New Cyclooxygenase-2/5-Lipoxygenase Inhibitors. 3. 7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzofuran Derivatives as Gastrointestinal Safe Antiinflammatory and Analgesic Agents: Variations at the 5 Position†

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We report an expansion of the scope of our initial discovery that 5-keto-substituted 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofurans (DHDMBFs) are antiinflammatory and analgesic agents. Several other functional groups have been introduced at the 5 position: amides, amidines, ureas, guanidines, amines, heterocycles, heteroaromatics, and heteroaryl ethenyl substituents in the 5 position all provide active compounds. These compounds are dual cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) inhibitors. They inhibit both COX-1 and COX-2 with up to 33-fold selectivity for COX-2.

Introduction

Di-*tert*-butylphenols are well-known antiinflammatory agents which are dual cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) inhibitors in vitro. The combination of COX/5-LOX inhibition and antioxidant properties has been proposed to account for the GI safety of some members of this class, as discussed in a preceding paper.[1]

The evolution of our work in the di-*tert*-butylphenol area began with the discovery of the antiinflammatory agent tebufelone (**1**). Among the metabolites of tebufelone was the 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (DHDMBF) **2**, a nonphenolic compound. In the first paper in this series,[1] we disclosed that several 5-keto-substituted DHDMBFs were active antiinflammatory agents as well as COX/5-LOX inhibitors with selectivity for COX-2. Compound **3** was of particular interest since it showed excellent gastric safety in a variety of in vivo tests. We also showed that a variety of structural changes in the dihydrobenzofuran moiety led to active compounds.[2] In both of these papers, all of the active compounds described were 5-keto-substituted compounds.

We now report results on a more extensive variation of the substituent in the 5 position of 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran. A variety of compounds (**4**) containing carboxyl, amido, heterocyclic, heteroaromatic, and othr substituents at the 5 position were prepared. Biological testing was done to evaluate the effects of these structural changes on in vivo antiinflammatory and analgesic activity and on in vitro COX/5-LOX inhibitory properties. Many of these new compounds showed significant in vivo antiinflammatory activity, thus greatly extending the scope of the substituted DHDMBF class of antiinflammatory agents.

Chemistry

The 5-carboxy-2,3-dihydro-3,3-dimethylbenzofuran **5** was the intermediate used for the preparation of ester **6** and amides **7**−**27** and **31**−**33** (Scheme 1). Compound **5** was prepared by lithium−halogen exchange of the 5-bromo compound **I**[1] with *tert*-butyllithium followed by carbonation with CO_2. Acid-catalyzed esterification gave the methyl ester **6**. Treatment of **5** with oxalyl chloride followed by addition of the appropriate amine gave the amides **7**−**27** and **31**−**33** (method A). The tertiary cyclopropyl amides **28**−**30** were prepared from the secondary cyclopropyl amide **13** by phase-transfer alkylation (method B).[3] The amidine **34** was prepared via the same lithio dihydrobenzofuran mentioned above by quenching with dimethylcyanamide.[4]

The nitrile **II** was an intermediate for the preparation of two analogues, **35** and **46** (Scheme 2). The amidine **35** was prepared by conversion of **II** (prepared from **I** with chlorosulfonylisocyanate[5]) to the imidate **III** followed by treatment with excess pyrrolidine. The 1,2,4-oxadiazole **46** was prepared via the oxime **IV** by treatment with acetyl chloride.[6]

The 5-amino dihydrobenzofuran **V** was the key starting material for the preparation of several different types of compounds (Scheme 2). It was prepared by nitration of 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran[1] with nitric acid in acetic acid followed by hydrogenation of the nitro compound over palladium. Acylation of **V** with acetyl chloride gave the "reversed" amide **36**. Reaction with the appropriate isocyanates gave the ureas **37** and **38** (method C). Reaction with imidazoline-2-sulfonic acid[7] gave the cyclic guanidine **39**, while treatment with diphenyliodonium-2-carboxylate and cupric acetate[8] gave the anthranilic acid derivative **40**.

The 5-bromoacetyl-substituted dihydrobenzofuran **VI**[1] was the starting material for the preparation of several other compounds (Scheme 3). Heating with formamide gave the oxazole **44**. Reaction with ethylthiooxamate followed by hydrolysis and decarboxylation gave the thiazole **45**, while reaction with thiourea gave the aminothiazole **47**. The guanidinothiazole **48** was prepared similarly by reaction with 1-amidinothiourea. Reaction with 2-aminothiazoline gave the imidazothia-

† Dedicated to the memory of our friend and colleague Hoang Do.

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Scheme 1

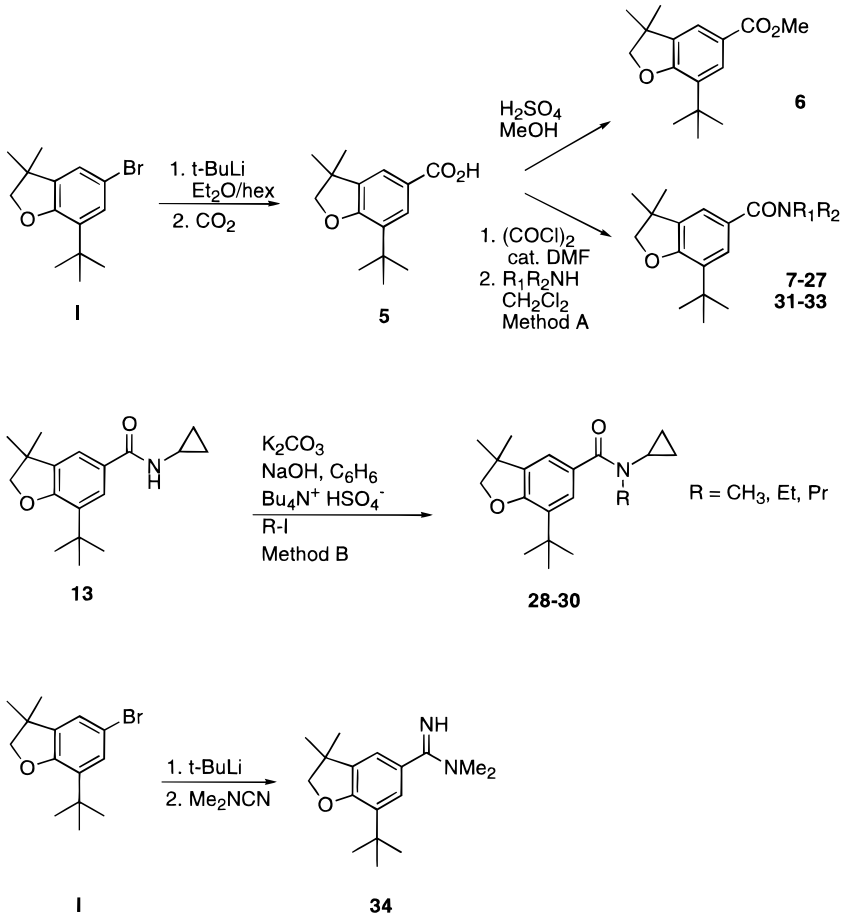
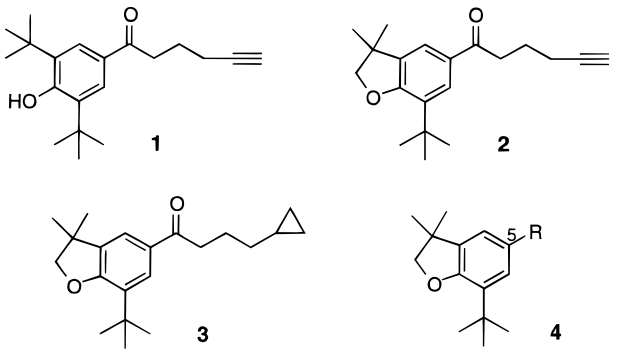


Chart 1



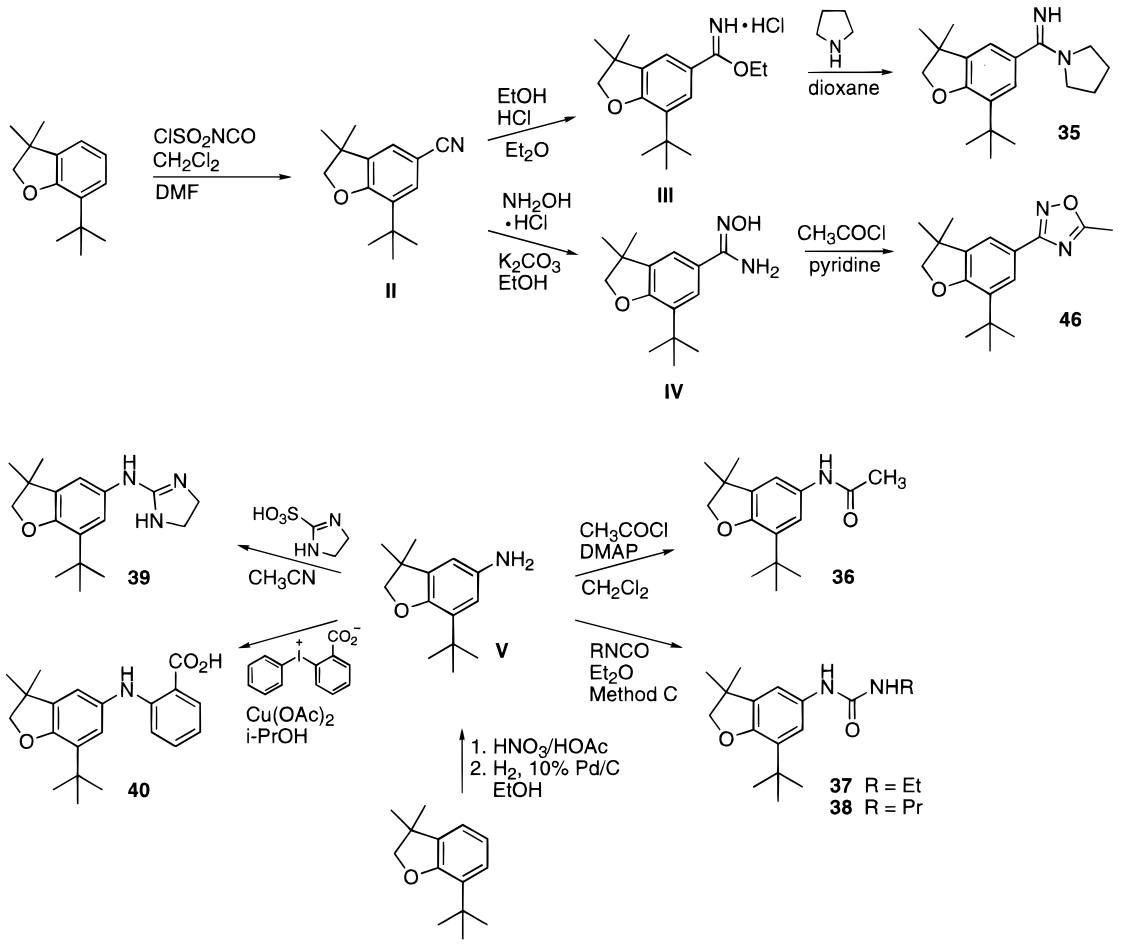
zoline **49** which could be oxidized to **50** and **51** by sequential addition of *m*-chloroperbenzoic acid.[9] Scheme 3 also shows the synthesis of the isoxazoline **41** which was prepared by reaction of the 3-chloro-3-methylbutanoyl-substituted dihydrobenzofuran[1] with hydroxylamine.

The 5-bromo compound **I** was also the source of additional analogues (Scheme 4). Stille coupling[10] of 2-tri-*n*-butyltin-substituted furan and thiophene with **I** gave compounds **42** and **43** (method D). The heterocyclic ketones **54**−**59** were prepared by addition of 5-lithio dihydrobenzofuran to the desired aldehyde followed by oxidation of the resulting alcohol with 4-methylmorpholine *N*-oxide (4-NMO) and a catalytic amount of tetrapropylammonium perruthenate (method E).[11] Conversion of **I** to 5-formyl dihydrobenzofuran **VII** (by lithium−halogen exchange followed by quenching with DMF) provided the starting material for the final group of compounds (Scheme 5). Wittig reaction of **VII** with 2-(triphenylphosphoranylidine)-γ-butyrolactone gave compound **52**. Condensations with psuedothiohydantoin or 2-thiopheneacetic acid[12] gave **53** and **60**, respectively. While **60** was resistant to thermal decarboxylation,[13] heating to 250 °C in the presence of copper[14] gave an 85/15 *E*/*Z* mixture of decarboxylated product **61**. A more convenient method for the stereoselective synthesis of **61** involved a Horner−Emmons[15] reaction with ethyl 2-thiophenemethylphosphonate. The pyridyl compounds **64** and **65** were also prepared from **VII** by Wittig reactions: the 2-picolyl ylide gave exclusively the *E* isomer **64**, while the 3-picolyl ylide gave a 40/60 *E*/*Z* mixture from which the *E* isomer **65** was separated by chromatography. The styrylisoxazole **62** was prepared by an isoxazolylmethyl carbanion approach. The carbanion generated by regioselective deprotonation at the 5-methyl position of 3,5-dimethylisoxazole with *n*-BuLi[16] was reacted with aldehyde **VII**. Dehydration of the resulting alcohol with toluenesulfonic acid gave **62**. Conversion of **62** to the styrylpyrazole **63** was carried out following Kobayashi's hydrogenolysis procedure[17] using $Mo(CO)_6$ followed by pyrazole ring formation using hydrazine.

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

Scheme 2



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.[18] 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 cyclopropyl ketone **3** was quite good (62%) in the rat.

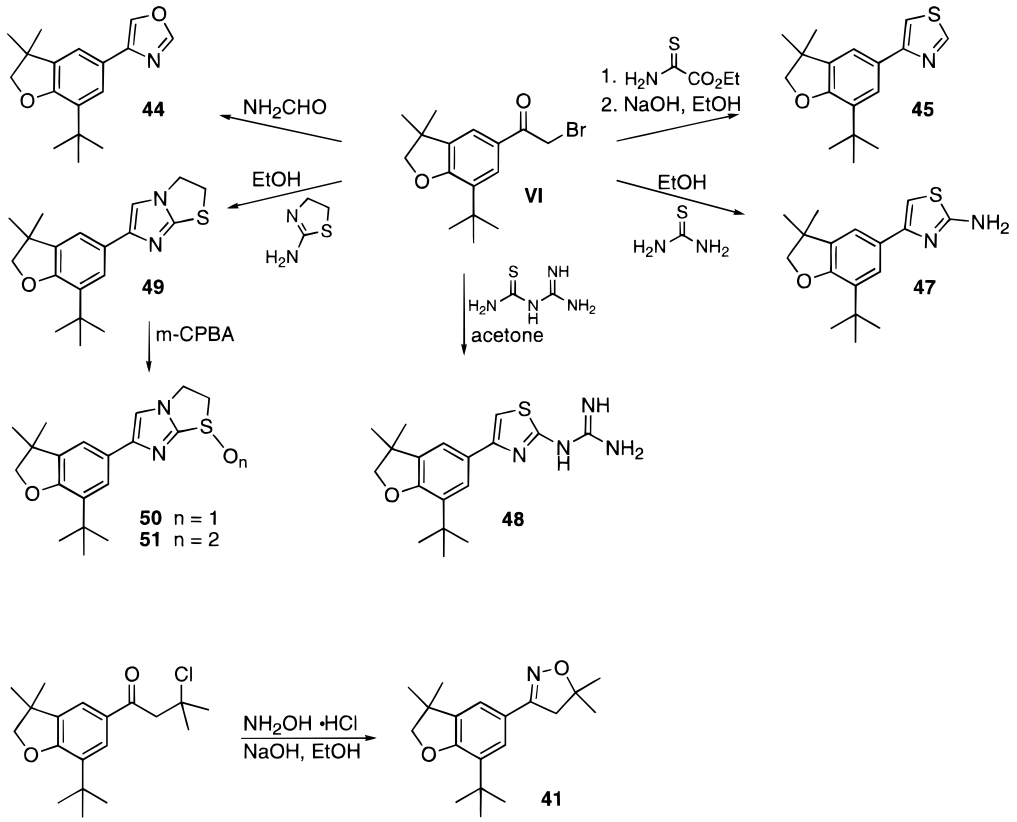
With the goal of defining the scope of the substituents in the 5 position that provide compounds with antiinflammatory activity, our work was guided by the structure−activity trends observed for the 5-keto dihydrobenzofurans[1] and by the type of substituents that led to activity in the di-*tert*-butylphenol series. We began with the 5-carboxylic acid **5** which had modest although significant activity. The corresponding ester **6** and primary amide **7**, however, were inactive. We next prepared a series of secondary amides. For *n*-alkyl amides, the ethyl and propyl compounds **8** and **9** were active, while the higher homologues **10** and **11** were not. The branched and cyclic C-3 alkyl compounds **12** and **13** were active, while the homologated cyclopropyl compounds **14** and **15** and the larger cycloalkyl compounds **16** and **17** as well as the aniline amide **18** were not. Similar trends were observed with the 5-keto dihydrobenzofurans where modest increases in alkyl chain length or ring size led to a loss of activity.[1] Many of the larger secondary amides were high melting compounds with limited solubility which may have contributed to their lack of in vivo activity.

In an effort to improve the solubility of our secondary amides, compounds incorporating heteroatoms in the amide substituent were prepared. While the hydroxyethyl amide **19** was inactive, the methoxyethyl compound **20** had very good activity. The dihydroxypropyl compound **21** had modest activity while the dimethylaminoethyl compound **22** was inactive. Incorporating heteroatoms into a 5-membered ring provided the active heterocyclic amides **23** and **24**. Thus, incorporation of heteroatoms into otherwise inactive secondary amides led to active compounds in four out of six cases.

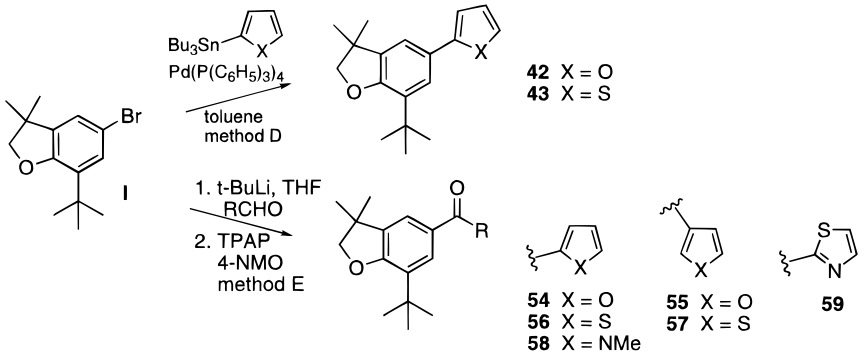
An alternative way to improve solubility was to prepare tertiary amides which lack the N−H bond. Intermolecular hydrogen bonding can lead to higher melting, less soluble compounds. Eight of the nine tertiary amides **25**−**33** were active. These included compounds with up to six carbons in the alkyl substituents (**30**) and five carbons in a cyclic ring (**32**) thereby extending the size of the alkyl substituents which lead to active compounds compared to secondary amides. The results for the tertiary amides prompted us to prepare the isosteric *N*,*N*-dialkyl amidines **34** and **35**, both of which were active.

A variety of compounds which bear a nitrogen rather than a carbon atom linked to C-5 were prepared. The reversed secondary amide **36** was active as was the

Scheme 3



Scheme 4



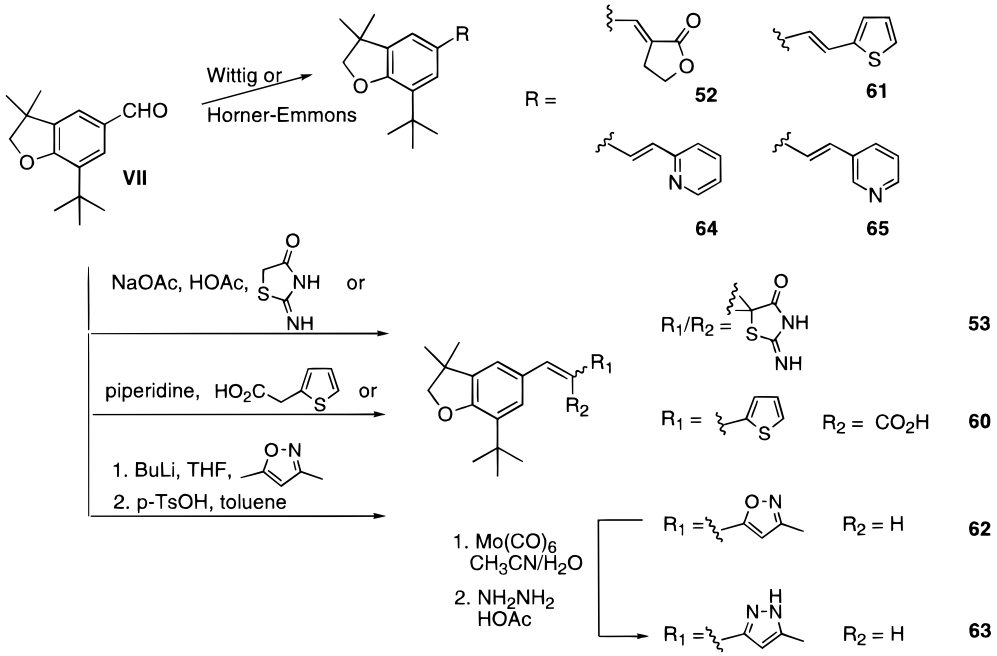
shorter of the two alkyl ureas, **37**. The guanidino compound **39** had very good activity. Finally, the anthranillic acid derived amine **40** was also active.

A series of compounds **41**−**51** with either a heteroaryl or heterocyclic groups directly attached to C-5 was prepared. In general, activity across this series was good. The active isoxazoline **41** was readily prepared from the acyclic β-chloroketone precursor which itself was an active compound.[1] Five unsubstituted or alkyl-substituted heteroaryl compounds **42**−**46** were prepared, and all except the oxazolyl compound **44** were active. Five additional substituted or fused-ring heterocycles, **47**−**51**, were prepared. While the amino-substituted thiazole **47** was inactive, the guanidino-substituted compound **48** was active. In the fused imidazothiazole series **49**−**51**, the sulfide and sulfoxide forms were active.

Two compounds with heterocycles fused to a double bond at the 5 position were prepared. The lactone **52**, which is the dihydrobenzofuran analogue of the active di-*tert*-butylphenol KME-4,[19] was active. In contrast, the iminothiazolidinone **53,** the dihydrobenzofuran analogue of the active di-*tert*-butylphenol CI-1004,[20] was inactive. The final group of compounds (**54**−**65**), all bear heteroaromatic groups which are linked to the dihydrobenzofuran via an intervening carbonyl group (**54**−**59**) or carbon−carbon double bond (**60**−**65**). The ketones **54**−**59** were all active. The olefin-linked heteroaromatics **60**−**65** were generally active with the exception of the 3-methylisoxazole **62** and the 2-pyridyl compound **64**.

The correlation of antiinflammatory activity in the CPE assay with analgesic activity in the phenylquinone-induced abdominal constriction assay (PAC) is quite good. Of the 32 compounds which were active in the CPE assay, 27 were likewise active in the PAC assay. The five outliers fall into different structural categories and it is difficult to find a common explanation for their inactivity. Among the compounds active in the PAC

Scheme 5



assay, the two most active were the anthranillic acid derivative **40** and the furyl ketone **55** both with ED_{50} < 10 mg/kg.

Finally, it is interesting to compare the antiinflammatory activity of the DHDMBFs with the corresponding di-*tert*-butylphenols (Table 2). It was, in fact, the correspondence of antiinflammatory activity in the two series for the hexynoyl side chain that led us to explore the DHDMBFs. This same correspondence holds for the thienyl ketone **56**.[21] However, for the new substituents at the 5 position, the correspondence is poor. For the carboxylate derivatives **5**, **7**, **25**, and **36**, only one compound gave consistent results in both series.[22] For heterocyclic groups that are directly attached to the phenyl ring of DHDMBF or di-*tert*-butylphenol, the activity of the oxdiazole **46** does not correlate,[6] while the imidazothiazoles **49**, **50**, and **51** do correlate.[9] For the remaining heterocycles, either fused to a methylene group (**52**[19] and **53**[20]) or attached via a carbonyl (**56**) or an ethenyl group (**61**−**65**),[12,17a] the correspondence is again random. Thus, while drawing analogies from the di-*tert*-butylphenol literature was a source of several active DHDMBFs, activity in the di-*tert*-butylphenol series was not accurately predictive of activity in the DHDMBF series.

In Vitro Results. Selected compounds were tested in vitro for inhibition of COX and 5-LOX (Table 3). The COX-2 selectivity that we observed for many of the 5-keto-substituted dihydrobenzofurans[1,2] prompted us to look for similar selectivity for compounds with different substituents at C-5. Potency and selectivity were determined using human platelet-derived COX-1 and recombinant human COX-2. In addition, selected compounds were assayed for inhibition of 5-lipoxygenase in RBL cells.

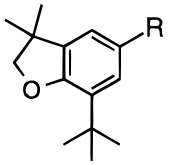
For the series of secondary amides (**8**−**20** and **36**), there was a trend for increasing COX-2 selectivity with increasing chain length as was observed for alkyl ketones.[1] The most selective compound in the series was the methoxyethyl amide **20** which was 33-fold selective. Tertiary amides (**26, 28, 30**) were less potent inhibitors of COX-2 and, therefore, had low selectivities. Curiously, the amidine and guanidine compounds **35** and **39** failed to inhibit either COX-1 or COX-2. Both were active in the CPE assay but not in the PAC assay, suggesting that some unknown pharmacology may be responsible for their antiinflammatory efficacy. The anthranillic acid derivative **40** had modest potency and little selectivity. Among the remaining tested compounds, all of which were heterocycles, COX-2 selectivity was generally quite low. Several compounds (**49, 52, 56, 58,** and **61**) were quite potent (ED_{50} < 100 nm) inhibitors of both COX-1 and COX-2. The most potent versus COX-2, **52** (3.5 nM), was also the most selective (13-fold). Compound **52** was also the most potent 5-LOX inhibitor. 5-LOX ED_{50} determinations ranged from 4 to >50 μM for those compounds tested. In general, the selectivity for COX-2 observed for the compounds in Table 3 was less than for the 5-keto compounds previously tested.[1,2]

Except for the two compounds noted above, all of the compounds inhibited COX-1 and or COX-2 with ED_{50}s in the low μM range or below. Thus, it was reasonable to expect that all of the compounds might show in vivo activity. This prediction was true except for three compounds, the secondary amides **10** and **11** and the iminothiazolidinone **53**. The poor solubility of the secondary amides, mentioned above, could result in poor bioavailability. A lack of bioavailability could also be the reason for the inactivity of compound **53**.

Conclusions

A large variety of substituents in the 5 position led to antiinflammatory and analgesic 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofurans. This observation has greatly expanded the scope of the dihydrobenzofuran lead. The substituents leading to active compounds include amides, amidines, ureas, guanidines, amines, heterocycles, heteroaromatics, heterocyclic ketones, and heteroaromatic ethenyl compounds. The in vivo activity

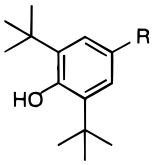
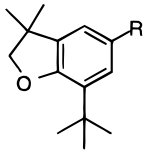
Table 1. Structure, Synthetic Methods, and in Vivo Activity of Dihydrodimethylbenzofurans



compd	R	method	yield, %	mp, °C	formula	CPE index[a]	PAC assay[b]
1, tebufelone						**1.00**[c]	**37**
naproxen						**1.06**[c]	**1.3**
5	CO_2H	Scheme 1	95	197−202	$C_{15}H_{20}O_3$	**0.47**	NT[d]
6	CO_2Me	Scheme 1	79	33−34	$C_{16}H_{22}O_3$	0.16	NT
7	$CONH_2$	A	100	182−184	$C_{15}H_{21}NO_2$	0.07	NT
8	CONHEt	A	77	204−205	$C_{17}H_{25}NO_2$	**0.88**	56%
9	CONHPr	A	42	195−197	$C_{18}H_{27}NO_2$	**1.17**	63%
10	CONHBu	A	68	185−186	$C_{19}H_{29}NO_2$	0.46	NT
11	CONHPen	A	45	165−168	$C_{20}H_{31}NO_2$	0.16	NT
12	CONH-*i*-Pr	A	55	226−227	$C_{18}H_{27}NO_2$	**1.09**	43%
13	CONH-c-Pr	A	93	>200 dec	$C_{18}H_{25}NO_2$	**0.68**	**20**
14	$CONHCH_2$-c-Pr	A	30	206−208	$C_{19}H_{27}NO_2$	0.44	NT
15	$CONH(CH_2)_2$-c-Pr	A	32	185−186	$C_{20}H_{29}NO_2$	0.06	NT
16	CONH-c-Bu	A	51	>200 dec	$C_{19}H_{27}NO_2$	0.00	NT
17	CONH-c-Pen	A	28	254−256	$C_{20}H_{29}NO_2$	0.00	NT
18	$CONHC_6H_5$	A	35	247−249	$C_{21}H_{25}NO_2$	0.01	NT
19	$CONH(CH_2)_2OH$	A	85	168−170	$C_{17}H_{25}NO_3$	0.33	NT
20	$CONH(CH_2)_2OMe$	A	69	150−152	$C_{18}H_{27}NO_3$	**1.47**	84%
21	$CONHCH_2CH(OH)CH_2OH$	A	69	140−142	$C_{18}H_{27}NO_4$	**0.51**	NT
22	$CONH(CH_2)_2NMe_2$	A	71	160−162	$C_{19}H_{30}N_2O_2$	0.00	NT
23	CONH-2-thiazole	A	61	230−232	$C_{18}H_{22}N_2O_2S$	**0.49**	NT
24	CONH-2-thiazoline	A	35	158−160	$C_{18}H_{24}N_2O_2S$	**0.81**	65%
25	$CONMe_2$	A	89	91−93	$C_{17}H_{25}NO_2$	0.36	NT
26	CONMeEt	A	86	61−62	$C_{18}H_{27}NO_2$	**0.86**	**19**
27	CONMePr	A	73	73−75	$C_{19}H_{29}NO_2$	**0.91**	36%
28	CONMe-c-Pr	B	57	70−72	$C_{19}H_{27}NO_2$	**1.82**	**10**
29	CONEt-c-Pr	B	59	81−83	$C_{20}H_{29}NO_2$	**1.14**	NT
30	CONPr-c-Pr	B	49	90−92	$C_{21}H_{31}NO_2$	**1.41**	NT
31	$CON(C_4H_8)$	A	74	90−92	$C_{19}H_{27}NO_2$	**0.78**	NT
32	$CON(C_5H_{10})$	A	87	105−107	$C_{20}H_{29}NO_2$	**0.52**	34%
33	$CON(C_4H_8S)$	A	91	143−145	$C_{19}H_{27}NO_2S$	**0.71**	29%
34	$C(=NH)NMe_2$	Scheme 1	20	>160 dec	$C_{17}H_{26}N_2O$	**0.47**	NT
35	$C(=NH)(C_4H_8N)$	Scheme 2	54	255−256	$C_{19}H_{28}N_2O$	**0.80**	0%[e]
36	NHCOMe	Scheme 2	22	154−155	$C_{16}H_{23}NO_2$	**0.66**	22%[e]
37	NHCONHEt	C	51	197−198	$C_{17}H_{26}N_2O_2$	**0.73**	36%
38	NHCONHPr	C	39	193−194	$C_{18}H_{28}N_2O_2$	0.41	NT
39	$NH(C_3H_5N_2)$	Scheme 2	32	>264 dec	$C_{17}H_{25}N_3O$	**1.49**	8%[e]
40	NH-*o*-$(CO_2H)C_6H_4$	Scheme 2	57	204−206	$C_{21}H_{25}NO_3$	**0.78**	<**10**
41	3-(5,5-di-Me)isoxazolinyl	Scheme 3	31	96−98	$C_{19}H_{27}NO_2$	**0.56**	80%
42	2-furyl	D	43	oil	$C_{18}H_{22}O_2$	**0.93**	7%[e]
43	2-thienyl	D	43	61−63	$C_{18}H_{22}OS$	**0.92**	52%
44	4-oxazolyl	Scheme 3	41	141−142	$C_{17}H_{21}NO_2$	0.19	NT
45	4-thiazolyl	Scheme 3	36	100−101	$C_{17}H_{21}NOS$	**1.53**	59%
46	3-(5-Me)-1,2,4-oxdiazolyl	Scheme 2	52	81−82	$C_{17}H_{22}N_2O_2$	**0.83**	NT
47	4-(2-amino)thiazolyl	Scheme 3	52	161−162	$C_{17}H_{22}N_2OS$	0.26	NT
48	4-(2-guanidino)thiazolyl	Scheme 3	35	237−238	$C_{18}H_{24}N_4OS$	**1.38**	77%
49	6-imidazo[2.1-*b*]thiazolyl	Scheme 3	63	189−190	$C_{19}H_{24}N_2OS$	**0.81**	68%
50	6-imidazo[2.1-*b*]thiazolyl-1-oxide	Scheme 3	75	217−219	$C_{19}H_{24}N_2O_2S$	**0.96**	NT
51	6-imidazo[2.1-*b*]thiazolyl-1,1-dioxide	Scheme 3	64	275−276	$C_{19}H_{24}N_2O_3S$	0.19	NT
52	3-methylene-γ-butyrolactonyl	Scheme 5	78	122−123	$C_{19}H_{24}O_3$	**0.93**	NT
53	5-methylene-2-imino-4-thiazolidinonyl	Scheme 5	29	>213 dec	$C_{18}H_{22}N_2O_2S$	0.07	NT
54	CO-2-furyl	E	84	103−104	$C_{19}H_{22}O_3$	**0.70**	**24**
55	CO-3-furyl	E	67	120−121	$C_{19}H_{22}O_3$	**0.68**	**3**
56	CO-2-thienyl	E	74	103−105	$C_{19}H_{22}O_2S$	**0.58**	**34**
57	CO-3-thienyl	E	80	89−90	$C_{19}H_{22}O_2S$	**0.62**	40%
58	CO-2-(N-Me)pyrrole	E	47	oil	$C_{20}H_{25}NO_2$	**1.24**	**57**
59	CO-2-thiazolyl	E	23	101−103	$C_{18}H_{21}NO_2S$	**0.75**	**28**
60	(*E*)-CH=C(CO_2H)-2-thienyl	Scheme 5	34	183−185	$C_{21}H_{24}O_3S$	**0.76**	19%[e]
61	(*E*)-CH=CH-2-thienyl	Scheme 5	86	113.5−115	$C_{20}H_{24}OS$	**0.77**	**13**
62	(*E*)-CH=CH-3-(3-Me)-5-isoxazolyl	Scheme 5	75	122−123	$C_{20}H_{25}NO_2$	0.00	NT
63	(*E*)-CH=CH-3-(5-Me)-1H-3-pyrazolyl	Scheme 5	42	145−147	$C_{20}H_{26}N_2O$	**0.56**	35%
64	(*E*)-CH=CH-2-pyridyl	Scheme 5	81	122−123	$C_{21}H_{25}NO$	0.50	NT
65	(*E*)-CH=CH-3-pyridyl	Scheme 5	38	72−74	$C_{21}H_{25}NO$	**0.78**	45%

[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 >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[1] for complete details. [b] PAC, phenylquinone-induced abdominal constriction assay. Values are ED_{50} in bold or the percent reduction of constrictions at a po dose of 70 mg/kg; maximal percent reduction is ∼90%. See Experimental Section[1] 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 not statistically different from vehicle control.

Table 2. Comparative Activity of Di-*tert*-butylphenols versus Dihydrodimethylbenzofurans in the CPE Assay

compd	R		
2	$CO(CH_2)_3CCH$	+[a]	+
5	CO_2H	−[b]	+
7	$CONH_2$	−	−
25	$CONMe_2$	+	−
36	NHCOMe	−	+
46	3-(5-Me)-1,2,4-oxdiazolyl	−	+
49	6-imidazo[2.1-*b*]thiazolyl	+	+
50	6-imidazo[2.1-*b*]thiazolyl-1-oxide	+	+
51	6-imidazo[2.1-*b*]thiazolyl-1,1-dioxide	−	−
52	3-methylene-γ-butyrolactonyl	+	+
53	5-methylene-2-imino-4-thiazolidinonyl	+	−
56	CO-2-thienyl	+	+
61	(*E*)-CH=CH-2-thienyl	+[c]	+
62	(*E*)-CH=CH-3-(3-Me)−5-isoxazolyl	+	−
63	(*E*)-CH=CH-3-(5-Me)−1H-3-pyrazolyl	+	+
64	(*E*)-CH=CH-2-pyridyl	+[c]	−
65	(*E*)-CH=CH-3-pyridyl	+	+

[a] A + indicates that the compound is orally active with an ED_{35} or ED_{50} ≤15 mg/kg or with ≥25% inhibition of paw swelling at a dose ≤50 mg/kg. [b] A − indicates an inactive compound. [c] Test results from an adjuvant arthritis model.

correlated reasonably well with the inhibition of cyclooxygenase. Active compounds inhibited both COX-1 and COX-2 with up to 33-fold selectivity for COX-2.

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. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively. NMR spectra were recorded in $CDCl_3$ unless indicated otherwise, and chemical shifts are reported relative to tetramethylsilane (δ = 0.00). Infrared spectra were recorded on a Perkin-Elmer instrument as a neat thin film on NaCl windows for oils or as KBr pellets for solids. 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 Procter & Gamble Pharmaceuticals (Norwich NY). 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.

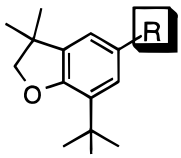
7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuran Carboxylic Acid (5). A solution of 5-bromo-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran **I**[1] (13.3 g, 48.2 mmol) in dry Et_2O (17 mL) and dry hexanes (150 mL) was cooled to −78 °C, and *t*-BuLi (59.0 mL, 1.59 M in pentane, 94 mmol, 2.0 equiv) was added dropwise over 10 min. The resulting yellow solution was allowed to stir at −78 °C for 45 min, and then CO_2 was slowly bubbled through for 30 min. Excess dry ice was added, and the reaction allowed to warm to 23 °C. The reaction was partitioned between Et_2O (150 mL) and 4 N NaOH (2 × 100 mL). The aqueous layer was acidified to pH 2 with concentrated HCl and extracted with Et_2O. The extracts were combined, dried ($MgSO_4$), and evaporated to give 11.63 g (95%) of **5** as a light yellow solid, mp 197−202 °C: ^{1}H NMR δ 12.40 (br s, 1 H), 7.95 (d, J = 2.0 Hz, 1 H), 7.80 (d, J = 2.0 Hz, 1 H), 4.35 (s, 2 H), 1.40 (s, 9 H), 1.39 (s, 6 H); ^{13}C NMR δ 172.8, 162.5, 137.7, 133.1, 128.5, 122.8, 121.5, 84.8, 41.1, 34.2, 29.1, 27.6; MS *m*/*z* 249 (MH^+), 231; IR 2959, 1676, 1603 cm^{-1}. Anal. ($C_{15}H_{20}O_3$) C, H.

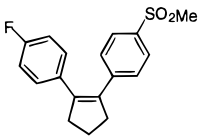
7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuran Carboxylic Acid Methyl Ester (6). A solution of acid **5** (995 mg, 4.01 mmol), MeOH (20 mL), and concentrated H_2SO_4 (0.1 mL) was heated at reflux for 14 h. The reaction was quenched with 10% aqueous $NaHCO_3$ (20 mL). The resulting mixture was extracted with hexanes, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a yellow oil that was purified by preparative TLC (2% EtOAc/hexanes) to give 840 mg (79%) of **6** as a colorless oil which solidified on standing, mp 33−34 °C: ^{1}H NMR δ 1.36 (s, 6 H), 1.38 (s, 9 H), 3.87 (s, 3 H), 4.35 (s, 2 H), 7.65 (d, J = 1.2 Hz, 1 H), 7.84 (d, J = 1.2 Hz, 1 H); ^{13}C NMR δ 167.0, 162.0, 137.4, 132.9, 127.5, 122.3, 122.0, 84.5, 51.7, 41.0, 34.1, 29.1, 27.5; MS 263 *m*/*z* (MH^+). Anal. ($C_{16}H_{22}O_3$) C, H.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-ethyl-5-benzofurancarboxamide (8). Method A. To a solution of acid **5** (21.5 g, 86.7 mmol), dry THF (300 mL), and DMF (5 mL) at 0 °C was added oxalyl chloride (11.4 mL, 130 mmol, 1.5 equiv) dropwise over 10 min, and gas evolution was observed. The reaction was allowed to warm to 23 °C and stirred for 2.5 h, at which time the solvent was evaporated to provide 27 g (110%) of crude acid chloride as a dark oil, suitable for use in subsequent reactions. The oil was stored under N_2 in the refrigerator. The acid chloride could also be prepared for each individual reaction and used without evaporation of the solvent: ^{1}H NMR δ 1.37 (s, 15 H), 4.37 (s, 2 H), 7.74 (d, J = 2.0 Hz, 1 H), 7.91 (d, J = 2.0 Hz, 1 H); IR 2961, 1747, 1683, 1598 cm^{-1}.

To a solution of acid chloride (950 mg, 3.56 mmol) in CH_2Cl_2 (10 mL) was added ethylamine (765 mg, 1.45 mL, 17.8 mmol, 5 equiv. Note: 5−10 equiv of amine were generally used) over 5 min. The reaction was stirred for 1 h at 23 °C, and then the solvent was evaporated. The residue was taken up in 1 N HCl (10 mL), and the insoluble material was collected by filtration and crystallized from 5:1 *i*-PrOH/H_2O to yield 754 mg (77%) of **8** as white needles, mp 204−205 °C (note: reaction time using method A varied from 1 h to overnight. An alternative workup was often used which involved quenching the reaction with 1 N HCl followed by extraction of the product into CH_2Cl_2, evaporation of the solvent, and purification): ^{1}H NMR δ 1.23 (t, J = 7.5 Hz, 3 H), 1.32 (s, 6 H), 1.35 (s, 9 H), 3.49 (dq, J = 7.5, 7.5 Hz, 2 H),

Table 3. In Vitro Activity of 5-Substituted Dihydrodimethylbenzofurans



compd		IC_{50}, μM[a] COX-1	COX-2	COX-1/COX-2	IC_{50}, μM 5-LOX[b]
8	CONHEt	20	6	3.33	NT
9	CONHPr	0.55	0.95	0.58	>50
10	CONHBu	2.5	0.22	11.4	NT
11	CONHPen	2.0	0.25	8.00	NT
13	CONH-c-Pr	0.29	0.55	0.53	>50
20	$CONH(CH_2)_2OMe$	1.0	0.03	33.0	~50
26	CONMeEt	2.5	4.5	0.55	22
28	CONMe-c-Pr	5	1	5.00	12
30	CONPr-c-Pr	4.5	4	1.13	NT
35	$C(=NH)(C_4H_8N)$	>100	>100	–	30
36	NHCOMe	3.5	3.5	1.00	NT
39	$NH(C_3H_5N_2)$	>100	>100	–	7.5
40	NH-*o*-$(CO_2H)C_6H_4$	2.5	4	0.63	NT
41	3-(5,5-di-Me)isoxazolinyl	0.07	0.2	0.35	NT
43	2-thienyl	0.2	0.07	2.85	9
48	4-(2-guanidino)thiazolyl	15	9	1.67	NT
49	6-imidazo[2.1-*b*]thiazolyl	0.075	0.015	5.00	10
52	3-methylene-*γ*-butyrolactonyl	0.045	0.0035	12.86	4
53	5-methylene-2-imino-4-thiazolidinonyl	5	3	1.60	NT
56	CO-2-thienyl	0.045	0.038	1.15	10
58	CO-2-(N-Me)pyrrole	0.035	0.045	0.77	NT
61	(*E*)-CH=CH-2-thienyl	0.02	0.035	0.57	6
1	tebufelone	0.25	0.10	2.5	3
benchmarks					
Ibuprofen		3	30	0.1	
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.

4.25 (s, 2 H), 6.00, (br s, 1 H), 7.40 (d, J = 1.5 Hz, 1 H), 7.50 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 167.8, 159.9, 137.4, 132.9, 127.2, 124.1, 119.1, 84.3, 41.2, 34.8, 34.1, 29.1, 27.4, 15.0; IR 3256, 3081, 2961, 2870, 1631 cm^{-1}; MS 276 m/z (MH^+). Anal. ($C_{17}H_{25}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (7). Method A was used with ammonium hydroxide, and the resulting compound **7** was recrystallized from 3:5 EtOAc/hexanes: ^{1}H NMR δ 7.58 (d, J = 2.1 Hz, 1 H), 7.50 (d, J = 2.1 Hz, 1 H), 5.95 (br s, 2 H), 4.32 (s, 2 H), 1.39 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR δ 168.0, 159.1, 137.0, 131.5, 126.6, 124.9, 120.0, 83.9, 40.7, 33.8, 29.0, 27.1; MS m/z 248 (MH^+), 232; IR 3346, 3195, 2959, 1656 cm^{-1}. Anal. ($C_{15}H_{21}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-propyl-5-benzofurancarboxamide (9). Method A was used with propylamine, and the resulting compound **9** was recrystallized from 8:1 EtOH/H_2O: ^{1}H NMR δ 0.94 (t, J = 7.7 Hz, 3 H), 1.35 (s, 6 H), 1.39 (s, 9 H), 1.65 (sextet, J = 7.7 Hz, 2 H), 3.40 (m, 2 H), 4.25 (s, 2 H), 6.10 (br s, 1 H), 7.40, (d, J = 2.0 Hz, 1 H), 7.50 (d, J = 2.0 Hz, 1 H); ^{13}C NMR δ 167.8, 159.9, 137.4, 132.9, 127.2, 124.1, 119.1, 84.3, 41.6, 41.2, 34.1, 29.0, 27.4, 23.0, 11.4; IR 3266, 3085, 2960, 2870, 1630, 1550 cm^{-1}; MS 290 m/z (MH^+). Anal. ($C_{18}H_{27}NO_2$) C, H, N.

***N*-Butyl-7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (10).** Method A was used with butylamine, and the resulting compound **10** was triturated with hot hexanes: ^{1}H NMR δ 0.95 (t, J = 6.8 Hz, 3 H), 1.35 (s, 6 H), 1.38 (s, 9 H), 1.38−1.45 (m, 2 H), 1.60 (m, 2 H), 3.43 (q, J = 6.8 Hz, 2 H), 4.28 (s, 2 H), 6.15 (br s, 1 H), 7.40 (d, J = 1.5 Hz, 1 H), 7.53 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 167.9, 159.9, 137.4, 133.0, 127.3, 124.3, 119.2, 84.4, 41.3, 39.8, 34.2, 32.0, 29.2, 27.5, 20.2, 13.8; IR 3306, 2958, 1633, 1606, 1548 cm^{-1}; MS m/z 304 (MH^+). Anal. ($C_{19}H_{29}O_2N$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-pentyl-5-benzofurancarboxamide (11). Method A was used with pentylamine, and the resulting compound **11** was triturated with hot hexanes: ^{1}H NMR δ 0.91 (t, J = 6.8 Hz, 3 H), 1.35 (s, 6 H), 1.38 (s, 9 H), 1.38−1.45 (m, 4 H), 1.60 (m, 2 H), 3.45 (q, J = 6.8 Hz, 2 H), 4.28 (s, 2 H), 6.15 (br s, 1 H), 7.40 (d, J = 1.5 Hz, 1 H), 7.54 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 167.9, 160.0, 137.5, 133.0, 127.3, 124.3, 119.2, 84.4, 41.3, 40.1, 34.2, 29.6, 29.2 (2), 27.5, 22.4, 14.0; IR 3279, 2956, 1628, 1547 cm^{-1}; MS m/z 318 (MH^+). Anal. ($C_{20}H_{31}O_2N$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-isopropyl-5-benzofurancarboxamide (12). Method A was used with isopropylamine, and the resulting compound **12** was recrystallized from EtOAc: ^{1}H NMR δ 1.27 (d, J = 6.4 Hz, 6 H), 1.33 (s, 6 H), 1.37 (s, 9 H), 4.28 (s, 2 H), 4.30 (m, 1 H), 6.03 (d, J = 7.5 Hz, 1 H), 7.40 (d, J = 2.0 Hz, 1 H), 7.53 (d, J = 2.0 Hz, 1 H); ^{13}C NMR δ 23.1, 27.7, 29.4, 34.4, 41.5, 42.0, 84.6, 119.3, 124.6, 127.6, 133.2, 137.6, 160.1, 167.3; IR 3250, 2954, 1628 cm^{-1}; MS m/z 290 (MH^+). Anal. ($C_{18}H_{27}NO_2$) C, H, N.

7-*tert*-Butyl-*N*-cyclopropyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (13). Method A was used with cyclopropylamine, and the resulting compound **13** was recrystallized from EtOAc: ^{1}H NMR δ 0.62 (m, 2 H), 0.83 (m, 2 H), 1.32 (s, 6 H), 1.38 (s, 9 H), 2.87 (m, 1 H), 4.26 (s, 2 H), 6.39 (br s, 1 H), 7.38 (d, J = 1.8 Hz, 1 H), 7.50 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 6.8, 23.2, 27.5, 29.2, 34.2, 41.3, 84.5, 119.3, 124.4, 126.9, 133.0, 137.5, 160.1, 169.3; IR 3243, 2949, 1630, 1522 cm^{-1}; MS m/z 288 (MH^+). Anal. ($C_{18}H_{25}NO_2$) C, H, N.

7-*tert*-Butyl-*N*-cyclopropylmethyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (14). Method A was used with aminomethylcyclopropane, and the resulting compound **14** was recrystallized from EtOAc: ^{1}H NMR δ 0.27 (m, 2 H), 0.53 (m, 2 H), 1.05 (m, 1 H), 1.33 (s, 6 H), 1.36 (s, 9 H), 3.30 (dd, J = 5.7, 5.6 Hz, 2 H), 4.27 (s, 2 H), 6.20 (br s, 1 H),

7.42 (d, J = 1.7 Hz, 1 H), 7.53 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 3.5, 10.9, 27.5, 29.2, 34.2, 41.3, 44.9, 84.4, 119.3, 124.4, 127.2, 133.0, 137.5, 160.0, 167.9; IR 3267, 2956, 1628 cm^{-1}; MS m/z 302 (MH$^+$). Anal. ($C_{19}H_{27}NO_2$) C, H, N.

7-*tert*-Butyl-*N*-(2-cyclopropylethyl)-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (15). Step 1. 2-Cyclopropylethylamine. Concentrated sulfuric acid (1.09 mL, 20.0 mmol) was added dropwise to a vigorously stirred solution of lithium aluminum hydride (1.53 g, 40.0 mmol) in 40 mL of ether at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h, and a solution of cyclopropylacetonitrile (1.06 g, 13.0 mmol, Lancaster) in 5 mL of ether was added dropwise. The resulting mixture was heated at reflux for 2 h, cooled to 0 °C, and slowly quenched with water. A solution of sodium hydroxide (2 g) in 18 mL of water was added, and the organic phase was decanted from the resulting aluminum hydroxide precipitate which was rinsed with three 20-mL portions of ether. All ethereal portions were combined, and the solvent was distilled off to leave 1.10 g (99%) of 2-cyclopropylethylamine as a colorless liquid: ^{1}H NMR δ 2.77 (t, J = 6.9 Hz, 2 H), 1.34 (q, J = 6.9 Hz, 2 H), 0.67 (m, 1 H), 0.42 (m, 2 H), 0.04 (m, 2 H).

Step 2. 7-*tert*-Butyl-*N*-(2-cyclopropylethyl)-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (15). Method A was used with 2-cyclopropylethylamine, and the resulting compound **15** was chromatographed with 10 → 20% EtOAc/hexanes: ^{1}H NMR δ 7.49 (d, J = 1.8 Hz, 1 H), 7.40 (d, J = 1.8 Hz, 1 H), 6.16 (br s,1 H), 4.26 (s, 2 H), 3.53 (q, J = 7.4 Hz, 2 H), 1.52 (q, J = 7.4 Hz, 2 H), 1.35 (s, 9 H), 1.32 (s, 6 H), 0.74 (m, 1 H), 0.50 (m, 2 H), 0.12 (m, 2 H); ^{13}C NMR δ 167.7, 160.0, 137.4, 132.8, 127.2, 124.0, 119.2, 84.3, 41.2, 40.2, 34.4, 34.1, 29.0, 27.4, 8.63, 4.08; IR 3266, 3079, 2956, 2869, 1630 cm^{-1}; MS m/z 316 (MH$^+$). Anal. ($C_{20}H_{29}NO_2$) C, H, N.

7-*tert*-Butyl-*N*-cyclobutyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (16). Method A was used with cyclobutylamine, and the resulting compound **16** was recrystallized from EtOAc: ^{1}H NMR δ 1.33 (s, 6 H), 1.35 (s, 9 H), 1.75 (m, 2 H), 1.96 (m, 2 H), 2.42 (m, 2 H), 4.27 (s, 2 H), 4.59 (m, 1 H), 5.99 (br s, 1 H), 7.39 (d, J = 1.5 Hz, 1 H), 7.50 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 15.2, 27.5, 29.2, 31.4, 34.2, 41.3, 45.3, 84.5, 119.3, 124.5, 126.9, 133.1, 137.5, 160.1, 167.1; IR 3243, 2955, 1627 cm^{-1}; MS m/z 302 (MH$^+$). Anal. ($C_{19}H_{27}NO_2$) C, H, N.

7-*tert*-Butyl-*N*-cyclopentyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (17). Method A was used with cyclopentylamine, and the resulting compound **17** was recrystallized from EtOAc: ^{1}H NMR δ 1.33 (s, 6 H), 1.36 (s, 9 H), 1.50 (m, 2 H), 1.70 (m, 4 H), 2.10 (m, 2 H), 4.27 (s, 2 H), 4.37 (m, 1 H), 5.99 (br s, 1 H), 7.36 (d, J = 1.8 Hz, 1 H), 7.49 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 23.8, 27.4, 29.0, 33.1, 34.1, 41.2, 51.5, 84.3, 119.0, 124.2, 127.3, 132.9, 137.3, 160.1, 167.3; IR 3265, 2954, 1624 cm^{-1}; MS m/z 316 (MH$^+$). Anal. ($C_{20}H_{29}NO_2$) C, H, N.,

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-phenyl-5-benzofurancarboxamide (18). Method A was used with aniline, and the resulting compound **18** was recrystallized from EtOAc: ^{1}H NMR δ 1.35 (s, 6 H), 1.38 (s, 9 H), 4.30 (s, 2 H), 7.12 (t, J = 7.4 Hz, 1 H), 7.35 (t, J = 8.4 Hz, 2 H), 7.66−7.56 (m, 3 H), 7.85 (s, 1 H); ^{13}C NMR δ 27.5, 29.0, 34.2, 41.2, 84.5, 119.4, 120.1, 124.1, 124.6, 127.2, 128.9, 133.2, 137.7, 138.2, 160.1, 166.1; IR 3278, 2959, 1645 cm^{-1}; MS m/z 324 (MH$^+$). Anal. ($C_{21}H_{25}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-(2-hydroxyethyl)-5-benzofurancarboxamide (19). Method A was used with ethanolamine, and the resulting compound **19** was chromatographed with 3:2 EtOAc/hexanes: ^{1}H NMR δ 7.53 (d, J = 1.8 Hz, 1 H), 7.42 (d, J = 1.8 Hz, 1 H), 6.58 (s, 1 H), 4.32 (s, 2 H), 3.84 (t, J = 6.9 Hz, 2 H), 3.65 (q, J = 6.9 Hz, 2 H), 1.38 (s, 9 H), 1.33 (s, 6 H); ^{13}C NMR δ 169.2, 160.2, 137.5, 132.0, 126.2, 124.5, 119.3, 84.4, 62.6, 43.0, 41.1, 34.1, 29.0, 27.4; MS m/z 292 (MH$^+$), 215, 140; IR 3410, 3275, 2958, 1610 cm^{-1}. Anal. ($C_{17}H_{25}NO_3$) C, H, N.,

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-(2-methoxyethyl)-5-benzofurancarboxamide (20). Method A was used with 2-methoxyethylamine, and the resulting compound **20** was chromatographed with 1:6 and then with 2:3 EtOAc/hexanes: ^{1}H NMR δ 7.54 (d, J = 1.8 Hz, 1 H), 7.41 (d, J = 1.8 Hz, 1 H), 6.48 (br, 1 H), 4.28 (s, 2 H), 3.64 (dt, J = 4.9 Hz, 2 H), 3.56 (t, J = 4.9 Hz, 2 H), 3.39 (s, 3 H), 1.36 (s, 9 H), 1.33 (s, 6 H); ^{13}C NMR δ 167.9, 160.1, 137.5, 133.0, 126.9, 124.5, 119.3, 84.4, 71.5, 58.8, 41.3, 39.7, 34.2, 29.2, 27.5; IR 3271, 2955, 1630, 1548 cm^{-1}; MS m/z 306 (MH$^+$). Anal. ($C_{18}H_{27}NO_3$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-*N*-(2,3-dihydroxypropyl)-3,3-dimethyl-5-benzofurancarboxamide (21). Method A was used with 2,3-dihydroxypropylamine, and the resulting compound **21** was chromatographed without workup with EtOAc and then with 10:1 EtOAc/MeOH, followed by recrystallization from EtOAc: ^{1}H NMR (CD_3OD) δ 7.65 (d, J = 1.9 Hz, 1 H), 7.54 (d, J = 1.9 Hz, 1 H), 4.90 (s, 2 H), 4.30 (s, 1 H), 3.83 (m, 1 H), 3.58−3.38 (m, 4 H), 1.36 (s, 9 H), 1.34 (s, 6 H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 170.1, 160.8, 137.9, 133.4, 126.1, 125.3, 119.8, 84.8, 71.4, 63.8, 42.8, 41.5, 34.5, 29.4, 27.7; IR 3442, 3324, 2959, 1649, 1545 cm^{-1}; MS m/z 322 (MH$^+$), 248. Anal. ($C_{18}H_{27}NO_4$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-(2-dimethylaminoethyl)-5-benzofurancarboxamide (22). Method A was used with *N*,*N*-dimethyethylenediamine, and the resulting compound **22** was chromatographed with 10:1 CH_2Cl_2/MeOH: ^{1}H NMR δ 7.53 (d, J = 1.9 Hz, 1 H), 7.41 (d, J = 1.9 Hz, 1 H), 6.66 (br, 1 H), 4.27 (s, 2 H), 3.54 (q, J = 5.8 Hz, 2 H), 2.54 (t, J = 6.0 Hz, 2 H), 2.28 (s, 6 H), 1.37 (s, 9 H), 1.34 (s, 6 H); ^{13}C NMR δ 168.0, 160.0, 137.4, 132.9, 127.2, 124.5, 119.3, 84.4, 58.1, 45.3, 41.3, 37.3, 34.2, 29.1, 27.5; IR 3297, 2961, 1630, 1547 cm^{-1}; MS m/z 319 (MH$^+$). Anal. ($C_{19}H_{30}N_2O_2$) C, H, N.

***N*-(2-Aminothiazolyl)-7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (23).** Method A was used with 2-aminothiazole, and the resulting compound **23** was chromatographed with 1:7 EtOAc/hexanes and then washed with hot hexane: ^{1}H NMR δ 12.6 (br, 1 H), 7.81 (d, J = 1.8 Hz, 1 H), 7.68 (d, J = 1.8 Hz, 1 H), 7.09 (d, J = 3.6 Hz, 1 H), 6.91 (d, J = 3.6 Hz, 1 H), 4.34 (s, 2 H), 1.34 (s, 15 H); ^{13}C NMR δ 166.1, 161.4, 160.7, 137.9, 137.2, 133.5, 126.2, 124.8, 120.6, 113.2, 84.7, 41.3, 34.3, 29.0, 27.6; IR 3235, 2961, 1640, 1547 cm^{-1}; MS m/z 331 (MH$^+$), 231. Anal. ($C_{18}H_{22}N_2O_2S$) C, H, N, S.

***N*-(2-Amino-2-thiazolinyl)-7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (24).** Method A was used with 2-aminothiazoline, and the resulting compound **24** was chromatographed with 2:3 EtOAc/hexanes and then triturated with hot ether: ^{1}H NMR δ 7.93 (d, J = 1.8 Hz, 1 H), 7.77 (d, J = 1.8 Hz, 1 H), 4.28 (s, 2 H), 3.68 (t, J = 7.6 Hz, 2 H), 3.22 (t, J = 7.6 Hz, 2 H), 1.35 (s, 9 H), 1.32 (s, 6 H); ^{13}C NMR δ 174.1, 173.1, 161.1, 137.3, 132.7, 128.0, 127.2, 121.6, 84.6, 47.4, 41.2, 34.2, 30.0, 29.2, 27.6; IR 3356, 2959, 1620, 1599 cm^{-1}; MS m/z 333 (MH$^+$) 247. Anal. ($C_{18}H_{24}N_2O_2S$) C, H, N, S.

7-*tert*-Butyl-2,3-dihydro-*N*,*N*-dimethyl-3,3-dimethyl-5-benzofurancarboxamide (25). Method A was used with dimethylamine, and the resulting compound **25** was chromatographed with 1:1 EtOAc/hexanes: ^{1}H NMR (CD_3OD) δ 7.17 (d, J = 1.8 Hz, 1 H), 7.11 (d, J = 1.8 Hz, 1 H), 4.26 (s, 2 H), 3.04 (s, 6 H), 1.34 (s, 9 H), 1.31 (s, 6 H); ^{13}C NMR (CD_3OD) δ 174.5, 160.0, 138.8, 134.1, 129.1, 125.9, 121.0, 85.4, 42.5, 40.5, 30.2, 29.8, 27.9; IR 2957, 1629, 1496 cm^{-1}; MS m/z 276 (MH$^+$), 275, 231. Anal. ($C_{17}H_{25}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-ethyl-*N*-methyl-5-benzofurancarboxamide (26). Method A was used with ethylmethylamine, and the resulting compound **26** was recrystallized from hexane: ^{1}H NMR δ 7.13 (d, J = 1.8 Hz, 1 H), 7.03 (d, J = 1.8 Hz, 1 H), 4.24 (s, 2 H), 3.42 (br s, 2 H), 3.01 (s, 3 H), 1.45 (s, 9 H) 1.41 (s, 6 H), 1.18 (t, J = 8.6 Hz, 3 H); ^{13}C NMR δ 172.2, 157.9, 136.7, 132.4, 128.4, 123.9, 118.9, 83.8, 45.8, 42.4, 41.1, 33.9, 29.3, 27.3, 13.4; IR 2964, 1620 cm^{-1}; MS m/z 290 (MH$^+$), 231. Anal. ($C_{18}H_{27}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-*N*-methyl-*N*-propyl-5-benzofurancarboxamide (27). Method A was used with methylpropylamine, and the resulting compound **27** was

chromatographed with 1:1 EtOAc/hexanes: ^{1}H NMR δ 7.12 (d, J = 1.8 Hz, 1 H), 7.02 (d, J = 1.8 Hz, 1 H), 4.24 (s, 2 H), 3.37 (br s, 2 H), 3.01 (s, 3 H), 1.65 (m, 2 H), 1.38 (s, 9 H), 1.31 (s, 6 H), 0.88 (br s, 3 H); ^{13}C NMR δ 174.1, 158.0, 136.8, 132.6, 128.5, 124.1, 119.1, 83.9, 51.3, 49.1, 41.2, 34.0, 29.1, 27.4, 21.0, 10.9; MS m/z 304 (MH^+), 303, 231; IR 2958, 1628, 1465 cm^{-1}. Anal. ($C_{19}H_{29}NO_2$) C, H, N.

7-*tert*-Butyl-*N*-cyclopropyl-*N*-methyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (28). Method B. To a stirring solution of cyclopropyl amide **13** (2.0 g, 6.97 mmol) in 25 mL of benzene at room temperature were added powdered K_2CO_3 (1.0 g, 7.0 mmol), powdered NaOH (1.1 g, 27.9 mmol), and tetrabutylammonium bisulfate (0.1 g, 0.3 mmol). The resulting mixture was stirred for 1 h at room temperature. To this stirring solution was added methyl iodide (0.5 mL, 7.7 mmol), and the reaction was then heated to reflux. The reaction was monitored by TLC for the absence of starting material. Upon completion, the reaction was diluted with 100 mL of ethyl ether and washed with water. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. Purification by silica gel flash chromatography with 1:3 EtOAc/hexanes gave 1.2 g (57%) of **28**, mp 70−72 °C: ^{1}H NMR δ 7.23 (d, J = 1.8 Hz, 1 H), 7.09 (d, J = 1.8 Hz, 1 H), 4.20 (s, 2 H), 2.98 (s, 3 H), 2.79 (m, 1 H), 1.37 (s, 9 H), 1.35 (s, 6 H), 0.58 (d, J = 8.0 Hz, 2 H), 0.40 (br s, 2 H); ^{13}C NMR δ 173.0, 158.3, 136.5, 132.2, 129.0, 125.2, 119.9, 84.1, 41.2, 35.5, 34.1, 33.0, 29.6, 29.2, 8.9; MS m/z 302 (MH^+), 262, 231; IR 2958, 1623 cm^{-1}. Anal. ($C_{19}H_{27}NO_2\cdot 0.5H_2O$) C, H, N.

7-*tert*-Butyl-*N*-cyclopropyl-*N*-ethyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (29). Method B was used with ethyl iodide. Additional ethyl iodide was used to drive the reaction to completion. Compound **29** was chromatographed with 1:3 EtOAc/hexanes, followed by recrystallization from hexanes: ^{1}H NMR δ 7.25 (d, J = 1.7 Hz, 1 H), 7.12 (d, J = 1.7 Hz, 1 H), 4.25 (s, 2 H), 3.56 (q, J = 7.2 Hz, 2 H), 2.77 (m, 1 H), 1.34 (s, 9 H), 1.31 (s, 6 H), 1.25 (t, J = 7.2 Hz, 3 H), 0.67 (m, 2 H), 0.50 (m, 2 H); ^{13}C NMR δ 173.0, 158.3, 136.6, 132.3, 129.4, 125.0, 119.8, 84.1, 42.7, 41.3, 34.2, 30.7, 29.3, 27.6, 13.6, 9.4; IR 3202, 2959, 1618 cm^{-1}; MS m/z 316 (MH^+). Anal. ($C_{20}H_{29}NO_2$) C, H, N.

7-*tert*-Butyl-*N*-cyclopropyl-*N*-*n*-propyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide (30). Method B was used with propyl iodide. Additional propyl iodide was used to drive the reaction to completion. Compound **30** was recrystallized from hexane, followed by chromatography of the mother liquors with 1:3 EtOAc/hexanes: ^{1}H NMR δ 7.25 (d, J = 1.7 Hz, 1 H), 7.12 (d, J = 1.7 Hz, 1 H), 4.24 (s, 2 H), 3.45 (t, J = 7.4 Hz, 2 H), 2.73 (m, 1 H), 1.71 (m, 2 H), 1.34 (s, 9 H), 1.31 (s, 6 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.65 (m, 2 H), 0.48 (m, 2 H); ^{13}C NMR δ 173.3, 158.3, 136.6, 132.3, 129.4, 125.1, 119.8, 84.1, 49.4, 41.3, 34.1, 31.1, 29.3, 27.6, 21.3, 11.5, 9.6; IR 3204, 2959, 1620 cm^{-1}; MS m/z 330 (MH^+). Anal. ($C_{21}H_{31}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethylpyrrolidinyl-5-benzofurancarboxamide (31). Method A was used with pyrrolidine, and the resulting compound **31** was chromatographed in 3:2 EtOAc/hexanes: ^{1}H NMR δ 7.28 (d, J = 1.8 Hz, 1 H), 7.18 (d, J = 1.8 Hz, 1 H), 4.24 (s, 2 H), 3.56 (br s, 4 H), 1.90 (br s, 4 H), 1.34 (s, 9 H), 1.31 (s, 6 H); ^{13}C NMR δ 170.3, 159.7, 136.7, 132.3, 129.0, 124.7, 119.6, 84.0, 48.2, 41.2, 34.1, 29.1, 27.4, 26.1; MS m/z 302 (MH^+), 301, 231; IR 2956, 2871, 1616 cm^{-1}. Anal. ($C_{19}H_{27}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethylpiperidinyl-5-benzofurancarboxamide (32). Method A was used with piperidine, and the resulting compound **32** was chromatographed in 3:2 EtOAc/hexanes: ^{1}H NMR δ 7.05 (d, J = 1.8 Hz, 1 H), 6.95 (d, J = 1.8 Hz, 1 H), 4.15 (s, 2 H), 3.43 (br s, 4 H), 1.58 (br s, 4 H), 1.51 (br s, 2 H), 1.29 (s, 9 H), 1.26 (s, 6 H); ^{13}C NMR δ 171.0, 159.2, 136.9, 132.5, 128.1, 124.3, 119.3, 83.9, 48.1, 41.2, 34.0, 29.1, 27.4, 26.0, 24.5; MS m/z 316 (MH^+), 231, 112; IR 2950, 2860, 1627 cm^{-1}. Anal. ($C_{20}H_{29}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethylthiomorpholinyl-5-benzofurancarboxamide (33). Method A was used with thiomorpholine, and the resulting compound **33** was chromatographed in 1:6 and then in 1:3 EtOAc/hexanes: ^{1}H NMR δ 7.10 (d, J = 1.8 Hz, 1 H), 7.02 (d, J = 1.8 Hz, 1 H), 4.25 (s, 2 H), 3.87 (br m, 4 H), 2.66 (br m, 4 H), 1.33 (s, 9 H), 1.31 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.7, 157.6, 136.4, 132.0, 126.5, 123.4, 118.5, 83.2, 45.3 (br), 40.3, 33.2, 28.2, 26.5, 25.6; IR 2959, 1630 cm^{-1}; MS m/z 334 (MH^+), 231. Anal. ($C_{19}H_{27}NO_2S$) C, H, N, S.

7-*tert*-Butyl-2,3-dihydro-*N*,*N*-dimethyl-3,3-dimethyl-5-benzofurancarboximidamide Hydrochloride (34). To a solution of the 5-bromo dihydrobenzofuran compound **I** (500 mg, 1.8 mmol) in Et_2O (0.6 mL) and hexanes (5.5 mL) at −78 °C was added *t*-BuLi (1.5 M in hexanes, 3.3 mL, 5.3 mmol, 2.9 equiv) at such a rate that the reaction temperature did not exceed −60 °C. This solution was stirred for 1 h and then was slowly cannulated into a −78 °C solution of dimethylcyanamide (0.15 mL, 1.8 mmol, 1.0 equiv) in Et_2O (5 mL). The reaction was kept at −78 °C for 0.5 h and then was allowed to warm to 0 °C. After 1.5 h, TLC (10% MeOH in $CHCl_3$) indicated the reaction to be complete. The reaction was quenched with H_2O (10 mL) and 1 N HCl (10 mL) and then extracted with Et_2O. The aqueous layer was brought to pH 9 with 1 N NaOH and extracted with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and evaporated to a yellow oil (410 mg). This oil was purified by preparative TLC (15% MeOH in $CHCl_3$) to give a yellow oil, which was stirred in EtOH (5 mL) and 1 N HCl (10 mL) for 5 min. The EtOH was evaporated, and the resulting solution was extracted with CH_2Cl_2. The dried organic layers were evaporated to a yellow oil, which was triturated with Et_2O to give 110 mg (20%) of **34** as a white powder, mp >160 °C dec: ^{1}H NMR δ 1.34 (s, 9 H), 1.33 (s, 6 H), 3.10 (s, 6 H), 4.27 (s, 2 H), 7.05 (d, J = 1.8 Hz, 1 H), 7.11 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 27.5, 29.2, 34.3, 40.1, 41.4, 84.3, 119.9, 125.0, 126.5, 133.5, 137.7, 158.0, 169.1; IR 2958, 1576 cm^{-1}; MS m/z 275 (MH^+). Anal. ($C_{17}H_{26}N_2O\cdot 1.75HCl$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(imino-1-pyrrolidinylmethyl)benzofuran Hydrochloride (35). Step 1. 7-*tert*-Butyl-5-cyano-2,3-dihydro-3,3-dimethylbenzofuran (II). A solution of 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (16.75 g, 82 mmol) in CH_2Cl_2 (175 mL) was heated to reflux, and chlorosulfonylisocyanate (25.4 mL, 287 mmol, 3.5 equiv) was added in a single portion. The reaction was judged to be complete by TLC (5% EtOAc/hexanes) after 2 h. The reaction mixture was then cooled to 0 °C, and DMF (65 mL, 0.82 mol, 10 equiv) was added. The solution was allowed to stir at ambient temperature for 1.5 h. The solvents were evaporated, and the resulting oil was partitioned between hexanes and H_2O. The aqueous phase was discarded, and the hexanes were dried ($MgSO_4$) and evaporated to a yellow oil which solidified upon sitting (18.2 g). This solid was purified by medium-pressure chromatography (5% EtOAc/hexanes) to give 8.58 g (46%) of **II** as a yellow oil of sufficient purity (∼85% by ^{1}H NMR) for the next reaction: ^{1}H NMR δ 1.35 (s, 15 H), 4.28 (s, 2 H), 7.25 (d, J = 1.0 Hz, 1 H), 7.39 (d, J = 1.0 Hz, 1 H).

Step 2. Ethyl 7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzofuran-5-carboximidic Acid Hydrochloride (III). Into a solution of **II** (4.90 g, 18.6 mmol) in Et_2O (30 mL) and EtOH (3.2 mL, 55.8 mmol, 3 equiv) was bubbled HCl gas for 10 min. The red solution was stirred at 23 °C for 4 days. (Using higher reaction temperatures to speed the reaction reduced the yield.) The solvents were evaporated, and the resulting red oil was triturated with hexanes (30 mL) to produce a red solid which was collected by filtration to give 3.55 g (62%) of **III** as a red powder of sufficient purity for the next reaction: ^{1}H NMR δ 1.6 (t, J = 6.8 Hz, 3 H) 1.39 (s, 15 H), 4.41 (s, 2 H), 4.65 (q, J = 6.8 Hz, 2 H), 4.95 (br s, 2 H), 7.85 (s, 2 H).

Step 3. 7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(imino-1-pyrrolidinylmethyl)benzofuran Hydrochloride (35). To a solution of **III** (400 mg, 1.29 mmol) in dioxane (10 mL) was added excess pyrrolidine (0.6 mL). A color change from red to yellow was observed during the addition, and a precipitate

formed. The reaction was also monitored by TLC (10% MeOH/$CHCl_3$). After 3 h, the yellow precipitate was collected by filtration and purified by preparative TLC (10% MeOH/$CHCl_3$) to give 210 mg (54%) of **35** as a white powder, mp 255−256 °C: ^{1}H NMR (CD_3OD) δ 1.39 (s, 9 H) 1.38 (s, 6 H), 1.95 (quintet, J = 7.3 Hz, 2 H), 2.15 (quintet, J = 7.3 Hz, 2 H), 3.55 (t, J = 7.3 Hz, 2 H), 3.60 (t, J = 7.3 Hz, 2 H), 4.35 (s, 2 H), 7.25 (s, 2 H); ^{13}C NMR (CD_3OD) δ 26.0, 26.7, 27.7, 29.5, 35.4, 42.6, 50.0, 53.5, 85.8, 121.7, 123.3, 126.5, 135.1, 140.0, 161.8, 165.0; IR 3418, 2958, 1656, 1607 cm^{-1}; MS *m*/*z* 301 (MH^+). Anal. ($C_{19}H_{28}N_2O$·1.7HCl) C, H, N.

***N*-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)ethanamide (36). Step 1. 7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-nitrobenzofuran.** To a solution of 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (10.0 g, 49.0 mmol) in glacial acetic acid (80 mL) was added dropwise 70% HNO_3 (4.0 mL, 5.7 g, 63.7 mmol). The reaction mixture darkened to a deep green color over the course of the addition. The reaction was monitored by TLC (2% EtOAc/hexanes) and was allowed to stir at 22 °C for 4 h. Then the reaction mixture was partitioned between Et_2O and H_2O. The ethereal layer was washed with saturated aqueous Na_2CO_3, dried ($MgSO_4$), filtered, and evaporated to a red solid (9.12 g). Crystallization from hexane provided the title compound as orange prisms (2.26 g, 18.5%), mp 93−94 °C. A second crop yielded slightly less pure material (4.93 g, 40.3%) which was used without further purification: ^{1}H NMR δ 1.38 (s, 15 H), 4.40 (s, 2 H), 7.91 (d, J = 1.5 Hz, 1 H), 8.12 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 163.5, 142.2, 138.4, 133.8, 122.4, 116.8, 85.4, 41.2, 34.4, 28.9, 27.6. Anal. ($C_{14}H_{19}NO_3$) C, H, N.

Step 2. 5-Amino-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (V). A suspension of 7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-nitrobenzofuran (2.2 g, 8.8 mmol) in absolute EtOH (60 mL) was hydrogenated over 10% palladium on charcoal at 40 psi of H_2 pressure on a Parr hydrogenation apparatus for 3 h at 22 °C. The reaction was judged to be complete by TLC (hexanes/EtOAc, 19:1; visualized with Dragendorff reagent). The reaction mixture was filtered through Celite and evaporated to yield 1.7 g (88%) of **V** as a purple solid which was used without further purification: ^{1}H NMR δ 1.28 (s, 6 H), 1.33 (s, 9 H), 3.32 (br s, 2 H), 4.13 (s, 2 H), 6.32 (d, J = 1.5 Hz, 1 H), 6.45 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 27.1, 29.3, 34.0, 41.7, 83.5, 107.5, 112.4, 133.3, 137.8, 139.5, 150.5; MS *m*/*z* 220 (MH^+).

Step 3. *N*-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)ethanamide (36). To a solution of **V** (800 mg, 3.68 mmol) and DMAP (494 mg, 4.05 mmol) in CH_2Cl_2 (40 mL) was added acetyl chloride (0.26 mL, 3.68 mmol). The reaction was monitored by TLC and was judged to be complete after 1 h. The reaction mixture was diluted with Et_2O, and the precipitated solids were filtered and discarded. The filtrate was evaporated, and the residue was purified by preparative TLC with 9:1 hexanes/EtOAc to yield 212 mg (22%) of **36** as a white solid, mp 154−155 °C: ^{1}H NMR δ 1.31 (s, 6 H), 1.35 (s, 9 H), 2.14 (s, 3 H), 4.20 (s, 2 H), 6.92 (d, J = 1.5 Hz, 1 H), 7.22 (br s, 1 H), 7.33 (d, J = 1.5 Hz, 1 H); ^{13}C NMR δ 24.2, 27.2, 29.1, 34.0, 41.6, 83.8, 113.3, 117.6, 130.7, 132.5, 136.5, 153.5, 167.5; IR 3313, 2960, 1664, 1619 cm^{-1}; MS *m*/*z* 262 (MH^+). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

***N*-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-*N*′-ethylurea (37). Method C.** Ethylisocyanate (0.18 mL, 2.28 mmol) was added dropwise to a solution of **V** (500 mg, 2.28 mmol) in Et_2O (5 mL). A solid formed after 10 min, and the reaction was quenched with H_2O (10 mL) after 40 min. The reaction was extracted with Et_2O, and the organic layers were dried ($MgSO_4$) and evaporated to a tan solid (657 mg). This solid was recrystallized from EtOAc to give 335 mg (51%) of **37** as white prisms, mp 197−198 °C: ^{1}H NMR δ (1.06 t, J = 7.9 Hz, 3 H), 1.28 (s, 6 H), 1.33 (s, 9 H), 3.23 (br s, 2 H), 4.20 (br s, 2 H), 5.20 (br s, 1 H), 6.91 (br s, 1 H), 6.95 (br s, 1 H), 7.00 (br s, 1 H); ^{13}C NMR δ 15.4, 27.2, 29.1, 34.0, 34.9, 41.5, 83.8, 114.9, 119.7, 131.0, 133.5, 137.7, 154.0, 157.2; IR 3326, 2960, 2869, 1643, 1571 cm^{-1}; MS *m*/*z* 291 (MH^+). Anal. ($C_{17}H_{26}N_2O_2$) C, H, N.

***N*-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-*N*′-propylurea (38).** Method C was followed using propylisocyanate, and the resulting compound **38** was recrystallized from EtOAc: ^{1}H NMR δ 0.89 (t, J = 7.9 Hz, 3 H), 1.27 (s, 6 H), 1.33 (s, 9 H), 1.49 (m, J = 7.8 Hz, 2 H), 3.18 (br s, 2 H), 4.20 (s, 2 H), 5.20 (br s, 1 H), 6.89 (br s, 1 H), 7.00 (br s, 1 H); ^{13}C NMR δ 11.3, 23.4, 27.3, 29.2, 34.1, 41.6, 41.9, 83.9, 115.3, 120.0, 131.0, 133.6, 137.8, 154.0, 156.9; IR 3323, 2960, 2870, 1639, 1562 cm^{-1}; MS *m*/*z* 305 (MH^+). Anal. ($C_{18}H_{28}N_2O_2$) C, H, N.

2-(*N*-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)amino)imidazoline (39). To a solution of **V** (0.3 g, 1.3 mmol) in 10 mL of CH_3CN at room temperature was added of imidazoline-2-sulfonic acid (0.2 g, 1.3 mmol). The reaction was then refluxed overnight. As the solution cooled to room temperature, the pure product precipitated out of solution and was filtered to give 120 mg (32%) of **39**, mp 264 °C dec: ^{1}H NMR (CD_3OD) δ 6.94 (d, J = 1.7 Hz, 1 H), 6.92 (d, J = 1.7 Hz, 1 H), 4.24 (s, 2 H), 3.67 (s, 4 H), 1.24 (s, 9 H), 1.21 (s, 6 H); ^{13}C NMR δ 173.2, 158.3, 137.4, 134.1, 129.7, 125.4, 120.0, 84.9, 41.0, 36.0, 34.5, 29.8, 26.8; MS *m*/*z* 288 (MH^+), 220, 205, 164; IR 3167, 2959, 1664 cm^{-1}. Anal. ($C_{17}H_{25}N_3O$·0.8H_2SO_4) C, H, N.

2-[5-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzofuranyl)amino]benzoic Acid (40). A mixture of **V** (1.05 g, 4.8 mmol), diphenyliodonium-2-carboxylate monohydrate (1.3 g, 4.0 mmol), cupric acetate (0.03 g, 0.2 mmol), and 7 mL of 2-propanol was heated at reflux for 4 h. The dark reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in ether, washed with 1 N NaOH solution and with 1 N HCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (5% MeOH/CH_2Cl_2) afforded 0.90 g (57%) of **40** as a light yellow solid, mp 204−206 °C: ^{1}H NMR δ 8.03 (dd, J = 8.0, 1.5 Hz, 1 H), 7.31 (m, 1 H), 6.97 (m, 2 H), 6.88 (d, J = 1.8 Hz, 1 H), 6.47 (t, J = 8.0 Hz, 1 H), 4.25 (s, 2 H), 1.37 (s, 9 H), 1.34 (s, 6 H); ^{13}C NMR δ 186.6, 173.7, 154.6, 150.9, 138.1, 135.1, 133.9, 132.4, 122.3, 117.1, 115.8, 113.5, 109.0, 83.9, 41.6, 34.1, 29.2, 27.3; IR 3338, 1660, 1605, 1577 cm^{-1}; MS *m*/*z* 340 (MH^+). Anal. ($C_{21}H_{25}NO_3$) C, H, N.

3-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-5,5-dimethylisoxazoline (41). A solution of 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-chloro-3-methylbutan-1-one (500 mg, 1.56 mmol), hydroxylamine hydrochloride (1.87 mmol, 1.2 equiv), EtOH (13 mL), and 2 N NaOH (0.78 mL, 1.56 mmol, 1 equiv) was heated to 50 °C and stirred for 36 h at which time TLC (10% EtOAc/hexanes) showed completion of the reaction. A white precipitate was removed by filtration and discarded. The filtrate was evaporated to a gummy, yellow solid (547 mg). This solid was purified by preparative TLC (10% EtOAc/hexanes) to give 145 mg (31%) of **41** as a white solid, mp 96−98 °C: ^{1}H NMR δ 1.33 (s, 6 H), 1.38 (s, 9 H), 1.50 (s, 6 H), 3.13 (s, 2 H), 4.24 (s, 2 H), 7.30 (d, J = 1.7 Hz, 1 H), 7.36 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 27.2, 27.4, 29.1, 34.1, 41.3, 47.2, 84.2, 84.2, 118.3, 122.6, 123.8, 133.2, 137.0, 156.6, 158.6; IR 2961, 1605, 1457 cm^{-1}; MS *m*/*z* 302 (MH^+). Anal. ($C_{19}H_{27}NO_2$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(2-furanyl)benzofuran (42). Method D. A mixture of **I** (1.13 g, 4.0 mmol), 2-(tributylstannyl)furan (1.71 g, 4.8 mmol, Aldrich), tetrakis(triphenylphosphine)palladium (0.46 g, 0.4 mmol), and 20 mL of toluene was heated under argon at reflux for 30 min. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with ether, washed with 10% NH_4OH and with brine, dried over anhydrous $MgSO_4$, and concentrated to give a dark oil. Purification by flash column chromatography on silica gel (1% EtOAc/hexanes) yielded 0.47 g (43%) of **42** as a light yellow oil: ^{1}H NMR δ 7.55 (d, J = 1.8 Hz, 1 H), 7.48 (dd, J = 1.8, 0.9 Hz, 1 H), 7.37 (d, J = 1.8 Hz, 1 H), 6.58 (dd, J = 3.4, 0.9 Hz, 1 H), 6.47 (dd, J = 3.4, 1.8 Hz, 1 H), 4.30 (s, 2 H), 1.50 (s, 9 H), 1.41 (s, 6 H); ^{13}C NMR δ 156.9, 155.0, 140.9, 137.6, 133.3, 123.9, 121.1, 116.0, 111.4, 102.8, 84.0, 41.4, 34.2, 29.3, 27.4; IR 2958, 2870, 1454 cm^{-1}; MS *m*/*z* 271 (MH^+). Anal. ($C_{18}H_{22}O_2$) C, H.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(2-thienyl)benzofuran (43). Method D was followed using 2-(tributylstannyl)thiophene (Aldrich). Purification by flash column chromatography on silica gel (0.5% EtOAc/hexanes) yielded 0.98 g (43%) of **43** as a colorless oil, which solidified upon standing, mp 61−63 °C: ^{1}H NMR δ 7.35 (d, J = 1.8 Hz, 1 H), 7.19 (m, 3 H), 7.07 (m, 1 H), 4.27 (s, 2 H), 1.43 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR δ 157.0, 145.5, 137.7, 133.3, 127.7, 127.0, 123.3, 123.3, 121.7, 118.0, 84.0, 41.4, 34.1, 29.2, 27.4; IR 3071, 2958, 2871, 1458 cm^{-1}; MS m/z 287 (MH$^+$). Anal. ($C_{18}H_{22}OS$) C, H, S.

4-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)oxazole (44). A mixture of the 5-bromoacetyl compound **VI**[1] (1.30 g, 4.0 mmol) and formamide (2.60 g, 57.8 mmol) was heated to 160 °C for 2 h. The reaction mixture was cooled to room temperature, poured into water, and extracted with ether. The ethereal extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (3% EtOAc/hexanes) to give 0.45 g (41%) of **44** as a white solid, mp 140.5−141.5 °C: ^{1}H NMR δ 7.90 (s, 1 H), 7.85 (s, 1 H), 7.44 (d, J = 1.8 Hz, 1 H), 7.35 (d, J = 1.8 Hz, 1 H), 4.24 (s, 2 H), 1.40 (s, 9 H), 1.33 (s, 6 H); ^{13}C NMR δ 157.3, 150.8, 140.7, 137.6, 133.3, 132.1, 122.9, 122.4, 117.4, 83.9, 41.3, 34.0, 29.1, 27.3; IR 3118, 2956, 1628, 1514 cm^{-1}; MS m/z 272 (MH$^+$). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

4-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzo-5-furanyl)thiazole (45). Step 1. 4-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-(ethoxycarbonyl)thiazole. A mixture of **VI**[1] (3.58 g, 11.0 mmol), ethyl thiooxamate (1.60 g, 12.0 mmol), and 60 mL of ethanol was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The solid residue was dissolved in CH_2Cl_2 and was washed with aqueous $NaHCO_3$ solution and with water, dried over $MgSO_4$, and concentrated in vacuo to yield 4.56 g of the crude product. Purification by flash column chromatography on silica gel (8% EtOAc/hexanes) gave 3.52 g (89%) of the title compound as a colorless solid, mp 125−126 °C: ^{1}H NMR δ 7.61 (d, J = 1.8 Hz, 1 H), 7.58 (m, 2 H), 4.48 (q, J = 7.0 Hz, 2 H), 4.24 (s, 2 H), 1.29 (t, J = 7.0 Hz, 3 H), 1.39 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 160.4, 159.0, 157.9, 157.3, 137.7, 133.2, 126.2, 123.5, 118.9, 116.5, 84.1, 62.4, 41.4, 34.1, 29.2, 27.4, 14.2; IR 3077, 2956, 1714, 1470 cm^{-1}; MS m/z 360 (MH$^+$).

Step 2. 4-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)thiazole (45). A mixture of 4-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-(ethoxycarbonyl)thiazole (2.80 g, 7.8 mmol), NaOH (0.6 g, 15.0 mmol), and 30 mL of ethanol was heated at reflux for 0.5 h. The reaction mixture was cooled to room temperature and concentrated to give 2.16 g of the crude product. Purification by flash column chromatography on silica gel (10% EtOAc/hexanes) afforded 0.80 g (36%) of **45** as a light yellow solid, mp 100−101 °C: ^{1}H NMR δ 8.86 (d, J = 1.9 Hz, 1 H), 7.64 (d, J = 1.9 Hz, 1 H), 7.56 (d, J = 1.8 Hz, 1 H), 7.38 (d, J = 1.8 Hz, 1 H), 4.27 (s, 2 H), 1.41 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR δ 157.5, 157.0, 152.5, 137.7, 133.4, 127.0, 123.5, 118.5, 110.2, 84.1, 41.5, 34.2, 29.3, 27.5; IR 3449, 3081, 2959, 1610, 1457 cm^{-1}; MS m/z 288 (MH$^+$). Anal. ($C_{17}H_{21}NOS$) C, H, N, S.

3-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-5-methyl-1,2,4-oxadiazole (46). Step 1. 7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofurancarboxamide Oxime (IV). A mixture of **II** (6.39 g, 27.9 mmol), K_2CO_3 (15.80 g, 114.0 mmol), hydroxylamine hydrochloride (7.93 g, 114.0 mmol), and 135 mL of ethanol was heated at reflux for 20 h. The reaction mixture was cooled to room temperature, filtered, and concentrated in vacuo to give a solid residue. Purification by flash column chromatography on silica gel (20% EtOAc/hexanes → 5% MeOH/CH_2Cl_2) furnished 3.13 g (43%) of **IV** as a colorless, foamy solid, mp 109−110 °C: ^{1}H NMR δ 7.36 (d, J = 1.8 Hz, 1 H), 7.26 (d, J = 1.8 Hz, 1 H), 4.88 (br s, 2 H), 4.25 (s, 2 H), 1.37 (s, 9 H), 1.33 (s, 6 H); ^{13}C NMR δ 158.8, 153.5, 137.5, 133.2, 124.8, 123.1, 118.1, 84.2, 41.4, 34.2, 29.2, 27.4; IR 3491, 3386, 2958, 2869, 1641, 1609, 1483 cm^{-1}; MS m/z 263 (MH$^+$). Anal. ($C_{15}H_{22}N_2O_2$) C, H, N.

Step 2. 3-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-5-methyl-1,2,4-oxadiazole (46). To a solution of **IV** (1.05 g, 4.0 mmol) in 20 mL of pyridine was added acetyl chloride (0.43 mL, 6.0 mmol). The reaction mixture was heated at 95 °C for 22 h and cooled to room temperature. The pyridine was removed in vacuo at 50 °C, and the residue was partitioned between water and EtOAc. The organic layer was washed with water and with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 1.33 g of the crude product. Purification by flash column chromatography on silica gel (10% EtOAc/hexanes) produced 0.60 g (52%) of **46** as a white solid, mp 81−82 °C: ^{1}H NMR δ 7.81 (d, J = 1.8 Hz, 1 H), 7.65 (d, J = 1.8 Hz, 1 H), 4.28 (s, 2 H), 2.62 (s, 3 H), 1.38 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 175.8, 168.6, 159.7, 137.8, 133.5, 124.6, 119.4, 118.7, 84.2, 41.2, 34.1, 29.0, 27.3, 12.2; IR 2959, 2871, 1585, 1437 cm^{-1}; MS m/z 287 (MH$^+$). Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

2-Amino-4-(7-*tert*-butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)thiazole (47). A mixture of **VI**[1] (1.03 g, 3.2 mmol), thiourea (0.42 g, 5.4 mmol), and 17 mL of ethanol was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, concentrated in vacuo, and poured into water. The resulting solution was adjusted to pH 9 with saturated aqueous K_2CO_3 and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (30% EtOAc/hexanes) gave 0.50 g (52%) of **47** as a white solid, mp 161−162 °C: ^{1}H NMR δ 7.51 (d, J = 1.8 Hz, 1 H), 7.39 (d, J = 1.8 Hz, 1 H), 6.55 (s, 1 H), 5.20 (br s, 2 H), 4.23 (s, 2 H), 1.39 (s, 9 H), 1.34 (s, 6 H); ^{13}C NMR δ 167.0, 157.1, 152.0, 137.3, 133.0, 127.4, 123.0, 117.9, 100.2, 84.0, 41.4, 34.1, 29.2, 27.4; IR 3465, 3276, 1633, 1520 cm^{-1}; MS m/z 303 (MH$^+$). Anal. ($C_{17}H_{22}N_2OS$) C, H, N, S.,

4-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-2-guanidinothiazole (48). A mixture of **VI**[1] (0.66 g, 2.0 mmol), 2-iminothiobiuret (0.24 g, 2.0 mmol), and 10 mL of acetone was heated at reflux for 24 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in 1:1 EtOAc/THF, and this solution was washed with aqueous K_2CO_3. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% MeOH/$CHCl_3$) afforded 0.24 g (35%) of **48** as a white solid, mp 237−238 °C: ^{1}H NMR (CD_3COCD_3) δ 7.60 (d, J = 1.8 Hz, 1 H), 7.54 (d, J = 1.8 Hz, 1 H), 6.86 (s, 1 H), 4.25 (s, 2 H), 1.40 (s, 9 H), 1.38 (s, 6 H); ^{13}C NMR (CD_3COCD_3) δ 175.8, 157.9, 157.6, 152.1, 138.2, 133.2, 129.5, 123.5, 118.5, 101.5, 84.7, 42.1, 34.7, 29.3, 27.6; IR 3446, 3400, 3118, 2960, 2872, 1717, 1663, 1604 cm^{-1}; MS m/z 345 (MH$^+$). Anal. ($C_{18}H_{24}N_4OS$) C, H, N.

6-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)imidazo[2.1-*b*]thiazoline (49). A mixture of **VI**[1] (0.81 g, 2.5 mmol), 2-aminothiazoline (0.25 g, 2.5 mmol), and 10 mL of ethanol was heated at reflux for 20 h. The reaction mixture was cooled to room temperature, concentrated to ca. 5 mL in volume, and poured into water. This solution was adjusted to pH 9 with 20% aqueous K_2CO_3 and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% ether/hexanes → ether) gave 0.52 g (63%) of **49** as a white solid, mp 189−190 °C: ^{1}H NMR δ 7.40 (d, J = 1.8 Hz, 1 H), 7.37 (s, 1 H), 7.14 (d, J = 1.8 Hz, 1 H), 4.23 (s, 2 H), 4.16 (t, J = 7.0 Hz, 2 H), 3.80 (t, J = 7.0 Hz, 2 H), 1.39 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR δ 156.4, 149.5, 148.1, 137.3, 132.9, 126.7, 121.3, 116.7, 110.9, 83.9, 46.1, 41.4, 34.5, 34.0, 29.2, 27.4; IR 2956, 1462, 1409 cm^{-1}; MS m/z 329 (MH$^+$). Anal. ($C_{19}H_{24}N_2OS$) C, H, N, S.

6-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)imidazo[2.1-*b*]thiazoline 1-Oxide (50). *m*-Chloroperbenzoic acid (0.82 g, ∼2.6 mmol, 50−60% pure) was added to a solution of **49** (0.87 g, 2.6 mmol) in 10 mL of $CHCl_3$ at 0 °C. The reaction was complete within 5 min. The reaction mixture

was washed with aqueous $NaHCO_3$ and with water, dried over $MgSO_4$, and concentrated to give a pink solid. Purification by flash column chromatography on silica gel (35% EtOAc/hexanes → 5% MeOH/$CHCl_3$) yielded 1.0 g of a pink solid, which was redissolved in $CHCl_3$. Treatment of this solution with hexane resulted in the precipitation of 0.67 g (75%) of **50** as a light pink solid, mp 217−219 °C: ^{1}H NMR δ 7.40 (s, 2 H), 7.34 (s, 1 H), 4.77 (m, 1 H), 4.35 (m, 1 H), 4.23 (s, 2 H), 3.70 (m, 2 H), 1.38 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 157.2, 152.8, 150.8, 137.6, 133.2, 125.7, 122.2, 117.3, 112.6, 84.0, 55.6, 43.1, 41.4, 34.1, 29.2, 27.4; IR 2958, 2869, 1446 cm^{-1}; MS *m*/*z* 345 (MH^+), 373 ($M + C_2H_5^+$), 385 ($M + C_3H_5^+$). Anal. ($C_{19}H_{24}N_2O_2S\cdot0.5H_2O$) C, H, N, S.

6-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)imidazo[2.1-*b*]thiazoline 1,1-Dioxide (51). *m*-Chloroperbenzoic acid (0.29 g, ∼1.0 mmol, 50−60% pure) was added to a solution of **50** (0.33 g, 1.0 mmol) in 10 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 16 h and quenched with aqueous $NaHCO_3$. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% → 10% MeOH/$CHCl_3$) yielded 0.23 g (64%) of **51** as a white solid, mp 275−276 °C: ^{1}H NMR (CD_3COCD_3) δ 7.70 (s, 1 H), 7.56 (d, J = 1.8 Hz, 1 H), 7.52 (d, J = 1.8 Hz, 1 H), 4.75 (t, J = 7.5 Hz, 2 H), 4.26 (s, 2 H), 4.10 (t, J = 7.5 Hz, 2 H), 1.39 (s, 9 H), 1.34 (s, 6 H); ^{13}C NMR (CD_3COCD_3) δ 157.9, 150.0, 144.2, 138.6, 133.6, 127.1, 122.8, 118.1, 114.5, 84.7, 54.0, 42.1, 41.3, 34.7, 29.3, 27.5; IR 3448, 3150, 2954, 1447 cm^{-1}; MS *m*/*z* 361 (MH^+). Anal. ($C_{19}H_{24}N_2O_3S$) C, H, N, S.

(*Z*)-3-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)methylene-γ-butyrolactone (52). Step 1. 7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-formylbenzofuran (VII). To aryl bromide **I** (20.2 g, 71.4 mmol) in Trapps solvent (4:1:1 THF/ether/hexanes, 180 mL) at −78 °C was added dropwise *t*-BuLi (1.7 M in pentane, 88.2 mL, 148 mmol) over 20 min. The mixture was stirred at −78 °C for 1 h. Anhydrous DMF (6.1 mL, 78.5 mmol) was added over 10 min. The resulting yellow solution was stirred at −78 °C for 30 min and warmed to room temperature over 40 min. The reaction mixture was quenched with water and extracted with ether. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and filtered. Evaporation of the solvent yielded a yellow oil (21.9 g) which was filtered through a silica gel pad with 10% ether in hexane to provide aldehyde **VII** as a yellow-brown oil (15.9 g, 96.5%). This product was estimated to be ∼90% pure on the basis of ^{1}H NMR analysis: ^{1}H NMR δ 9.83 (s, 1 H), 7.61 (d, J = 1.5 Hz, 1 H), 7.53 (d, J = 1.5 Hz, 1 H), 4.33 (s, 2 H), 1.37 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 191.1, 162.9, 138.4, 133.6, 130.3, 129.4, 121.4, 84.8, 40.8, 34.1, 29.0, 27.5; IR 2960, 2869, 1688, 1593, 1454 cm^{-1}; MS *m*/*z* 233 (MH^+).

Step 2. (*Z*)-3-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)methylene-γ-butyrolactone (52). A mixture of **VII** (0.77 g, 3.3 mmol), 2-(triphenylphosphoranylidene)-γ-butyrolactone (prepared according to the procedure of Lyga[23] et al., 1.19 g, 3.4 mmol), and 30 mL of benzene was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated to afford a brown solid. Purification by flash column chromatography on silica gel (10% → 75% ether/hexane) gave 0.77 g (78%) of **52** as a white solid, mp 122−123 °C: ^{1}H NMR δ 7.55 (t, J = 2.8 Hz, 1 H), 7.28 (d, J = 1.8 Hz, 1 H), 7.12 (d, J = 1.8 Hz, 1 H), 4.45 (t, J = 7.4 Hz, 2 H), 4.29 (s, 2 H), 3.24 (dt, J = 2.8, 7.4 Hz, 2 H), 1.36 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 173.2, 159.1, 138.2, 137.6, 133.7, 128.1, 127.5, 122.1, 119.2, 84.5, 65.3, 41.2, 34.2, 29.1, 27.6, 27.5; IR 2958, 1748, 1649, 1601, 1455 cm^{-1}; MS *m*/*z* 301 (MH^+). Anal. ($C_{19}H_{24}O_3$) C, H.

(*Z*)-5-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)methylene-2-imino-4-thiazolidinone (53). A mixture of **VII** (0.62 g, 2.7 mmol), pseudothiohydantoin (0.29 g, 2.5 mmol), sodium acetate (0.51 g, 6.2 mmol), and 12 mL of acetic acid was heated at reflux for 22 h. The reaction mixture was cooled to room temperature and poured into cold water. The resulting orange precipitate was collected, washed with water, and air-dried to give 0.81 g of the crude product, which was washed with ether to furnish 0.26 g (29%) of **53** as a yellow solid, mp 213-215 °C dec: ^{1}H NMR (CD_3COCD_3) δ 7.64 (s, 1 H), 7.36 (d, J = 1.8 Hz, 1 H), 7.29 (d, J = 1.8 Hz, 1 H), 4.33 (s, 2 H), 1.39 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR (CD_3SOCD_3) δ 182.2, 174.2, 158.2, 138.3, 132.8, 131.3, 126.7, 126.3, 123.2, 122.5, 84.0, 40.7, 33.8, 28.9, 27.0; IR 3150, 2959, 1737, 1672, 1582, 1456 cm^{-1}; MS (ion spray) *m*/*z* 331 (MH^+), 353 ($M + Na^+$), 369 ($M + K^+$). Anal. ($C_{18}H_{22}N_2O_3S\cdot0.25H_2O$) C, H, N, S; S: calcd, 9.57; found, 9.02.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(2-furoyl)benzofuran (54). Method E. *tert*-Butyllithium (5.5 mL, 9.4 mmol, 1.7 M in pentane) was added dropwise to a solution of **I** (1.13 g, 4.0 mmol) in 16 mL of anhydrous THF at −78 °C. The resulting yellow solution was stirred at −78 °C for 10 min, and 2-furaldehyde (0.50 mL, 6.0 mmol) was introduced. The reaction mixture was warmed to 0 °C, stirred for 30 min, quenched with water, and extracted with ether. The extract was dried over $MgSO_4$ and concentrated to give 1.55 g of an oily residue, which was dissolved in 25 mL of CH_2Cl_2 and reacted for 2 h with 4-methylmorpholine *N*-oxide (0.90 g, 7.7 mmol) and tetrapropylammonium perruthenate (0.16 g, 0.46 mmol). The reaction mixture was filtered through a short column of silica gel and concentrated to yield 1.57 g of the crude product. Purification by flash column chromatography on silica gel (2.5% → 4% EtOAc/hexanes) gave 1.0 g (84%) of **54** as a white solid, mp 103−104 °C: ^{1}H NMR δ 7.83 (d, J = 1.8 Hz, 1 H), 7.66 (d, J = 1.8 Hz, 2 H), 7.17 (d, J = 3.4 Hz, 1 H), 6.57 (dd, J = 3.4, 1.8 Hz, 1 H), 4.29 (s, 2 H), 1.38 (s, 9 H), 1.36 (s, 6 H); ^{13}C NMR δ 181.6, 161.5, 152.7, 146.3, 137.5, 132.8, 130.0, 127.9, 122.0, 119.3, 111.8, 84.6, 41.0, 34.2, 29.1, 27.5; IR 2959, 1640, 1593, 1562, 1507, 1464 cm^{-1}; MS *m*/*z* 299 (MH^+). Anal. ($C_{19}H_{22}O_3$) C, H.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(3-furoyl)benzofuran (55). Method E was followed using 3-furaldehyde, and the resulting compound **55** was purified by flash column chromatography on silica gel (2.5% EtOAc/hexanes): ^{1}H NMR δ 7.88 (dd, J = 1.5, 0.9 Hz, 1 H), 7.70 (d, J = 1.8 Hz, 1 H), 7.54 (d, J = 1.8 Hz, 1 H), 7.48 (dd, J = 1.8, 1.5 Hz, 1 H), 6.87 (dd, J = 1.8, 0.9 Hz, 1 H), 4.32 (s, 2 H), 1.37 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 188.3, 161.4, 147.3, 143.5, 137.7, 132.9, 131.5, 127.5, 126.7, 121.6, 110.5, 84.6, 41.0, 34.1, 29.1, 27.5; IR 2959, 2870, 1642, 1595 cm^{-1}; MS *m*/*z* 299 (MH^+). Anal. ($C_{19}H_{22}O_3$) C, H.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(2-thenoyl)benzofuran (56). Method E was followed using 2-thiophenecarboxaldehyde, and the resulting compound **56** was purified by flash column chromatography on silica gel (10% EtOAc/hexanes): ^{1}H NMR δ 7.75 (d, J = 1.8 Hz, 1 H), 7.66 (m, 2 H), 7.58 (d, J = 1.8 Hz, 1 H), 7.15 (dd, J = 4.8, 3.5 Hz, 1 H), 4.33 (s, 2 H), 1.40 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR δ 186.9, 161.0, 144.0, 137.6, 133.5, 132.9, 132.8, 130.9, 128.0, 127.6, 122.1, 84.7, 41.2, 34.3, 29.2, 27.6; IR 2958, 2869, 1727, 1632, 1594 cm^{-1}; MS *m*/*z* 315 (MH^+). Anal. ($C_{19}H_{22}O_2S$) C, H, S.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(3-thenoyl)benzofuran (57). Method E was followed using 3-thiophenecarboxaldehyde, and the resulting compound **57** was purified by flash column chromatography on silica gel (3% EtOAc/hexanes): ^{1}H NMR δ 7.88 (dd, J = 2.8, 1.0 Hz, 1 H), 7.71 (d, J = 1.8 Hz, 1 H), 7.56 (m, 2 H), 7.37 (dd, J = 4.8, 2.8 Hz, 1 H), 4.33 (s, 2 H), 1.40 (s, 9 H), 1.38 (s, 6 H); ^{13}C NMR δ 189.3, 161.3, 142.0, 137.3, 132.5, 132.0, 131.1, 128.6, 128.1, 125.6, 122.1, 84.5, 41.0, 34.0, 29.0, 27.4; IR 2958, 1642, 1594 cm^{-1}; MS *m*/*z* 315 (MH^+). Anal. ($C_{19}H_{22}O_2S$) C, H, S.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-[2-(*N*-methylpyrroloyl)]benzofuran (58). Method E was followed using 1-methyl-2-pyrrolecarboxaldehyde except that *n*-BuLi was used, and the stoichiometry of *n*-BuLi/**I**/aldehyde was 1/1/0.8. **58** was purified by flash column chromatography on silica gel (5% EtOAc/hexanes): ^{1}H NMR δ 7.68 (d, J = 1.8 Hz, 1 H), 7.52 (d, J = 1.8 Hz, 1 H), 6.85 (br s, 1 H), 6.70 (m, 1 H), 6.15 (m, 1 H), 4.30 (s, 2 H), 3.99 (s, 3 H), 1.34 (s, 9 H), 1.32 (s, 6 H); ^{13}C NMR δ 185.5, 160.5, 136.9, 132.4, 132.2, 130.7, 130.3, 127.6, 121.9, 121.2, 107.6, 84.4, 41.0, 36.9, 34.0, 29.0, 27.4; IR

2958, 2869, 1623, 1592 cm^{-1}; MS *m*/*z* 312 (MH^+). Anal. ($C_{20}H_{25}NO_2 \cdot 0.25H_2O$) C, H, N.

7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-(2-thiazoloyl)-benzofuran (59). Method E was followed using 2-thiazolecarboxaldehyde. **59** was purified by flash column chromatography on silica gel (2.5% EtOAc/hexanes): ^1H NMR δ 8.45 (d, $J = 1.8$ Hz, 1 H), 8.22 (d, $J = 1.8$ Hz, 1 H), 8.05 (d, $J = 3.2$ Hz, 1 H), 7.67 (d, $J = 3.2$ Hz, 1 H), 4.33 (s, 2 H), 1.40 (s, 9 H), 1.38 (s, 6 H); ^{13}C NMR δ 182.5, 169.0, 162.5, 144.4, 137.6, 133.0, 130.2, 128.0, 125.2, 124.0, 84.8, 41.0, 34.2, 29.1, 27.6; IR 2959, 1634, 1589 cm^{-1}; MS *m*/*z* 316 (MH^+). Anal. ($C_{18}H_{21}NO_2S$) C, H, N, S.

***E*-3-(7′-*tert*-Butyl-2′,3′-dihydro-3′,3′-dimethyl-5′-benzofuranyl)-2-(2″-thiophene)propenoic Acid (60).** To a mixture of aldehyde **VII** (1.064 g, 4.59 mmol) and 2-thiopheneacetic acid (978 mg, 6.88 mmol) was added piperidine (1.5 mL). The mixture was heated at 140 °C (oil bath temperature) for 4 h, cooled to room temperature, quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give a brown semisolid. Silica gel chromatography (5% MeOH/CH_2Cl_2) provided 543 mg (34.0%) of **60** as a yellow solid, mp 183−185 °C: ^1H NMR δ 8.00 (s, 1 H), 7.41 (dd, $J = 5.0$, 1.0 Hz, 1 H), 7.08 (dd, $J = 5.0$, 3.5 Hz, 1 H), 7.05 (d, $J = 2.0$ Hz, 1 H), 6.97 (dd, $J = 3.5$, 1.0 Hz, 1 H), 6.70 (d, $J = 2.0$ Hz, 1 H), 4.21 (s, 2 H), 1.20 (s, 9 H), 1.19 (s, 6 H); ^{13}C NMR δ 172.4, 159.3, 146.3, 137.4, 136.6, 132.9, 129.5, 127.9, 127.3, 126.8, 126.4, 123.4, 119.8, 84.3, 40.8, 33.9, 28.9, 27.3; IR 2959 (v br), 1678, 1594 cm^{-1}; MS *m*/*z* 374 (MNH_4^+), 357 (MH^+). Anal. ($C_{21}H_{24}O_3S$) C, H, S.

5-[*E*-2′-(2″-Thiophene)ethenyl]-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (61). 2-Thiophenemethyl Chloride. To 2-thiophenemethanol (9.5 mL, 100 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added thionyl chloride (14.6 mL, 200 mmol), followed by the addition of pyridine (9.7 mL, 120 mmol). The mixture was stirred at room temperature for 30 min and concentrated via rotary evaporation. The resulting brown oil was filtered through a silica gel pad, washed with 5% ether/hexanes, and evaporated to give the title compound as an orange oil (6.50 g, 48.9%) which was stored in the cold and in the dark, and was used within a week: ^1H NMR δ 7.35−6.97 (m, 3 H), 4.85 (s, 2 H).

Diethyl 2-Thiophenemethyl Phosphonate. A mixture of 2-thiophenemethyl chloride (1.1 g, 8.3 mmol) and triethyl phosphite (2.07 mL, 12.1 mmol) was heated at 130 °C for 4 h. The resulting mixture was subjected to Kugelrohr distillation to remove the excess triethyl phosphite (50 °C/0.005 mm) followed by the title phosphonate as a clear oil (90−130 °C/0.005 mm, 1.00 g, 51.8%): ^1H NMR δ 7.18−6.92 (m, 3 H), 4.05 (dq, $J = 7.5$, 7.5 Hz, 4 H), 3.36 (d, $J = 20.5$ Hz, 2 H), 1.27 (t, $J = 7.0$ Hz, 6 H); MS *m*/*z* 235 (MH^+).

5-[*E*-2′-(2″-Thiophene)ethenyl]-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (61). A mixture of aldehyde **VII** (90%, 8.76 g, 33.95 mmol), diethyl 2-thiophenemethylphosphonate (8.04 mL, 40.7 mmol), and NaH (60% in mineral oil (3.26 g, 81.5 mmol) washed with hexanes three times and dried in vacuo prior to use) in anhydrous DME (68 mL) was heated at reflux under nitrogen for 2 h (vigorous evolution of H_2 started at ∼5−10 min of heating; therefore, good ventilation should be ensured). Upon completion of the reaction, the mixture was quenched carefully with water and extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated via rotary evaporation. The resulting residue was recrystallized from a 1:1 mixture of CH_2Cl_2/hexanes to provide 7.05 g (65.9%) of **61** as a white solid. Silica gel chromatography (5% CH_2Cl_2/hexanes) of the mother liquid afforded more **61** (2.04 g, total 86% yield), mp 113.5−115 °C: ^1H NMR δ 7.16−7.11 (m, 3 H), 7.03 (d, $J = 16.0$ Hz, 1 H), 7.02−6.96 (m, 2 H), 6.91 (d, $J = 16.0$ Hz, 1 H), 4.24 (s, 2 H), 1.38 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 152.1, 138.4, 132.5, 128.0, 124.4, 123.9, 122.2, 119.7, 118.8, 118.1, 113.6, 112.2, 78.9, 36.1, 28.9, 24.0, 22.2; IR 2958, 2871, 1600, 1455 cm^{-1}; MS *m*/*z* 313 (MH^+), 257. Anal. ($C_{20}H_{24}OS$) C, H, S.

5-[*E*-2′-(3″-Methylisoxazol-5″-yl)ethenyl]-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (62). Step 1. 1-(7′-*tert*-Butyl-2′,3′-dihydro-3′,3′-dimethyl-5-benzofuranyl)-2-(3″methylisoxazol-5″-yl)ethanol. To 3,5-dimethylisoxazole (1.47 mL, 15.0 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (1.47 M in hexanes, 10.0 mL, 14.7 mmol). The mixture was stirred at −78 °C for 2 h. To the resulting yellow solution at −78 °C was added dropwise aldehyde **VII** (3.48 g, 15.0 mmol) in THF (60 mL). The reaction mixture was stirred at room temperature for 5 h and evaporated. The residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a brown oil. Silica gel chromatography afforded the title alcohol as a thick yellow oil (4.36 g, 88.2%) which solidified, mp 71−72 °C: ^1H NMR δ 7.03 (d, $J = 1.5$ Hz, 1 H), 6.97 (d, $J = 1.5$ Hz, 1 H), 5.88 (s, 1 H), 4.98 (m, 1 H), 4.21 (br s, 2 H), 3.21−3.01 (m, 2 H), 2.24 (s, 3 H), 1.33 (s, 9 H), 1.31 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR δ 169.8, 159.6, 156.8, 137.3, 134.8, 132.9, 122.4, 117.1, 103.1, 83.8, 72.5, 41.3, 36.6, 34.0, 29.1, 27.3, 27.2, 11.2; IR 3378 (br), 2958, 2869, 1606 cm^{-1}; MS *m*/*z* 330 (MH^+). Anal. ($C_{20}H_{27}NO_3$) C, H, N.

Step 2. 5-[*E*-2′-(3″-Methylisoxazol-5″-yl)ethenyl]-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (62). To the above alcohol (3.23 g, 9.80 mmol) in toluene (50 mL) was added *p*-toluenesulfonic acid monohydrate (9 mg). The mixture was heated at reflux for 2 h with removal of water via a Dean−Stark trap. After concentration, the residue was purified by silica gel chromatography (65% CH_2Cl_2 in hexanes), followed by recrystallization from hexanes/CH_2Cl_2 (15 mL/1 mL) to provide a 15:1 mixture, as determined by ^1H NMR analysis, of olefin **62** and the *Z*-isomer (2.28 g, 74.8%), mp 121.5−123 °C: ^1H NMR δ 7.36−7.15 (m, 3 H), 6.77 (d, $J = 16.5$ Hz, 1 H), 6.02 (s, 1 H), 4.26 (s, 2 H), 2.30 (s, 3 H), 1.38 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 168.8, 159.9, 158.4, 137.9, 135.1, 133.4, 128.2, 125.0, 118.2, 109.9, 100.9, 84.2, 41.2, 34.0, 29.1, 27.4, 11.4; IR 2959, 2872, 1640, 1590 cm^{-1}; MS *m*/*z* 312 (MH^+). Anal. ($C_{21}H_{25}NO_2$) C, H, N.

5-[*E*-2′-(5″-Methyl-1H-pyrazol-3″-yl)ethenyl]-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (63). To a mixture of isoxazole **62** (1.54 g, 4.96 mmol) and molybdenum hexacarbonyl (982 mg, 3.72 mmol) was added acetonitrile (58 mL) and water (89 μL, 4.96 mmol). The mixture was heated at reflux for 14 h and then concentrated. To the residue were added MeOH (30 mL) and 2 N HCl (0.8 mL) until the pH = 1. The mixture was stirred for 5 h, concentrated again, and then treated with water (30 mL) and neutralized with 1 N NaOH. EtOAc and brine were added. The separated aqueous layer was extracted with EtOAc. The combined organic layers were filtered through a silica gel pad with $CHCl_3$ washing. The organic filtrate was concentrated, and the residue was taken up with EtOAc and filtered through a silica gel pad with EtOAc washing. The organic layer was treated with acetic acid (78 mL) and 97% hydrazine (0.779 mL, 24.8 mmol). The mixture was stirred for 20 h, followed by removal of acetic acid via vacuum evaporation. The residue was washed with water and filtered. The resulting brown cake was purified by silica gel chromatography (1% MeOH/CH_2Cl_2), followed by recrystallization from hexanes to provide 645 mg (42%) of **63** as a light yellow solid, mp 145−147 °C: ^1H NMR δ 7.27 (d, $J = 1.5$ Hz, 1 H), 7.10 (d, $J = 1.5$ Hz, 1 H), 7.01 (d, $J = 16.5$ Hz, 1 H), 6.87 (d, $J = 16.5$ Hz, 1 H), 6.23 (br s, 1 H), 4.21 (s, 2 H), 2.19 (br s, 3 H), 1.31 (s, 9 H), 1.27 (s, 6 H); ^{13}C NMR (CD_3OD) δ 159.0 (br), 139.6, 134.5, 132.5 (br), 131.7 (br), 125.4, 122.3 (br), 119.1, 113.6, 103.3 (br), 102.2 (br), 85.6, 42.8, 35.4, 30.6, 30.2, 28.1; IR 3190, 3100, 2956, 2869, 1583 cm^{-1}; MS *m*/*z* 311 (MH^+). Anal. ($C_{20}H_{26}N_2O$) C, H, N.

5-[*E*-2′-(2″-Pyridinyl)ethenyl]-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (64). To a mixture of 2-picolyl triphenylphosphonium chloride (1.29 g, 3.3 mmol, prepared from 2-picolyl chloride and triphenylphosphine) and sodium amide (90%, 143 mg, 3.3 mmol) was added THF (8 mL). The mixture was stirred at room temperature for 1 h and then was cooled to −78 °C. To this pink slurry at −78 °C was added aryl aldehyde **VII** (690 mg, 3.00 mmol) in THF (2 mL). The

mixture was stirred at −78 °C for 10 min and then at room temperature for 30 min. The solvent was removed via rotary evaporation. The residue was extracted with ether and filtered. The extract was concentrated, and the residue was purified via silica gel chromatography (20% ether/hexanes), followed by recrystallization from a hexanes/CH_2Cl_2 mixture to afford 750 mg (81%) of **64** as a white solid, mp 122−123 °C; ^{1}H NMR δ 8.56 (m, 1 H), 7.63 (m, 1 H), 7.57 (d, J = 16.0 Hz, 1 H), 7.37 (m, 1 H), 7.29 (d, J = 1.6 Hz, 1 H), 7.24 (d, J = 1.5 Hz, 1 H), 7.13 (m, 1 H), 7.03 (d, J = 16.0 Hz, 1 H), 4.25 (s, 2 H), 1.37 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR δ 158.1, 156.5, 149.8, 138.0, 136.6, 133.5, 133.4, 129.5, 125.4, 125.1, 121.6, 121.5, 118.4, 84.4, 41.5, 34.3, 29.5, 27.7; IR 2958, 2872, 1634, 1584 cm^{-1}; MS m/z 308 (MH^+). Anal. ($C_{21}H_{25}NO$) C, H, N.

5-[*E*-2′-(3″-Pyridinyl)ethenyl]-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (65). The procedure described for the preparation of **64** was followed using 3-picolyl triphenylphosphonium chloride (prepared from 3-picolyl chloride and triphenylphosphine) except that 0.4 equiv of aldehyde **VII** was used. The crude product consisted of a 40:60 mixture of the *E*/*Z* double bond isomers. Separation of the isomers was performed via silica gel chromatography (20−25% EtOAc/hexanes) to afford the *Z*-isomer (788 mg, 51%) and the *E*-isomer **65** (580 mg, 38%) both as a white solids. For **65**: mp 72−74 °C; ^{1}H NMR δ 8.70 (br s, 1 H), 8.43 (br s, 1 H), 7.79 (br d, J = 8.0 Hz, 1 H), 7.25 (m, 1 H), 7.21 (d, J = 2.0 Hz, 1 H), 7.18 (d, J = 2.0 Hz, 1 H), 7.13 (d, J = 16.0 Hz, 1 H), 6.90 (d, J = 16.0 Hz, 1 H), 4.25 (s, 2 H), 1.38 (s, 9 H), 1.36 (s, 6 H); ^{13}C NMR δ 157.6, 148.1, 147.7, 137.7, 133.4, 133.1, 132.0, 131.2, 129.2, 124.4, 123.3, 121.5, 117.6, 84.0, 41.2, 34.0, 29.1, 27.3; IR 3024, 2957, 2868, 1633, 1603 cm^{-1}; MS m/z 308 (MH^+). Anal. ($C_{21}H_{25}NO$) C, H, N.

Biological Procedures. The procedures for the carrageenan-induced paw edema (CPE) assay, the phenylquinone-induced abdominal constriction (PAC) assay, the human COX-1/COX-2 isolated enzyme assays, and the RBL-2H3 intact cell assay for LTB_4 inhibition are given in a preceding publication.[1]

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