.73; found, 53.20. [b] PAF receptor antagonist activity was determined by competition of [^{3}H]PAF specific binding to human platelet membranes. [c] 5-LO inhibitory activity was determined by measuring the conversion of [^{14}C]arachidonic acid to leukotrienes in RBL-2H3 cell using thin-layer chromatography. [d] HWB assay was done by measuring the production of LTB_4 in calcium ionophore (A 23187)-activated human whole blood by the enzyme immunoassay. The percent inhibition was measured at 3 μM. [e] Obtained from Merck Research Laboratories. [f] Obtained from Boehringer-Ingelheim laboratories. [g] Obtained from Abbott Research Laboratories. *ND = not determined.

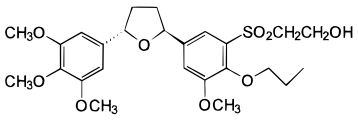
were retained, and further modifications were made at C-4 of ring B. When the C-4 propoxyl group on ring B was replaced by a substituted phenylthioethoxyl group (compounds **26**−**32**), the 5-LO activity was significantly increased while the PAF activity remained undiminished (Table 1).



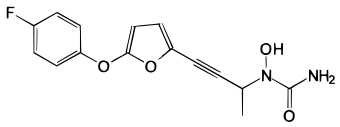
41



zileuton



MK 287



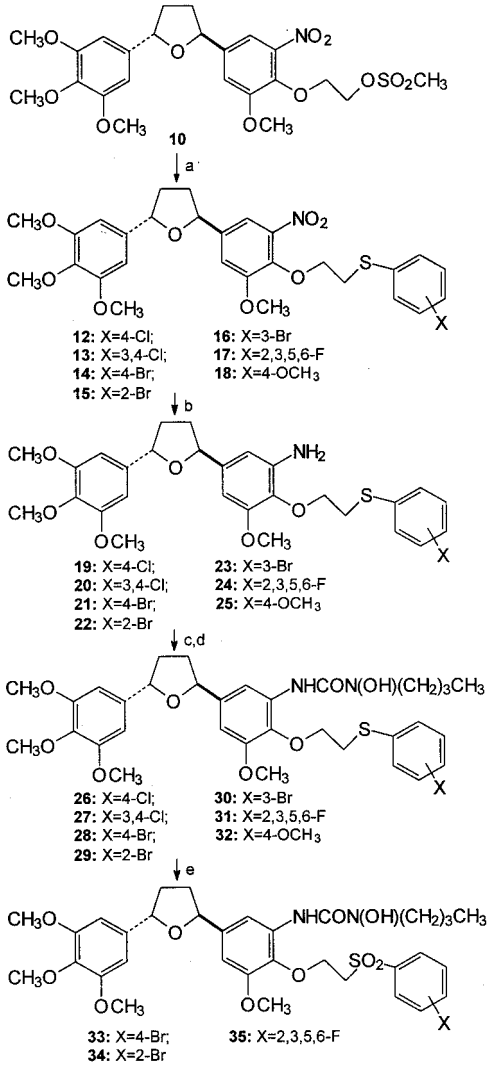
A-78773

In Vitro Assays. The in vitro activity of the compounds are listed in Table 1. All of the compounds tested are potent PAF receptor antagonists. The 2,3,5,6-tetrafluoro-substituted compound (**31**) is the most potent PAF receptor antagonist (IC_{50} = 2 nM) among those prepared, being about 3 times more potent than MK 287. However, **31** is less potent in 5-LO inhibition with an IC_{50} value of 118 nM in the RBL assay and only 3% inhibition at 3 μM in the HWB assay. The corresponding sulfone derivative **35** showed much lower potency both in PAF binding (IC_{50} = 285 nM) and 5-LO inhibition (IC_{50} = 520 nM) assays. The compounds with a halogen (X = Cl, Br, F) substituted phenylthioethoxy chain on ring B (**26**−**31**) are more potent than the methoxy substituted analogue (**32**) in overall 5-LO inhibition and PAF binding assays.

In Vivo Models. The compounds were further tested in in vivo models (Table 2). The 4- bromo analogue **28**, which is very active in the HWB assay, showed no activity in both PAF-induced hemoconcentration and arachidonic acid-induced ear edema models. To test the hypothesis that this might be caused by metabolic oxidation of thioether to sulfone, the corresponding sulfone derivative **33** was made and tested in these two models and showed increased activity. To determine if a sulfone substituent might generally offer more advantages in vivo, two other pairs of sulfide and sulfone analogues were synthesized (**31** and **35**, **29** and **34**). The data shows that **31** and **35** have almost the same activity in PAF-induced hemoconcentration model, but the thioether **31** has higher potency in the arachidonic acid-induced ear edema model and in in vitro assays. Compound **34** is inactive in the arachidonic acid-induced ear edema model while compound **29** is active. Furthermore, **29** is 5 times more potent than **34** in the in vitro 5-LO assay (Tables 1 and 2). These results diminished our further interests in pursuing the sulfone analogues.

In the design of a dual functional molecule, a balanced activity profile with both 5-LO inhibition and PAF antagonism is desirable. An analysis of our structure−activity data indicated that monohalogen substitution is preferable and a para substituent in the sulfur-attached phenyl ring is also important for stabilizing

Scheme 2[a]



[a] (a) Et_3N, EtOH, HS-C_6H_4-R, R = 4-Cl or 3,4-Cl or 4-Br or 2-Br or 3-Br or 2,3,5,6-F or 4-OCH_3, reflux; (b) Zn, $CaCl_2$, EtOH, reflux; (c) $(Cl_3CO)_2CO$, EtOH, CH_2Cl_2, reflux; (d) $CH_3(CH_2)_3NHOH$, Et_3N, CH_2Cl_2; (e) MMPP, CH_3CN, H_2O.

the compound against metabolism. Therefore, compound **26** was considered to be a good lead candidate in this series meeting both of these criteria.

Compound 40. The next attempts were made to improve the activity of compound **26**, especially in the in vivo models. We focused on the hydroxyurea side chain on ring B. Compound **39** was formed by inserting a methylene group between ring B and the hydroxyurea side chain of compound **26**. As a consequence, however, the PAF receptor binding affinity of **39** decreased significantly. Compound **39** also showed only 26% inhibition at 3 μM in the human whole blood assay. However, when the *n*-butyl chain was replaced by a methyl group to form compound **40**, it showed very potent and balanced activities against both 5-LO and PAF. Compared with reference compounds, **40** is more potent than zileuton and A-78773 in 5-LO inhibitory activity and is more potent than WEB 2086 and almost equally potent as MK 287 in PAF receptor antagonist activity.

Compound **40** was further studied in several 5-LO inhibition and PAF antagonism assays, including acute and chronic TPA-induced mouse ear edema assays, as summarized in Table 3. Topical treatment of compound **40** in the acute and chronic TPA models resulted in a significant decrease of ear weight, inflammatory cell infiltration (as assessed by MPO content), and histological examination (data not shown).

Compound **40** was also tested in the arachidonic acid-induced mouse ear edema model in comparison with a 5-LO inhibitor (zileuton), a PAF receptor antagonist (BN 50739)[25] and a combination of zileuton and BN 50739 (Figure 2). The results indicate that **40** is more potent than either zileuton or BN 50739 and that **40** achieves an equivalent inhibitory effect as a physical combination of the latter two. These results suggest that a dual function compound which both inhibits 5-LO and antagonizes PAF receptor binding may provide therapeutic advantages over agents with only single biological activity (5-LO or PAF). Compound **40** has accordingly been advanced to clinical development as a novel antiinflammatory agent.

Experimental Section

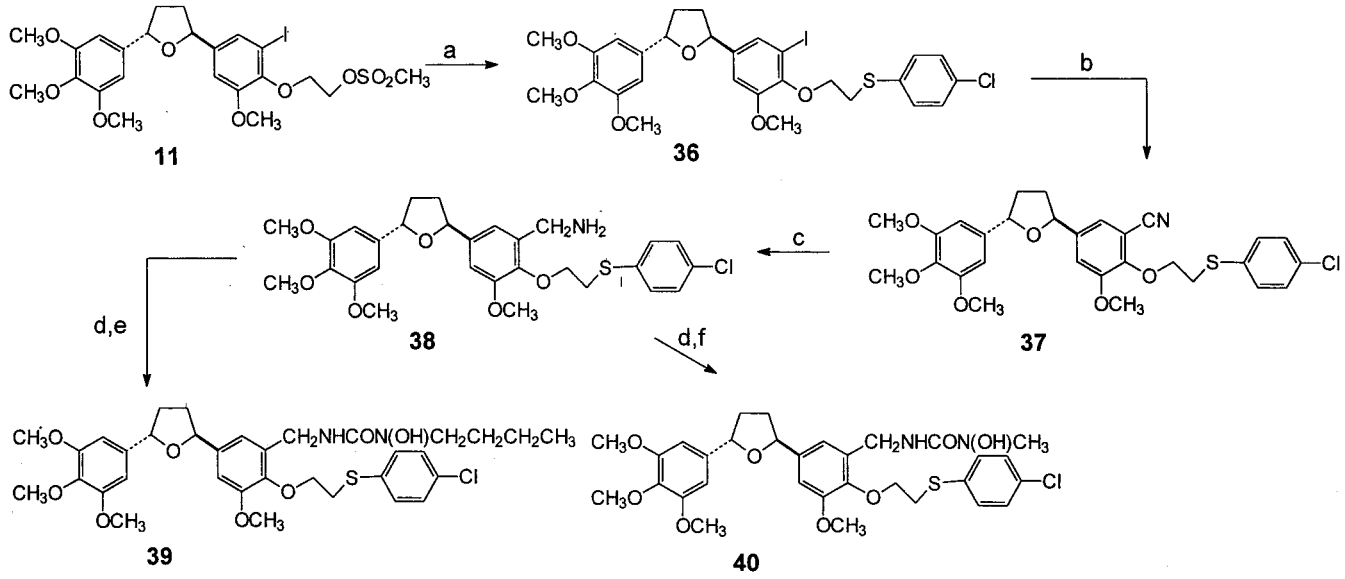
Chemistry. General. Proton nuclear magnetic resonance spectra were recorded on a Varian Gemini-300 spectrometer at ambient temperature in $CDCl_3$ and proton chemical shifts are relative to tetramethylsilane (TMS) as an internal standard. Melting points were determined on a Electrothermal IA 9100 melting point apparatus in open capillary tube and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Silica gel 60 (E. Merck, 230−400 mesh) was used for flash column chromatography. THF was freshly distilled from sodium benzophenone ketyl. DMF and ethanol were anhydrous grade. Other solvents were HPLC grade. All the other chemicals were from commercial suppliers and used without further purification.

3-Methoxy-4-hydroxyethoxy-5-nitrobenzaldehyde (2). To a solution of 5-nitrovanillin (25 g, 126.8 mmol) in DMF (650 mL) was added potassium carbonate (21.0 g, 152.2 mmol) and 18 crown-6 (3.35 g, 12.68 mmol). The mixture was heated to 80 °C to make a clear solution. 2-Iodoethanol (43.61 g, 253.6 mmol) was added, and the reaction mixture was stirred at 80 °C for 48 h. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give the title compound as an oil (7.1 g, 23%): ^{1}H NMR δ 3.68 (bs, 1H), 3.94 (m, 2H), 4.02 (s, 3H), 4.45 (t, J = 4.1 Hz, 2H), 7.65 (d, J = 1.6 Hz, 1H), 7.92 (d, J = 1.6 Hz, 1H), 9.95 (s, 1H).

3-Methoxy-4-hydroxyethoxy-5-iodobenzaldehyde (3). To a stirred suspension of NaH (60% dispersion in mineral oil) (3.60 g, 90.0 mmol) in dimethylformamide (25 mL) was added dropwise a solution of 5-iodovanillin (25 g, 90.0 mmol) in DMF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. 2-Iodoethanol (23.1 g, 134.3 mmol) was added dropwise. After the addition, the reaction mixture was stirred at 50 °C for 20 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with aqueous NaOH (10%), water, and saturated NaCl, dried over $MgSO_4$, filtered, and evaporated in vacuo to yield **3** as a tan solid (26.8 g, 93%) which was used without further purification: ^{1}H NMR δ 3.91 (m, 2H), 3.94 (s, 3H), 4.29 (t, J = 4.1 Hz, 2H), 7.42 (s, 1H), 7.88 (s, 1H), 9.84 (s, 1H).

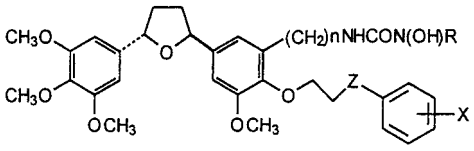
1-(3-Methoxy-4-hydroxyethoxy-5-nitrophenyl)-4-(3,4,5-trimethoxyphenyl)-1,4-butanedione (4). A mixture of **1** (22 g, 99.1 mmol), **2** (19.9 g, 82.6 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (8.9 g, 33.1 mmol) in triethylamine (105 mL) were stirred at 60 °C for 16 h. The reaction was then acidified with 10% HCl and extracted with dichloromethane and the organic layer washed with 10% HCl, water, and saturated NaCl solution. The extract was dried over $MgSO_4$, filtered, and evaporated in vacuo to yield **4** as a crude solid (23 g, 60%) which was used for the next reaction

Scheme 3[a]



[a] (a) HS-C_6H_4-*p*-Cl, Et_3N, EtOH, reflux; (b) CuCN, DMF, △; (c) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, reflux or BH_3THF, THF, reflux; (d) $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, reflux; (e) $CH_3CH_2CH_2CH_2NHOH$, Et_3N, CH_2Cl_2; (f) $CH_3NHOHHCl$, Et_3N, CH_2Cl_2.

Table 2. In Vivo Activity of Selected Hydroxyurea Compounds



					inhibition (%), 3 mg/kg	
compd	*n*	Z	R	X	PAF-Htc[a]	AA-Ed[b]
26	0	S	$CH_3CH_2CH_2CH_2$	4-Cl	43	39
27	0	S	$CH_3CH_2CH_2CH_2$	3,4-Cl	26	26
28	0	S	$CH_3CH_2CH_2CH_2$	4-Br	−11	−3
29	0	S	$CH_3CH_2CH_2CH_2$	2-Br	34	26
30	0	S	$CH_3CH_2CH_2CH_2$	3-Br	28	40
31	0	S	$CH_3CH_2CH_2CH_2$	2,3,5,6-F	59	30
32	0	S	$CH_3CH_2CH_2CH_2$	4-OMe	24	3
33	0	SO_2	$CH_3CH_2CH_2CH_2$	4-Br	29	35
34	0	SO_2	$CH_3CH_2CH_2CH_2$	2-Br	60	−9
35	0	SO_2	$CH_3CH_2CH_2CH_2$	2,3,5,6-F	50	12
40	1	S	CH_3	4-Cl	56	46

[a] PAF-induced hemoconcentration in mice was evaluated by measuring the hematocrit. Animals were challenged with PAF, iv, 15 min after dosing with compound, iv. [b] Arachidonic acid-induced ear edema in mice was determined by measuring the ear weight following the topical application of arachidonic acid 15 min after intravenous administration of compound.

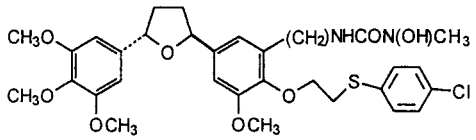
without further purification: ^{1}H NMR δ 3.43 (m, 4H), 3.92 (m, 2H), 3.93 (s, 9H), 4.00 (s, 3H), 4.42 (t, J = 4.2 Hz, 2H), 7.29 (s, 2H), 7.80 (d, J = 1.8 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H).

1-(3-Methoxy-4-hydroxyethoxy-5-iodophenyl)-4-(3,4,5-trimethoxyphenyl)-1,4-butanedione (5). A mixture of **1** (4.8 g, 21.6 mmol), **3** (5.7 g, 17.8 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (1.9 g, 7.0 mmol) in triethylamine (20 mL) was stirred at 60 °C for 16 h. The reaction was then acidified with 10% HCl and extracted with dichloromethane. The organic layer was washed with 10% HCl, water, and saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **5** as a crude solid (9.7 g, 51%) which was carried to the next step without further purification: ^{1}H NMR δ 3.41 (m, 4H), 3.90 (m, 2H), 3.92 (s, 3H), 3.93 (s, 9H), 4.26 (t, J = 4.4 Hz, 2H), 7.29 (s, 2H), 7.57 (d, J = 1.8 Hz, 1H), 8.08(d, J = 1.8 Hz, 1H).

1-(3-Methoxy-4-hydroxyethoxy-5-nitrophenyl)-4-(3,4,5-trimethoxyphenyl)-1,4-butanediol (6). To a stirred solution of **4** (8.0 g, 17.3 mmol) in tetrahydrofuran (120 mL) and methanol (240 mL) was added dropwise sodium borohydride (1.18 g, 31.2 mmol) in water (60 mL). The reaction was stirred at room temperature for 3 h, the reaction mixture was cooled in an ice−water bath and quenched with water, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to provide **6** as a foam (8.0 g, 99%) which was used directly in the next step.

1-(3-Methoxy-4-hydroxyethoxy-5-iodophenyl)-4-(3,4,5-trimethoxyphenyl)-1,4-butanediol (7). To a stirred solution of **5** (11.6 g, 21.3 mmol) in tetrahydrofuran (120 mL) and methanol (240 mL) was added dropwise the sodium borohydride (1.45 g, 38.4 mmol) in water (60 mL). The reaction was stirred at room temperature for 2.5 h, cooled in an ice−water bath, and quenched with water, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to provide the title product as a foam (11.8 g, 99%) which was used directly in the next step: ^{1}H NMR δ 1.86 (m, 4H), 3.83 (s, 3H), 3.86 (m, 2H), 3.87 (s, 9H), 4.15 (m, 2H), 4.68 (m, 2H), 6.57 (s, 2H), 6.90 (s, 1H), 7.32 (s, 1H).

Table 3. In Vitro and in Vivo Activity of Compound **40**



	IC_{50}	ED_{50}	$T_{1/2}$
human whole blood (LTB_4)	7.8 μM		
RBL (5-LO)	100 nM		
PAF receptor binding (^{3}H-PAF)	10 nM		
PAF-induced mouse hemoconcentration		2.2 mg/kg	30 min
arachidonic acid-induced mouse ear edema		1.8 mg/kg	
TPA-induced mouse ear edema (edema)[a]		269 μg/ear (acute) 552 μg/ear (chronic)	
TPA-induced mouse ear edema (MPO)[b]		299 μg/ear (acute) 580 μg/ear (chronic)	

[a] Acute TPA-induced ear edema in mice was determined by topically applying TPA to the ears of mice. Mice were sacrificed after 6 h and the ear punch biopsies were weighed. Chronic TPA-induced ear edema in mice was determined by topically applying TPA once a day every 2 days for a total of 10 days. Compound **40** was topically administered twice daily on the last 3 days of the experiment. Mice were then sacrificed and the ear punch biopsies were weighed. [b] Biopsies were homogenized and MPO content was determined via spectrophotometric assay.[24]

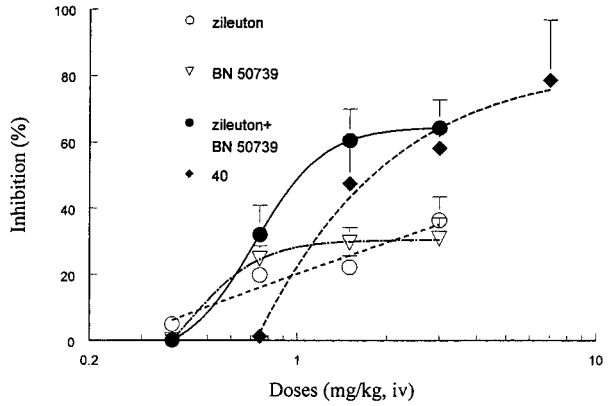


Figure 2. Comparison of compound **40** with a PAF receptor antagonist (BN 50739), a 5-LO inhibitor (zileuton) and the combination in arachidonic acid-induced mouse ear edema model. Arachidonic acid-induced ear edema in mice was determined by measuring the ear weight following the topical application of arachidonic acid 15 min after intravenous administration of compound.

(±)-*trans*-2-(3-Methoxy-4-hydroxyethoxy-5-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (8). To a stirred solution of **6** (8.0 g, 17.1 mmol) in chloroform (80 mL) at 0 °C was added dropwise trifluoroacetic acid (7.81 g, 68.5 mmol) in chloroform (80 mL) over 30 min. The solution was stirred at 0 °C for 2 h and then at room temperature for 1 h. The reaction was diluted with dichloromethane, washed with 10% NaOH solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated in vacuo to an oil which was a cis and trans mixture. The trans isomer **8** was isolated as a foam by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) (1.64 g, 21%) as the faster eluting isomer: ^{1}H NMR δ 2.00 (m, 2H), 2.51 (m, 2H), 3.85 (s, 3H), 3.89 (s, 6H), 3.90 (m, 2H), 3.95 (s, 3H), 4.31 (t, J = 4.5 Hz, 2H), 5.23 (m, 2H), 6.62 (s, 2H), 7.21 (s, 1H), 7.43 (s, 1H).

(±)-*trans*-2-(3-Methoxy-4-hydroxyethoxy-5-iodophenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (9). To a stirred solution of **7** (11.8 g, 21.5 mmol) in chloroform (100 mL) at 0 °C was added dropwise trifluoroacetic acid (9.82 g, 86.1 mmol) in chloroform (100 mL) over 30 min. The solution was stirred at 0 °C for 2 h and then at room temperature for 1 h. The reaction was quenched with 1 N NaOH, and chloroform (100 mL) was added. The organic layer was washed with 1 N NaOH solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated in vacuo to an oil which was a cis and trans mixture. The *trans* isomer **9** was isolated as an oil by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) (4.7 g, 41%) as the faster eluting isomer: ^{1}H NMR δ 1.98 (m, 2H), 2.45 (m, 2H), 3.83 (s, 3H), 3.86 (m, 2H), 3.88 (s, 9H), 4.15 (t, J = 4.4 Hz, 2H), 5.17 (m, 2H), 6.61 (s, 2H), 6.96 (s, 1H), 7.38(d, 1H).

(±)-*trans*-2-(3-Methoxy-4-methanesulfonylethoxy-5-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (10). To a stirred solution of **8** (1.64 g, 3.65 mmol) in dichloromethane (80 mL) at 0 °C were added methanesulfonyl chloride (627.5 mg, 5.48 mmol) and triethylamine (553.3 mg, 5.48 mmol). The reaction was stirred at 0 °C for 2 h, water was added, and the reaction was extracted with ethyl acetate. The organic layer was washed with water and brine and evaporated to an oil which was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to yield **10** as an oil (1.9 g, 99%): ^{1}H NMR δ 2.00 (m, 2H), 2.50 (m, 2H), 3.10 (s, 3H), 3.86 (s, 3H), 3.89 (s, 6H), 3.96 (s, 3H), 4.42 (t, J = 4.5 Hz, 2H), 4.58 (t, J = 4.5 Hz, 2H), 5.23 (m, 2H), 6.62 (s, 2H), 7.20 (s, 1H), 7.38 (s, 1H).

(±)-*trans*-2-(3-Methoxy-4-methanesulfonylethoxy-5-iodophenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (11). To a stirred solution of **9** (4.7 g, 8.87 mmol) in dichloromethane (50 mL) at 0 °C were added methanesulfonyl chloride (3.05 g, 26.6 mmol) and triethylamine (2.69 g, 26.60 mmol). The reaction was stirred at 0 °C for 2 h and room temperature overnight. The solvent was evaporated, and the residue was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to yield **11** as an oil (4.17 g, 77%): ^{1}H NMR δ 1.98 (m, 2H), 2.45 (m, 2H), 3.14 (s, 3H), 3.82 (s, 3H), 3.88 (s, 9H), 4.23 (t, J = 4.5 Hz, 2H), 4.60 (t, J = 4.5 Hz, 2H), 5.18 (m, 2H), 6.60 (s, 2H), 6.92 (s, 1H), 7.38 (s, 1H).

(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-nitrophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (12). To a solution of **10** (50.0 mg, 0.095 mmol) in 5 mL of ethanol were added 4-chlorothiophenol (41.2 mg, 0.285 mmol) and triethylamine (28.7 mg, 0.285 mmol). The reaction was refluxed for 16 h, quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to yield an oil which was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to give **12** as an oil (51 mg, 93%): ^{1}H NMR δ 2.00 (m, 2H), 2.49 (m, 2H), 3.31 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.89 (s, 9H), 4.25 (t, J = 7.2 Hz, 2H), 5.20 (m, 2H), 6.61 (s, 2H), 7.16 (s, 1H), 7.26 (d, J = 8.5 Hz, 2H), 7.32 (s, 1H), 7.34 (d, J = 8.5 Hz, 2H).

(±)-*trans*-2-[3-Methoxy-4-(3,4-dichlorophenylthioethoxy)-5-nitrophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (13). In a similar manner as for **12** but using 3,4-dichlorothiophenol (51.0 mg, 0.285 mmol) in place of 4-chlorothiophenol, **10** (50.0 mg, 0.095 mmol) was converted to **13** as an oil (52.6 mg, 91%): ^{1}H NMR δ 2.00 (m, 2H), 2.50 (m, 2H), 3.33 (t, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.89 (s, 6H), 3.91 (s, 3H), 4.27 (t, J = 7.1 Hz, 2H), 5.22 (m, 2H), 6.61 (s, 2H), 7.17 (s, 1H), 7.24 (m, 1H), 7.36 (m, 2H), 7.47 (s, 1H).

(±)-*trans*-2-[3-Methoxy-4-(4-bromophenylthioethoxy)-5-nitrophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (14). In a similar manner as for **12** but using 4-bromothiophenol (594.4 mg, 3.144 mmol) in place of 4-chlorothiophenol, **10** (552.1 mg, 1.048 mmol) was converted to **14** as an oil (609.9 mg, 94%): ^{1}H NMR δ 2.00 (m, 2H), 2.50 (m, 2H), 3.32 (t, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.90 (s, 9H), 4.25 (t, J = 7.1 Hz, 2H), 5.21 (m, 2H), 6.61 (s, 2H), 7.15 (s, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.35 (s, 1H), 7.41 (d, J = 8.2 Hz, 2H).

(±)-*trans*-2-[3-Methoxy-4-(2-bromophenylthioethoxy)-5-nitrophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (15). In a similar manner as for **12** but using 2-bo-

mothiophenol (53.8 mg, 0.285 mmol) in place of 4-chlorothiophenol, **10** (50.0 mg, 0.095 mmol) was converted to **15** as an oil (48 mg, 82%): ^{1}H NMR δ 2.00 (m, 2H), 2.50 (m, 2H), 3.39 (t, J = 7.4 Hz, 2H), 3.85 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 4.32 (t, J = 7.4 Hz, 2H), 5.22 (m, 2H), 6.62 (s, 2H), 7.04 (m, 1H), 7.16 (s, 1H), 7.31 (m, 1H), 7.36 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.55(d, J = 8.0 Hz, 1H).

(±)-*trans*-2-[3-Methoxy-4-(3-bromophenylthioethoxy)-5-nitrophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (16). In a similar manner as for **12** but using 3-bromothiophenol (53.8 mg, 0.285 mmol) in place of 4-chlorothiophenol, **10** (50.0 mg, 0.095 mmol) was converted to **16** as an oil (56 mg, 95%): ^{1}H NMR δ 2.00 (m, 2H), 2.50 (m, 2H), 3.34 (t, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 4.28 (t, J = 7.1 Hz, 2H), 5.21 (m, 2H), 6.62 (s, 2H), 7.16 (m, 2H), 7.33 (m, 3H), 7.52 (s, 1H).

(±)-*trans*-2-[3-Methoxy-4-(2,3,5,6-tetrafluorophenylthioethoxy)-5-nitrophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (17). In a similar manner as for **12** but using 2,3,5,6-tetrafluorothiophenol (51.8 mg, 0.285 mmol) in place of 4-chlorothiophenol, **10** (50.0 mg, 0.095 mmol) was converted to **17** as an oil (51 mg, 88%): ^{1}H NMR δ 2.00 (m, 2H), 2.50 (m, 2H), 3.37 (t, J = 7.1 Hz, 2H), 3.86 (s, 6H), 3.90 (s, 6H), 4.27 (t, J = 7.1 Hz, 2H), 5.22 (m, 2H), 6.62 (s, 2H), 7.08 (m, 1H), 7.17 (m, 1H), 7.33(m, 1H).

(±)-*trans*-2-[3-Methoxy-4-(4-methoxyphenylthioethoxy)-5-nitrophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (18). In a similar manner as for **12** but using 4-methoxythiophenol (123.7 mg, 0.882 mmol) in place of 4-chlorothiophenol, **10** (155.0 mg, 0.294 mmol) was converted to **18** as an oil (135 mg, 91%): ^{1}H NMR δ 2.00 (m, 2H), 2.49 (m, 2H), 3.22 (t, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89 (s, 6H), 4.22 (t, J = 7.1 Hz, 2H), 5.20 (m, 2H), 6.61 (s, 2H), 6.87 (d, J = 8.2 Hz, 2H), 7.14 (s, 1H), 7.34 (s, 1H), 7.41 (d, J = 8.2 Hz, 2H).

(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-aminophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (19). To a stirred solution of **12** (50.0 mg, 0.087 mmol) in ethanol (3 mL) was added zinc powder (125.1 mg, 1.91 mmol) and calcium chloride (9.65 mg, 0.087 mmol). The reaction mixture was heated at reflux for 16 h. The reaction was filtered and the filtrate was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated to give **19** as an oil (42 mg, 88.6%): ^{1}H NMR δ 1.98 (m, 2H), 2.44 (m, 2H), 3.25 (t, J = 6.3 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.88 (s, 6H), 4.14 (t, J = 6.3 Hz, 2H), 5.15 (m, 2H), 6.38 (s, 1H), 6.43 (s, 1H), 6.63 (s, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.34(d, J = 8.5 Hz, 2H).

(±)-*trans*-2-[3-Methoxy-4-(3,4-dichlorophenylthioethoxy)-5-aminophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (20). Following the same procedure as for **19**, **13** (52.4 mg, 0.086 mmol) was converted to **20** as an oil (39 mg, 78%): ^{1}H NMR δ 1.97 (m, 2H), 2.43 (m, 2H), 3.26 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 6H), 4.15 (t, J = 6.4 Hz, 2H), 5.14 (m, 2H), 6.37 (d, J = 1.8 Hz, 1H), 6.43 (d, J = 1.8 Hz, 1H), 6.62 (s, 2H), 7.22 (m, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.45 (s, 1H).

(±)-*trans*-2-[3-Methoxy-4-(4-bromophenylthioethoxy)-5-aminophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (21). Following the same procedure as for **19**, **14** (194.0 mg, 0.313 mmol) was converted to **21** as a foam (170 mg, 92%): ^{1}H NMR δ_1.98 (m, 2H), 2.45 (m, 2H), 3.27 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 6H), 4.12 (t, J = 6.4 Hz, 2H), 5.15 (m, 2H), 6.38 (s, 1H), 6.44 (s, 1H), 6.64 (s, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H).

(±)-*trans*-2-[3-Methoxy-4-(2-bromophenylthioethoxy)-5-aminophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (22). Following the same procedure as for **19**, **15** (47.8 mg, 0.077 mmol) was converted to **22** as an oil (39 mg, 85.7%): ^{1}H NMR δ 1.98 (m, 2H), 2.44 (m, 2H), 3.30 (m, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.88 (s, 6H), 4.20 (m, 2H), 5.14 (m, 2H), 6.37 (s, 1H), 6.43 (s, 1H), 6.63 (s, 2H), 7.20 (m, 1H), 7.29 (m, 1H), 7.40 (m, 1H), 7.55 (m, 1H).

(±)-*trans*-2-[3-Methoxy-4-(3-bromophenylthioethoxy)-5-aminophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (23). Following the same procedure as for **19**, **16** (56.0 mg, 0.090 mmol) was converted to **23** as an oil (48 mg, 90%): ^{1}H NMR δ 1.97 (m, 2H), 2.43 (m, 2H), 3.28 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.88 (s, 9H), 4.16 (t, J = 6.4 Hz, 2H), 5.13 (m, 2H), 6.38 (d, J = 1.8 Hz, 1H), 6.44 (d, J = 1.8 Hz, 1H), 6.63 (s, 2H), 7.16 (t, J = 8.0 Hz, 1H), 7.29 (m, 2H), 7.51 (s, 1H).

(±)-*trans*-2-[3-Methoxy-4-(2,3,5,6-tetrafluorophenylthioethoxy)-5-aminophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (24). Following the same procedure as for **19**, **17** (50.0 mg, 0.082 mmol) was converted to **24** as an oil (33 mg, 69.3%): ^{1}H NMR δ 1.97 (m, 2H), 2.43 (m, 2H), 3.30 (t, J = 6.3 Hz, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 3.88 (s, 6H), 4.11 (t, J = 6.3 Hz, 2H), 5.13 (m, 2H), 6.36 (s, 1H), 6.42 (s, 1H), 6.62 (s, 2H), 7.04 (m, 1H).

(±)-*trans*-2-[3-Methoxy-4-(4-methoxyphenylthioethoxy)-5-aminophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (25). Following the same procedure as for **19**, **18** (130.0 mg, 0.228 mmol) was converted to **25** as an oil (116 mg, 94%): ^{1}H NMR δ 1.98 (m, 2H), 2.43 (m, 2H), 3.15 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.88 (s, 6H), 4.10 (t, J = 6.0 Hz, 2H), 5.13 (m, 2H), 6.36 (s, 1H), 6.43 (s, 1H), 6.62 (s, 2H), 6.83 (d, J = 7.4 Hz, 2H), 7.42 (d, J = 7.4 Hz, 2H).

(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (26). To a solution of **19** (38.0 mg, 0.070 mmol) in dry dichloromethane (3 mL) was added triphosgene (6.83 mg, 0.023 mmol) and triethylamine (8.47 mg, 0.084 mmol). The reaction mixture was heated to reflux for 2 h and then cooled with an ice bath. To this mixture was then added *n*-butylhydroxylamine (18.6 mg, 0.209 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed and the product was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to yield **26** a foam (35 mg, 76%): ^{1}H NMR δ 0.93 (t, J = 7.2 Hz, 3H), 1.36 (m, 2H), 1.64 (m, 2H), 2.00 (m, 2H), 2.45 (m, 2H), 3.21 (t, J = 6.4 Hz, 2H), 3.58 (t, J = 7.2 Hz, 2H), 3.84 (s, 6H), 3.87 (s, 6H), 4.16 (t, J = 6.4 Hz, 2H), 5.20 (m, 2H), 6.33 (bs, 1H), 6.62 (s, 2H), 6.74 (s, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.89 (s, 1H), 8.65 (s, 1H). Anal. ($C_{33}H_{41}O_8N_2SCl$) C, H, N, S.

(±)-*trans*-2-[3-Methoxy-4-(3,4-dichlorophenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (27). Following the same procedure as for **26**, **20** (39.0 mg, 0.067 mmol) was converted to **27** as a foam (40 mg, 85%): ^{1}H NMR δ 0.93 (t, J = 7.2 Hz, 3H), 1.35 (m, 2H), 1.63 (m, 2H), 1.98 (m, 2H), 2.46 (m, 2H), 3.23 (t, J = 6.3 Hz, 2H), 3.59 (t, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.88 (s, 6H), 4.17 (t, J = 6.3 Hz, 2H), 5.20 (m, 2H), 6.62 (s, 2H), 6.75 (s, 1H), 7.18 (m, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.43 (m, 1H), 7.90 (s, 1H), 8.61 (s, 1H). Anal. ($C_{33}H_{40}O_8N_2SCl_2$) C, H, N.

(±)-*trans*-2-[3-Methoxy-4-(4-bromophenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (28). Following the same procedure as for **26**, **21** (40.0 mg, 0.068 mmol) was converted to **28** as a foam (20.3 mg, 43%): ^{1}H NMR δ 0.91 (t, J = 7.2 Hz, 3H), 1.34 (m, 2H), 1.60 (m, 2H), 1.98 (m, 2H), 2.43 (m, 2H), 3.20 (t, J = 6.3 Hz, 2H), 3.56 (t, J = 7.2 Hz, 2H), 3.83 (s, 6H), 3.87 (s, 6H), 4.14 (t, J = 6.3 Hz, 2H), 5.20 (m, 2H), 6.61 (s, 2H), 6.72 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.88 (s, 1H), 8.61 (s, 1H). Anal. ($C_{33}H_{41}O_8N_2SBr$) C, H, N.

(±)-*trans*-2-[3-Methoxy-4-(2-bromophenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (29). Following the same procedure as for **26**, **22** (39.0 mg, 0.066 mmol) was converted to **29** as an oil (35 mg, 75%): ^{1}H NMR δ 0.92 (t, J = 7.1 Hz, 3H), 1.36 (m, 2H), 1.64 (m, 2H), 2.00 (m, 2H), 2.45 (m, 2H), 3.26 (m, 2H), 3.58 (t, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 4.18 (m, 2H), 5.20 (m, 2H), 6.62 (s, 2H), 6.75 (s, 1H), 7.26 (m, 2H), 7.37 (m, 1H), 7.53 (m, 1H), 7.92 (s, 1H), 8.68 (s, 1H). Anal. ($C_{33}H_{41}O_8N_2SBr$) C, H, N.

(±)-*trans*-2-[3-Methoxy-4-(3-bromophenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (30). Following the same procedure as for **26**, **23** (48.0 mg, 0.082 mmol) was converted to **30** as an oil (46 mg, 80%): ^{1}H NMR δ 0.91 (t, J = 7.1 Hz,,3H), 1.35 (m, 2H), 1.61 (m, 2H), 2.00 (m, 2H), 2.46 (m, 2H), 3.22 (t, J = 6.3 Hz, 2H), 3.57 (t, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 4.16 (t, J = 6.3 Hz, 2H), 5.20 (m, 2H), 6.55 (bs, 1H), 6.62 (s, 2H), 6.73 (s, 1H), 7.12 (m, 1H), 7.26 (m, 2H), 7.48 (s, 1H), 7.89 (s, 1H), 8.61 (s, 1H). Anal. ($C_{33}H_{41}O_8N_2$SBr) C, H, N, S.

(±)-*trans*-2-[3-Methoxy-4-(2,3,5,6-tetrafluorophenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (31). Following the same procedure as for **26**, **24** (33.0 mg, 0.057 mmol) was converted to **31** as an oil (28 mg, 71%): ^{1}H NMR δ 0.95 (t, J = 7.2 Hz, 2H), 1.38 (m, 2H), 1.62 (m, 2H), 2.00 (m, 2H), 2.46 (m, 2H), 3.29 (t, J = 6.1 Hz, 2H), 3.61 (t, J = 7.2 Hz, 2H), 3.84 (s, 6H), 3.88 (s, 6H), 4.18 (t, J = 6.1 Hz, 2H), 5.20 (m, 2H), 6.62 (s, 2H), 6.74 (s, 1H), 7.06 (m, 1H), 7.91 (s, 1H), 8.63 (s, 1H). Anal. ($C_{33}H_{38}O_8N_2SF_4$) C, H, N.

(±)-*trans*-2-[3-Methoxy-4-(4-methoxyphenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (32). Following the same procedure as for **26**, **25** (31.0 mg, 0.057 mmol) was converted to **32** as a foam (25.8 mg, 70%): ^{1}H NMR δ 0.93 (t, J = 7.3 Hz, 3H), 1.37 (m, 2H), 1.63 (m, 2H), 2.00 (m, 2H), 2.45 (m, 2H), 3.11 (t, J = 6.1 Hz, 2H), 3.60 (t, J = 7.3 Hz, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 3.88 (s, 6H), 4.14 (t, J = 6.1 Hz, 2H), 5.20 (m, 2H), 6.62 (s, 2H), 6.73 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.91 (s, 1H), 8.75 (s, 1H). Anal. ($C_{34}H_{44}O_9N_2$S) C, H, N.

(±)-*trans*-2-[3-Methoxy-4-(4-bromophenylsulfonylethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (33). To a stirred solution of **28** (10.0 mg, 0.014 mmol) in acetonitrile (1 mL) was added magnesium monoperoxyphthalic acid (MMPP) in water (0.1 mL). The reaction was stirred at room temperature for 2 h, diluted with water, and extracted with ethyl acetate. The extract was washed with water and brine. The product was separated by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **33** as an oil (5.6 mg, 53%): ^{1}H NMR δ 0.95 (t, J = 7.4 Hz, 3H), 1.40 (m, 2H), 1.68 (m, 2H), 2.00 (m, 2H), 2.47 (m, 2H), 3.53 (t, J = 5.0 Hz, 2H), 3.64 (t, J = 7.4 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3.89 (s, 6H), 4.43 (t, J = 5.0 Hz, 2H), 5.21 (m, 2H), 6.63 (s, 2H), 6.76 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.91 (s, 1H), 8.60 (s, 1H). Anal. ($C_{33}H_{41}O_{10}N_2$SBr) C, H, N; C: calcd, 53.73; found, 53.20.

(±)-*trans*-2-[3-Methoxy-4-(2-bromophenylsulfonylethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (34). Following the same procedure described above for converting **28** to **33**, **29** (20.0 mg, 0.028 mmol) was transformed to **34** as a foam (14 mg, 67%): ^{1}H NMR δ 0.95 (t, J = 7.4 Hz, 3H), 1.40 (m, 2H), 1.68 (m, 2H), 2.01 (m, 2H), 2.47 (m, 2H), 3.54 (t, J = 4.5 Hz, 2H), 3.65 (t, J = 7.4 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.88 (s, 6H), 4.43 (t, J = 4.5 Hz, 2H), 5.22 (m, 2H), 6.64 (s, 2H), 6.75 (s, 1H), 7.61 (m, 2H), 7.71 (m, 1H), 7.92 (m, 1H), 7.96 (s, 1H), 8.66 (s, 1H). Anal. ($C_{33}H_{41}O_{10}N_2$SBr) C, H, N.

(±)-*trans*-2-[3-Methoxy-4-(2,3,5,6-tetrafluorophenylsulfonylethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (35). Following the same procedure described above for converting **28** to **33**, **31** (38.0 mg, 0.054 mmol) was transformed to **35** as an oil (25 mg, 63%): ^{1}H NMR δ 0.93 (t, J = 7.4 Hz, 3H), 1.38 (m, 2H), 1.65 (m, 2H), 2.00 (m, 2H), 2.47 (m, 2H), 3.51 (m, 2H), 3.61 (m, 2H), 3.84 (s, 3H), 3.88 (s, 9H), 4.45 (m, 2H), 5.21 (m, 2H), 6.62 (s, 2H), 6.80 (s, 1H), 7.31 (m, 1H), 7.82 (s, 1H), 8.32 (s, 1H). Anal. ($C_{33}H_{38}O_{10}N_2SF_4$) C, H, N.

(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (36). To a stirred solution of **11** (2.5 g, 4.11 mmol) in ethanol (50 mL) was added 4-chlorothiophenol (1.19 g, 8.22 mmol) and triethylamine (0.831 g, 8.22 mmol). The reaction mixture was heated at reflux for 16 h, and then the solvent was removed. The residue was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield **36** as an oil (2.35 g, 87%): ^{1}H NMR δ 1.96 (m, 2H), 2.45 (m, 2H), 3.35 (t, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.88 (s, 6H), 4.11 (t, J = 7.1 Hz, 2H), 5.17 (m, 2H), 6.61 (s, 2H), 6.92 (s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.35 (s, 1H).

(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-cyanophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (37). A mixture of **36** (2.35 g, 3.58 mmol) and CuCN (0.36 g, 4.30 mmol) in DMF (20 mL) was heated with stirring at 140 °C for 16 h. The reaction was cooled, diluted with water, and extracted with ethyl acetate. The extract was washed with water and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. The title compound was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) as an oil (1.79 g, 90.0%): ^{1}H NMR δ 1.99 (m, 2H), 2.49 (m, 2H), 3.36 (t, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.89 (s, 6H), 4.28 (t, J = 7.2 Hz, 2H), 5.20 (m, 2H), 6.61 (s, 2H), 7.16 (s, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H).

(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-aminomethylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (38). To a solution of **37** (300.0 mg, 0.54 mmol) in THF (10 mL) were added sodium borohydride (36.8 mg, 0.97 mmol) and boron trifluoride etherate (191.8 mg, 1.35 mmol) dropwise. The reaction mixture was heated at reflux for 1 h and cooled with an ice−water bath, and then a few drops of 10% HCl was added. The reaction mixture was poured into 10% K_2CO_3 and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. The title compound was purified by flash column chromatography (silica gel, 93:7 CH_2Cl_2/MeOH) as a gum (64 mg, 21.2%): ^{1}H NMR δ 1.98 (m, 2H), 2.46 (m, 2H), 2.50 (m, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.83 (s, 3 H), 3.84 (s, 3H), 3.88 (s, 6H), 3.90 (m, 2H), 4.17 (t, J = 6.6 Hz, 2H), 5.18 (m, 2H), 6.62 (s, 2H), 6.91 (s, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H).

(+)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-butyl-*N*-hydroxyureidyl)methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (39). To a stirred solution of **38** (390.0 mg, 0.70 mmol) in dry dichloromethane (30 mL) were added triphosgene (68.8 mg, 0.23 mmol) and triethylamine (71.7 mg, 0.70 mmol). The reaction mixture was heated at reflux for 2 h and then cooled to room temperature. To this solution was then added *n*-butylhydroxylamine (187.6 mg, 2.11 mmol), with further stirring at room temperature overnight. The reaction was quenched with water and extracted with dichloromethane. The organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated in vacuo. The product **39** was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give a solid (151 mg, 32%): mp 55−57 °C; ^{1}H NMR δ 0.92 (t, J = 7.4 Hz, 3H), 1.33 (m, 2H), 1.55 (m, 2H), 1.98 (m, 2H), 2.45 (m, 2H), 3.29 (t, J = 6.6 Hz, 2H), 3.50 (t, J = 7.4 Hz, 2H), 3.84 (s, 6H), 3.88 (s, 6H), 4.17 (t, J = 6.6 Hz, 2H), 4.43 (d, J = 5.8 Hz, 2H), 5.18 (m, 2H), 6.41 (t, J = 5.8 Hz, 1H), 6.62 (s, 2H), 6.92 (s, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H). Anal. ($C_{34}H_{43}O_8N_2$SCl) C, H, N, S.

(±)-*trans*-2-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-methyl-*N*-hydroxyureidyl)methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (40). To a stirred solution of **38** (54.0 mg, 0.10 mmol) in dry dichloromethane (4 mL) were added triphosgene (9.46 mg, 0.03 mmol) and triethylamine (9.77 mg, 0.10 mmol). The reaction mixture was heated at reflux for 2 h and then cooled to room temperature. To this mixture were then added triethylamine (35.2 mg, 0.35 mmol) and methylhydroxylamine hydrochloride (24.2 mg, 0.29 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with water and saturated NaCl solution, dried over

$MgSO_4$, filtered, and evaporated. The product **40** was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) (49 mg, 80%) to give a solid: mp 68−70 °C; ^{1}H NMR δ 1.98 (m, 2H), 2.44 (m, 2H), 3.08 (s, 3H), 3.27 (t, J = 6.6 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 3.87 (s, 6H), 4.15 (t, J = 6.6 Hz, 2H), 4.40 (d, J = 5.7 Hz, 2H), 5.17 (m, 2H), 6.41 (m, 1H), 6.61 (s, 2H), 6.77 (bs, 1H), 6.90 (s, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 33.9, 35.6, 35.7, 39.1, 39.8, 55.8, 56.2, 60.9, 70.9, 81.2, 81.6, 102.5, 109.1, 118.7, 129.1, 130.8, 132.2, 139.2, 139.6, 152.1, 153.5, 161.8. Anal. ($C_{31}H_{37}O_8N_2SCl$) C, H, N, S.

PAF Receptor Binding Assay. CHO cells expressing the human PAF receptor were grown to confluence (2×10^6/mL) in spinner flasks, harvested, and washed with 20 nM Tris, 5 mM EDTA, 0.15 M NaCl, pH 7.4. Cells were resuspended in homogenization buffer (20 mM Tris pH 7.4, 5 mM EDTA, 225 mM sucrose, 1 mM PMSF) at 1×10^8/mL and lysed by sonication. Five milliliters of extract was layered over a sucrose gradient containing 5 mL each of 0.25, 1.03, and 1.5 M sucrose in homogenization buffer and centrifuged (48000*g*, 2 h, 4 °C). The membrane fractions located at the interface of the 1.5 and 1.03 M sucrose layers and the membrane pellet at the bottom of the tube were pooled; the protein concentration was determined by solubilization in 1% SDS and quantitation using the BCA reagent (Pierce).

The membrane preparation, compound, and 3 nM [^{3}H]PAF in 0.25 mL of binding buffer (10 mM Tris pH 7.0, 0.25% BSA, 30 mM $MgCl_2$) were incubated (3 h, 4 °C) in a microtiter plate. The reaction was then transferred to glass fiber plate filters using a Packard Filtermate 196 plate harvester. Filters were washed three times with ice cold 10 mM Tris pH 7.0, 0.25% BSA. Packard Microscint-20 scintillation fluid (25 μL) was added to each well, and the plate was counted using a Packard Top Count. Specific binding was determined by subtracting the value obtained in the presence of excess unlabeled PAF from that obtained in the absence of unlabeled PAF. Percent inhibition at each dose of compound was determined from the decrease in specific binding, and IC_{50} value was calculated.

5-LO Assay in RBL Cell Extracts. RBL-2H3 cells were grown to confluence according to literature protocols. Cells were harvested and washed twice in buffer. Cells were suspended at 2×10^7/mL in 10 mM BES, 10 mM PIPES, 1 mM EDTA, pH 6.8 buffer and sonicated. The cell lysate was centrifuged (20000*g*, 20 min, 4 °C); the supernatant was removed and stored in aliquots at −70 °C.

5-LO activity in cell lysate was determined as follows: 0.1 mL reactions consisting of 10 mM BES, 10 mM PIPES, 0.1 M NaCl, 1 mM EDTA, 0.7 mM $CaCl_2$, pH 6.8, test compound (in DMSO), and an amount of cell lysate that will convert ∼15% of [^{14}C]AA substrate mix to oxygenated products were incubated (20 min, room temperature). A substrate mix containing [^{14}C]AA was added and incubated further (5 min, 37 °C).

The reaction was terminated by adding 0.2 mL of an organic extraction solution containing triphenylphosphine, followed by microcentrifugation. The organic phase (50 μL) was spotted onto silica gel TLC plates. The plates were developed in ethyl ether/acetic acid (100:0.1) (25 min, room temperature). Plates were exposed to film for 36 h. The film was developed and scanned using a densitometer, and the peak areas of AA and its products were calculated. Percent inhibition was determined from the amount of [^{14}C]AA converted into oxygenated products in samples containing test compound relative to that of control samples (no test compound), and an IC_{50} value was obtained via regression analysis.

LTB_4 Production from Human Whole Blood. Human blood was drawn into heparinized blood collection tubes and aliquoted in 1 mL portions into 1.5 mL microfuge tubes. Five microliters of test compound (at selected concentration in DMSO) was added to the blood sample and incubated for 15 min at 37 °C. Calcium ionophore (A23187 in DMSO, 50 μM final concentration) and the samples were incubated (30 min, 37 °C). The samples were centrifuged (1100*g*, 10 min, 4 °C), and the supernatant was assayed for LTB_4 using an EIA kit (Cayman Chemical). The percent inhibition for each sample was calculated and an IC_{50} value obtained via regression analysis.

PAF-Induced Hemoconcentration in Mice. PAF was dissolved in 0.25% BSA in 0.9% NaCl. Except for dose−response studies, 10 μg (10 mL/kg) was injected into the tail vein. All test compounds were dissolved in 0.5% DMSO saline solution and intravenously injected at 3 mg (10 mL/kg) body weight at various times prior to PAF challenge. Blood (30−50 μL) was collected by cutting the tail end into a heparinized microhematocrit tube (O.D. 1.50 mm) 15 min after PAF administration. The percent inhibition of PAF-induced hemoconcentration for each experimental assay was calculated with respect to the hematocrit observed in the vehicle control.

Arachidonic Acid-Induced Ear Edema in Mice. Arachidonic acid was applied to both ears of mice in 0.025 mL of freshly prepared vehicle (acetone/pyridine/water (97:2:1 v/v/v) and dried under a Sun-Lite Hitensity bulb. Except for dose−response studies, 0.5 mg of arachidonic acid was used for all applications. All test compounds were dissolved in 0.5% DMSO saline solution and intravenously injected at 3 mg/kg body weight 15 min prior to arachidonic acid treatment. Animals were sacrificed by cervical dislocation at 1 h after topical application of arachidonic acid. A 7-mm-diameter disk of tissue was removed from each ear by means of a metal punch. Edema was measured by the average wet weight of both ear tissue.

Acute TPA-Induced Ear Edema in Mice. Eight mice per group were administered 10 μL of TPA solution (acetone) or vehicle (acetone) with or without drug on both surfaces of each ear for each animal. All animals within the group were sacrificed after 6 h. Tissues were taken with a biopsy punch and weighed. The left ear was then placed in a fixative solution for later histological analysis. The right ear was placed into a 5 mL centrifuge tube and stored at −80 °C for later analysis of MPO activity. Experimental treatment group responses were compared to the maximal control for inhibition of edema by analysis of ear mass, dermal histology, and MPO production.

Chronic TPA-Induced Ear Edema in Mice. Eight mice per group were administered 10 μL of TPA solution (acetone) or vehicle (acetone) with or without drug on both surfaces of each ear for each animal. All animals within the group were dosed with TPA once a day every 2 days for a total of 10 days in order to induce the chronic inflammatory response. Drugs were administered twice daily on the last 3 days of the experiment. Animals were sacrificed by CO_2 asphyxiation. Tissues were taken with a biopsy punch and weighed. The left ear was then placed in a fixative solution for histological analysis. The right ear was stored at −80 °C for later analysis of MPO activity. Representative ear samples from each group were subjected to histological evaluation. Experimental treatment group responses were compared to the maximal control for inhibition of edema by analysis of ear mass, dermal histology, and MPO production.

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