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New Cyclooxygenase-2/5-Lipoxygenase Inhibitors. 1. 7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzofuran Derivatives as Gastrointestinal Safe Antiinflammatory and Analgesic Agents: Discovery and Variation of the 5-Keto Substituent

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A series of 5-keto-substituted 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofurans (DHDMBFs) were prepared and evaluated as potential nonsteroidal antiinflammatory and analgesic agents. Interest in this class of compounds arose when a DHDMBF was found to be an active metabolite of the di-*tert*-butylphenol antiinflammatory agent tebufelone. We have now found that a variety of 5-keto-substituted DHDMBFs have good in vivo antiinflammatory and analgesic activity after oral administration. These compounds inhibit both cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) in vitro. The cyclooxygenase inhibition was found to be selective for the cyclooxygenase-2 isoform, and this combination of COX-2/5-LOX inhibition may be responsible for the gastrointestinal safety of compounds such as **30**.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for the treatment of pain, inflammation, and fever.[1] The mechanism of action of these drugs is proposed to involve the inhibition of cyclooxygenase (COX) which converts arachidonic acid to proinflammatory prostaglandins. However, since prostaglandins are also cytoprotective, common mechanism-based side effects of NSAID use are gastric ulceration and nephrotoxicity.

In recent years, several approaches have been proposed to minimize the toxicities of NSAIDs. Among these is the development of dual cyclooxygenase/5-lipoxygenase (COX/5-LOX) inhibitors. LTB_4, one of the leukotrienes formed from arachidonic acid by 5-LOX, has been proposed to play a role in the formation of gastric ulcers.[2]

The di-*tert*-butylphenol class of antiinflammatory agents is one source of dual COX/5-LOX inhibitors. Representative compounds include R-830 (**1**),[3] KME-4 (**2**),[4] E-5110 (**3**),[5] and CI-1004 (**4**)[6] (Chart 1). The antioxidant and radical scavenging properties of these compounds have been proposed to be relevant to their antiinflammatory efficacy and low ulcerogenic potential.[7]

Another approach to gastrointestinal (GI) safe NSAIDs involves selective inhibition of COX isozymes: COX-1, thought to be the constitutive form essential for normal gastric and kidney function, and COX-2, an isozyme that is upregulated during inflammation. Selective inhibitors of COX-2 such as NS-398 (**5**) and SC-57666 (**6**) (Chart 1) have indeed been found to have reduced GI side effects in animal models.[8,9]

The di-*tert*-butylphenol tebufelone (**7**) (Chart 1) was previously identified as a promising member of the di-*tert*-butylphenol class.[10−12] Among the metabolites of tebufelone was the dihydrodimethylbenzofuran **8**[13] (Chart 1). Although **8** is no longer a phenol and is not an antioxidant, it nonetheless displays antiinflammatory activity equivalent to tebufelone in the rat carrageenan paw edema assay. Herein we report that the antiinflammatory activity of this new class of agents is general and that certain of these compounds are dual COX/5-LOX inhibitors, some with >50-fold selectivity for COX-2. This combination of two potential mechanisms for reduced GI side effects may be responsible for the GI safety displayed by these compounds.

Chemistry

The original six-step route[14] to the requisite DHDMBF starting material **12** was inconvenient for scale-up, so an improved synthesis was devised. The key reaction was the free radical cyclization of β-methallyl 2,4-dibromo-6-*tert*-butylphenyl ether to the desired 2,3-dihydrobenzofuran nucleus (Scheme 1).[15] Thus, 2,4-dibromo-6-*tert*-butylphenol (**9**)[16] was allylated with 3-chloro-2-methylpropene. The resulting ether **10** underwent a 5-exo-trig radical cyclization reaction under the influence of various radical reaction initiators and reductants. Operationally, aqueous hypophosphorus acid[17,18] proved to be a superior hydrogen source over either *n*-Bu_3SnH or $(TMS)_3SiH$, both of which required extensive chromatography to remove Sn- or Si-based byproducts. This cyclization reaction was carried out on multikilogram quantities, with yields ranging from 60% to 70%, and provided 5-bromo-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (**11**) as a 70:30 mixture with **12**. Debromination of **11** to **12** was reliably achieved by transfer hydrogenation of this mixture with cyclohexene in refluxing EtOH in the presence of 10% Pd on charcoal and an acid scavenger such as K_2CO_3.

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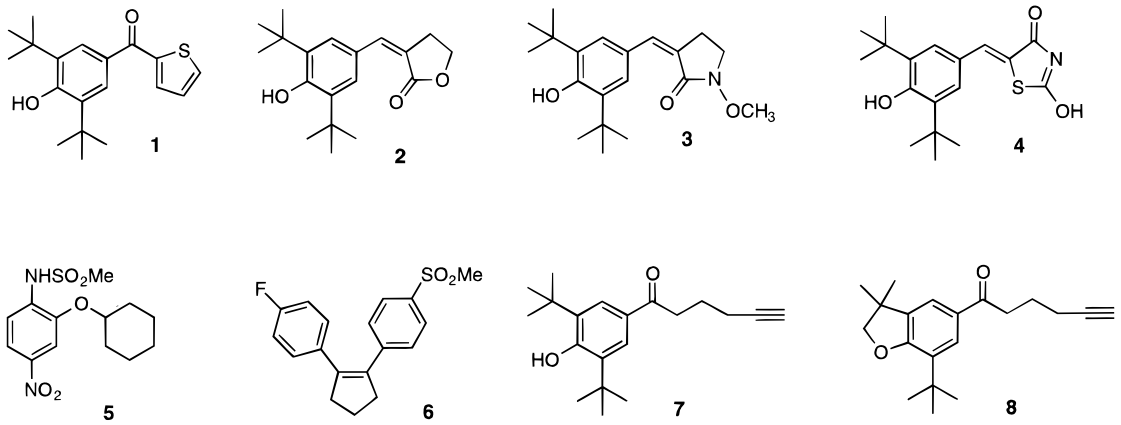
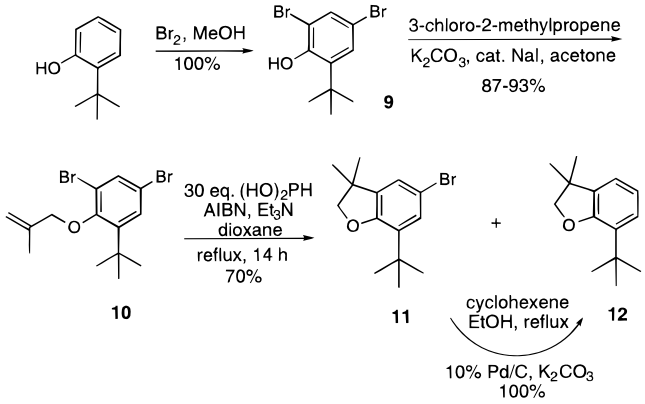
Chart 1



Scheme 1



The 5-keto derivatives of the dihydrobenzofurans were generally prepared by Friedel−Crafts acylation of **12** with an appropriately activated carboxylic acid. An acylation method developed for the large-scale preparation of tebufelone proved to be a convenient and quite general method here.[19] Addition of trifluoroacetic anhydride (TFAA) at −20 °C to a 1:1.1 mixture of **12** and the appropriate carboxylic acids gave the desired ketones generally in modest to good isolated yields (Scheme 2, method A). Reduction of ketone **13** with $NaBH_4$ provided the corresponding alcohol **14**. The TFAA reaction failed for preparation of the dioxa acid-derived compound **20,** but the addition of 5-lithio DHDMBF to the Weinreb amide[20] of the oxa acid (method B) was successful. Preparation of compound **31** involved the oxidation of the trimethylsilyl enol ether (LDA, TMSCl) of **30** with palladium acetate and benzoquinone (method C).[21]

The preparations of several sulfur-, nitrogen-, and chlorine-containing analogues are shown in Scheme 3. The sulfide **33** was prepared by the TFAA method and then subsequently oxidized with *m*-chloroperbenzoic acid to the sulfoxide **34** and sulfone **35** (method D). The sulfoxide **37** and the sulfone **38** were prepared similarly from the sulfide **36** (method F) which, in turn, was prepared by ammonolysis/alkylation of the thioacetyl compound **43** (method E). The amine **39** and sulfide **41** were prepared via substitution reactions of **47** (method G), itself prepared via the TFAA reaction. The *β*-chloro ketone **44** was prepared by addition of HCl to the olefin **46** (method H) which also derives from the TFAA-mediated acylation.

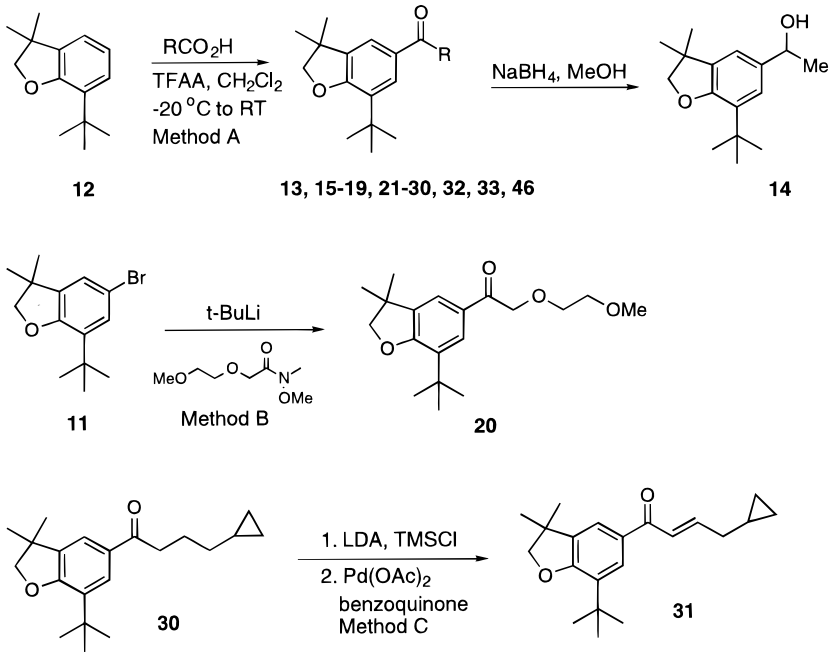
The acetylated analogue **13** was the starting material for four analogues (Scheme 4). Bromination of the trimethylsilyl enol ether with *N*-bromosuccinimide followed by reaction with potassium thioacetate gave the thioester **43** (method I). Chlorination of **13** was accomplished by reaction with benzyltrimethylammonium dichloroiodate.[22] Subsequent substitution reactions provided the amine **40** (method J) and ester **42** (method K). Mukaiyama aldol reaction[23] of **13** with acetone provided the alcohol **45** (method L).

Results and Discussion

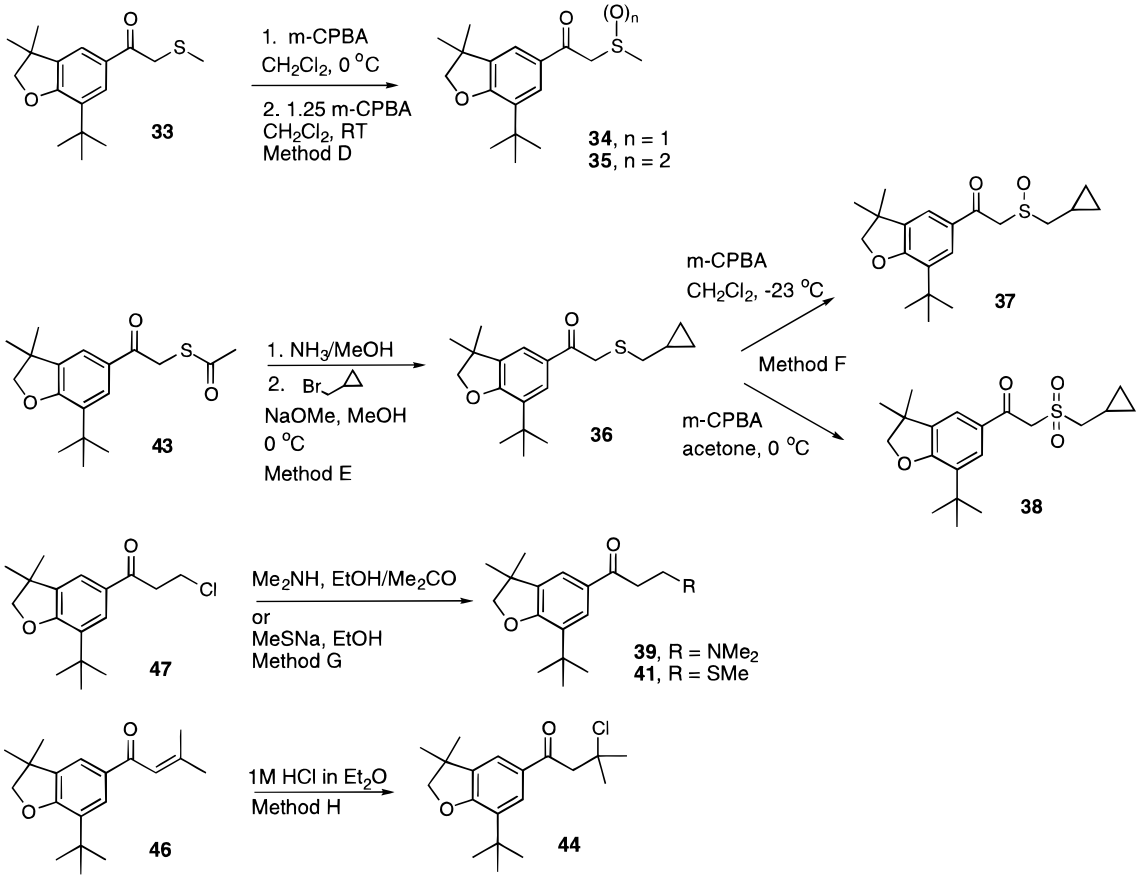
In Vivo Activity. The carrageenan paw edema (CPE) assay was the primary screen used to assess in vivo antiinflammatory activity. Compounds were tested for their ability to inhibit paw swelling relative to tebufelone (positive control) after a single oral screening dose (50 mg/kg). The CPE data in Table 1 are given in terms of a CPE index which is the ratio of a compound's percent inhibition of paw edema versus control to tebufelone's percent inhibition of paw edema versus control.[24] At the 50 mg/kg screening dose, both naproxen, a marketed nonsteroidal antiinflammatory agent, and tebufelone exhibited about the same antiinflammatory activity. While uncertainties about bioavailability complicate the interpretation of the CPE results, the bioavailability of **30** was quite good (62%) in the rat.

The prototypical DHDMBF **8** had activity equivalent to tebufelone. The parent unsubstituted DHDMBF **12** was inactive. A series of aliphatic and cyclic ketones were prepared to determine chain length and size limitations. Activity was observed for ketones with two to five carbons in the chain (compounds **13** and **15**−**18**) with the exception of the *tert*-butyl ketone **21**. The two-carbon alcohol **14**, however, was inactive. The six-carbon ketone **19** was inactive, although the longer dioxa ketone **20** retained activity. Among cycloalkyl ketones, the cyclopropyl and cyclopentyl compounds **22** and **23** were active while the cyclohexyl ketone **24** was not. Systems with extended conjugation were investigated with the synthesis of aromatic ketones. The phenyl ketone **25** was active, while 2- and 4-halogenated versions **26** and **27** were not. Terminally unsaturated compounds such as tebufelone and the corresponding DHDMBF **8** were among the most active compounds but have the potential to inhibit liver enzymes.[25] The cyclopropyl group offered an alternative terminating group with some of the characteristics of terminal

Scheme 2

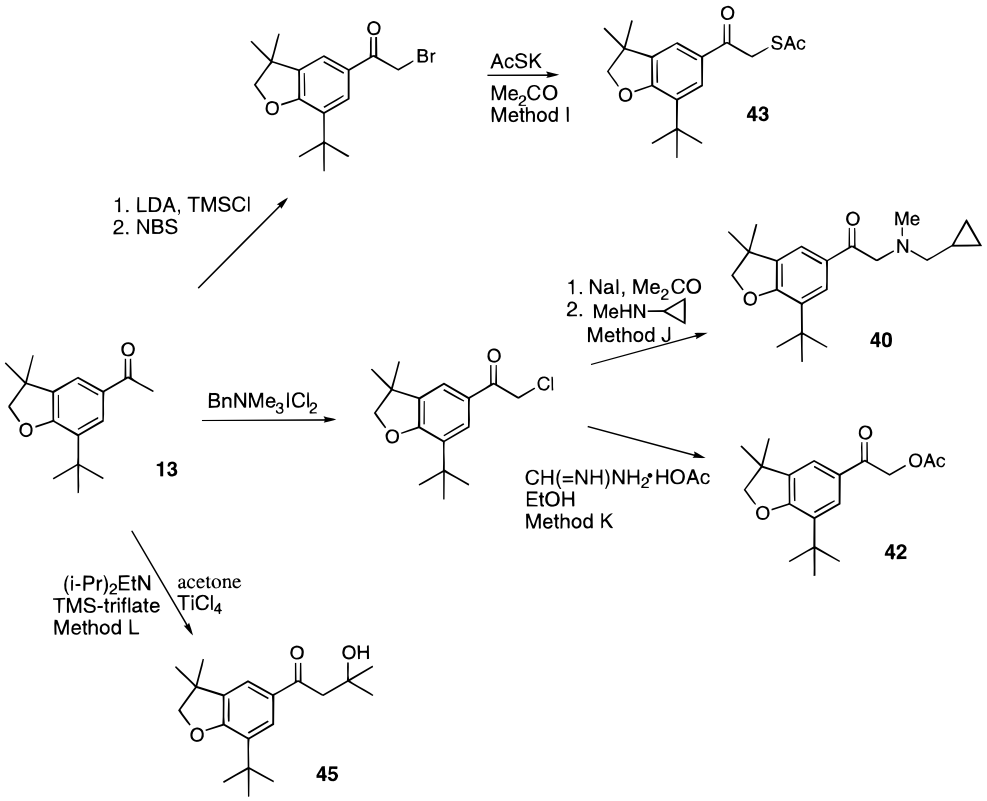


Scheme 3



unsaturation. A series of three cyclopropylalkyl ketones (**28**−**30**) were prepared and were active with the curious exception of the middle compound in the series, **29**. The 4-cyclopropylbutanoyl compound **30** proved to be of particular interest (vide infra), and several analogues of **30** were prepared. The trans α,β-unsaturated derivative **31** proved inactive. The terminally branched compound **32** formally derived by addition of hydrogen across the unsubstituted cyclopropyl bond, was also inactive. In contrast, some heteroatoms could be incorporated into the cyclopropylbutanoyl side chain with retention of activity: the sulfide **36** (but not the corresponding sulfoxide **37** and sulfone **38**) was active as was the amine **40** (but less active than tebufelone). These results prompted us to prepare other heteroatom-containing analogues. In general, these analogues

Scheme 4

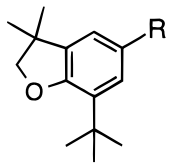


would be more hydrophilic and perhaps have somewhat greater water solubility than the extremely hydrophobic all-carbon analogues. Among sulfur-containing analogues, the sulfide and sulfoxide **33** and **34** were active, the latter compound's activity contrasting with the inactivity of the sulfoxide **37**. The sulfone **35** was inactive, consistent with the results for the sulfone **38**. The thioether **41** was active as was the thioester **43**. In contrast, the corresponding ester **42** was inactive. The β-halo and β-hydroxy compounds **44** and **45** were active as was the α,β-unsaturated analogue **46**.

Most of the active compounds from the CPE assay were evaluated for analgesic activity in the mouse phenylquinone-induced abdominal constriction (PAC) assay. The correlation of antiinflammatory and analgesic activity was generally good. All the compounds active in the CPE assay had an ED_{50} of <35 mg/kg or ≥50% inhibition at 70 mg/kg in the PAC assay with the exception of compounds **18** and **33**. Compound **30** was the most potent analogue with an ED_{50} of 11 mg/kg. Selected compounds were progressed to subsequent testing tiers for additional assessment of safety and efficacy. Table 2 shows some of these data for compound **30** in comparison to a standard NSAID, naproxen. Compound **30** was active in the therapeutic rat adjuvant arthritis assay with an ED_{50} of 6.6 mg/kg. The acute ulcerogenic dose (UD_{50}) was much higher, with no GI lesions observed at oral doses up to 1000 mg/kg. Thus, the therapeutic index for **30** is much greater than that of the benchmark NSAID, naproxen. Additional testing confirmed the high GI safety for compound **30**: in a refed rat antral damage model,[26] its UD_{50} was greater than that for naproxen and nabumetone, and no GI damage was seen in 13-day studies in dogs and rats at doses up to 200 mg/kg/day, po (data not shown).

In Vitro Results. The lack of GI toxicity for compound **30** prompted us to probe the in vitro pharmacology of the dihydrodimethylbenzofurans. With the discovery of COX-2 (well after our program began), we examined the potency and selectivity for inhibition of human platelet-derived COX-1 and recombinant human COX-2, as well as RBL lipoxygenase, as possible explanations for the observed in vivo antiinflammatory activity and GI safety. Thirteen compounds in three groups (active, less active, or inactive in the CPE assay) were tested (Table 3). Among the seven compounds which were active in the CPE assay, all were potent inhibitors of COX-1 and/or COX-2 with IC_{50} values < 1 μM. Compound **31** was also a potent inhibitor in vitro but was inactive in the CPE assay perhaps due to bioavailability and/or metabolism effects. Among the six compounds that were inactive or less active in the CPE assay, all were weak inhibitors of COX-1 and COX-2 with IC_{50} values > 1 μM except for compound **31**, discussed above, and compound **19**. Compound **19**, while still potent against COX-2 (IC_{50} = 0.09 μM) had little activity against COX-1 (IC_{50} > 10 μM). The compounds tested were moderately COX-2-selective with IC_{50} ratios from 1 to >111. The most selective compound was analogue **19**, mentioned above. A trend for increasing COX-2 selectivity with increasing chain length was noted in comparing analogues **16**, **18**, and **19** where the selectivity ranges from 1 to 50 to >111. The IC_{50} values for two benchmark compounds were determined for comparison. The marketed NSAID ibuprofen was a modestly selective COX-1 inhibitor,[27] while SC-57666 (Searle) was a highly selective (>100-fold) COX-2 inhibitor,[9] results consistent with literature reports. The 5-keto dihydrodimethylbenzofurans con-

Table 1. Structure, Synthetic Methods, and in Vivo Activity of Dihydrodimethylbenzofurans



compd	R	method	yield, %	mp, °C	formula	CPE index[a]	PAC assay[b]
7, tebufelone						**1.00**[c]	**26**
naproxen						**1.06**[c]	**1.3**
8	$CO(CH_2)_3CCH$	ref 13				**0.94**	NT[d]
12	H	Scheme 1	75	oil	$C_{14}H_{20}O$	0.31	NT
13	COMe	A	57	86−87	$C_{16}H_{22}O_2$	**0.92**	78%
14	CH(OH)Me	A	96	oil	$C_{16}H_{24}O_2$	0.00	NT
15	COEt	A	67	oil	$C_{17}H_{24}O_2$	**1.14**	**20**
16	COPr	A	66	oil	$C_{18}H_{26}O_2$	**1.16**	85%
17	CO-*i*-Pr	A	61	oil	$C_{18}H_{26}O_2$	**1.25**	**22**
18	COBu	A	41	54−56	$C_{19}H_{28}O_2$	**0.92**	38%
19	COpentyl	A	27	oil	$C_{20}H_{30}O_2$	0.40	NT
20	$COCH_2O(CH_2)_2OMe$	B	8	oil	$C_{19}H_{28}O_4$	**0.52**	NT
21	CO-*t*-Bu	A	47	oil	$C_{19}H_{28}O_2$	0.30	NT
22	CO-*c*-Pr	A	76	61−63	$C_{18}H_{24}O_2$	**0.67**	85%
23	CO-*c*-pentyl	A	34	62−63	$C_{20}H_{28}O_2$	**0.65**	56%
24	CO-*c*-hexyl	A	26	131−132	$C_{21}H_{30}O_2$	0.36	NT
25	COphenyl	A	29	oil	$C_{21}H_{24}O_2$	**0.72**	**34**
26	CO-4-F-phenyl	A	12	98−100	$C_{21}H_{23}O_2F$	0.52	NT
27	CO-2-Cl-phenyl	A	36	117−118	$C_{21}H_{23}O_2Cl$	0.00	NT
28	$COCH_2$-*c*-Pr	A	100	62−63	$C_{19}H_{26}O_2$	**1.06**	NT
29	$CO(CH_2)_2$-*c*-Pr	A	9	oil	$C_{20}H_{28}O_2$	0.18	58%
30	$CO(CH_2)_3$-*c*-Pr	A	53	33−34	$C_{21}H_{30}O_2$	**0.72**	**11**
31	CO-*E*-CH=$CHCH_2$-*c*-Pr	C	56	76−77	$C_{21}H_{28}O_2$	0.18	NT
32	$CO(CH_2)_3CHMe_2$	A	22	41−42	$C_{21}H_{32}O_2$	0.36	NT
33	$COCH_2SMe$	A	11	oil	$C_{17}H_{24}O_2S$	**1.77**	35%
34	$COCH_2SOMe$	D	32	96−97	$C_{17}H_{24}O_3S$	**1.01**	**20**
35	$COCH_2SO_2Me$	D	68	112−113	$C_{17}H_{24}O_4S$	0.00	NT
36	$COCH_2SCH_2$-*c*-Pr	E	37	oil	$C_{20}H_{28}O_2S$	**0.62**	54%
37	$COCH_2SOCH_2$-*c*-Pr	F	61	107−108	$C_{20}H_{28}O_3S$	0.04	NT
38	$COCH_2SO_2CH_2$-*c*-Pr	F	59	84−86	$C_{20}H_{28}O_4S$	0.00	NT
39	$CO(CH_2)_2NMe_2$	G	14	oil	$C_{19}H_{29}NO_2$	0.32[e]	NT
40	$COCH_2N(Me)CH_2$-*c*-Pr	J	29	oil	$C_{21}H_{31}NO_2$	0.38[e]	NT
41	$CO(CH_2)_2SMe$	G	34	80−81	$C_{18}H_{26}O_2S$	**0.70**	NT
42	$COCH_2OAc$	K	31	83−84	$C_{18}H_{24}O_4$	0.21	NT
43	$COCH_2SAc$	I	51	61−63	$C_{18}H_{24}O_3S$	**0.95**	64%
44	$COCH_2C(Cl)Me_2$	H	42	87−88	$C_{19}H_{27}O_2Cl$	**1.20**	**16**
45	$COCH_2C(OH)Me_2$	L	21	86−88	$C_{19}H_{28}O_3$	0.49[e]	NT
46	$COCH=CMe_2$	A	86	56−58	$C_{19}H_{26}O_2$	**1.22**	50%

[a] CPE index, carrageenan paw edema index, is defined as the ratio of the reduction in paw volume for test compounds relative to tebufelone. A value of >1 means more active than tebufelone, <1 means less active; dose = 50 mg/kg po. Bold faced values are statistically greater than vehicle control and not statistically different from tebufelone. See Experimental Section for complete details. [b] PAC, phenylquinone-induced abdominal constriction assay. Values are ED_{50}'s in bold or the percent reduction of constrictions at a po dose of 70 mg/kg. Maximal percent reduction is ~90%. See Experimental Section for complete details. [c] Percent inhibition of paw swelling for a 50 mg/kg po dose was 51.1 ± 10.0 for tebufelone (33−75%, $n = 65$) and 54% for naproxen (44−64%, $n = 2$). [d] NT, not tested. [e] Activity is statistically greater than vehicle control but less than tebufelone.

Table 2. Additional Efficacy and Safety Testing

compd	adjuvant arthritis ED_{50}, mg/kg	acute GI safety UD_{50}, mg/kg	therapeutic index (UD_{50}/ED_{50})
30	6.6	>1000	>152
naproxen	1.9	31	16.3

sistently showed low micromolar IC_{50} values as inhibitors of 5-LOX.

It is interesting to compare the above results with related results in the di-*tert*-butylphenol series. There are conflicting literature reports on the importance of the phenolic group for biological activity. In the CPE assay, acetylation of the phenol or replacement with a methoxy group provides compounds with equivalent or slightly reduced activity[28] or with greatly reduced potency.[7] Replacement of the phenolic group with hydrogen reduced[7] or eliminated[6] antiinflammatory activity. Together these data suggest that the phenolic group is not required for in vivo antiinflammatory activity although it often improves potency. A similar trend is observed for in vitro COX inhibition.[29] In contrast, until recently, 5-LOX inhibition was thought to be associated with the antioxidant properties of the phenol. A recent report[6] has shown that 5-LOX (and COX) activity can be retained in the absence of the phenolic group, although in this case the resulting dual inhibitor lacked antiinflammatory activity. Our compounds appear to be the first nonphenolic compounds related to di-*tert*-butylphenols which are both dual inhibitors of COX and 5-LOX in vitro and good antiinflammatory/analgesic agents in vivo.

Conclusions

5-Substituted dihydrodimethylbenzofurans represent a new class of antiinflammatory/analgesic agents. Despite the lack of antioxidant properties, these com-

Table 3. In Vitro Activity of Dihydrodimethylbenzofurans

compd	IC_{50}, μM[a] COX-1	COX-2	COX-1/COX-2	5-LOX[b] IC_{50}, μM
Active in CPE				
8	0.06	0.015	4	6
16	0.095	0.095	1	8.5
18	2.00	0.04	50	12
25	0.15	0.007	21.4	5
30	7.00	0.22	31.8	8
36	0.65	0.40	1.6	NT
44	1.00	0.10	10	8
7, tebufelone	0.25	0.10	2.5	3
Less Active in CPE[c]				
40	30	2.5	12	NT
Inactive in CPE				
19	>10	0.09	>111	NT
31	0.8	0.25	3.2	NT
32	15	4.5	3.3	15
37	20	4.0	5	NT
38	5	2.0	2.5	NT
Benchmarks				
ibuprofen	3	30	0.1	
6, SC-57666	30	<0.3	>100	

[a] COX testing was done by testing duplicate samples in duplicate. [b] 5-LOX testing was done by testing single samples in triplicate. [c] Activity is statistically less than tebufelone but greater than vehicle.

pounds are potent inhibitors of COX and 5-LOX with moderate selectivity for COX-2.[30] This combination of COX-2 selectivity and 5-LOX inhibition may be responsible for the high GI safety observed in this class. In the companion paper, the scope of this lead was investigated by varying the dihydrobenzofuran "core".

Experimental Section

General Procedures. Reagents and solvents were generally used as received from the commercial supplier. Dry THF and dry Et_2O were obtained by distillation from sodium/benzophenone ketyl under a N_2 atmosphere. Dry hexanes, CH_2Cl_2, and DMF were obtained by distillation from CaH_2 under a N_2 atmosphere. Reactions were routinely performed under a N_2 atmosphere in oven-dried glassware. Melting points were determined with an electrothermal heating block and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on either a Bruker AC300 or a Nicolet QE300 spectrometer. NMR spectra were recorded in $CDCl_3$ unless indicated otherwise, and chemical shifts are reported relative to tetramethylsilane ($\delta = 0.00$). Infrared spectra were recorded on a Perkin-Elmer instrument as a neat thin film on NaCl windows, unless indicated otherwise. Routine mass spectra were obtained using chemical ionization with NH_3 or CH_4 gas. Elemental microanalyses were performed by Oneida Laboratories, Inc. (Whitesboro, NY) or in-house at P&G Pharmaceuticals in Norwich, NY. High-resolution mass spectral data were obtained using EI as the ionization method. HPLC was performed on a Spectra Physics system using a 300-mm C18 reverse-phase column and isocratic elution with 9:1 MeOH−H_2O and a flow rate of 1 mL/min. Low- and medium-pressure column chromatographies were performed using Merck silica gel 60 (270−400 mesh). TLC was performed on 250-μm precoated Merck silica gel 60 F_{254} glass-backed plates. Preparative TLC was performed using 20- × 20-cm 1500-μm precoated Analtech silica gel GF plates. Spots were visualized under 254-nm UV light or by staining with phosphomolybdate spray reagent.

2-*tert*-Butyl-4,6-dibromophenyl 2-Methylallyl Ether (10). In a 3-L three-neck flask, equipped with Ar inlet and magnetic stirrer, were placed **9** (70.0 g, 226 mmol), K_2CO_3 (37.6 g, 276 mmol), NaI (3.38 g, 22.6 mmol), β-methallyl chloride (33.9 mL, 339 mmol), and acetone (1500 mL). The reaction mixture was vigorously stirred at 23 °C for 56 h. Subsequent TLC analysis showed the reaction to be complete. The solids were removed by filtration, and the acetone was evaporated to give a dark oil. This oil partially decomposed to starting material when stored at 23 °C over a period of 24 h. When stored at −20 °C, no decomposition was detected by NMR after 56 h. Immediately before use, the oil was dissolved in hexanes (100 mL) and stirred with silica gel (80 g). The slurry was filtered through a pad of Celite and eluted with additional hexanes (6 × 100 mL). The filtrate was evaporated to give 77 g (94%) of **10** as a yellow oil suitable for the next reaction: ^1H NMR δ 1.39 (s, 9 H), 1.90 (s, 3 H), 4.48 (s, 2 H), 5.03 (s, 1 H), 5.21 (s, 1 H), 7.41 (d, $J = 2.4$ Hz, 1 H), 7.58 (d, $J = 2.4$ Hz, 1 H); ^{13}C NMR δ 19.50, 30.47, 35.69, 75.61, 112.06, 116.51, 118.80, 129.82, 134.00, 140.42, 147.02, 154.23.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzofuran (12). A mixture of aqueous hypophosphorus acid (550 g) and toluene (5 × 500 mL) was cautiously evaporated on a rotovap to provide azeotropically dried hypophosphorus acid as a clear liquid (275 g, 4.16 mol). In a 5-L three-neck flask, equipped with Ar inlet, submersed N_2 inlet, reflux condenser, and magnetic stirrer, were placed dioxane (3000 mL), **10** (50.3 g, 0.14 mol), the anhydrous hypophosphorus acid (275 g, 4.16 mol), and Et_3N (585 mL, 4.16 mol). The mixture was degassed by bubbling with N_2 for 30 min and then was maintained under an N_2 atmosphere. A solution of azobis(isobutyrylnitrile) (AIBN; 20 mL of a 0.7 M solution in degassed dioxane) was added via syringe, and the stirred solution was brought to reflux. Every 0.5 h, an additional 20 mL of the AIBN solution was injected. After 3 h, TLC indicated complete consumption of starting material, and addition of AIBN was discontinued. The reaction was allowed to reflux for an additional 14 h and then was allowed to cool to 24 °C. The reaction mixture was twice extracted with a mixture of brine (250 mL) and 1 N HCl (100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 41.2 g of a yellow oil admixed with a white solid. This was triturated with hexanes (300 mL), and the insolubles were filtered off, rinsed with fresh hexanes (50 mL), and discarded. The combined filtrates were evaporated to give 27.4 g (75%) of a clear-yellow oil. NMR analysis showed the product to consist of a 30:70 mixture of **12** and its 5-bromo derivative **11**.

In a 250-mL round-bottom flask, equipped with magnetic stir bar, reflux condenser, and N_2 inlet, were suspended a 15-g sample of this crude product and 10% Pd on charcoal (3.94 g) in absolute EtOH (70 mL). K_2CO_3 (8.8 g, 63.5 mmol) was added, and the mixture was degassed by bubbling with N_2 for 15 min. Cyclohexene (33 mL) was added, and the mixture was heated at reflux for 8 h. The reaction mixture was allowed to cool to 23 °C and was filtered through a pad of Celite. Evaporation of the solvent at reduced pressure provided a dark oil, which was taken up in hexanes (50 mL), stirred with fresh silica gel (5 g), filtered, and evaporated to yield **12** as a dark-yellow oil, of sufficient purity for subsequent reactions: ^1H NMR δ 1.30 (s, 6 H), 1.36 (s, 9 H), 4.18 (s, 2 H), 6.94 (t, $J = 7.0$ Hz, 1 H), 7.05 (dd, $J = 7.0$, 1.4 Hz, 1 H), 7.08 (dd, $J = 7.0$, 1.4 Hz, 1 H); ^{13}C NMR δ 27.46, 29.32, 34.36, 41.32, 83.62, 119.91, 120.24, 124.59, 133.02, 136.91, 157.02; IR 2858, 1590, 1460 cm^{-1}; MS m/z 205 (MH^+).

For **11**: ^1H NMR δ 1.36 (s, 6 H), 1.39 (s, 9 H), 4.26 (s, 2 H), 7.11 (d, $J = 1.8$ Hz, 1 H), 7.22 (d, $J = 1.8$ Hz, 1 H); ^{13}C NMR δ 27.30, 29.04, 34.24, 41.65, 83.93, 112.26, 122.97, 127.60, 135.21, 139.23, 156.21; IR 2958, 2870, 1441 cm^{-1}; MS m/z 283 (MH^+).

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)ethan-1-one (13). Method A. To a solution of **12** (2.0 g, 9.8 mmol) and acetic acid (0.56 mL, 9.8 mmol) at 0 °C was added trifluoroacetic anhydride (1.5 mL, 9.8 mmol). The reaction mixture was cooled to −20 °C and allowed to slowly warm to room temperature overnight. The reaction was monitored by TLC (2% EtOAc/hexanes). The reaction was quenched with H_2O (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with water and brine and dried over $MgSO_4$ to provide a yellow oil (3.1 g). Medium-pressure chromotography (2%

EtOAc/hexanes) gave 1.37 g (57%) of **13** as a white solid: mp 86−87 °C; ^{1}H NMR δ 1.20 (s, 6 H), 1.25 (s, 9 H), 2.38 (s, 3 H), 4.15 (s, 2 H), 7.50 (d, J = 1.7 Hz, 1 H), 7.60 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 26.33, 27.49, 29.04, 34.10, 40.97, 84.65, 120.82, 126.73, 130.57, 132.55, 137.59, 162.50, 197.10; IR 2959, 2874, 1674, 1596 cm^{-1}; MS m/z 247 (MH$^+$). Anal. ($C_{16}H_{22}O_2$) C, H.

(±)-7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(1-hydroxyethyl)dihydrobenzofuran (14). To a solution of **13** (463 mg, 1.88 mmol) in absolute EtOH (5 mL) was added $NaBH_4$ (75 mg, 1.98 mmol). The reaction mixture was allowed to stir at 23 °C for 18 h. The solvent was evaporated, and the oily residue was partitioned between water and EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to provide 450 mg (96%) of **14** as a faint-yellow oil: ^{1}H NMR δ 1.33 (s, 3 H), 1.34 (s, 3 H), 1.39 (s, 9 H), 1.51 (d, J = 7.2 Hz, 3 H), 4.86 (q, J = 7.2 Hz, 1 H); ^{13}C NMR δ 24.02, 24.79, 27.34, 29.10, 33.96, 41.28, 70.61, 83.76, 116.84, 117.24, 133.22, 137.34, 137.56, 155.99; IR 3408, 2959, 2869, 1456 cm^{-1}; MS m/z 249 (MH$^+$). Anal. ($C_{16}H_{24}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)propan-1-one (15): method A; ^{1}H NMR δ 1.22 (t, J = 7 Hz, 6 H), 1.38 (s, 6 H), 1.40 (s, 9 H), 2.95 (q, J = 7 Hz, 2 H), 4.30 (s, 2 H), 7.63 (d, J = 1.7 Hz, 1 H), 7.80 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 8.57, 27.48, 29.04, 31.33, 34.09, 40.98, 84.60, 120.48, 126.27, 130.21, 132.75, 137.50, 162.00, 199.7; IR 2960, 1676, 1598, 1456 cm^{-1}; MS m/z 261 (MH$^+$). Anal. ($C_{17}H_{24}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)butan-1-one (16): method A; ^{1}H NMR δ 1.00 (t, J = 7 Hz, 1 H), 1.35 (s, 6 H), 1.42 (s, 9 H), 1.75 (m, J = 7 Hz, 2 H), 2.88 (t, J = 7 Hz, 2 H), 4.30 (s, 2 H), 7.62 (d, J = 1.7 Hz, 1 H), 7.80 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 14.00, 18.11, 27.55, 29.14, 34.16, 40.14, 41.05, 84.66, 120.62, 126.39, 130.53, 132.78, 137.55, 162.03, 199.11; IR 2959, 1673, 1596, 1455 cm^{-1}; MS m/z 275 (MH$^+$), 231. Anal. ($C_{18}H_{26}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-methylpropan-1-one (17): method A; ^{1}H NMR δ 1.15 (d, J = 7 Hz, 6 H), 1.25 (s, 6 H), 1.35 (s, 9 H), 3.47 (m, 1 H), 4.25 (s, 2 H), 7.60 (d, J = 1.7 Hz, 1 H), 7.80 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 19.37, 27.39, 29.03, 34.01, 34.60, 40.90, 84.51, 120.74, 126.45, 129.30, 132.67, 137.45, 161.28, 202.70; IR 2963, 1671, 1595, 1455 cm^{-1}; MS m/z 275 (MH$^+$). Anal. ($C_{18}H_{26}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)pentan-1-one (18): method A; mp 54−56 °C; ^{1}H NMR δ 0.91 (t, J = 7.7 Hz, 3 H), 1.35−1.45 (s, 19 H), 1.75 (m, 2 H), 2.91 (t, J = 7.7 Hz, 2 H), 4.28 (s, 2 H), 7.65 (d, J = 1.5 Hz, 1 H), 7.78 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 13.92, 22.48, 26.85, 27.49, 29.06, 34.11, 37.89, 40.99, 84.61, 120.56, 126.37, 130.43, 132.73, 137.51, 161.5, 199.32; IR 2958, 1674, 1596, 1457 cm^{-1}; MS m/z 289 (MH$^+$). Anal. ($C_{19}H_{28}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)hexan-1-one (19): method A; ^{1}H NMR δ 0.90 (m, 3 H), 1.30−1.45 (s, 19 H), 1.73 (m, 2 H), 2.92 (t, J = 7.7 Hz, 2 H), 4.31 (s, 2 H), 7.63 (d, J = 1.5 Hz, 1 H), 7.78 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 13.89, 22.47, 24.39, 27.48, 29.06, 31.58, 34.10, 38.14, 40.98, 84.60, 120.56, 126.36, 130.43, 136.5, 137.0, 161.5, 199.0; IR 2958, 1672, 1589, 1553, 1535, 1455 cm^{-1}; MS m/z 303 (MH$^+$). Anal. ($C_{20}H_{30}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-1-oxo-3,6-dioxaheptane (20). Method B. To 1.0 g (3.5 mmol) of **11** in 2 mL of ether and 18 mL of hexanes at −78 °C was added 4.4 mL (7.1 mmol) of 1.6 M *t*-BuLi. After 30 min at −78 °C, the in situ generated aryllithio species was added to 0.9 g (5.3 mmol) of *N*-methyl-*N*-methoxy(methoxyethoxy)-acetamide in 10 mL of Et_2O at −78 °C in a slow steady stream. The resulting solution was allowed to slowly reach room temperature, and the reaction was then quenched with H_2O. The reaction mixture was then diluted with 200 mL of Et_2O, washed with H_2O (3 × 30 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated. Purification by flash chromatography (60% EtOAc/hexanes) afforded 90 mg (8.4%) of **20** as a yellow oil: ^{1}H NMR δ 1.34 (s, 6 H), 1.35 (s, 9 H), 3.38 (s, 3 H), 3.62 (t, J = 4.4 Hz, 2 H), 3.75 (t, J = 4.3 Hz, 2 H), 4.30 (s, 2 H), 4.76 (s, 2 H), 7.72 (d, J = 1.9 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H); ^{13}C NMR δ 27.5, 29.1, 34.2, 41.1, 58.9, 70.7, 72.0, 74.2, 84.7, 120.7, 126.4, 128.4, 133.1, 137.8, 162.0, 195.1, 231; IR ($CDCl_3$) 2960, 1689, 1597, 1456 cm^{-1}; MS m/z 321 (MH$^+$); HRMS (EI, MH$^+$) calcd for $C_{19}H_{28}O_4$ 320.1988, found 320.1987; HPLC 96.7%.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2,2-dimethylpropan-1-one (21): method A; ^{1}H NMR δ 1.30 (s, 6 H), 1.38 (s, 9 H), 1.41 (s, 9 H), 4.29 (s, 2 H), 7.55 (d, J = 1.7 Hz, 1 H), 7.76 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 27.57, 28.72, 29.21, 34.20, 41.15, 43.70, 84.51, 121.56, 127.13, 129.92, 132.09, 136.99, 160.14, 206.24; IR 2959, 1664, 1593, 1456 cm^{-1}; MS m/z 289 (MH$^+$). Anal. ($C_{19}H_{28}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)cyclopropylmethanone (22): method A; mp 61−63 °C; ^{1}H NMR δ 0.98 (m, 2 H), 1.20 (m, 2 H), 1.38 (s, 6 H), 1.44 (s, 9 H), 2.65 (m, 1 H), 4.34 (s, 2 H), 7.70 (d, J = 1.7 Hz, 1 H), 7.85 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 11.06, 16.54, 27.52, 29.07, 34.14, 41.02, 84.62, 120.54, 126.29, 131.25, 132.54, 137.50, 162.30, 197.80; IR 2959, 2869, 1660, 1597, 1455 cm^{-1}; MS m/z 273 (MH$^+$). Anal. ($C_{18}H_{24}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)cyclopentylmethanone (23): method A; mp 62−63 °C; ^{1}H NMR δ 1.33 (s, 6 H), 1.40 (s, 9 H), 1.50−1.80 (m, 4 H), 1.90 (m, 4 H), 3.70 (m, 1 H), 4.30 (s, 2 H), 7.66 (d, J = 1.5 Hz, 1 H), 7.81 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 26.30, 27.51, 29.09, 30.25, 40.99, 45.88, 84.61, 120.92, 126.75, 130.13, 132.64, 137.45, 161.0, 201.62; IR 2957, 2869, 1669, 1595, 1454 cm^{-1}; MS m/z 301 (MH$^+$). Anal. ($C_{20}H_{28}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)cyclohexylmethanone (24): method A; mp 131−132 °C; ^{1}H NMR δ 1.38 (s, 6 H), 1.40 (s, 9 H), 1.45−1.60 (m, 5 H), 1.75 (m, 1 H), 1.87 (m, 4 H), 3.20 (m, 1 H), 4.30 (s, 2 H), 7.62 (d, J = 1.5 Hz, 1 H), 7.80 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 25.85, 25.92, 27.51, 29.06, 29.65, 34.10, 41.01, 45.22, 84.62, 120.70, 126.51, 129.44, 132.76, 137.54, 161.5, 202.61; IR 2929, 1669, 1593, 1452 cm^{-1}; MS m/z 315 (MH$^+$). Anal. ($C_{21}H_{30}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)phenylmethanone (25): method A; ^{1}H NMR δ 1.32 (s, 6 H), 1.38 (s, 9 H), 4.35 (s, 2 H), 7.44−7.55 (m, 4 H), 7.64 (d, J = 1.7 Hz, 1 H), 7.65 (d, J = 1.7 Hz, 1 H), 7.78 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 27.51, 29.10, 34.14, 41.02, 84.65, 122.90, 128.02, 128.98, 129.56, 130.19, 131.54, 132.70, 137.43, 138.74, 161.41, 195.78; IR 2958, 1650, 1595 cm^{-1}; MS m/z 309 (MH$^+$). Anal. ($C_{21}H_{24}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)(4′-fluorophenyl)methanone (26): method A; mp 98−100 °C; ^{1}H NMR δ 1.36 (s, 15 H), 4.34 (s, 2 H), 7.16 (m, 2 H), 7.48 (d, J = 1.8 Hz, 1 H), 7.60 (d, J = 1.7 Hz, 1 H), 7.79 (m, 2 H); ^{13}C NMR δ 27.6, 29.2, 34.3, 41.1, 84.8, 122.9 (115.4, 115.1, d, J = 22.5 Hz), 128.9, 130.1, 132.9 (132.3, 132.2, d, J = 7.5 Hz), 135.2, 137.6, 161.6 (166.6, 163.2, d, J = 255 Hz), 194.6; IR (KBr) 2957, 2882, 1655, 1599 cm^{-1}; MS m/z 327 (MH$^+$). Anal. ($C_{21}H_{23}FO_2$) C, H, F.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)(2′-chlorophenyl)methanone (27): method A; mp 117−118 °C; ^{1}H NMR δ 1.30 (s, 9 H), 1.32 (s, 6 H), 4.32 (s, 2 H), 7.30−7.47 (m, 4 H), 7.51 (d, J = 1.6 Hz, 1 H), 7.61 (d, J = 1.6 Hz, 1 H); ^{13}C NMR δ 27.47, 28.95, 34.06, 40.88, 84.36, 122.67, 126.39, 128.80, 129.24, 129.42, 129.82, 130.46, 131.09, 132.52, 137.84, 139.32, 162.41, 193.87; IR 2959, 1654, 1592, 1458 cm^{-1}; MS m/z 343 (MH$^+$). Anal. ($C_{21}H_{23}ClO_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-cyclopropylethan-1-one (28): method A; mp 62−63 °C; ^{1}H NMR δ 0.20 (m, 2 H), 0.59 (m, 2 H), 1.16 (m, 1 H), 1.35 (s, 6 H), 1.38 (s, 9 H), 2.83 (d, J = 6.8 Hz, 1 H), 4.31 (s, 2 H), 7.62 (d, J = 1.8 Hz, 1 H), 7.77 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 4.5, 7.0, 27.5, 29.0, 34.1, 41.0, 43.5, 84.6, 120.6, 126.5, 130.2, 132.8, 137.5, 161.5, 198.7; IR 2959, 2870, 1674, 1596, 1455 cm^{-1}; MS m/z 287 (MH$^+$). Anal. ($C_{19}H_{26}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-cyclopropylpropan-1-one (29): method A; ^{1}H NMR δ −0.01 (m, 2 H), 0.38 (m, 2 H), 0.69 (m, 1 H), 1.35 (s, 9 H),

1.30 (s, 6 H), 1.55 (q, J = 7.5 Hz, 2 H), 2.95 (t, J = 7.5 Hz, 2 H), 4.21 (s, 2 H), 7.54 (d, J = 1.7 Hz, 1 H), 7.75 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 4.58, 10.73, 22.55, 27.49, 29.07, 34.12, 38.27, 40.98, 84.71, 120.58, 126.40, 130.45, 132.62, 137.51, 161.49, 199.21; IR 2959, 2869, 1874, 1596, 1455 cm^{-1}; MS m/z 301 (MH^+). HRMS (EI, MH^+) calcd for $C_{20}H_{28}O_2$ 301.2167, found 301.2130; HPLC 96.6%. Anal. ($C_{20}H_{28}O_2$) C, H; C: calcd, 79.96; found, 78.92. H: calcd, 9.39; found, 8.95.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-4-cyclopropylbutan-1-one (30). 4-Cyclopropylbutan-1-ol. *Caution*: Neat $AlMe_3$ is extraordinarily pyrophoric, and this reaction should be carried out only by well-trained technical personnel! Particular attention should be paid to the *Aldrich Technical Bulletin* accompanying commercial $AlMe_3$, describing proper techniques for handling air- and moisture-sensitive reagents. This reaction was performed with a sand-filled secondary container underneath the reaction vessel and large quantities of dry ice at hand to smother any spill to allow time for personnel to evacuate should the necessity arise. In a 12-L four-neck flask, equipped with mechanical stirrer, 1-L addition funnel, efficient steel-coil condensor funnel and 4-mm bore gas outlet, internal thermometer, and ice bath, were placed 5-hexen-1-ol (378.6 g, 3.78 mol), CH_2I_2 (1265 g, 4.73 mol), and CH_2Cl_2 (2200 mL). The reaction flask was purged with N_2 for 0.5 h, and then neat $AlMe_3$ (approximately 600 g, 8.3 mol) was transferred via cannula into the addition funnel. The $AlMe_3$ was added dropwise to the stirred reaction mixture. *Caution*: Strong exotherm and gas (CH_4) evolution! The temperature rose to 40 °C during the addition. After approximately 150 g of $AlMe_3$ had been added, the exotherm and gas evolution subsided, and the remainder $AlMe_3$ was added over the course of 45 min, along with a 100-mL CH_2Cl_2 rinse of the addition funnel. The reaction mixture was heated at reflux for 10 h. Completion of the reaction was confirmed by ^{1}H NMR analysis of a 1-mL aliquot. The reaction mixture was diluted to a volume of 12 L with fresh CH_2Cl_2 and then transferred via glass tube siphon into a stirred mixture of 50% NaOH (1.8 L, 22.7 mol) in ice (10 L). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 2 L). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to provide the title compound as a yellow oil (442.8 g, 102%) which was used without further purification: ^{1}H NMR δ −0.08 (m, 2 H), 0.31 (m, 2 H), 0.58 (m, 1 H), 1.13 (q, J = 6.8 Hz, 2 H), 1.36 (m, 2 H), 1.50 (m, 2 H), 3.41 (s, 1 H), 3.50 (t, J = 6.8 Hz, 2 H).

4-Cyclopropylbutanoic Acid. In a 500-mL three-neck flask, equipped with mechanical stirrer, addition funnel, and an internal thermometer, was placed a solution of 4-cyclopropylbutan-1-ol (20 g, 175 mmol), in acetone (100 mL). The solution was cooled to 0 °C, and Jones reagent (prepared by the careful addition of concentrated H_2SO_4 (40 mL) to a solution of CrO_3 (35 g, 350 mmol) in H_2O (75 mL)) was added dropwise at a rate such that the temperature of the reaction mixture did not exceed 10 °C. The reaction was monitored by TLC (hexane−EtOAc, 19:1); after approximately two-thirds of the Jones reagent had been added, the reaction was judged complete and was quenched by the addition of 2-propanol (10 mL). The pH was adjusted to above pH 10 with 4 N NaOH, and the reaction mixture was partitioned between H_2O (200 mL) and EtOAc (4 × 100 mL). The organic phase was separated, washed with H_2O and brine, dried ($MgSO_4$), filtered, and evaporated to provide 3-cyclopropylpropyl 4-cyclopropylbutyrate (7.22 g). The aqueous phase was acidified with concentrated H_2SO_4 to pH 2 and extracted with EtOAc (6 × 100 mL). The organic phases were dried ($MgSO_4$), filtered, and evaporated to provide the title compound as a colorless oil (12.1 g, 54.2%). The ester (7.2 g) was hydrolyzed with aqueous 2 N NaOH (32 mL) in MeOH (30 mL) at 23 °C. Workup as above provided 4-cyclopropylbutan-1-ol (3.45 g) and the title compound (3.20 g) as colorless oils. The combined yield of the desired acid was 15.3 g (68.2%): ^{1}H NMR δ −0.08 (m, 2 H), 0.28 (m, 2 H), 0.61 (m, 1 H), 1.20 (m, 2 H), 1.75 (quintet, J = 7.7 Hz, 2 H), 2.35 (t, J = 7.7 Hz, 2 H), 10.80 (bs, 1 H); ^{13}C NMR δ 0.01, 6.07, 20.42, 29.41, 29.55, 176.04; IR 2932, 1709 cm^{-1}; MS m/z 129 (MH^+).

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-4-cyclopropylbutan-1-one (30): method A; mp 33−34 °C; ^{1}H NMR δ −0.03 (m, 2 H), 0.41 (m, 2 H), 0.69 (q, J = 7.5 Hz, 1 H), 1.29 (m, 2 H), 1.34 (s, 6 H), 1.37 (s, 9 H), 1.83 (m, 2 H), 2.95 (t, J = 7.5 Hz, 2 H), 4.29 (s, 2 H), 7.62 (d, J = 1.7 Hz, 1 H), 7.72 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 4.42, 10.72, 24.89, 27.59, 29.15, 34.21, 34.39, 38.02, 41.09, 84.71, 120.65, 126.49, 130.49, 132.82, 137.62, 161.49, 199.45; IR 2958, 1674, 1596, 1455 cm^{-1}; MS m/z 315 (MH^+). Anal. ($C_{21}H_{30}O_2$) C, H.

(*E*)-1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-4-cyclopropyl-2-buten-1-one (31). Method C. Lithium diisopropylamide (4.0 mL, 8.0 mmol, 2.0 M solution in heptane−THF−ethylbenzene) was added dropwise to a solution of **30** (1.26 g, 4.0 mmol) in 20 mL of anhydrous THF at −78 °C. The resulting solution was stirred at −78 °C for 15 min, and chlorotrimethylsilane (1.0 mL, 8.0 mmol) was introduced. The reaction mixture was stirred at −78 °C for 10 min, warmed to 0 °C, stirred for 1 h, quenched with H_2O, and extracted with Et_2O. The extract was dried over anhydrous Na_2SO_4 and concentrated to give 1.90 g of a yellowish oil, which was added under argon to a clear-brown solution of palladium acetate (0.89 g, 4.0 mmol) and benzoquinone (0.43 g, 4.0 mmol) in 40 mL of CH_3CN. The resulting dark solution was stirred for 18 h and filtered through a short column of silica gel. The filtrate was diluted with 100 mL of H_2O and extracted with 10% EtOAc/hexanes. The extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated to afford 1.36 g of the crude product as a brown oil. Purification by flash column chromatography on silica gel (1% → 2% Et_2O/hexanes) gave 0.70 g (56%) of **31** as a colorless solid: mp 76−77 °C; ^{1}H NMR δ 0.14 (m, 2 H), 0.52 (m, 2 H), 0.85 (m, 1 H), 1.33 (s, 6 H), 1.36 (s, 9 H), 2.19 (t, J = 6.3 Hz, 2 H), 4.29 (s, 2 H), 7.09−6.91 (m, 2 H), 7.61 (d, J = 1.8 Hz, 1 H), 7.76 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 4.37, 9.41, 27.5, 29.2, 34.2, 37.3, 41.1, 84.7, 121.1, 126.1, 127.0, 131.3, 132.9, 137.7, 147.0, 161.4, 189.7; IR 2959, 1665, 1619, 1592, 1455 cm^{-1}; MS m/z 313 (MH^+). Anal. ($C_{21}H_{28}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-5-methylhexan-1-one (32): method A; mp 41−42 °C; ^{1}H NMR δ 1.06 (d, J = 6.7 Hz, 6 H), 1.28 (m, 1 H), 1.55 (s, 6 H), 1.57 (s, 9 H), 1.72 (m, 2 H), 1.76 (m, 2 H), 2.90 (t, J = 7.3 Hz, 2 H), 4.31 (s, 2 H), 7.62 (d, J = 1.8 Hz, 1 H), 7.78 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 22.5, 22.6, 27.5, 27.9, 29.2, 34.2, 38.5, 38.8, 41.1, 84.7, 120.6, 126.4, 130.6, 132.9, 137.6, 161.4, 199.3; IR (KBr) 2957, 1675, 1597 cm^{-1}; MS m/z 317 (MH^+), 301, 246, 231. Anal. ($C_{21}H_{32}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-thiabutan-1-one (33): method A; ^{1}H NMR δ 1.30 (s, 6 H), 1.35 (s, 9 H), 2.15 (s, 3 H), 3.70 (s, 2 H), 4.25 (s, 2 H), 7.60 (d, 1 H), 7.75 (d, 1 H); ^{13}C NMR δ 15.9, 27.5, 29.0, 34.1, 38.8, 41.0, 84.7, 121.3, 127.2, 128.3, 132.9, 137.7, 161.9, 193.1. Anal. ($C_{17}H_{24}O_2S$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-sulfinylbutan-1-one (34). Method D. Compound **33** (1.08 g, 3.7 mmol) was dissolved in CH_2Cl_2 (8 mL) in a flame-dried flask under argon and then cooled in an ice/H_2O bath. mCPBA (85%, 826 mg, 4.1 mmol) was added carefully, and the reaction mixture was stirred for 45 min. The reaction mixture was then poured into saturated $NaHCO_3$, separated, and extracted twice with CH_2Cl_2. The organic extracts were combined and evaporated. The crude product was purified by filtration flash chromatography with 10% and then 50% EtOAc/hexanes followed by crystallization from EtOAc/hexanes to give 363 mg (32%) of **34** as a white powder: mp 96−97 °C; ^{1}H NMR δ 1.30 (s, 6 H), 1.35 (s, 9 H), 2.75 (s, 3 H), 4.10 (d, 1 H), 4.30 (s, 2 H), 4.50 (d, 1 H), 7.60 (d, 1 H), 7.75 (d, 1 H); ^{13}C NMR δ 27.5, 28.9, 34.2, 39.7, 40.9, 62.3, 84.9, 121.5, 127.5, 129.2, 133.4, 138.2, 163, 190.1; MS m/z 309 (MH^+), 247. Anal. ($C_{17}H_{24}O_3S$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-sulfonylbutan-1-one (35). Method D. Compound **34** (500.1 mg, 1.62 mmol) was dissolved in 8 mL of CH_2Cl_2 in a

dry flask under argon. mCPBA (~75%, 467.6 mg, 2.03 mmol) was added, and the reaction mixture was allowed to stir at room temperature. After 2.5 h, the reaction mixture was poured into dilute sodium bisulfite and extracted with CH_2Cl_2. The organics were washed with another portion of bisulfite and then 2 × 35 mL of 0.5 N $NaHCO_3$. The combined organics were dried over molecular sieves; then the solvent was evaporated. Flash chromatography with 10% and then 50% EtOAc/hexanes followed by crystallization from EtOAc/hexanes gave 354.9 mg (67.5%) of white crystals: mp 112−113 °C; ^{1}H NMR δ 1.40 (s, 16 H), 3.15 (s, 3 H), 4.40 (s, 2 H), 4.60 (s, 2 H), 7.70 (d, 1 H), 7.80 (d, 1 H); ^{13}C NMR δ 27.8, 29.2, 34.5, 41.2, 42.0, 61.4, 85.3, 122.5, 128.4, 129.2, 133.8, 138.5, 163.5, 187.7; MS *m*/*z* 325 (MH^+), 247. Anal. ($C_{17}H_{24}O_4S_1$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-thia-4-cyclopropylbutan-1-one (36). 1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-mercapto-1-ethanone. Method E. A stirring solution of **43** (0.5 g, 1.6 mmol) in 20 mL of MeOH was purged with argon for 30 min at room temperature. Then NH_3 gas was bubbled in for 60 min. The resulting yellow solution was stirred for 30 min until completion by TLC, diluted with Et_2O (150 mL), and washed with H_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to give a yellow oil. Purification by flash chromatography (12% EtOAc/hexanes) resulted in 0.3 g (67%) of the title compound as a light-yellow solid: mp 42−44 °C; ^{1}H NMR δ 1.34 (s, 6 H), 1.35 (s, 9 H), 2.14 (t, J = 7.2 Hz, 1 H), 3.90 (d, J = 7.2 Hz, 2 H), 4.31 (s, 2 H), 7.60 (d, J = 1.8 Hz, 1 H), 7.75 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 28.2, 29.7, 31.5, 34.9, 41.7, 85.5, 121.9, 127.7, 128.9, 133.9, 138.6, 162.8, 194.2; MS *m*/*z* 279 (MH^+), 280, 318. Anal. ($C_{16}H_{22}O_2S$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-thia-4-cyclopropylbutan-1-one (36). To 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-mercapto-1-ethanone (0.2 g, 0.7 mmol) in 3 mL of MeOH was added NaOMe (0.1 g, 1.8 mmol). The resulting solution was stirred at 0 °C for 15 min at which time bromomethylcyclopropane (0.2 g, 1.8 mmol) was added via syringe. The reaction mixture was allowed to warm to room temperature over 16 h, and the reaction was followed by TLC until no starting material was present. The organic layer was diluted with 100 mL of Et_2O and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Flash chromatography with 5% EtOAc/hexanes resulted in 0.1 g (37%) of **36** as an orange oil: ^{1}H NMR δ 0.20 (bd d, 2 H), 0.51 (bd d, 2 H), 0.96 (m, 1 H), 1.33 (s, 6 H), 1.39 (s, 9 H), 2.48 (d, J = 7.0 Hz, 2 H), 3.59 (s, 2 H), 4.26 (s, 2 H), 7.61 (d, J = 1.5 Hz, 1 H), 7.77 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 5.2, 10.5, 27.4, 28.9, 34.0, 36.4, 37.4, 40.8, 84.5, 121.2, 127.1, 128.4, 132.7, 137.5, 161.6, 193.4; IR (KBr) 2958, 1654, 1594 cm^{-1}; MS *m*/*z* 333 (MH^+), 247. Anal. ($C_{20}H_{28}O_2S$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-sulfinyl-4-cyclopropylbutan-1-one (37). Method F. To a stirring solution of **36** (0.3 g, 0.8 mmol) in 10 mL of CH_2Cl_2 was added mCPBA (0.2 g, 0.8 mmol). The resulting solution was stirred at −23 °C for 2 h, at which time no starting material was present by TLC. The reaction was quenched with aqueous sodium bisulfite and diluted with H_2O. The organic layer was extracted with 100 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ (3 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to yield a brown oil. Purification by flash chromatography in 25% EtOAc/hexanes and further recrystallization from hexanes resulted in 0.2 g (61%) of **37** as a white solid: mp 107−108 °C; ^{1}H NMR δ 0.41 (m, 2 H), 0.73 (m, 2 H), 1.28 (m, 1 H), 1.35, (s, 6 H), 1.37 (s, 9 H), 2.87 (m, 2 H), 4.37 (s, 2 H), 4.40 (d, J = 14.5 Hz, 1 H), 4.45 (d, J = 14.5 Hz, 1 H), 7.63 (d, J = 1.9 Hz, 1 H), 7.78 (d, J = 1.9 Hz, 1 H); ^{13}C NMR δ 4.3, 5.4, 27.4, 28.7, 34.1, 40.8, 58.21, 59.4, 84.8, 121.5, 127.5, 129.2, 133.3, 138.1, 163.5, 190.5; IR (KBr) 2963, 1667, 1597, 1457 cm^{-1}; MS *m*/*z* 349 (MH^+), 333, 247. Anal. ($C_{20}H_{28}O_3S\cdot0.25H_2O$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-sulfonyl-4-cyclopropylbutan-1-one (38). Method F. To a stirring solution of **36** (0.4 g, 1.2 mmol) in 11 mL of acetone at 0 °C was added mCPBA (1.0 g, 6.0 mmol). The resulting solution was allowed to warm to room temperature over 12 h and was monitored by TLC until conversion to sulfone was about complete. The reaction was quenched with aqueous sodium bisulfite and diluted with H_2O. The organic layer was extracted with 100 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine (3 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaported. Purification by flash chromatography in 16% EtOAc/hexanes resulted in 0.3 g (59%) of **38** as a white solid: mp 84−86 °C; ^{1}H NMR δ 0.53 (m, 2 H), 0.75 (m, 2 H), 1.28 (m, 1 H), 1.36 (s, 6 H), 1.37 (s, 9 H), 3.23 (d, J = 6.8 Hz, 2 H), 4.35 (s, 2 H), 4.61 (s, 2 H), 7.63 (d, J = 1.8 Hz, 1 H), 7.80 (d, J = 1.9 Hz, 1 H); ^{13}C NMR δ 4.2, 4.3, 27.3, 27.4, 28.8, 34.1, 40.8, 58.4, 84.9, 122.0, 128.0, 129.0, 133.4, 138.1, 163.1, 187.6; IR (KBr) 2957, 2907, 1672, 1593 cm^{-1}; MS *m*/*z* 365 (MH^+), 247. Anal. ($C_{20}H_{28}O_4S$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-(dimethylamino)propan-1-one (39). Method G. Compound **12** (2.45 g, 12.0 mmol) and 3-chloropropionic acid (1.3 g, 12.0 mmol) were reacted with trifluoroacetic anhydride in the usual way (method A). Purification of the crude product by flash chromatography on silica gel (1% EtOAc/hexanes) gave 0.85 g (35%) of a light-yellow oil, which was dissolved in 20 mL of acetone and reacted for 18 h with Me_2NH (6 mL, 33.0 mmol, 33% ethanolic solution). The reaction mixture was evaporated. The residue was purified by flash chromatography on silica gel (10% EtOAc/hexanes → 10% MeOH/$CHCl_3$) to give 0.50 g (14%) of **39** as a brown oil: ^{1}H NMR δ 1.29 (s, 6 H), 1.32 (s, 9 H), 2.26 (s, 6 H), 2.72 (t, J = 7.4 Hz, 2 H), 3.07 (t, J = 7.4 Hz, 2 H), 4.26 (s, 2 H), 7.58 (d, J = 1.8 Hz, 1 H), 7.74 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 27.4, 28.9, 34.0, 36.3, 40.8, 45.2, 54.6, 84.5, 120.5, 126.3, 130.1, 132.7, 137.5, 161.6, 197.6; IR 2958, 1671, 1595 cm^{-1}; MS *m*/*z* 304 (MH^+). Anal. ($C_{19}H_{29}NO_2\cdot0.25H_2O$) C, H, N; H: calcd, 9.66; found 9.15.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-(*N*-methyl-*N*-(cyclopropylmethyl)amino)ethan-1-one (40). 1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-chloroethan-1-one. Method J. A mixture of benzyltrimethylammonium dichloroiodate (31.70 g, 91.0 mmol), **13** (12.35 g, 50.2 mmol), 300 mL of 1,2-dichloroethane, and 120 mL of MeOH was heated at reflux for 13 h. The reaction mixture was cooled to room temperature and concentrated in vacuo; 5% aqueous sodium bisulfite solution (125 mL) was added to the residue obtained. This mixture was extracted with Et_2O; the extract was washed with aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and concentrated to produce 14.09 g (100%) of the title compound as a reddish solid: mp 76−77 °C; ^{1}H NMR δ 1.32 (s, 6 H), 1.34 (s, 9 H), 4.32 (s, 2 H), 4.63 (s, 2 H), 7.61 (d, J = 1.8 Hz, 1 H), 7.74 (d, J = 1.8 Hz, 1 H).

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-(*N*-methyl-*N*-(cyclopropylmethyl)amino)ethan-1-one (40). 1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-chloroethan-1-one (1.47 g, 5.2 mmol) was added in portions to a solution of NaI (0.86 g, 5.8 mmol) in acetone. The reaction mixture was stirred for 0.5 h and filtered through a short column of Celite to give a solution of 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-iodoethan-1-one in acetone, which was immediately reacted for 0.5 h with *N*-methyl-*N*-(cyclopropylmethyl)amine (1.50 g, 17.6 mmol). The reaction mixture was evaporated, and the residue was dissolved in EtOAc; this solution was washed with aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated to give 1.92 g of the crude product. Purification by flash chromatography on silica gel (20% → 25% EtOAc/hexanes) produced 0.50 g (29%) of **40** as a yellow oil: ^{1}H NMR δ 0.38 (m, 2 H), 0.51 (m, 2 H), 0.94 (m, 1 H), 1.33 (s, 6 H), 1.35 (s, 9 H), 2.43 (s, 3 H), 2.44 (d, J = 6.6 Hz, 2 H), 3.86 (s, 2 H), 4.28 (s, 2 H), 7.67 (d, J = 1.8 Hz, 1 H), 7.86 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 3.7, 8.7, 27.4, 28.9, 34.0, 40.9, 42.7, 62.4, 62.8,

84.5, 120.7, 126.5, 129.4, 132.6, 137.4, 161.5, 196.0; IR 2959, 2871, 1673, 1596 cm^{-1}; MS *m/z* 330 (MH^+). Anal. ($C_{21}H_{31}NO_2 \cdot 1.33H_2O$) C, H, N; H: calcd, 9.60; found, 8.76.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-methylthiapropan-1-one (41). Method G. Compound **12** was reacted with 3-chloropropionic acid and trifluoroacetic anhydride in the usual manner (method A). The crude product was purified by flash chromatography on silica gel (0.5% EtOAc/hexanes) to give 1.55 g (35%) of 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-chloropropan-1-one as a colorless oil. To a solution of this oil (0.76 g, 2.6 mmol) in 15 mL of MeOH was added sodium thiomethoxide (0.54 g, 6.4 mmol). The reaction mixture was stirred for 5 h and evaporated. The residue was dissolved in Et_2O; the resulting solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated to give 1.40 g of the crude product as a syrup. Purification by flash chromatography on silica gel (1 → 2% EtOAc/hexanes) yielded 0.78 g (34% for two steps) of **41** as a light-yellow solid: mp 80−81 °C; ^{1}H NMR δ 1.34 (s, 6 H), 1.36 (s, 9 H), 2.15 (s, 3 H), 2.88 (t, J = 7.4 Hz, 2 H), 3.22 (t, J = 7.4 Hz, 2 H), 4.30 (s, 2 H), 7.61 (d, J = 1.8 Hz, 1 H), 7.76 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 15.8, 27.4, 28.7, 28.9, 34.0, 38.1, 40.9, 84.6, 120.5, 126.3, 129.9, 132.9, 137.6, 161.6, 197.0; IR 2959, 1673, 1595, 1455 cm^{-1}; MS *m/z* 307 (MH^+). Anal. ($C_{18}H_{26}O_2S$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-acetoxyethan-1-one (42). Method K. A mixture of 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-chloroethan-1-one, described in the preparation of **40** (1.12 g, 4.0 mmol), formamidine acetate (0.50 g, 4.8 mmol), and 10 mL of EtOH was heated at reflux for 19 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was treated with aqueous Na_2CO_3 solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give 1.2 g of a dark-brown oil. Purification by flash chromatography on silica gel (5% EtOAc/hexanes) gave 0.38 g (31%) of **42** as a light-green solid: mp 83−84 °C; ^{1}H NMR δ 1.35 (s, 6 H), 1.37 (s, 9 H), 2.23 (s, 3 H), 4.33 (s, 2 H), 5.31 (s, 2 H), 7.56 (d, J = 1.8 Hz, 1 H), 7.71 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 20.6, 27.5, 29.0, 34.2, 41.0, 65.8, 84.7, 120.4, 126.1, 127.5, 133.3, 138.0, 162.3, 170.5, 190.7; IR 2959, 1749, 1694, 1599 cm^{-1}; MS *m/z* 305 (MH^+). Anal. ($C_{18}H_{24}O_4$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-thioacetoxyethan-1-one (43). 1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-bromoethan-1-one. Method I. A solution of **13** (2.46 g, 10.0 mmol) in 25 mL of anhydrous THF was added dropwise to LDA (6.0 mL, 12.0 mmol, 2.0 M solution in heptane−THF−ethylbenzene) at −78 °C. The resulting solution was stirred at −78 °C for 15 min, and chlorotrimethylsilane (1.5 mL, 12.0 mmol) was introduced. The reaction mixture was stirred at −78 °C for 15 min, warmed to room temperature, stirred for 1.5 h, quenched with H_2O, and extracted with Et_2O. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo; the residue was dissolved in 25 mL of anhydrous THF and reacted at 0 °C with *N*-bromosuccinimide (1.78 g, 10.0 mmol). The resulting yellowish solution was kept at 0 °C for 0.5 h, warmed to room temperature, stirred for 0.5 h, quenched with H_2O, and extracted with Et_2O. The extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (5% → 20% Et_2O/hexanes) afforded 2.85 g (88%) of the title compound as a yellowish solid: mp 54−56 °C; ^{1}H NMR δ 1.36 (s, 6 H), 1.38 (s, 9 H), 4.34 (s, 2 H), 4.40 (s, 2 H), 7.64 (d, J = 1.8 Hz, 1 H), 7.80 (d, J = 1.8 Hz, 1 H).

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-thioacetoxyethan-1-one (43). A mixture of 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-bromoethan-1-one (0.63 g, 1.9 mmol) and potassium thioacetate (0.22 g, 1.9 mmol) in 10 mL of anhydrous acetone was heated at reflux for 2 h. The acetone was evaporated, and the residue was partitioned between $Et_2O$and H_2O; the ethereal layer was dried over anhydrous $MgSO_4$ and evaporated. Purification by flash chromatography on silica gel (10% EtOAc/hexanes) afforded 0.31 g (51%) of **43** initially as a yellowish oil which upon storage in a refrigerator became a light-yellow solid: mp 61−63 °C; ^{1}H NMR δ 1.33 (s, 6 H), 1.35 (s, 9 H), 2.38 (s, 3 H), 4.30 (s, 2 H), 4.36 (s, 2 H), 7.64 (d, J = 1.8 Hz, 1 H), 7.80 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 27.5, 29.0, 30.1, 34.2, 36.2, 41.0, 84.7, 121.2, 127.0, 128.6, 133.1, 137.8, 162.2, 191.8, 194.3; IR 2960, 1694, 1597 cm^{-1}; MS *m/z* 321 (MH^+). Anal. ($C_{18}H_{24}O_3S$) C, H, S.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-chloro-3-methylbutan-1-one (44). Method H. A solution of **46** (9.4 g, 32.7 mmol) in 1 M ethereal HCl (80 mL) was stirred for 24 h at room temperature. The reaction was quenched with H_2O (80 mL) and the mixture extracted with CH_2Cl_2 (3×). The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and evaporated to provide a tan solid (11.2 g). This solid was recrystallized twice from hexanes to provide **44** (3.54 g 33%): mp 87−88 °C; ^{1}H NMR δ 1.37 (s, 6 H), 1.40 (s, 9 H), 1.83 (s, 6 H), 3.50 (s, 2 H), 4.33 (s, 2 H), 7.64 (d, J = 1.7 Hz, 1 H), 7.83 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 27.55, 29.09, 32.48, 34.19, 41.01, 51.91, 68.48, 84.75, 120.96, 126.79, 130.59, 132.98, 137.64, 161.96, 195.18; IR 2980, 1675, 1594 cm^{-1}; MS *m/z* 323 (MH^+). Anal. ($C_{19}H_{27}O_2Cl$) C, H, Cl.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-hydroxy-3-methylbutan-1-one (45). Method L. To a solution of **13** (1.07 g, 3.19 mmol) in dry CH_2Cl_2 (65 mL) at −78 °C were added *i*-Pr_2NEt (0.97 mL, 5.6 mmol) and then trimethylsilyl triflate (1.1 mL, 5.6 mmol). The solution was stirred at −78 °C for 10 min, brought to 23 °C for 45 min, and then cooled to −78 °C. Acetone (0.54 mL, 7.3 mmol) and $TiCl_4$ (1 M, 4.3 mmol, 4.3 mL) were added sequentially via syringe. The reaction, judged complete by TLC (15% EtOAc/hexanes) after 1 h, was warmed to 23 °C and the solvent evaporated. The resulting dark oil was dissolved in MeOH (25 mL) and stirred with 1 N HCl (4.3 mL) for 30 min. The MeOH was removed, the H_2O was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layers were washed with $NaHCO_3$, dried ($MgSO_4$), and evaporated to a gummy orange solid (1.10 g). This solid was taken up in hexanes, filtered to remove insoluble *i*-Pr_2NEt HCl, and evaporated to an oil. This oil was purified by medium-pressure chromatography to give 276 mg (21%) of **45** as a white solid: mp 86−88 °C; ^{1}H NMR δ 1.30 (s, 6 H), 1.33 (s, 9 H), 1.35 (s, 9 H), 3.10 (s, 2 H), 4.35 (s, 2 H), 7.10 (d, J = 1.5 Hz, 1 H), 7.75 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 27.51, 29.00, 29.53, 34.15, 40.97, 47.81, 69.87, 84.76, 120.72, 126.53, 130.53, 133.07, 137.77, 162.17, 200.51; IR 3464, 2963, 1721, 1656, 1594 cm^{-1}; MS *m/z* 305 (MH^+). Anal. ($C_{19}H_{28}O_3$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-methyl-2-buten-1-one (46): method A; mp 56−58; ^{1}H NMR δ 1.33 (s, 6 H), 1.36 (s, 9 H), 2.05 (s, 3 H), 2.18 (s, 3 H), 4.35 (s, 2 H), 6.70 (s, 1 H), 7.60 (d, J = 1.7 Hz, 1 H), 7.77 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 21.04, 27.61, 27.86, 29.21, 34.24, 41.13, 84.68, 120.89, 121.64, 132.43, 126.65, 132.86, 137.50, 154.28, 161.21, 190.84; IR 2958, 1797, 1659, 1614 cm^{-1}; MS *m/z* 287 (MH^+). Anal. ($C_{19}H_{26}O_2$) C, H.

Biological Procedures. 1. Carrageenan-Induced Paw Edema (CPE) Assay. After a 16-h food fast, left hindpaw volumes of 180−200-g rats (male Sprague−Dawley rats obtained from Charles River Laboratories) were measured using a Ugo Basile model 7150 plethysmometer (Stoelting Inc., Wood Dale, IL). Immediately thereafter, animals (N = 7/group) were dosed orally with vehicle (5 mL/kg), tebufelone (positive control), or test compound at 50 mg/kg. Solid test compounds were micronized with 25% microcrystalline cellulose (Avicel, FMC, Philadelphia, PA) and subsequently suspended in a vehicle of 0.25% methylcellulose (4000 cpi) and 1% Tween 80 (both from Sigma) in double-distilled water. Compounds which were oils were added directly to the vehicle and vortexed vigorously to suspend; 1 h later, 50 λ of a 1% suspension of carrageenan lambda (Sigma) in physiological saline was injected into the plantar surface of the left hindpaw to induce inflammation. Paw edema was allowed to develop for 4 h, and posttreatment paw volumes were determined. The percent

inhibition (%I) of paw edema by each compound was calculated using the following formula:

$$\%I = [(C - T)/C] \times 100$$

where C is the average difference in paw volume (posttreatment − pretreatment) in the control (vehicle) group and T is the average difference in test compound-treated animals. Statistical analysis comparing paw volume ratios (post/pre) across treatment groups was performed using either least-squares or robust (*M*-test) one-way analysis of variance (ANOVA). Variability in the percent inhibition of paw swelling in either controls or test compounds affected the statistical significance such that similar CPE values may or may not be statistically different from controls.

2. Phenylquinone-Induced Abdominal Constriction (PAC) Assay. Male CD-1 mice (18−22 g; Harlan Laboratories) were food-deprived for 4 h and orally dosed with vehicle (10 mL/kg), tebufelone (positive control, 70 mg/kg), or test compound at 10, 40, and 70 mg/kg ($N = 6$/group). Dosing solutions were prepared as described for the CPE assay; 1 h later, 10 mL/kg of a 0.02% solution of phenylquinone (Sigma) was injected intraperitoneally, and abdominal constrictions were counted for the ensuing 10 min. Results are expressed as percent inhibition of writhing using the formula indicated in the CPE methodology above. Maximal inhibition was about 90%. Statistical analysis comparing responses across treatment groups was performed using either least-squares or robust ANOVA, and ED_{50} values were determined using regression analysis.

3. Therapeutic Adjuvant Arthritis Assay. After baseline paw volumes were measured using a mercury plethysmometer, male Lewis rats (190−210 g; Charles River, Portage, MI) were injected subcutaneously into the base of the tail with an 8 mg/mL suspension of *Mycobacterium butyricum* (Difco, Detroit, MI) in mineral oil at a dose volume of 0.5 mL/kg. On day 14, paw volumes were again determined, and animals were randomly divided into treatment groups ($N = 6$). From days 14 to 28, animals were orally dosed with vehicle (5 mL/kg/day), tebufelone (1, 3, or 10 mg/kg/day, positive control), or test compound (3, 10, or 30 mg/kg/day). Dosing solutions were prepared as described for the CPE assay. On day 28, paw volumes and animal weights were measured, and animals were euthanized. For graphical representation, data are expressed as percent inhibition of paw volume increase from days 14 to 28 using the formula:

$$\%I = [(C - T)/(C - H)] \times 100$$

where C is the average difference in paw volume (day 28 − day 14) in the control (vehicle) group, T is the average difference in test compound-treated animals, and H is the average difference in healthy (nonadjuvant-injected) animals. For statistical analysis, the mean of the right and left paw volumes on day 28 was compared across groups using an ANOVA. ED_{50} values were calculated using linear regression of paw volumes vs log(dose).

4. Acute Gastric Safety. Rats weighing 180−200 g ($N =$ 6/group) were dosed orally once with vehicle (5 mL/kg), naproxen (50 mg/kg), or test compound (200, 500, and 1000 mg/kg) and euthanized 4 h later using CO_2 asphyxiation. In a separate study, naproxen was tested in a dose-response of 20, 50, and 100 mg/kg and found to have a UD_{50} of 31 mg/kg. Dosing solutions were prepared as described for the CPE assay. Stomachs were removed, cut open along the greater curvature, rinsed clean in physiological saline, and spread out on cards. Both the length and the area of hemorrhagic lesions were measured using the Image Pro Plus analysis program (Media Cybernetics, Silver Spring, MD), and both parameters were statistically compared across treatment groups using a nonparametric method (Wilcoxon rank-sum test).

5. Human COX-1/COX-2 Isolated Enzyme Assays. a. Enzyme Isolation. COX-1 Enzyme: Outdated human platelet concentrate (1 unit) was obtained from local hospitals/blood banks. The platelet suspension was centrifuged at 1000*g* for 10 min. The cell pellet was washed once with the same volume of phosphate-buffered saline, and the suspension was again centrifuged. The platelets were suspended in 5 volumes of 50 mM Tris-HCl buffer (pH 7.5) and subjected to sonication for 3 × 20 s at 4 °C. The suspension was centrifuged at 5000*g* for 10 min. The supernatant was further centrifuged at 100,000*g* for 60 min. The pellet (microsomes) was suspended in 5 mL of 50 mM Tris-HCl buffer (pH 7.5) and stored in 500-μL aliquots at −70 °C. This fraction was used as the source of COX-1.

COX-2 Enzyme: Recombinant human COX-2 was obtained from Sf9 cells infected with recombinant baculovirus carrying COX-2 cDNA. Briefly, Sf9 cells (1×10^7) were seeded in 75-cm^2 tissue culture flasks in 20 mL of complete TNF−FH medium. Cells were allowed to attach for 1 h. The medium was removed, and 4 mL of Grace's medium containing recombinant virus at a multiplicity of infection of about 10 was added. After the cells were incubated for 1 h at 27 °C, the medium was removed and 20 mL of fresh TNM-FH medium was added. The cells were allowed to grow continuously for 72 h. The cells were then collected by centrifugation at 5000*g* for 10 min. The cells were then suspended in 1.0 mL of 50 mM Tris-HCl (pH 7.5) and sonicated for 2 × 10 s at 0 °C. The crude homogenate was centrifuged at 10000*g* for 10 s. The supernatant was then stored at −80 °C and was used as the source of COX-2

b. Enzyme Assay Protocol. Cyclooxygenase enzyme activity, either COX-1 or COX-2, was assayed by the ability of the enzyme to convert arachidonic acid (AA) to prostaglandin H_2 (PGH_2), which was then reduced to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) by $SnCl_2$ added during the reaction. The reaction mixture contained AA (33 μM), $SnCl_2$ (0.5 mg/mL), inhibitor (5-keto dihydromethylbenzofurans or controls) at various concentrations (compounds were dissolved in DMSO at the 1 mg/mL level and then diluted with DMSO to provide working stock solutions; an aliquot of the appropriate DMSO working stock solution was then added to the enzyme preparation to give the desired concentration of inhibitor), and the enzyme in 0.5 mL of 50 mM Tris-HCl buffer (pH 7.5). The amounts of COX-1 and COX-2 enzyme activities used for the assay were adjusted to give comparable conversion of AA to PGH_2. The reaction was initiated by the addition of the enzyme preparation and was allowed to continue for 5 min at 37 °C. The reaction was terminated by the addition of 40 μL of 1 N HCl. The reaction mixture was neutralized by the addition of 60 μL of 1 M Tris base. A portion (30 μL) of the reaction mixture was diluted to 1 mL with enzyme immunoassay (EIA) buffer, and 50 μL of the diluted sample was assayed for $PGF_{2\alpha}$ by EIA. Duplicate samples were run for each inhibitor concentration including the zero concentration sample. Each sample was assayed for immunoreactive $PGF_{2\alpha}$ in duplicate. The EIA was carried out in 96-microwell plates precoated with protein A (1 mg/well) which served to capture the antibody molecules. Appropriately diluted $PGF_{2\alpha}$ antibodies, samples, or standards and $PGF_{2\alpha}$-horseradish peroxidase conjugate were added to each well. Incubation was allowed to proceed for 1 h. After unbound materials were removed by washing, the bound enzyme activity was determined by adding substrate (3,3′,5,5′-tetramethylbenzidine plus H_2O_2). The concentrations of the unknown samples were determined from the standard curve. The dose-dependent inhibition curve for COX-1 and COX-2 for each compound was constructed by plotting the percent inhibition of $PGF_{2\alpha}$ production versus the concentration of the NoPAIN analogue using the FigP software package (BioSoft, Cambridge, U.K.). The concentration that gives 50% inhibition (IC_{50}) was calculated for each analogue. The ratio of the IC_{50} for COX-1 versus COX-2 (IC_{50} COX-1/IC_{50} COX-2) provides an indication of the specificity of the inhibition. A ratio that is greater than 1 indicates specificity for COX-2, while a ratio less than 1 indicates a greater specificity for COX-1.

6. RBL-2H3 Intact Cell Assay for LTB_4 Inhibition. Rat basophilic leukemia cells (RBL-2H3) were grown overnight in spinner culture in S-MEM (minimum essential media for suspension culture) with 16% fetal bovine serum, L-glutamine

(2 mM), and penicillin/streptomycin (100 U/100 μg/mL) to a density of 2.0×10^6 cells/mL. LTB_4 inhibitory activity was assayed for 10 min at 37 °C with controls/test agents (25 μL preincubated with 1.0×10^7 cells/sample for 30 min at 37 °C) in 5-mL reaction volumes consisting of assay buffer (140 mM NaCl, 5 mM KCl, 0.6 mM $MgCl_2$, 2 mM $CaCl_2$, 5 mM glucose, and 5 mM HEPES, pH 7.4) and 10 μM calcium ionophore A23187. The reaction was quenched with EDTA, and samples were centrifuged. Sample supernatant was removed and stored in 25% methanol at −70 °C until quantitative analysis by a stable-isotope-based high-performance liquid chromatography/electrospray mass spectrometry/mass spectrometry (LC/MS/MS) method. The samples were prepared for analysis by spiking a known volume with LTB_4-d_4, mixing, and performing solid-phase extraction on octadecylsilane (ODS) cartridges. Chromatographic isolation of LTB_4 and LTB_4-d_4 from matrix components was performed on a Waters Symmetry ODS column (2.1 mm × 150 mm) with a mobile phase of methanol/1 mM ammonium acetate/formic acid (78/22/0.1; v/v/v) at a flow rate of 0.25 mL/min. The MS/MS detection utilized a selected-reaction-monitoring scheme where LTB_4 and the LTB_4-d_4 were monitored using parent-to-daughter transitions of m/z 354.3 → 301.0 and m/z 358.3 → 305.0. The methodology was able to detect LTB_4 at the 100 pg/mL level with an accuracy of 100 ± 10%.

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