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Inhibition of E-Selectin-, ICAM-1-, and VCAM-1-Mediated Cell Adhesion by Benzo[b]thiophene-, Benzofuran-, Indole-, and Naphthalene-2-carboxamides: Identification of PD 144795 as an Antiinflammatory Agent

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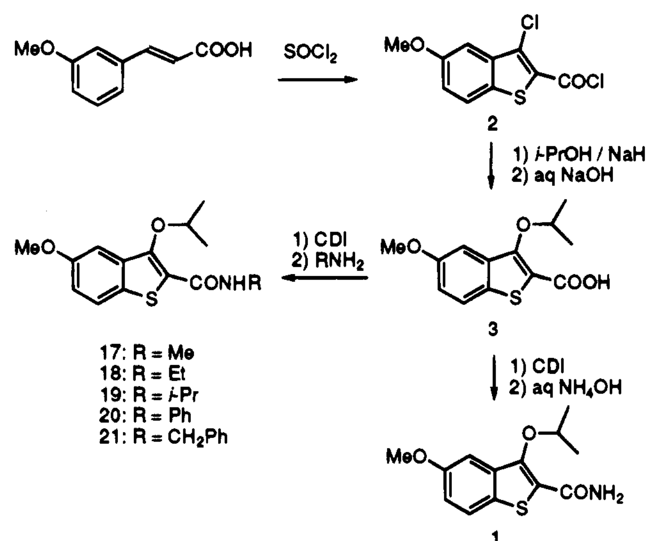
It was previously reported that 3-alkoxybenzo[b]thiophene-2-carboxamides exemplified by **1**, 5-methoxy-3-(1-methylethoxy)benzo[b]thiophene-2-carboxamide, decreased the adherence of neutrophils to activated endothelial cells by inhibiting the upregulation of the adhesion molecules E-selectin and ICAM-1 on the surface of the endothelium. This finding is extended here to a series of 3-thiobenzo[b]thiophene-2-carboxamides and also heterocyclic analogs of **1**, including benzofurans, indoles, and naphthalenes. The compounds that inhibited the expression of E-selectin and ICAM-1 had the same effect on the expression of VCAM-1. PD 144795, 5-methoxy-3-(1-methylethoxy)benzo[b]thiophene-2-carboxamide 1-oxide (**44**), the sulfoxide analog of **1**, was orally active in several models of inflammation. The *in vitro* and *in vivo* activity of PD 144795 resided predominately in the *S*-enantiomer.

Introduction

The adherence of neutrophils to vascular endothelium is essential to the pathogenesis of acute inflammation. The initial adherence of the neutrophils is followed by their migration from the vasculature into the surrounding tissue, resulting in tissue damage, swelling, and pain. The steps in this cascade of events are mediated by the interaction of specific cell surface proteins, termed adhesion molecules.[1-3] E-Selectin (ELAM-1, endothelial leukocyte adhesion molecule-1),[4] ICAM-1 (intercellular adhesion molecule-1),[5] and VCAM-1 (vascular cell adhesion molecule-1)[6,7] are adhesion molecules whose expression on endothelial cells is upregulated upon treatment with inflammatory stimuli. Lipopolysaccharide (LPS) or cytokines such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), or interferon-γ (INF-γ) induce mRNA and protein synthesis with elevated levels of ICAM-1 and E-selectin appearing on the cell surface after 4–6 h, and maximal expression of VCAM-1 occurring at 12–24 h. Adhesion molecules on the neutrophils that recognize ICAM-1 include the β2 integrins, Mac-1 (macrophage antigen-1, CD11b/CD18), and LFA-1 (lymphocyte function related antigen-1, CD11a/CD18). Carbohydrates, such as the tetrasaccharide sialyl Lewis X (sLe^x), displayed by proteins on the neutrophil surface, recognize the lectin domain of E-selectin. Since neutrophils do not contain the counter ligands for VCAM-1, the key adhesion molecules on the endothelium responsible for neutrophil adherence are ICAM-1 and E-selectin.

The inhibition of cell adhesion as a therapeutic strategy for the treatment of inflammation is validated by the activity of monoclonal antibodies to adhesion molecules in various animal models[8,9] and by the efficacy of an antibody to ICAM-1 in a clinical trial of rheumatoid arthritis.[10] Further support comes from the reports of the *in vivo* activity of sLe^x and related carbohydrates, antagonists of E-selectin mediated adhesion.[11,12] This *in vivo* activity is shared by the leumedins, low molecular weight compounds from Scios-Nova that affect Mac-1/ICAM-1 mediated adhesion.[13,14]

Scheme 1



Cell adhesion can also be prevented by inhibiting the upregulation of the inducible adhesion molecules on the endothelium. In an approach to identify such an agent, an *in vitro* assay was used wherein a monolayer of human umbilical vein endothelial cells (HUVECs) was stimulated with TNF-α in the presence of the test compound for 4 h. Freshly isolated human neutrophils, labeled with either ^{51}Cr or calcein-AM, were added to the HUVECs and the cells were allowed to adhere. The nonadherent neutrophils were removed by washing, and the resultant radioactivity or fluorescence was measured.

We previously reported that 5-methoxy-3-(1-methylethoxy)benzo[b]thiophene-2-carboxamide (**1**) strongly

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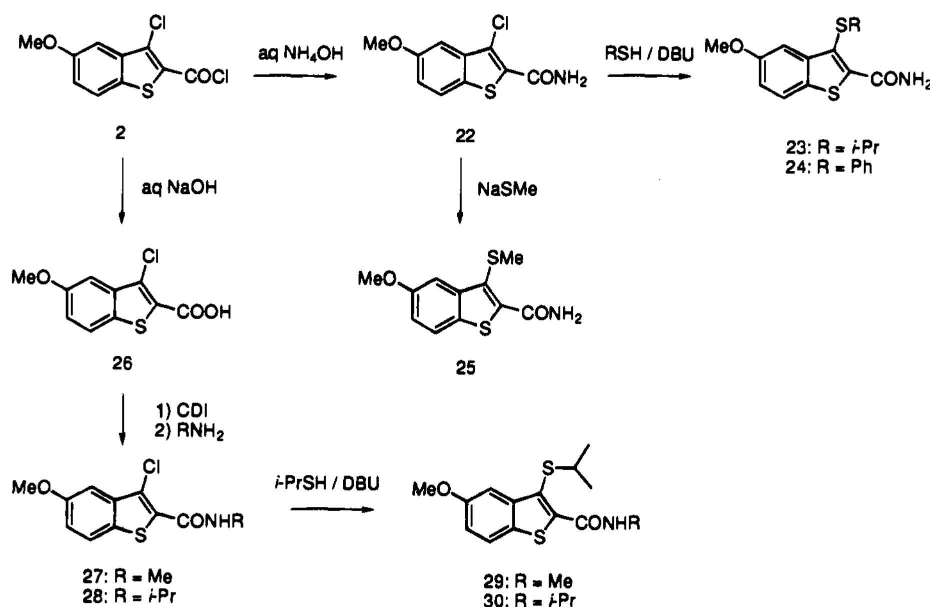
Scheme 2



inhibited the adhesion of neutrophils to the activated HUVECs in this assay (IC_{50} = 3.8 μM).[15] Optimum activity was observed when **1** was added within the first 60 min of TNF-α activation. No effect was seen when **1** was added 4 h postactivation of the HUVECs, suggesting that this compound influences early events in TNF-α-induced adhesion molecule expression. Similar results were obtained when either LPS or IL-1 were used as the stimulus instead of TNF-α.

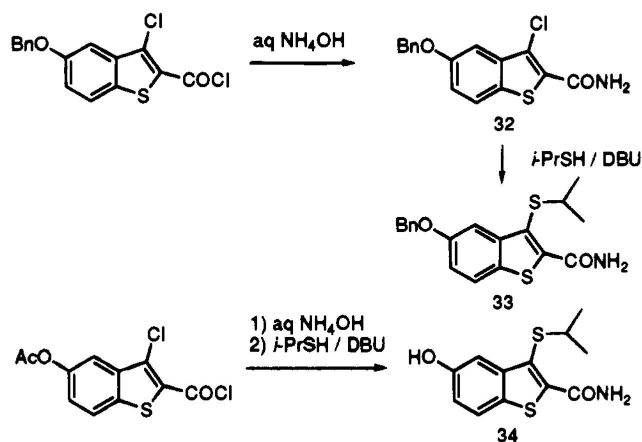
Chemistry

The preparation of **1** is shown in Scheme 1. Reaction of 3-methoxycinnamic acid with thionyl chloride gave 3-chloro-5-methoxybenzo[*b*]thiophene-2-carbonyl chloride (**2**) as first reported by Higa.[16] Treatment of **2** with 2-propanol under basic conditions resulted in displacement of the 3-chloro with isopropoxide and also converted the acid chloride group to the isopropyl ester.[17] Hydrolysis to the acid **3**, followed by the addition of 1,1′-carbonyldiimidazole formed the imidazolide which was directly subjected to aqueous ammonium hydroxide to give the desired primary carboxamide **1**.

Several related 3-alkoxybenzo[*b*]thiophene-2-carboxamides, **4**–**8**, **11**, and **13**–**15**, were prepared in an analogous fashion from the corresponding known 3-alkoxybenzo[*b*]thiophene-2-carboxylic acids.[17] Two exceptions are **16**, which was prepared via the acid chloride, and **12**, which was prepared via treatment of the corresponding ester with lithium amide. Catalytic reduction of the 5-nitro derivative **7** provided the 5-amino analog **9**. The 5-hydroxy derivative **10** was obtained by deprotection of the 5-benzyloxy analog **8**. The secondary amides **17**–**21** resulted from the reaction of the imidazolide of **3** with primary amines (Scheme 1).

A series of analogs of **1** where the alkoxy group at C-3 was replaced by a thioether were prepared, as shown in Scheme 2. Addition of **2** to an aqueous solution of ammonium hydroxide gave amide **22**. Displacement of the chloro group of **22** with 2-propanethiol in dimethylformamide in the presence of 1,8-diazobicyclo[5.4.0]undec-7-ene provided **23**. The corresponding

Scheme 3

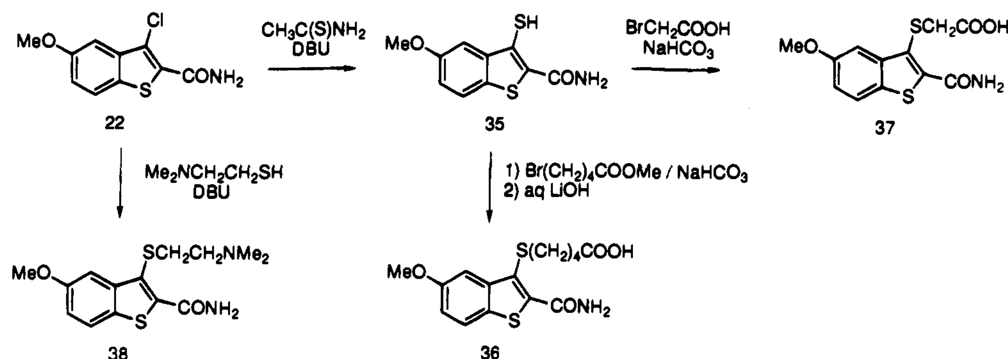


3-thiophenyl analog **24** was similarly obtained by reaction of **22** with thiophenol, while the thiomethyl derivative **25** was obtained by the action of sodium thiomethoxide on **22**. Hydrolysis of **2** with aqueous sodium hydroxide in tetrahydrofuran provided the corresponding acid **26**. Reaction of the imidazolide of **26** with methylamine and isopropylamine gave **27** and **28**, which were treated with 2-propanethiol to provide amides **29** and **30**.

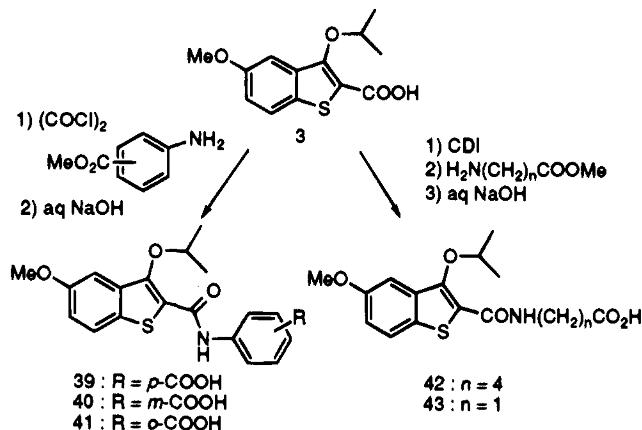
Analogs of **23** were prepared with aromatic substituents other than 5-methoxy. The unsubstituted derivative **31** was obtained from the known acid[18] and the 5-benzyloxy derivative **33** was obtained via **32**, the product of the reaction of 3-chloro-5-(benzyloxy)benzo[*b*]thiophene-2-carbonyl chloride[17] and ammonium hydroxide (Scheme 3). While the benzyl group of **8** was readily removed by hydrogenation, we could not generate the 5-hydroxy derivative **34** directly from **33**. An intermediate 5-acetoxy derivative, obtained in the reaction of 3-acetoxycinnamic acid[19] with thionyl chloride, was therefore used to prepare **34**.

Analogs of **1** containing functionalities that would allow for salt formation were synthesized. One site chosen was the C-3 position. Due to the milder conditions that could be used to displace the 3-chloro group of **22** with thiols vs alcohols, C-3 substituted thioethers

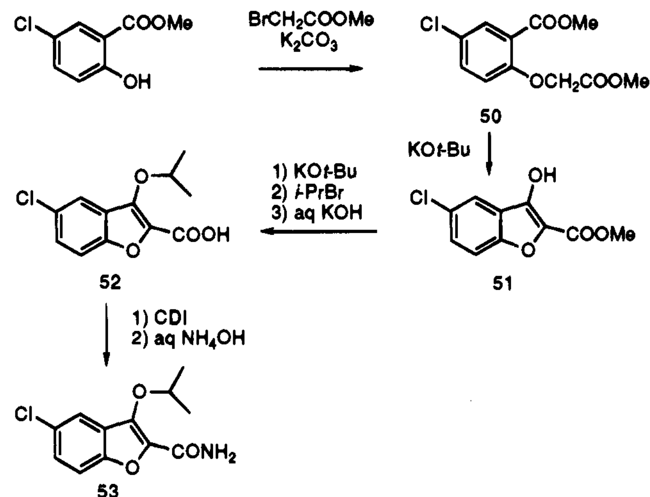
Scheme 4



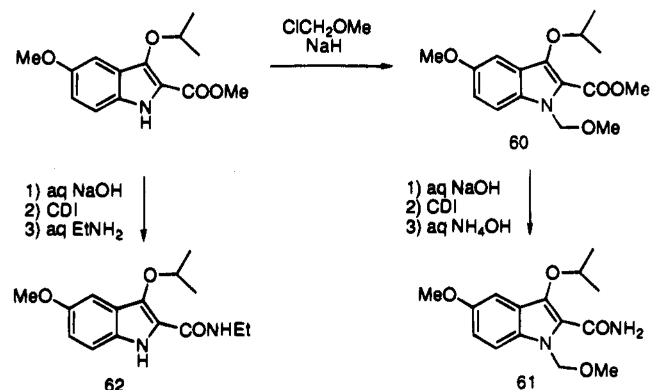
Scheme 5



Scheme 6



Scheme 7



were selected as opposed to C-3 substituted alkoxides. The desired products could also be obtained via the thiol **35**, the product of the reaction of **22** with thioacetamide (Scheme 4). Alkylation of **35** with methyl bromovalerate provided the intermediate ester which was hydrolyzed to give **36**. Direct treatment of **35** with bromoacetic acid gave **37**, which like **36** contains a carboxylic acid group. Reaction of **22** with 2-(dimethylamino)ethanethiol gave **38**, which contains a tertiary amine in its side chain.

Ionizable groups were also introduced into the amide functionality of **1**. These compounds were prepared as shown in Scheme 5. For the carboxylate-substituted benzamides, **3** was converted to its acid halide with oxalyl chloride and then treated with the esters of 2-, 3-, or 4-aminobenzoate. The resulting esters were then hydrolyzed to give the desired acids **39**, **40**, and **41**. The analogs containing alkyl carboxylic acids, **42** and **43**, were prepared via conversion of **3** to its imidazolide derivative followed by addition of an amine containing an ester substituent. Treatment of these intermediates with aqueous base provided the desired amides substituted with an acid functionality.

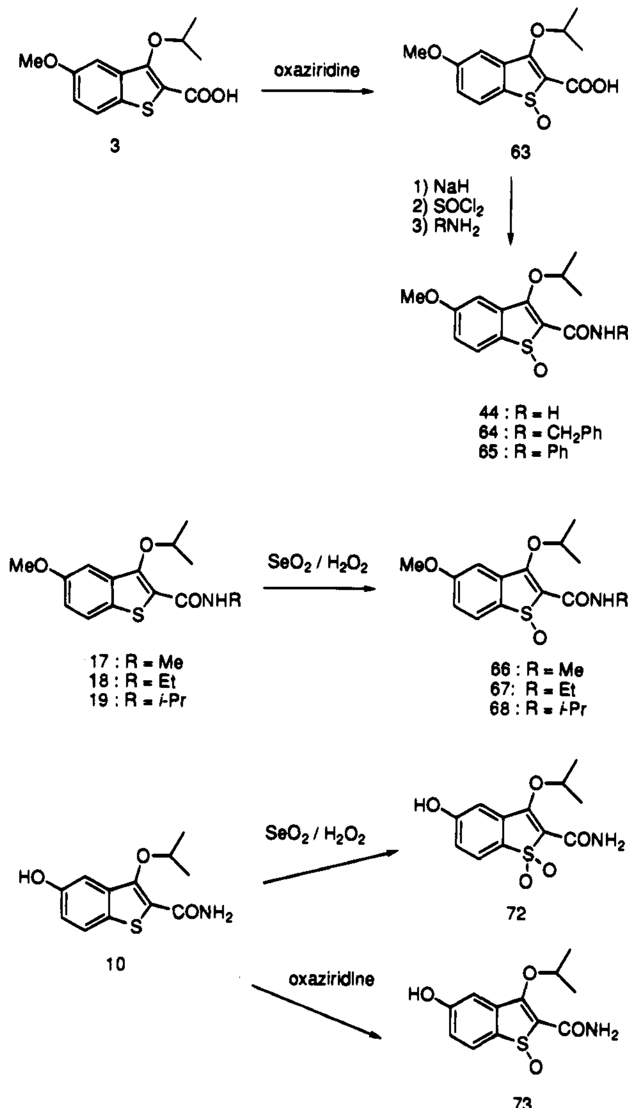
By varying the reaction conditions, it was possible to oxidize **1** with hydrogen peroxide in acetic acid and obtain either the sulfoxide **44** or sulfone **45** as the major product. The corresponding benzofuran **46**, naphthalene **47**, indole **48**, and *N*-methylindole **49** analogs were all prepared via conversion of the previously reported acids[17,20] to the imidazolides followed by addition of aqueous ammonium hydroxide.

Other benzofuran analogs of **46** were prepared as shown in Scheme 6. Reaction of methyl 5-chlorosalicylate[21] with methyl bromoacetate gave the diester **50** which was cyclized with potassium *tert*-butoxide to provide benzofuran **51**. Alkylation of **51** followed by ester hydrolysis gave **52**. Treatment of **52** with 1,1′-carbonyldiimidazole and aqueous ammonium hydroxide resulted in **53**. The unsubstituted derivative **54** was prepared in an analogous fashion from methyl 3-hydroxy-2-benzofurancarboxylate.[22] The ethyl- and phenylamides (**55** and **56**) were synthesized via the conditions employed in the benzo[*b*]thiophene series.

The additional naphthalenes **57**–**59** and the *N*-ethyl indole **62** were prepared by standard methods from the known acids.[20,23] The *N*-methoxymethyl derivative **61** was obtained via the corresponding methyl ester **60**[24] as shown in Scheme 7. Direct alkylation of **48** with sodium hydride and chloromethyl methyl ether also provided **61**, albeit in low yield.

While **44** could be obtained via oxidation of **1** with hydrogen peroxide, the yield was low due to the dif-

Scheme 8



ficulty in stopping the oxidation at the sulfoxide stage. An extensive study was made to find the optimal conditions for the conversion of either **1** or **3** to the corresponding sulfoxide. Success was achieved in the reaction of **3** with *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine[25] in chloroform. Under these conditions the polar sulfoxide **63** precipitated out of solution removing it from the oxidant, circumventing further oxidation to the sulfone (Scheme 8). Formation of the sodium salt of **63** with sodium hydride followed by the addition of thionyl chloride gave the acid chloride, which was not isolated. Addition of ammonia gas at low temperature yielded the primary amide **44**. When benzylamine or aniline were added to this acid chloride, the *N*-benzyl- and *N*-phenyl-substituted amides **64** and **65** were obtained.

Additional secondary amides were prepared via oxidation of the corresponding benzo[*b*]thiophenes with selenium dioxide and hydrogen peroxide (Scheme 8). This direct oxidation route was used to prepare the *N*-methyl, *N*-ethyl and *N*-isopropyl analogs **66**, **67**, and **68** and also to convert **4** to **69**. Alternatively, *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine was used to directly oxidize the benzothiophene at the amide stage, as in the preparation of **70** from **14**, or to oxidize the benzothiophene at the acid stage, with subsequent formation of the amide, as in the preparation of **71**. Surprisingly, oxidation of the 5-hydroxy derivative **10** with selenium dioxide and hydrogen peroxide gave the sulfone **72**. The desired sulfoxide **73** was obtained by reaction of **10** with *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine.

Table 1. Inhibition of Cell Adhesion by 3-(1-Methylethoxy)benzo[*b*]thiophene-2-carboxamides

compd	R^{Ar}	adhesion[a]
1	5-OMe	3.8
4	5-H	60%
5	5-Cl	72%
6	5-Me	61%
7	5-NO_2	40%
8	5-OCH_2Ph	NA[b]
9	5-NH_2	49%
10	5-OH	6.4
11	7-OMe	35%
12	6-OMe	24%

[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 100 μM. Each percentage value is from a single assay that was run in triplicate. The mean standard error is less than 5%. Neutrophils were labeled with $Na^{51}CrO_4$. [b] NA: less than 4% inhibition at the testing concentration.

Table 2. Inhibition of Cell Adhesion by Additional 3-Alkoxy-5-methoxybenzo[*b*]thiophene-2-carboxamides

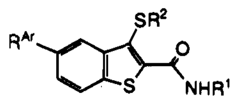
compd	R^1	R^2	adhesion[a]
13	H	*t*-Bu	97%
14	H	Me	60%
15	H	CH_2Ph	57%
16	H	Ph	59%
17	Me	*i*-Pr	15
18	Et	*i*-Pr	64%
19	*i*-Pr	*i*-Pr	26%[b]
20	Ph	*i*-Pr	12%
21	CH_2Ph	*i*-Pr	35%[b]

[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 100 μM. Each percentage value is from a single assay that was run in triplicate. The mean standard error is less than 5%. Neutrophils were labeled with $Na^{51}CrO_4$. [b] Neutrophils were labeled with calcein-AM.

Results and Discussion

In compounds **4** through **10**, the substituent at C-5 was varied to include hydrogen, chloro, methyl, nitro, benzyloxy, amino, and hydroxy (Table 1). The most active of these analogs in inhibiting cell adhesion was **10**, which contains a 5-hydroxy group. The least active compound was the 5-benzyloxy analog, **8**. Moving the aromatic methoxy group from position 5 to either position 7 or 6, compounds **11** and **12** respectively, markedly decreased the activity. In analogs **13** to **16**, the C-3 1-methylethoxy group of **1** was replaced by other alkoxy or phenoxy substitutents. Compound **13**, containing a 1,1-dimethylethoxy group at C-3, provided 97% inhibition of cell adhesion at a testing concentration of 100 μM (Table 2). The C-3 methoxy, phenoxy, and benzyloxy analogs **14**, **15**, and **16** were equipotent and less effective than **1** or **13**.

Table 3. Inhibition of Cell Adhesion by 3-Thiobenzo[*b*]thiophene-2-carboxamides



compd	R^{Ar}	R^1	R^2	adhesion[a]
23	OMe	H	*i*-Pr	12
24	OMe	H	Ph	48% at 100 μM
25	OMe	H	Me	81% at 100 μM
29	OMe	Me	*i*-Pr	61% at 33 μM[b]
30	OMe	*i*-Pr	*i*-Pr	22% at 33 μM[b]
31	H	H	*i*-Pr	34% at 100 μM
33	OCH_2Ph	H	*i*-Pr	24% at 33 μM[b]
34	OH	H	*i*-Pr	3.6[b]
36	OMe	H	$(CH_2)_4COOH$	37% at 33 μM[b]
37	OMe	H	CH_2COOH	7% at 33 μM[b]
38	OMe	H	$CH_2CH_2NH_2$	NA[c] at 33 μM[b]

[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 100 or 33 μM. Each percentage value is from a single assay that was run in triplicate. The mean standard error is less than 5%. Neutrophils were labeled with $Na^{51}CrO_4$. [b] Neutrophils were labeled with calcein-AM. [c] NA: less than 4% inhibition at the testing concentration.

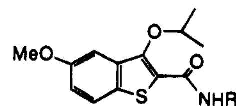
Increasing the size of the substituent on the amide nitrogen was detrimental to the *in vitro* activity. While the methyl-substituted amide **17** was less potent than **1**, it was more potent than the ethyl analog **18**. The more highly substituted isopropyl, phenyl, and benzyl analogs **19**, **20**, **21** were all less active than **18**. It should be noted that the analogs of **1** with a substituent other than an amide at C-2, including an acid or an ester, were not active (data not shown).

Compound **23**, the direct 3-thio analog of **1**, had an IC_{50} of 12 μM. The corresponding phenyl thioether analog, **24**, was less active than either **23** or the methyl thioether analog, **25** (Table 3). Mirroring the results seen in the 3-alkoxy series, increasing the size of the substituent on the amide nitrogen decreased the activity as demonstrated with **29** and **30**, the methyl- and phenylamide analogs of **23**. Substitution of the 5-methoxy group of **23** by a proton or benzyloxy group gave **31** and **33**, which were less active, while *in vitro* activity was retained with the 5-hydroxy derivative **34**. The SAR of the 3-thiobenzo[*b*]thiophenes paralleled that of the 3-alkoxy derivatives with the general structural requirements being a primary carboxamide at C-2, and a lower alkoxy or hydroxy substituent at C-5.

At this stage, the most potent compounds *in vitro* were tested in an *in vivo* model of thioglycollate-induced migration of neutrophils into the peritoneal cavity of mice (THIOPMN). Of compounds **1**, **10**, **17**, and **23**, the most efficacious in THIOPMN was **1**, which provided 55% inhibition after an oral dose of 100 mg/kg. Compound **1** was next tested in the reverse passive Arthus reaction (RPAR), a model of neutrophil influx into the pleural cavity resulting from immune complex formation. In this model, a 100 mg/kg oral dose of **1** weakly inhibited the accumulation of neutrophils (44%) and exudate (42%). When **1** was administered *iv*, a 3 mg/kg dose provided inhibitions of 38% and 52%, respectively. In order to improve the bioavailabilty of these compounds, a series of analogs containing ionizable functionalities was synthesized. If *in vitro* potency was maintained, these compounds could be converted to salts for *in vivo* testing.

Unfortunately, the compounds that contained an

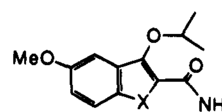
Table 4. Inhibition of Cell Adhesion by 5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamides containing a Carboxylic Acid Group



compd	R^1	adhesion[a]
39	C_6H_4-*p*-COOH	50
40	C_6H_4-*m*-COOH	28%
41	C_6H_4-o-COOH	35%
42	$(CH_2)_4COOH$	9%
43	CH_2COOH	NA[b]

[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 100 μM. Each percentage value is from a single assay that was run in triplicate. The mean standard error is less than 5%. Neutrophils were labeled with $Na^{51}CrO_4$. [b] NA: less than 4% inhibition at the testing concentration.

Table 5. Inhibition of Cell Adhesion by Heterocyclic Analogs of 1



compd	X	adhesion[a]
44	SO	8.7
45	SO_2	NA[b]
46	O	14
47	$(CH)_2$	11
48	NH	8.0
49	NMe	10

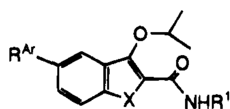
[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 100 μM. Each percentage value is from a single assay that was run in triplicate. The mean standard error is less than 5%. Neutrophils were labeled with $Na^{51}CrO_4$. [b] NA: less than 4% inhibition at the testing concentration.

ionizable group at C-3 (**36**–**38**) had weak *in vitro* activity in the cell adhesion assay (Table 3) and the derivatives with a carboxylic acid substituent within an alkyl amide at C-2 (**42** and **43**) were inactive (Table 4). However, the *p*-carboxylate benzamide **39**, had an IC_{50} of 50 μM. The isomeric ortho and meta analogs, **40** and **41**, were less potent. When the sodium salt of **39** was tested in THIOPMN, an oral dose of 100 mg/kg gave only 34% inhibition. Since this compound should be bioavailable, its poor activity *in vivo* is probably due to its decreased *in vitro* activity when compared to **1**.

With the exception of the sulfone **45**, all the direct heterocyclic analogs of **1** inhibited cell adhesion (Table 5). The sulfoxide **44**, the benzofuran **46**, the naphthalene **47**, and the indoles **48** and **49** all had IC_{50}s between 8.0 and 14 μM. The most active compound in RPAR was the sulfoxide **44**, which gave 68% and 93% inhibition at an oral dose of 10 mg/kg.[26] The only other analog active in RPAR was the *N*-methyl indole **49**, which gave 74 and 45% inhibition at 50 mg/kg. In the THIOPMN model **44** had an ID_{50} of 63 mg/kg when dosed orally.

As shown in Table 6, replacement of the 5-methoxy group of benzofuran **46** with a chloro, or proton substituent, **53** and **54**, decreased the *in vitro* activity and the ethyl- and phenylamide (**55** and **56**) analogs were inactive. A similar trend was observed in the naphthalene series. Compound **57**, which is devoid of aromatic substitution, was inactive. The ethylamide **58**, was less effective than the corresponding primary amide and the

Table 6. Inhibition of Cell Adhesion by Benzofuran, Naphthalene and Indole Analogs of 1



compd	X	R^{Ar}	R^1	adhesion[a]
53	O	Cl	H	52% at 100 μM
54	O	H	H	20% at 100 μM
55	O	OMe	Et	NA[b] at 100 μM
56	O	OMe	Ph	NA at 100 μM
57	CH=CH	H	H	NA at 33 μM
58	CH=CH	OMe	Et	73% at 100 μM
59	CH=CH	OMe	Ph	NA at 100 μM
61	NCH_2OMe	OMe	H	34
62	NH	OMe	Et	NA at 33 μM

[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 100 or 33 μM. Each percentage value is from a single assay that was run in triplicate. The mean standard error is less than 5%. Neutrophils were labeled with calcein-AM. [b] NA: less than 4% inhibition at the testing concentration.

phenylamide **59** was inactive. While the *N*-methyl **49** and unsubstituted indoles **48** were active, larger substituents on the indole nitrogen were detrimental, as was seen with the *N*-methoxymethyl derivative **61**. This was unfortunate since this position would be a third site to introduce an ionizable group. As in all the other series, indoles containing a secondary amide, such as **62**, were less active. Therefore, while the heteroatom of **1** could be varied, the structure requirements of a primary amide at C-2, and a lower alkoxy or hydroxy at C-5 were retained.

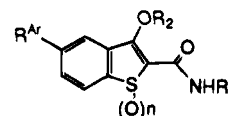
Due to the similar SAR observed with the benzo[*b*]thiophenes, benzofurans, indoles, and naphthalenes, it did not appear that ionizable functionality could be introduced into any of the new series and retain *in vitro* potency. Due to the oral activity of **44** in both THIO-PMN and RPAR, attention was focused on additional sulfoxides. The *in vivo* activity of **44** is attributed to the lower log *P* of this compound compared with **1** (1.5 vs 2.6), and also its 20-fold increase in water solubility, resulting in enhanced bioavailability.

A series of benzo[*b*]thiophene 1-oxides was prepared with the intention of increasing both the *in vitro* potency and *in vivo* activity. As is shown in Table 7, while the 5-hydroxy analog **73** blocked the adhesion of neutrophils to activated HUVECs, the 5-unsubstituted derivative **69** was inactive. Increasing the size of the amide substituent of **44** from methyl to ethyl to isopropyl to benzyl to phenyl (**66**, **67**, **68**, **64**, **65**) once again decreased the activity. Replacement of the 1-methylethoxy group of **44** with methoxy, **70**, or phenoxy, **71**, also resulted in decreased activity. An additional sulfone **72**, the 5-hydroxy analog of **45**, was not active *in vitro*.

After **44**, the two most active sulfoxides *in vitro* were the *N*-methyl analog **66** and the 5-hydroxy analog **73**. When these two compounds were tested orally in RPAR, **66** gave only marginal inhibition (20% and 39% at 50 mg/kg) and **73** was inactive. While the weak *in vivo* activity of **66** can be explained by its poor *in vitro* activity, **73** showed *in vitro* activity comparable to **44**, and was therefore expected to show *in vivo* activity.

Compound **44**, designated PD 144795, was tested in additional animal models of inflammation. When dosed orally in *Mycobacterium butyricum*-induced footpad

Table 7. Inhibition of Cell Adhesion by 3-Alkoxybenzo-[*b*]thiophene-2-carboxamide 1-Oxides and 1,1-Dioxides



compd	*n*	R^1	R^2	R^{Ar}	adhesion[a]
64	1	CH_2Ph	*i*-Pr	OMe	15%
65	1	Ph	*i*-Pr	OMe	NA[b]
66	1	Me	*i*-Pr	OMe	43%
67	1	Et	*i*-Pr	OMe	36%
68	1	*i*-Pr	*i*-Pr	OMe	8%
69	1	H	*i*-Pr	H	NA
70	1	H	Me	OMe	40%
71	1	H	Ph	OMe	15%
72	2	H	*i*-Pr	OH	NA
73	1	H	*i*-Pr	OH	80%

[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 100 μM. Each percentage value is from a single assay that was run in triplicate. The mean standard error is less than 5%. Neutrophils were labeled with calcein-AM. [b] NA: less than 4% inhibition at the testing concentration.

Table 8. Inhibition of Adhesion Molecule Expression via ELISA

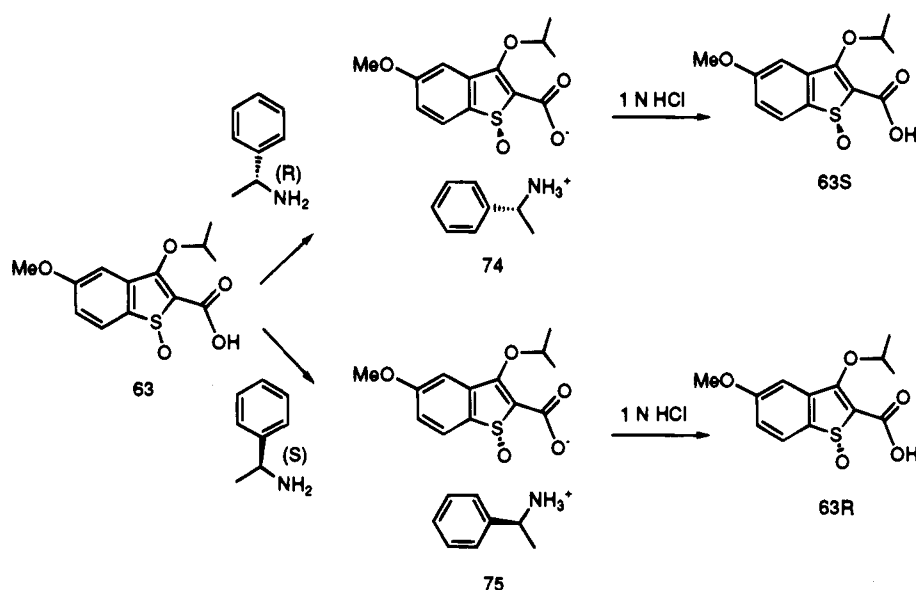
compd	adhesion[a]	ICAMH[b]	ESELH[c]	ICAMA[d]	VCAMA[e]
1	3.8	0.39	0.70	91%	84%
10	6.4	3.5	3.3	91%	not tested
11	35%	27%	NA[f]	21%	NA
12	24%	16%	21%	12%	NA
17	15	6.6	1.4	85%	83%
44	8.7	4.0	6.6	10	4.0
45	NA	15%	25%	not tested	not tested
46	14	5.0	7.9	not tested	not tested
47	11	5.2	8.6	86%	81%
48	8.0	2.5	7.9	89%	83%
49	10	3.7	9.2	92%	84%
73	80%	2.7	5.0	not tested	not tested
72	NA	21%	NA	not tested	not tested

[a] % Inhibition of adhesion at 100 μM or the IC_{50} (μM). [b] HUVEC assay, data reported as % inhibition of ICAM-1 surface expression at 30 μM or the IC_{50} (μM). Data shown is the average of two assays each performed in triplicate. The mean standard error is less than 10%. [c] HUVEC assay, data reported as % inhibition of E-selectin surface expression at 30 μM or the IC_{50} (μM). Data shown is the average of two assays each performed in triplicate. The mean standard error is less than 10%. [d] HAEC assay, data reported as % inhibition of ICAM-1 surface expression at 50 μM or the IC_{50} (μM). Data shown is the average of assays performed in duplicate or triplicate. The variation between the duplicates or triplicates was less than 10%. [e] HAEC assay, data reported as % inhibition of VCAM-1 surface expression at 50 μM or the IC_{50} (μM). Data shown is the average of assays performed in duplicate or triplicate. The variation between the duplicates or triplicates was less than 10%. [f] NA: less than 4% inhibition at the testing concentration.

edema, (MFE), a 3-day subacute model in the rat, PD 144795 inhibited swelling with an ID_{40} of 10.9 mg/kg.[26] When dosed orally in adjuvant-induced polyarthritis (AIP), a rat model of chronic inflammation, this compound had an ID_{50} of 12.0 mg/kg. Pharmacokinetic studies showed that PD 144795 was well absorbed and was not readily metabolized. PD 144795 was not an inhibitor of cyclooxygenase or 5-lipoxygenase and did not possess any activity in a wide variety of additional *in vitro* screens.

From the conditions employed in the *in vitro* assay, the adhesion molecules on the HUVECs responsible for neutrophil adherence would be E-selectin and ICAM-1. To confirm that these compounds were modulating the expression of these proteins, ELISAs (enzyme-linked immunosorbant assays) were developed. In these as-

Scheme 9



says, the HUVECs were treated with TNF-α in the presence of the compound for 4 h, and the level of surface E-selectin and ICAM-1 expression was measured via a double antibody technique. As shown in Table 8, **1** inhibited the expression of both adhesion molecules, as did **10**, the 5-hydroxy analog of **1**. The 7- and 6-methoxy analogs **11** and **12** did not have a strong effect on either E-selectin or ICAM-1 expression, while the methylamide, **17**, showed inhibition in both ELISAs. Of the heterocylic analogs of **1**, only the sulfone **45**, the analog not active in the adhesion assay, was inactive in the ELISAs. PD 144795 and the 5-hydroxy sulfoxide **73** showed good activity in the ELISA assays, while sulfone **72** was inactive.

The ability of PD 144795 to inhibit TNF-α-induced upregulation of E-selectin and ICAM-1 on HUVECs was confirmed by flow cytometry.[27] These studies also showed that PD 144795 blocked the induction of VCAM-1. While VCAM-1 is not involved in neutrophil adhesion to the endothelium, VCAM-1 does recognize the integrin VLA-4 (very late antigen-4) found on monocytes that also express LFA-1, a ligand for ICAM-1. Pretreatment of human aortic endothelial cells (HAECs) with TNF-α overnight resulted in the upregulation of VCAM-1 and ICAM-1 leading to an increase in the number of adherent U937 monocytic cells.[28] This monocyte adhesion was reduced when the HAECs were preincubated with both TNF-α and PD 144795 (IC_{50} = 8.8 μM).

In ELISAs measuring the expression of adhesion molecules on the surface of TNF-α activated HAECs, PD 144795 prevented the upregulation of VCAM-1 and ICAM-1 with IC_{50}s of 4.0 and 10 μM respectively.[29] When several analogs of PD 144795 were tested in these ELISAs (Table 8) those compounds that blocked ICAM-1 and E-selectin expression in the HUVECs also blocked VCAM-1 and ICAM-1 expression in the HAECs. Northern blot analysis of the mRNA of HAECs and HUVECs treated with PD 144795 and TNF-α indicated reduced levels of both ICAM-1 and VCAM-1 mRNA compared to the TNF-α treated controls.[29,30] The HUVECs treated with PD 144795 also showed reduced mRNA levels for E-selectin.[30]

NF-kB transcriptional factors are protein subunits which recognize the kB regulatory sequences found in several genes including E-selectin, ICAM-1, and VCAM-1.[31] A compound that inhibited the activation of this common transcription factor would result in decreased synthesis of these adhesion molecules. Mobililty shift assays using nuclear extracts from HAECs treated with PD 144795 and TNF-α showed no decrease in NF-kB activation compared to controls.[29] This same effect was observed in HUVECs,[30] implying that in both these cell types PD 144795 modulates the expression of TNF-α responsive genes with no apparent effect on NF-kB.

Table 9. Activity of the S and R Enantiomers of PD 144795 (**44**)

compd	adhesion[a]	ICAMH/ESELH[a]	MFE[b]
44-rac	8.7	4.0/6.6	10.9
44*S*	4.0	5.7/9.6	83%
44*R*	20%	24%/25%	5%

[a] Data reported as IC_{50} (μM) or as the % inhibition at a testing concentration of 50 μM. [b] Data reported as ID_{40} (mg/kg) or the % inhibition at a dose of 50 mg/kg.

Assays were performed to ensure that PD 144795 was not cytotoxic to the endothelial cells. Morphological evaluation of the PD 144795 treated HUVECs by light microscopy did not reveal any adverse effects on cell structure or monolayer integrity. PD 144795 did not induce the HUVECs to release lactate dehydrogenase, suggesting that the compound was not cytotoxic. In calcein-AM and ethidium homodimer uptake studies in HUVECs, no toxicity was noted up to 30 μM concentrations of PD 144795. Incorporation of tritiated leucine into the HAECs was not affected at concentrations of PD 144795 up to 50 μM.

The sulfoxide group of PD 144795 imparts chirality to the molecule. The precursor acid **63** was readily separated into its enantiomers via a classical resolution with α-methylbenzylamine (Scheme 9). The intermediate salts **74** and **75** were subjected to single-crystal X-ray analysis to determine the configuration of the sulfoxide. The salts were hydrolyzed to provide **63*S*** and **63*R***, which were converted into the corresponding enantiomers of PD 144795, **44*S*** and **44*R***. When the enantiomers were tested *in vitro*, in the neutrophil adhesion and ELISA assays for ICAM-1 and E-selectin expression, activity was found to reside in **44*S*** (Table

9). This same separation of activity was observed *in vivo*. When tested in MFE, a 50 mg/kg oral dose of **44S** provided 83% inhibition of swelling, while a similar dose of **44R** was inactive.

Conclusions

Benzo[*b*]thiophene-2-carboxamides and related benzofurans, naphthalenes, and indoles were found to inhibit the adhesion of neutrophils and monocytes to stimulated endothelium by modulating the expression of E-selectin, ICAM-1, and VCAM-1. The prototype compound, PD 144795, was orally active in models of inflammation, with the activity residing predominately in the *S*-enantiomer. Continuing studies are underway to elucidate the mechanism of action of PD 144795 and additional compounds.

Experimental Section

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

5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (1). To a solution of 5-methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic acid (**3**,[17] 20.0 g, 75.2 mmol) in 270 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (15.2 g, 94.0 mmol). The solution was heated at reflux for 1 h and then allowed to cool to room temperature and concentrated aqueous ammonium hydroxide (20 mL) was added. The solution was stirred at room temperature for 25 min and then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallization from methanol gave 16.4 g (82%) of **1**: mp 152–154 °C; ^{1}H NMR (DMSO-d_6) δ 1.38 (d, J = 6 Hz, 6H), 3.86 (s, 3H), 4.78 (heptet, J = 6 Hz, 1H), 7.14 (dd, J = 8.5, 2 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 7.34 (br s, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.86 (br s, 1H). Anal. ($C_{13}H_{15}NO_3S$) C, H, N.

General Procedure for the Preparation of Benzo[*b*]thiophene-2-carboxamides from the Corresponding Benzo[*b*]thiophene-2-carboxylic Acids; Used To Prepare 4–8, 11, and 13–15. To 1.0 mmol of a substituted benzo[*b*]thiophene-2-carboxylic acid[17] in 10 mL of tetrahydrofuran was added 1.3 mmol of 1,1′-carbonyldiimidazole. The solution was heated at reflux for 1 h and then allowed to cool to room temperature. An excess of concentrated aqueous ammonium hydroxide was added and the solution was stirred at room temperature for 0.5 to 2.0 h. The mixture was partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Analytical products were obtained via column chromatography and/or recrystallization.

3-(1-Methylethoxy)benzo[*b*]thiophene-2-carboxamide (4): Yield 62%; mp 162–164 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (d, J = 6 Hz, 6H), 4.79 (heptet, J = 6 Hz, 1H), 7.37 (br s, 1H), 7.42–7.55 (m, 2H), 7.85–7.89 (m, 2H), 7.97 (dd, J = 8.5, 2 Hz, 1H). Anal. ($C_{12}H_{13}NO_2S$) C, H, N, S.

5-Chloro-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (5): Yield 92%; mp 165–167 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (d, J = 6 Hz, 6H), 4.76 (heptet, J = 6 Hz, 1H), 7.36 (br s, 1H), 7.50 (dd, J = 8.5, 2 Hz, 1H), 7.84 (d, J = 2 Hz, 1H), 7.93 (br s, 1H), 8.00 (d, J = 8.5 Hz, 1H). Anal. ($C_{12}H_{12}ClNO_2S$) C, H, N.

5-Methyl-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (6): Yield 94%; mp 153–154 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (d, J = 6 Hz, 6H), 2.45 (s, 3H), 4.79 (heptet, J = 6 Hz, 1H), 7.31–7.33 (m, 2H), 7.64 (s, 1H), 7.83 (br s, 1H), 7.84 (d, J = 8.5 Hz, 1H). Anal. ($C_{13}H_{15}NO_2S$) C, H, N.

3-(1-Methylethoxy)-5-nitrobenzo[*b*]thiophene-2-carboxamide (7): Yield 85%; mp 205–207 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (d, J = 6 Hz, 6H), 4.82 (heptet, J = 6 Hz, 1H), 7.46 (br s, 1H), 8.04 (br s, 1H), 8.28 (s, 2H), 8.56 (s, 1H). Anal. ($C_{12}H_{12}N_2O_4S$) C, H, N.

3-(1-Methylethoxy)-5-(phenylmethoxy)benzo[*b*]thiophene-2-carboxamide (8): Yield 64%; mp 172–173 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, J = 6 Hz, 6H), 4.66 (heptet, J = 6 Hz, 1H), 5.24 (s, 2H), 7.21 (dd, J = 9, 2 Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 7.31 (br s, 1H), 7.34 (d, J = 7 Hz, 1H), 7.40 (m, 2H), 7.49 (d, J = 7 Hz, 2H), 7.83 (br s, 1H), 7.85 (d, J = 9 Hz, 1H). Anal. ($C_{19}H_{19}NO_3S$) C, H, N.

7-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (11): Yield 91%; mp 157–159 °C; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 6 Hz, 6H), 3.97 (s, 3H), 4.78 (heptet, J = 6 Hz, 1H), 7.06 (dd, J = 6.5, 2 Hz, 1H), 7.38 (br s, 1H), 7.43 (m, 2H), 7.87 (br s, 1H). Anal. ($C_{13}H_{15}NO_3S$) C, H, N.

3-(1,1-Dimethylethoxy)-5-methoxybenzo[*b*]thiophene-2-carboxamide (13): Yield 74%; mp 180–181 °C; ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 9H), 3.83 (s, 3H), 7.11 (dd, J = 9, 2.5 Hz, 1H), 7.15 (br s, 1H), 7.24 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 9 Hz, 1H), 7.87 (br s, 1H). Anal. ($C_{14}H_{17}NO_3S$) C, H, N.

3,5-Dimethoxybenzo[*b*]thiophene-2-carboxamide (14): Yield 70%; mp 184–185 °C; ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H), 4.07 (s, 3H), 7.14 (dd, J = 9, 2.5 Hz, 1H), 7.32 (d, J = 2.5 Hz, 1H), 7.46 (br s, 1H), 7.83 (br s, 1H), 7.85 (d, J = 9 Hz, 1H). Anal. ($C_{11}H_{11}NO_3S$) C, H, N.

5-Methoxy-3-(phenylmethoxy)benzo[*b*]thiophene-2-carboxamide (15): Yield 72%; mp 149–151 °C; ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 3H), 5.35 (s, 2H), 7.12 (dd, J = 9, 2.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.30 (br s, 1H), 7.3–7.4 (m, 3H), 7.50–7.53 (m, 2H), 7.80 (br s, 1H), 7.84 (d, J = 9 Hz, 1H). Anal. ($C_{17}H_{15}NO_3S$) C, H, N.

5-Amino-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (9). A mixture of **7** (104 mg, 0.37 mmol) and 5% palladium on carbon (10 mg) in 20 mL of acetic acid was sealed under a hydrogen atmosphere in a Parr apparatus and shaken for 1.5 h. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The crude product was chromatographed eluting with 1:2 hexane/ethyl acetate providing 62 mg (67%) of **10**: mp 150–151 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, J = 6 Hz, 6H), 4.70 (heptet, J = 6 Hz, 1H), 5.29 (br s, 2H), 6.83 (dd, J = 8.5, 2 Hz, 1H), 6.93 (d, J = 2 Hz, 1H), 7.27 (br s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.73 (br s, 1H). Anal. ($C_{12}H_{14}N_2O_2S{\cdot}0.05EtOAc$) C, H, N.

5-Hydroxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (10). A mixture of **8** (120 mg, 0.35 mmol) and 20% palladium on carbon (50 mg) in 40 mL of acetic acid was sealed under a hydrogen atmosphere in a Parr apparatus and shaken at 50 psi for 72 h. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The crude product was chromatographed eluting with a gradient of 1:1 to 1:2 hexane/ethyl acetate providing 49 mg (56%) of **10**: mp 237–240 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 6 Hz, 6H), 4.68 (heptet, J = 6 Hz, 1H), 6.98 (dd, J = 8.5, 2 Hz, 1H), 7.12 (d, J = 2 Hz, 1H), 7.30 (br s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.80 (br s, 1H), 9.71 (s, 1H). Anal. ($C_{12}H_{13}NO_3S$) C, H, N.

6-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (12). Lithium (74 mg, 10 mmol) was added portionwise to a −78 °C solution of a catalytic amount of ferric nitrate in 10 mL of liquid ammonia. The dry ice/acetone bath was removed and the reaction mixture allowed to warm to reflux. When the gray color of lithium amide remained for 10 min, 2 mL of freshly distilled tetrahydrofuran was slowly added followed by a solution of methyl 6-methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylate[17] (200 mg, 0.71 mmol) in 2 mL of tetrahydrofuran. The ammonia was allowed to evaporate and the reaction solution was diluted with ethyl acetate and washed with aqueous HCl, followed by water and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crystalline residue was suspended

in 1:9 ethyl acetate/hexane and filtered to afford 125 mg (66%) of **12**: mp 164–166 °C; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 6 Hz, 6H), 3.84 (s, 3H), 4.76 (heptet, J = 6 Hz, 1H), 7.04 (dd, J = 9, 2 Hz, 1H), 7.23 (br s, 1H), 7.53 (d, J = 2 Hz, 1H), 7.74 (d, J = 9 Hz, 1H), 7.7 (br s, 1H). Anal. ($C_{13}H_{15}NO_3S$) C, H, N.

5-Methoxy-3-phenoxybenzo[*b*]thiophene-2-carboxamide (16). Oxalyl chloride (8.3 g, 65.3 mmol) was added dropwise to a solution of 5-methoxy-3-phenoxybenzo[*b*]thiophene-2-carboxylic acid[17] (13.12 g, 43.7 mmol) in 150 mL of tetrahydrofuran. Four drops of dimethylformamide were added, and the solution was stirred at room temperature for 1 h and then concentrated *in vacuo*. The resulting solid was dissolved in 60 mL of tetrahydrofuran and added dropwise to 250 mL of cold concentrated aqueous ammonium hydroxide. The reaction mixture was stirred for 1 h and then poured into 800 mL of cold water. The resultant solid was collected by filtration and recrystallized from ethyl acetate to provide 11.0 g (84%) of **16**: mp 197.5–198.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 3H), 6.72 (d, J = 2 Hz, 1H), 7.03 (d, J = 8 Hz, 2H), 7.12–7.17 (m, 2H), 7.28 (br s, 1H), 7.35–7.39 (m, 2H), 7.86 (br s, 1H), 7.94 (d, J = 9 Hz, 1H). Anal. ($C_{16}H_{13}NO_3S$) C, H, N.

5-Methoxy-*N*-methyl-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (17). To a solution of **3** (1.0 g, 4.0 mmol) in 40 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (0.7 g, 4.4 mmol). The reaction was stirred for 2 h at room temperature, and then ethylamine was passed through the reaction solution for 10 min. The solution was stirred overnight, diluted with ethyl acetate, and washed with 1 N HCl, saturated aqueous $NaHCO_3$, water, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate/hexane to give 660 mg (59%) of **17**: mp 104–105 °C; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 6 Hz, 6H), 2.85 (d, J = 5 Hz, 3H), 3.85 (s, 3H), 4.69 (heptet, J = 6 Hz, 1H), 7.13 (dd, J = 9, 2 Hz, 1H), 7.18 (d, J = 2 Hz, 1H), 7.84 (d, J = 9 Hz, 1H), 7.8 (br s, 1H). Anal. ($C_{14}H_{17}NO_3S$) C, H, N.

General Procedure for the Preparation of N-Substituted 5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamides from 5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid;[17] Used To Prepare 18–21. To 1.0 mmol of **3** in 10 mL of tetrahydrofuran was added 1.3 mmol of 1,1′-carbonyldiimidazole. The solution was heated at reflux for 1 h then allowed to cool to room temperature. An excess of a primary amine was added and the solution was stirred at room temperature for 0.5 to 2.0 h. The mixture was partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Analytical products were obtained via column chromatography and/or recrystallization.

***N*-Ethyl-5-methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide (18):** Yield 62%; mp 60–62 °C; ^{1}H NMR (DMSO-d_6) δ 1.56 (t, J = 7 Hz, 3H), 1.37 (d, J = 6 Hz, 6H), 3.3–3.4 (m, 2H), 3.85 (s, 3H), 4.72 (heptet, J = 6 Hz, 1H), 7.13 (dd, J = 9, 2.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.84 (d, J = 9 Hz, 1H), 7.90 (t, J = 6 Hz, 1H). Anal. ($C_{15}H_{19}NO_3S$) C, H, N.

5-Methoxy-3-(1-methylethoxy)-*N*-(1-methylethyl)benzo[*b*]thiophene-2-carboxamide (19): Yield 76%; mp 64.5–65.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J = 6.5 Hz, 6H), 1.37 (d, J = 6 Hz, 6H), 3.85 (s, 3H), 4.0–4.2 (m, 1H), 4.78 (heptet, J = 6 Hz, 1H), 7.14 (dd, J = 9, 2.5 Hz, 1H), 7.21 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.85 (d, J = 9 Hz, 1H). Anal. ($C_{16}H_{21}NO_3S$) C, H, N.

5-Methoxy-3-(1-methylethoxy)-*N*-phenylbenzo[*b*]thiophene-2-carboxamide (20): [Note: An equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene was added to the reaction mixture.] Yield 27%; mp 116–118 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (d, J = 6 Hz, 6H), 3.88 (s, 3H), 4.80 (heptet, J = 6 Hz, 1H), 7.12–7.16 (m, 1H), 7.19 (dd, J = 9, 2 Hz, 1H), 7.27 (d, J = 2 Hz, 1H), 7.40 (t, J = 8 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.91 (d, J = 9 Hz, 1H), 9.89 (s, 1H). Anal. ($C_{19}H_{19}NO_3S$) C, H, N.

5-Methoxy-3-(1-methylethoxy)-*N*-(phenylmethyl)benzo[*b*]thiophene-2-carboxamide (21): Yield 81%; mp 85–86 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (d, J = 6 Hz, 6H), 3.85 (s, 3H), 4.53 (d, J = 6 Hz, 2H), 4.70 (heptet, J = 6 Hz, 1H), 7.14 (dd, J = 9, 2.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.2–7.4 (m, 5H), 7.86 (d, J = 9 Hz, 1H), 8.30 (t, J = 6 Hz, 1H). Anal. ($C_{20}H_{21}NO_3S$) C, H, N.

3-Chloro-5-methoxybenzo[*b*]thiophene-2-carboxamide (22). To a suspension of 3-chloro-5-methoxybenzo[*b*]thiophene-2-carbonyl chloride[16] (**2**, 1.52 g, 5.82 mmol) in 80 mL of toluene at 50 °C was added dropwise 10 mL of concentrated aqueous ammonium hydroxide. The resulting precipitate was collected by filtration and recrystallized from methanol to provide 267 mg (19%) of **22**: mp 220–222 °C; ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H), 7.22 (dd, J = 9, 2.5 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.79 (br s, 1H), 7.98 (d, J = 9 Hz, 1H), 8.07 (br s, 1H). Anal. ($C_{10}H_8ClNO_2S$) C, H, N.

5-Methoxy-3-[(1-methylethyl)thio]benzo[*b*]thiophene-2-carboxamide (23). 2-Propanethiol (1.1 mL, 12.4 mmol) was added to a suspension of **22** (3.00 g, 12.4 mmol) in 24 mL of dimethylformamide. 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.8 mL, 12.4 mmol) was added and the mixture was warmed to 80 °C. After 6 h, additional 2-propanethiol (110 μL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (180 μL) were added and heating was continued for 1 h. The reaction mixture was cooled, diluted with ethyl acetate and washed with 1 N NaOH, 1 N HCl, water and brine. The organic layer was dried over $MgSO_4$. Filtration followed by concentration *in vacuo* and recrystallization from ethyl acetate/hexane gave 235 mg (80%) of **23**. An analytical sample was obtained by a second recrystallization from ethyl acetate/hexane: mp 143–143.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (d, J = 6.5 Hz, 6H), 3.41 (heptet, J = 6.5 Hz, 1H), 3.87 (s, 3H), 7.18 (dd, J = 9, 2.5 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 8.23 (br s, 1H), 8.32 (br s, 1H). Anal. ($C_{13}H_{15}NO_2S_2$) C, H, N.

5-Methoxy-3-(phenylthio)benzo[*b*]thiophene-2-carboxamide (24). Thiophenol (116 μL, 1.13 mmol) was added to a suspension of **22** (250 mg, 1.03 mmol) in 2 mL of dimethylformamide. 1,8-Diazabicyclo[5.4.0]undec-7-ene (169 μL, 1.13 mmol) was added and the mixture warmed to 80 °C. After 2 h the reaction mixture was cooled, diluted with ethyl acetate and washed with 1 N NaOH, 1 N HCl, water, and brine. The organic layer was dried over $MgSO_4$. Filtration followed by concentration *in vacuo* and recrystallization from ethyl acetate/hexane gave 270 mg (84%) of **24**: mp 194–196 °C; ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 3H), 7.1–7.4 (m, 7H), 7.9–8.0 (m, 1H), 8.09 (br s, 1H), 8.12 (br s, 1H). Anal. ($C_{16}H_{13}NO_2S_2$) C, H, N.

5-Methoxy-3-(methylthio)benzo[*b*]thiophene-2-carboxamide (25). Sodium thiomethoxide (93 mg, 1.32 mmol) was added to a suspension of **22** (250 mg, 1.03 mmol) in 2 mL of dimethylformamide. After 1 h an additional amount of sodium thiomethoxide (13 mg) was added. The reaction mixture was diluted with ethyl acetate and washed with 1 N NaOH, 1 N HCl, water, and brine. The organic layer was dried over $MgSO_4$. Filtration followed by concentration *in vacuo* and recrystallization from ethyl acetate/hexane gave 190 mg (72%) of **25**: mp 171–173 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H), 3.89 (s, 3H), 7.18 (dd, J = 9, 2.5 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 8.15 (br s, 1H), 8.23 (br s, 1H). Anal. ($C_{11}H_{11}NO_2S_2$) C, H, N.

3-Chloro-5-methoxybenzo[*b*]thiophene-2-carboxylic Acid (26). To a solution of **2** (10.0 g, 38.3 mmol) in 80 mL of tetrahydrofuran was added sodium hydroxide (3.1 g, 76.6 mmol) in 400 mL of water. The solution was stirred at room temperature overnight, heated at 50 °C for 15 min, and then cooled to room temperature. HCl (1 N) was added until a pH of 1 was reached. The acidic solution was cooled to 0 °C and the resultant solid collected to give 7.5 g (81%) of **26**: mp >260 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 7.28 (d, J = 9 Hz, 1H), 7.33 (s, 1H), 7.99 (d, J = 9 Hz, 1H). Anal. ($C_{10}H_7ClO_3S$) C, H.

3-Chloro-5-methoxy-*N*-methylbenzo[*b*]thiophene-2-carboxamide (27). To a solution of **26** (1.5 g, 6.2 mmol) in 100 mL of acetonitrile was added 1,1′-carbonyldiimidazole (1.1 g, 6.8 mmol). The reaction was heated at reflux for 1.5 h and then cooled to room temperature. Methylamine gas was blown through a 33.3 mL aliquot of this reaction solution. After a few minutes the reaction was diluted with diethyl ether and washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and

concentrated *in vacuo* to a volume of 10 mL. This solution was cooled, and the precipitated crystals collected to give 310 mg (58%) of **27**: mp 147.5–148.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.84 (d, *J* = 4.5 Hz, 3H), 3.88 (s, 3H), 7.21 (dd, *J* = 9, 2.5 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 1H), 7.98 (d, *J* = 9 Hz, 1H), 8.3–8.4 (m, 1H). Anal. ($C_{11}H_{10}ClNO_2S$) C, H, N.

3-Chloro-5-methoxy-*N*-(1-methylethyl)benzo[*b*]thiophene-2-carboxamide (28). To a 33.3 mL aliquot removed from the above reaction solution (preparation of **27**) was added isopropylamine (640 μL, 7.40 mmol). After 30 min the reaction was diluted with diethyl ether and washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a volume of 10 mL. The precipitated crystals were collected to give 437 mg (74%) of **28**: mp 157–158 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (d, *J* = 6.5 Hz, 6H), 3.88 (s, 3H), 4.0–4.2 (m, 1H), 7.21 (dd, *J* = 9, 2.5 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 1H), 7.97 (d, *J* = 9 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H). Anal. ($C_{13}H_{14}ClNO_2S$) C, H, N.

5-Methoxy-*N*-methyl-3-[(1-methylethyl)thio]benzo[*b*]thiophene-2-carboxamide (29). To a solution of **27** (150 mg, 0.59 mmol) and 2-propanethiol (163 μL, 1.76 mmol) in 1.7 mL of dimethylformamide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (351 μL, 2.35 mmol). The reaction was stirred for 24 h then diluted with ethyl acetate and washed with 1 N NaOH, 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by crystallization from ethyl acetate/hexane then by chromatography eluting with 1:9 ethyl acetate/hexane to give 95 mg (54%) of **29**: mp 125–126 °C; ^{1}H NMR (DMSO-d_6) δ 1.19 (d, *J* = 6.5 Hz, 6H), 2.89 (d, *J* = 5 Hz, 3H), 3.38 (heptet, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 7.17 (dd, *J* = 9, 2.5 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.94 (d, *J* = 9 Hz, 1H), 8.6–8.7 (m, 1H). Anal. ($C_{14}H_{17}NO_2S_2$) C, H, N.

5-Methoxy-*N*-(1-methylethyl)-3-[(1-methylethyl)thio]benzo[*b*]thiophene-2-carboxamide (30). To a solution of **28** (175 mg, 0.62 mmol) and 2-propanethiol (172 μL, 1.85 mmol) in 2.0 mL of dimethylformamide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (369 μL, 2.47 mmol). The reaction was stirred for 24 h and then diluted with ethyl acetate and washed with 1 N NaOH, 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography eluting with 5:95 ethyl acetate/hexane to give 119 mg (59%) of **30**: mp 77.5–78 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (d, *J* = 6.5 Hz, 6H), 1.24 (d, *J* = 6.5 Hz, 6H), 3.3–3.4 (m, 1H), 3.87 (s, 3H), 4.0–4.2 (m, 1H), 7.17 (dd, *J* = 9, 2 Hz, 1H), 7.41 (d, *J* = 2 Hz, 1H), 7.95 (d, *J* = 9 Hz, 1H), 8.66 (d, *J* = 7.5 Hz, 1H). Anal. ($C_{16}H_{21}NO_2S_2$) C, H, N.

3-[(1-Methylethyl)thio]benzo[*b*]thiophene-2-carboxamide (31). To 3-[(1-methylethyl)thio]benzo[*b*]thiophene-2-carboxylic acid[18] (133 mg, 0.53 mmol) in 6 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (99 mg, 0.61 mmol). The mixture was heated at reflux for 1.5 h and then cooled slightly. Concentrated aqueous ammonium hydroxide (1 mL) was added and the reaction mixture stirred at room temperature for 30 min and then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography eluting with 1:1 hexane/ethyl acetate to provide 110 mg (83%) of **31**: mp 183–185 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (d, *J* = 6.5 Hz, 6H), 3.40 (heptet, *J* = 6.5 Hz, 1H), 7.54 (m, 2H), 8.03 (m, 2H), 8.20 (br s, 1H), 8.25 (br s, 1H). Anal. ($C_{12}H_{13}NOS_2$) C, H, N.

3-Chloro-5-(phenylmethoxy)benzo[*b*]thiophene-2-carboxamide (32). To a warm solution of 3-chloro-5-(phenylmethoxy)benzo[*b*]thiophene-2-carbonyl chloride (2.0 g, 6 mmol)[17] in 20 mL of toluene was added dropwise 10 mL of concentrated aqueous ammonium hydroxide. The resulting precipitate was collected by filtration washing with ethyl alcohol to provide 1.6 g (84%) of **32**: mp 205.5–206 °C; ^{1}H NMR (DMSO-d_6) δ 5.25 (s, 2H), 7.27–7.52 (m, 7H), 7.79 (br s, 1H), 7.98 (d, *J* = 9 Hz, 1H), 8.07 (br s, 1H). Anal. ($C_{16}H_{12}ClNO_2S_2$) C, H, N.

3-[(1-Methylethyl)thio]-5-(phenylmethoxy)benzo[*b*]thiophene-2-carboxamide (33). 2-Propanethiol (0.8 mL, 8 mmol) was added to a solution of **32** (1.0 g, 3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.6 mL, 17 mmol) in 10 mL of dimethylformamide and the mixture warmed to 55 °C for 1 h. The reaction mixture was cooled, poured into water, and stirred. After 1 h the precipitate was collected by filtration and washed with water to provide 1.1 g (98%) of **33**: mp 150–152 °C; ^{1}H NMR (DMSO-d_6) δ 1.14 (d, *J* = 6.5 Hz, 6H), 3.25 (heptet, *J* = 6.5 Hz, 1H), 5.26 (s, 2H), 7.23–7.53 (m, 7H), 7.95 (d, *J* = 9 Hz, 1H), 8.17 (br s, 1H), 8.21 (br s, 1H). Anal. ($C_{19}H_{19}NO_2S_2$) C, H, N.

5-Hydroxy-3-[(1-methylethyl)thio]benzo[*b*]thiophene-2-carboxamide (34). Thionyl chloride (17.9 mL, 245 mmol) was added dropwise to a stirred solution of 3-acetoxycinnamic acid[19] (10.0 g, 49 mmol), dimethylformamide (3.8 mL, 4.9 mmol), and pyridine (400 μL, 0.5 mmol) in 75 mL of chlorobenzene at 95–105 °C, and the mixture was slowly heated to vigorous reflux (125–130 °C) with provision for scrubbing the copious outgas. After 6 h the mixture was cooled and concentrated *in vacuo*. The solid residue was triturated with methyl *tert*-butyl ether and filtered. Recrystallization from toluene gave 10.6 g of a mixture of the 5- and 7-acetoxy isomers. Repeated recrystallization from acetonitrile gave 3-chloro-5-acetoxybenzo[*b*]thiophene-2-carbonyl chloride: mp 155–157 °C; ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H), 7.44 (dd, *J* = 8.5, 2 Hz, 1H), 7.71 (d, *J* = 2 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H). Anal. ($C_{11}H_6Cl_2O_3S$) C, H.

Concentrated aqueous ammonium hydroxide (1 mL) was added to a solution of the above acid chloride (250 mg, 0.90 mmol) in 5 mL of tetrahydrofuran. The solution was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was triturated with 30 mL of water and filtered to afford 200 mg of 3-chloro-5-hydroxybenzo[*b*]thiophene-2-carboxamide: mp 278 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.07 (dd, *J* = 8.5, 2 Hz, 1H), 7.17 (d, *J* = 2 Hz, 1H), 7.73 (br s, 1H), 7.86 (d, *J* =8.5 Hz, 1H), 8.02 (br s, 1H), 9.92 (s, 1H).

2-Propanethiol (160 μL, 1.70 mmol) was added to a solution of the above amide (160 mg, 0.70 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (700 μL, 4.70 mmol) in 5 mL of dimethylformamide. The mixture was stirred at 55 °C for 2 h, poured into 70 mL of water, and acidified with 4 N HCl. After 1 h the precipitate was collected and washed with water to afford 180 mg (96%) of **34**, which was purified by recrystallization from ethanol: mp 218–219 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (d, *J* = 6.5 Hz, 6H), 3.35 (m, obscured by water peak), 7.02 (d, *J* = 8.5 Hz, 1H), 7.35 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 8.12 (br s, 1H), 8.20 (br s, 1H), 9.75 (s, 1H). Analysis for $C_{12}H_{13}NO_2S_2$ requires: C, 53.91; H, 4.90; N, 5.24. Found: C, 53.38; H, 4.82; N, 5.26.

3-Mercapto-5-methoxybenzo[*b*]thiophene-2-carboxamide (35). 1,8-Diazabicyclo[5.4.0]undec-7-ene (4.38 mL, 29.28 mmol) was added to a room temperature solution of **24** (2.36 g, 9.76 mmol) and thioacetamide (2.35 g, 31.24 mmol) in 25 mL of dimethylformamide. The mixture was warmed to 80 °C for 5.5 h, then cooled, diluted with ethyl acetate, and washed with 1 N HCl and water. The organic layer was extracted 4 times with 1 N NaOH followed by water. The basic layers were combined and acidified with 6 N HCl. The precipitate was filtered and washed with water. Recrystallization from ethyl acetate/hexane gave 1.67 g (71%) of **35**: mp 205 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.54 (s, 3H), 6.88 (d, *J* = 2 Hz, 1H), 7.05 (dd, *J* = 9, 2 Hz, 1H), 7.87 (d, *J* = 9 Hz, 1H), 7.6–8.0 (br s, 2H). Anal. ($C_{10}H_9NO_2S_2$) C, H, N.

5-[[2-(Aminocarbonyl)-5-methoxybenzo[*b*]thien-3-yl]thio]pentanoic Acid (36). Methyl 5-bromovalerate (144 μL, 1.00 mmol) was added to a room temperature solution of **35** (200 mg, 0.84 mmol) in 8 mL of tetrahydrofuran followed by sodium bicarbonate (351 mg, 4.18 mmol) and the reaction mixture stirred at room temperature overnight. Additional methyl 5-bromovalerate (100 μL) was added and the reaction mixture stirred at room temperature for 3 days, then diluted with ethyl acetate, and washed with 1 N HCl, water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$. Filtration, followed by concentration *in vacuo* and recrystallization from ethyl acetate/hexane gave methyl 5-[[2-

(aminocarbonyl)-5-methoxybenzo[*b*]thien-3-yl]thio]pentanoate in 30% yield; mp 134.5–135.5 °C.

A mixture of this ester (150 mg, 0.42 mmol) and lithium hydroxide monohydrate (18 mg, 0.42 mmol) in 2 mL of water and 2 mL of methanol was heated at reflux for 6.5 h during which time additional lithium hydroxide monohydrate (5 mg) was added. The reaction mixture was cooled, diluted with ethyl acetate, and washed with 1 N HCl, water and brine. The organic layer was dried over $MgSO_4$. Filtration followed by concentration *in vacuo* and recrystallization from ethyl acetate/hexane gave 126 mg (88%) of **36**: mp 171.5–172 °C; ^{1}H NMR (DMSO-d_6) δ 1.4–1.7 (m, 4H), 2.17 (t, J = 7 Hz, 2H), 2.89 (t, J = 7 Hz, 2H), 3.88 (s, 3H), 7.18 (dd, J = 9, 2.5 Hz, 1H), 7.41 (d, J = 2.5 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 8.17 (br s, 1H), 8.21 (br s, 1H). Anal. ($C_{15}H_{17}NO_4S_2$) C, H, N.

[[2-(Aminocarbonyl)-5-methoxybenzo[*b*]thien-3-yl]thio]acetic Acid (37). Sodium bicarbonate (219 mg, 2.60 mmol) was added to a room temperature solution of bromoacetic acid (72 mg, 0.52 mmol) and **35** (50 mg, 0.21 mmol) in 3 mL of tetrahydrofuran. The reaction mixture was stirred at room temperature for 4 h, then diluted with ethyl acetate, and washed with 1 N HCl and brine. The organic layer was dried over $MgSO_4$. Filtration followed by concentration *in vacuo* and recrystallization from ethyl acetate/hexane provided 34 mg (54%) of **37**: mp 126–127 °C; ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 2H), 3.89 (s, 3H), 7.17 (dd, J = 9, 2.5 Hz , 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 8.17 (br s, 1H), 8.36 (br s, 1H), 12.90 (br s, 1H). Anal. ($C_{12}H_{11}NO_4S_2$) C, H, N.

3-[[2-(Dimethylamino)ethyl]thio]-5-methoxybenzo[*b*]thiophene-2-carboxamide (38). To a solution of **22** (250 mg, 1.03 mmol) and 2-(dimethylamino)ethanethiol hydrochloride (810 mg, 5.70 mmol) in 3 mL of dimethylformamide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (3.4 mL, 22.7 mmol). The reaction was warmed to 50 °C, stirred overnight, then diluted with ethyl acetate, and washed four times with water, followed by 1 N NaOH and an aqueous solution of citric acid. Saturated aqueous $NaHCO_3$ was added to the acidic layer and the resultant basic solution was extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a solid which was recrystallized from methanol/water to give 155 mg (48%) of **38**: mp 135.0–135.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.09 (s, 6H), 2.28 (t, J = 6 Hz, 2H), 3.05 (t, J = 6 Hz, 2H), 3.88 (s, 3H), 7.14–7.20 (m, 1H), 7.41 (s, 1H), 7.94 (d, J = 9 Hz,1H), 8.05 (br s, 1H), 8.97 (br s, 1H). Anal. ($C_{14}H_{18}N_2O_2S_2$) C, H, N.

4-[[[5-Methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]benzoic Acid (39). To a solution of **3** (353 mg, 1.32 mmol) in 5 mL of tetrahydrofuran was added oxalyl chloride (140 mL, 1.60 mmol) followed by one drop of dimethylformamide. The solution was stirred at room temperature for 1 h and then concentrated *in vacuo*. The resulting solid was added in portions to a 0 °C solution of methyl 4-aminobenzoate (250 mg, 1.65 mmol) and triethylamine (220 μL, 1.58 mmol) in 10 mL of tetrahydrofuran. The mixture was stirred at room temperature for 1 h and then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography eluting with 3:1 hexane/ethyl acetate provided 284 mg of methyl 4-[[[5-methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]benzoate: mp 138–142 °C.

A mixture of 4.0 g of this ester and 2 g of 50% aqueous sodium hydroxide in 100 mL of 10% aqueous methanol was heated on a steam bath for 15 min, then poured onto ice, and acidified with 10% HCl. The resulting gum was extracted into 500 mL of diethyl ether. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude solid was triturated with *tert*-butyl methyl ether to provide 2.5 g of **39**: mp 236–239 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.39 (d, J = 6 Hz, 6H), 3.88 (s, 3H), 4.78 (heptet, J = 6 Hz, 1H), 7.20 (dd, J = 9, 2 Hz, 1H), 7.28 (d, J = 2 Hz, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 9 Hz, 1H), 7.97 (d, J = 8.5 Hz, 2H), 10.17 (s, 1H), 12.81 (br s, 1H). Anal. ($C_{20}H_{19}NO_5S$) C, H, N, S.

Sodium Salt of 4-[[[5-Methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]benzoic Acid (39). To a suspension of **39** (542 mg, 1.40 mmol) in 14 mL of methanol was added 1.3 mL of 1 N NaOH. The reaction mixture was stirred at room temperature for 1 h. A small amount of solid was removed by filtration, and the filtrate was concentrated *in vacuo*. This solid was dried *in vacuo* to provide 576 mg of the sodium salt of **39**: mp > 255 °C; ^{1}H NMR (TFA) δ 1.42 (d, J = 6 Hz, 6H), 3.89 (s, 3H), 4.82 (heptet, J = 6 Hz, 1H), 7.21 (dd, J = 9, 2 Hz, 1H), 7.30 (d, J = 2 Hz, 1H), 7.85–7.98 (m, 5H). Anal. ($C_{20}H_{18}NO_5SNa \cdot 2H_2O$) C, H, N.

3-[[[5-Methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]benzoic Acid (40). Following a procedure analogous to example **39**, **3** (7.0 g, 26 mmol) and ethyl 3-aminobenzoate (4.3 g, 26 mmol) provided 8.5 g (78%) of the intermediate ester. Saponification of the crude ester followed by recrystallization from aqueous ethanol gave 4.2 g (53%) of **40**: mp 197–200 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.39 (d, J = 6 Hz, 6H), 3.88 (s, 3H), 4.77 (heptet, J = 6 Hz, 1H), 7.20 (dd, J = 9, 2 Hz, 1H), 7.28 (d, J = 2 Hz, 1H), 7.52 (m, 1H), 7.72 (d, J = 7 Hz, 1H), 7.88–7.94 (m, 2H), 8.40 (s, 1H), 10.05 (s, 1H). Anal. ($C_{20}H_{19}NO_5S$) C, H, N, S.

2-[[[5-Methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]benzoic Acid (41). Following a procedure analogous to example **39**, **3** (1.04 g, 3.9 mmol) and ethyl 2-aminobenzoate (670 mg, 4.1 mmol) provided 810 mg (51%) of the intermediate ester: mp 105–106 °C. Saponification of 250 mg of the ester gave 170 mg (72%) of 41: mp 239–242 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.39 (d, J = 6 Hz, 6H), 3.88 (s, 3H), 4.76 (heptet, J = 6 Hz, 1H), 7.18–7.25 (m, 3H), 7.64 (m, 1H), 7.90 (d, J = 9 Hz, 1H), 8.05 (dd, J = 8, 1.5 Hz, 1H), 8.67 (d, J = 8 Hz, 1H), 12.05 (s, 1H), 13.60 (br s, 1H). Anal. ($C_{20}H_{18}NO_5S$) C, H, N.

5-[[[5-Methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]pentanoic Acid (42). A solution of **3** (500 mg, 2.00 mmol) and 1,1′-carbonyldiimidazole (421 mg, 2.60 mmol) in 20 mL of tetrahydrofuran was heated at reflux for 1 h. After cooling to 0 °C, methyl 5-aminovalerate hydrochloride (787 mg, 4.7 mmol) was added followed by triethylamine (836 μL, 6.0 mmol). The mixture was heated at reflux overnight and then partitioned between ethyl acetate and 1 N HCl. The organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 1:9 ethyl acetate/hexane providing 530 mg (70%) of methyl 5-[[[5-methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]valerate: mp 82–84 °C.

A mixture of this ester (250 mg, 0.66 mmol) and 83 mg of lithium hydroxide monohydrate in 5 mL of methanol and 2 mL of water was stirred at room temperature for 7 h. The reaction mixture was partitioned between ethyl acetate and aqueous HCl. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Recrystallization from ethyl acetate/hexane gave 205 mg (85%) of **42**: mp 135–137 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 6 Hz, 6H), 1.5–1.7 (m, 4H), 2.2–2.3 (m, 2H), 2.2–3.4 (m, 2H), 3.85 (s, 3H), 4.74 (heptet, J = 6 Hz, 1H), 7.14 (dd, J = 9, 2.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.8–8.0 (m, 2H), 12.0 (br s, 1H). Anal. ($C_{18}H_{23}NO_5S$) C, H, N.

[[[5-Methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]acetic Acid (43). A solution of **3** (1.024 g, 3.84 mmol) and 1,1′-carbonyldiimidazole (772 mg, 4.76 mmol) in 40 mL of tetrahydrofuran was heated at reflux for 45 min. After cooling to 0 °C, the solution was added via a cannula to a solution of glycine methyl ester hydrochloride (638 mg, 5.08 mmol) and triethylamine (2.6 mL, 9.34 mmol) in 20 mL of tetrahydrofuran. The mixture was heated at reflux for 2 h and then partitioned between ethyl acetate and 1 N HCl. The organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with a large volume of 1 N HCl followed by saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 225 mg (17%) of methyl [[[5-methoxy-3-(1-methylethoxy)benzo[*b*]thien-2-yl]carbonyl]amino]acetate: mp 135–137 °C. Anal. ($C_{16}H_{19}NO_5S$) C, H, N.

To a room temperature suspension of this ester (129 mg, 38 mmol) in 10 mL of methanol was added 1 mL of 1 N NaOH.

The mixture was heated at reflux for several hours. The methanol was removed *in vacuo* and the residue partitioned between ethyl acetate and 10% aqueous HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 115 mg (93%) of **43**: mp 162–165 °C; ^1H NMR (DMSO-d_6) δ 1.40 (d, J = 6 Hz, 6H), 3.86 (s, 3H), 4.07 (d, J = 5.5 Hz, 2H), 4.86 (heptet, J = 6 Hz, 1H), 7.15 (dd, J = 9, 2.5 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 9 Hz, 1H), 8.17 (t, J = 5.5 Hz, 1H). Anal. ($C_{15}H_{17}NO_5S{\cdot}0.25H_2O$) C, H, N.

5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide 1-Oxide (44). A solution of 1 (250 mg, 0.94 mmol) and 30% aqueous hydrogen peroxide (4 mL, 40 mmol) in acetic acid (9.5 mL) was stirred at room temperature for 8 h. The reaction solution was diluted with water, and the pH was adjusted to 7 with aqueous sodium hydroxide and saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with saturated aqueous $NaHCO_3$, water, and brine, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized twice from ethyl acetate/hexane to give 60 mg (23%) of **44**: mp 163–164 °C; ^1H NMR (DMSO-d_6) δ 1.30 (d, J = 6 Hz, 3H), 1.40 (d, J = 6 Hz, 3H), 3.85 (s, 3H), 5.18 (heptet, J = 6 Hz, 1H), 7.10 (d, J = 2 Hz, 1H), 7.20 (dd, J = 8, 2 Hz, 1H), 7.80 (br s, 1H), 7.87 (br s, 1H), 7.90 (d, J = 8 Hz, 1H). Anal. ($C_{13}H_{15}NO_4S$) C, H, N.

5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide 1,1′-Dioxide (45). A solution of 1 (250 mg, 0.94 mmol) and 30% hydrogen peroxide (4 mL, 40 mmol) in 9.5 mL of acetic acid was heated at reflux for 6 h. The reaction solution was diluted with ethyl acetate and washed several times with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was crystallized from ethyl acetate/hexane to give 67 mg (24%) of **45**: mp 151–153 °C; ^1H NMR (DMSO-d_6) δ 1.37 (d, J = 6 Hz, 6H), 3.90 (s, 3H), 5.18 (heptet, J = 6 Hz, 1H), 7.16 (d, J = 2 Hz, 1H), 7.24 (dd, J = 8, 2 Hz, 1H), 7.62 (br s, 1H), 7.86 (d, J = 8 Hz, 1H), 8.00 (br s, 1H). Anal. ($C_{13}H_{15}NO_5S$) C, H, N.

5-Methoxy-1-(1-methylethoxy)-2-benzofurancarboxamide (46). To a room temperature solution of 5-methoxy-1-(1-methylethoxy)-2-benzofurancarboxylic acid[17] (520 mg, 2.08 mmol) in 15 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (386 mg, 2.38 mmol). The solution was heated at reflux for 1 h and cooled slightly. Aqueous ammonium hydroxide (2.5 mL) was added and the reaction mixture was heated at reflux for 2 h, then cooled, and partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed eluting with 1:1 hexane/ethyl acetate. Recrystallization from hexane/ethyl acetate gave 209 mg (40%) of **46**: mp 126–127 °C; ^1H NMR (DMSO-d_6) δ 1.33 (d, J = 6 Hz, 6H), 3.82 (s, 3H), 4.97 (heptet, J = 6 Hz, 1H), 7.07 (d, J = 9, 2.5 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 7.31 (br s, 1H), 7.49 (d, J = 9 Hz, 1H), 7.60 (br s, 1H). Anal. ($C_{13}H_{15}NO_4$) C, H, N.

7-Methoxy-1-(1-methylethoxy)-2-naphthalenecarboxamide (47). To a room temperature solution of 7-methoxy-1-(1-methylethoxy)-2-naphthalenecarboxylic acid[17] (141 mg, 0.54 mmol) in 10 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (105 mg, 0.65 mmol). The solution was heated at reflux for 1 h and cooled slightly. Concentrated aqueous ammonium hydroxide (2.5 mL) was added, and the reaction mixture was stirred at room temperature for 40 min and then partitioned between 1:1 hexane/ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was recrystallized from hexane/ethyl acetate to provide 94 mg (68%) of **47**: mp 172–174 °C; ^1H NMR (DMSO-d_6) δ 1.31 (d, J = 6 Hz, 6H), 3.91 (s, 3H), 4.45 (heptet, J = 6 Hz, 1H), 7.25 (dd, J = 9, 2.5 Hz, 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.63 (br s, 1H), 7.70 (br s, 1H), 7.87 (d, J = 9 Hz, 1H). Anal. ($C_{15}H_{17}NO_3$) C, H, N.

5-Methoxy-3-(1-methylethoxy)-1*H*-indole-2-carboxamide (48). To 5-methoxy-3-(1-methylethoxy)-1*H*-indole-2-carboxylic acid[20] (610 mg, 2.45 mmol) in 12 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (422 mg, 2.60 mmol). The mixture was heated at reflux for 1.5 h and then cooled slightly. Concentrated aqueous ammonium hydroxide (3 mL) was added, and the reaction mixture was stirred at room temperature for 1.5 h and then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was recrystallized from hexane/ethyl acetate to provide 347 mg (57%) of **48**: mp 141–142 °C; ^1H NMR (DMSO-d_6) δ 1.33 (d, J = 6 Hz, 6H), 3.77 (s, 3H), 4.71 (heptet, J = 6 Hz, 1H), 6.85 (dd, J = 9, 2 Hz, 1H), 6.9–7.0 (m, 2H), 7.26 (d, J = 9 Hz, 1H), 7.52 (br s, 1H), 11.0 (s, 1H). Anal. ($C_{13}H_{16}N_2O_3$) C, H, N.

5-Methoxy-1-methyl-3-(1-methylethoxy)-1*H*-indole-2-carboxamide (49). To 5-methoxy-1-methyl-3-(1-methylethoxy)-1*H*-indole-2-carboxylic acid[20] (164 mg, 0.62 mmol) in 8 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (422 mg, 2.60 mmol). The mixture was heated at reflux for 1 h and then cooled slightly. Concentrated aqueous ammonium hydroxide (1 mL) was added, and the reaction mixture was stirred at room temperature for 30 min and then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was recrystallized twice from hexane/ethyl acetate to provide 89 mg (55%) of **49**: mp 135–137 °C; ^1H NMR (DMSO-d_6) δ 1.31 (d, J = 6 Hz, 6H), 3.79 (s, 3H), 3.92 (s, 3H), 4.62 (heptet, J = 6 Hz, 1H), 6.94 (dd, J = 9, 2.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.30 (br s, 1H), 7.44 (d, J = 9 Hz, 1H), 7.54 (br s, 1H). Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

Methyl 5-Chloro-2-(2-methoxy-2-oxoethoxy)benzoate (50). Methyl bromoacetate (5.47 mL, 58.9 mmol) was added to a slurry of methyl 5-chlorosalicylate[21] (10.0 g, 53.6 mmol) and potassium carbonate (14.8 g, 107.2 mmol) in 100 mL of dimethylformamide. The reaction was stirred for 18 h at room temperature, then poured into 500 mL of ice water, and stirred for 1 h. The precipitate was collected by filtration. The mother liquor afforded additional product to give a total of 8.81 g (63%) of **50**. Recrystallization from methanol gave an analytically pure sample: mp 60–61 °C; ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H), 3.80 (s, 3H), 4.92 (s, 2H), 7.10 (d, J = 9 Hz, 1H), 7.56 (dd, J = 9, 3 Hz, 1H), 7.66 (d, J = 3 Hz, 1H). Anal. ($C_{11}H_{11}ClO_5$) C, H.

Methyl 5-Chloro-3-hydroxy-2-benzofurancarboxylate (51). A solution of **50** (8.50 g, 32.9 mmol) in 70 mL of tetrahydrofuran was added dropwise to a solution of potassium *tert*-butoxide (4.06 g, 36.2 mmol) in 70 mL of tetrahydrofuran cooled with an ice bath. The mixture was stirred at room temperature for 20 h, then quenched with 10 mL of 1 N HCl, and partitioned between ethyl acetate and 1 N HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized from methanol to give 5.79 g (78%) of **51**: mp 149–151 °C; ^1H NMR (DMSO-d_6) δ 3.84 (s, 3H), 7.52–7.64 (m, 2H), 7.97 (s, 1H), 11.05 (s, 1H). Anal. ($C_{10}H_7ClO_4$) C, H.

5-Chloro-3-(1-methylethoxy)-2-benzofurancarboxylic Acid (52). To a solution of potassium *tert*-butoxide (3.71 g, 112.2 mmol) in 60 mL of dimethyl sulfoxide was added **51** (5.00 g, 22.1 mmol). After the solution was stirred for 2 h, 2-bromopropane (2.1 mL, 123.0 mmol) was added and the reaction stirred for 18 h at room temperature followed by warming on a water bath for 2 h. The mixture was poured into 400 mL of ice water and stirred for 1 h. The precipitate was collected to provide 3.59 g (69%) of methyl 5-chloro-3-(1-methylethoxy)-2-benzofurancarboxylate.

A solution of this ester (3.59 g, 13.4 mmol) and potassium hydroxide (3.76 g, 67.0 mmol) in 60 mL of methanol was heated at reflux for 1 h. Upon cooling to room temperature, the reaction was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The ethyl acetate layer was washed with saturated aqueous $NaHCO_3$, and the aqueous layers were combined and acidified with 1 N HCl. The acidic solution was extracted twice with ethyl acetate, and the organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and washed with hexane to give 2.25 g (66%) of **52**: mp 175–176 °C; ^1H NMR (DMSO-d_6) δ 1.31 (d, J = 6 Hz, 6H), 4.85 (heptet, J = 6 Hz, 1H), 7.54 (dd, J = 9, 2 Hz, 1H), 7.69 (d, J = 9 Hz, 1H), 7.83 (d, J = 2 Hz, 1H). Anal. ($C_{12}H_{11}ClO_4$) C, H.

5-Chloro-3-(1-methylethoxy)-2-benzofurancarboxamide (53). To **52** (200 mg, 0.79 mmol) in 5 mL of dry tetrahydrofuran was added 1,1′-carbonyldiimidazole (167 mg,

1.03 mmol). The reaction solution was heated at reflux for 1 h and then cooled to room temperature. Concentrated aqueous ammonium hydroxide (3 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 169 mg (84%) of **53**: mp 154–155 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, *J* = 6 Hz, 6H), 4.85 (heptet, *J* = 6 Hz, 1H), 7.38 (br s, 1H), 7.51 (dd, *J* = 9, 2 Hz, 1H) 7.64 (d, *J* = 9 Hz, 1H), 7.72 (br s, 1H), 7.85 (d, *J* = 2 Hz, 1H). Anal. ($C_{12}H_{11}ClNO_3$) C, H, N.

3-(1-Methylethoxy)-2-benzofurancarboxamide (54). Following procedures analogous to the preparation of **52** and **53**, methyl 3-hydroxy-2-benzofurancarboxylate[22] (3.00 g, 15.6 mmol) was converted to 3.63 g (99%) of methyl 3-(1-methylethoxy)-2-benzofurancarboxylate. This ester (3.33 g, 14.2 mmol) was hydrolyzed to give 1.93 g (62%) of 3-(1-methylethoxy)-2-benzofurancarboxylic acid: mp 134–137 °C. The acid (200 mg, 0.91 mmol) was converted to 154 mg (77%) of the corresponding primary amide **54**: mp 82–83 °C; 1H NMR (DMSO-d_6) δ 1.34 (d, *J* = 6 Hz, 6H), 4.99 (heptet, *J* = 6 Hz, 1H), 7.33 (t, *J* = 8 Hz, 1H), 7.48 (t, *J* = 8 Hz, 1H) 7.59 (d, *J* = 8 Hz, 1H), 7.64 (s, 2H), 7.79 (d, *J* = 8 Hz, 1H). Anal. ($C_{12}H_{13}NO_3$) C, H, N.

***N*-Ethyl-5-methoxy-3-(1-methylethoxy)-2-benzofurancarboxamide (55).** A solution of 5-methoxy-3-(1-methylethoxy)-2-benzofurancarboxylic acid[17] (250 mg, 1.00 mmol) and 1,1′-carbonyldiimidazole (211 mg, 1.30 mmol) in 7 mL of tetrahydrofuran was heated at reflux for 1 h. Upon cooling of the solution to room temperature, 70% aqueous ethylamine (810 μL, 10.00 mmol) was added, and the reaction mixture was stirred for 10 min. The reaction was diluted with 20 mL of ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by chromatography eluting with a gradient of 1:2 to 1:1 ethyl acetate/hexane, to give 230 mg (83%) of **55**: mp 81–82 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (t, *J* = 6 Hz, 3H), 1.32 (d, *J* = 6 Hz, 6H), 3.29 (m, 2H), 3.82 (s, 3H), 4.92 (heptet, *J* = 6 Hz, 1H), 7.06 (d, *J* = 8 Hz, 1H), 7.12 (s, 1H), 7.48 (d, *J* = 8 Hz, 1H), 8.00 (t, *J* = 6 Hz, 1H). Anal. ($C_{15}H_{19}NO_4$) C, H, N.

5-Methoxy-3-(1-methylethoxy)-*N*-phenyl-2-benzofurancarboxamide (56). Oxalyl chloride (110 μL, 1.20 mmol) and 20 μL of dimethylformamide were added to a solution of 5-methoxy-3-(1-methylethoxy)-2-benzofurancarboxylic acid[17] (250 mg, 1.00 mmol) in 7 mL of tetrahydrofuran and stirred for 1.75 h. Aniline (550 μL, 6.00 mmol) was added and the mixture stirred for 18 h. The reaction was diluted with 20 mL of ethyl acetate and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by chromatography, eluting with 1:3 ethyl acetate/hexane, to provide 254 mg (78%) of **56**: mp 124–125 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (d, *J* = 6 Hz, 6H), 3.85 (s, 3H), 4.99 (heptet, *J* = 6 Hz, 1H), 7.12–7.20 (m, 3H), 7.35 (t, *J* = 8 Hz, 2H), 7.57 (d, *J* = 9 Hz, 1H), 7.76 (d, *J* = 9 Hz, 2H), 9.91 (s, 1H). Anal. ($C_{19}H_{19}NO_4$) C, H, N.

1-(1-Methylethoxy)-2-naphthalenecarboxamide (57). To a room temperature solution of 1-(1-methylethoxy)-2-naphthalenecarboxylic acid[23] (203 mg, 0.88 mmol) in 5 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (158 mg, 0.98 mmol). The solution was heated at reflux for 2 h and cooled slightly. Concentrated aqueous ammonium hydroxide (1.5 mL) was added, and the reaction mixture was stirred at room temperature for 2 h and then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed eluting with 1:1 hexane/ethyl acetate followed by recrystallization from hexane/ethyl acetate to give 99 mg (48%) of **57**: mp 141–142 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (d, *J* = 6 Hz, 6H), 4.46 (heptet, *J* = 6 Hz, 1H), 7.58–7.72 (m, 6H), 7.94 (br s, 1H), 8.18 (br s, 1H). Anal. ($C_{14}H_{15}NO_2$) C, H, N.

***N*-Ethyl-7-methoxy-1-(1-methylethoxy)-2-naphthalenecarboxamide (58).** To a room temperature solution of 7-methoxy-1-(1-methylethoxy)-2-naphthalenecarboxylic acid[17] (200 mg, 0.77 mmol) in 5 mL of tetrahydrofuran was added 1,1-carbonyldiimidazole (162 mg, 1.00 mmol). The solution was heated at reflux for 1 h and cooled slightly. Ethylamine (440 μL of a 70% aqueous solution) was added, and the reaction mixture stirred at room temperature for 30 min, followed by partitioning between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed on silica gel eluting with 2:1 hexane/ethyl acetate to provide 154 mg (70%) of **58**: mp 78–79 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, *J* = 7 Hz, 3H), 1.27 (d, *J* = 6 Hz, 6H), 3.33 (m 2H), 3.90 (s, 3H), 4.38 (heptet, *J* = 6 Hz, 1H), 7.24 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.42–7.45 (m, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 9 Hz, 1H), 8.25 (t, *J* = 5.5 Hz, 1H). Anal. ($C_{17}H_{21}NO_3$) C, H, N.

7-Methoxy-1-(1-methylethoxy)-*N*-phenyl-2-naphthalenecarboxamide (59). A solution of 7-methoxy-1-(1-methylethoxy)-2-naphthalenecarboxylic acid (200 mg, 0.77 mmol), oxalyl chloride (800 μL, 0.92 mmol), and 15 μL of dimethylformamide in 7 mL of tetrahydrofuran was stirred for 1.75 h. Aniline (420 μL, 4.62 mmol) was added and the mixture stirred for 18 h. The reaction was diluted with 20 mL of ethyl actetate and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography, eluting with 1:3 ethyl acetate/hexane, gave 202 mg (78%) of **59**: mp 138–140 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (d, *J* = 6 Hz, 6H), 3.92 (s, 3H), 4.39 (heptet, *J* = 6 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 1H), 7.27–7.51 (m, 5H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8 Hz, 2H), 7.91 (d, *J* = 9 Hz, 1H), 10.32 (s, 1H). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

Methyl 5-Methoxy-1-(methoxymethyl)-3-(1-methylethoxy)-1*H*-indole-2-carboxylate (60). To a room temperature suspension of sodium hydride (77 mg of a 60% suspension of sodium hydride in oil, 1.93 mmol) in 5 mL of dimethylformamide was added via cannula methyl 5-methoxy-3-(1-methylethoxy)-1*H*-indole-2-carboxylate[24] (417 mg , 1.59 mmol) in 3 mL of dimethylformamide. The solution was stirred at room temperature for 1 h then cooled to 0 °C. Chloromethyl methyl ether (180 μL, 2.37 mmol) was added, and the solution was stirred at room temperature overnight. The reaction was partitioned between brine and a 1:1 mixture of hexane/ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed eluting with 1:1 hexane/ethyl acetate to provide 380 mg (78%) of **60** as an oil: ^{1}H NMR (DMSO-d_6) δ 1.29 (d, *J* = 6 Hz, 6H), 3.07 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 4.43 (heptet, *J* = 6 Hz, 1H), 5.79 (s, 2H), 7.02–7.04 (m, 2H), 7.59 (d, *J* = 9 Hz, 1H). Anal. ($C_{16}H_{21}NO_5$) C, H, N.

5-Methoxy-1-(methoxymethyl)-3-(1-methylethoxy)-1*H*-indole-2-carboxamide (61). To a solution of **60** (280 mg, 0.91 mmol) in 8 mL of methanol was added 4 mL of 1 N NaOH. The reaction was heated at reflux for 3 h, cooled, and poured into water. A solution of 10% aqueous HCl was added resulting in the formation of a precipitate. The mixture was extracted with ethyl acetate, and the organic layer washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave 254 mg of 5-methoxy-1-methoxymethyl-3-(1-methylethoxy)-1*H*-indole-2-carboxylic acid that was not purified.

To this acid (218 mg, 0.85 mmol) in 10 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (150 mg, 0.92 mmol). The mixture was heated at reflux for 2 h and then cooled slightly. Concentrated aqueous ammonium hydroxide (2 mL) was added, and the reaction mixture was stirred at room temperature for 1 h, then partitioned between brine and a 1:1 mixture of hexane/ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed eluting with 1:1 hexane/ethyl acetate to provide 105 mg (48%) of **61**. An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 145–147 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, *J* = 6 Hz, 6H), 3.08 (s, 3H), 3.80 (s, 3H), 4.66 (heptet, *J* = 6 Hz, 1H), 5.91 (s, 2H), 6.96 (dd, *J* = 9, 2.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 7.35 (br s, 1H), 7.53 (d, *J* = 9 Hz, 1H), 7.58 (br s, 1H). Anal. ($C_{15}H_{20}N_2O_4$) C, H, N.

***N*-Ethyl-5-methoxy-3-(1-methylethoxy)-1*H*-indole-2-carboxamide (62).** To 5-methoxy-3-(1-methylethoxy)-1*H*-indole-2-carboxylic acid[20] (201 mg, 0.81 mmol) in 5 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (154 mg, 0.95 mmol). The mixture was heated at reflux for 1.5 h and then cooled slightly. A 70% aqueous ethylamine solution (1 mL) was added and the reaction mixture stirred at room temperature for 30 min and then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was recrystallized from hexane/ethyl acetate to provide 167 mg (75%) of **62**. An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 159–160 °C; ^1H NMR (DMSO-d_6) δ 1.16 (t, J = 7 Hz, 3H), 1.34 (d, J = 6 Hz, 6H), 3.37 (m, 2H), 3.77 (s, 3H), 4.66 (m, J = 6 Hz, 1H), 6.84 (dd, J = 9, 2 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 7.26 (d, J = 9 Hz, 1H), 7.50 (t, J = 5.5 Hz, 1H), 11.05 (s, 1H). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid 1-Oxide (63). A solution of **3** (30 g, 112 mmol) and (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine[25] (35 g, 135 mmol) in chloroform (500 mL) was stirred at room temperature for 20 h. The reaction mixture was filtered and the solid washed with 2 portions of 1:1 chloroform/hexane. The filtrate was stirred at room temperature for 8 h. Additional (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (17 g, 66 mmol) was added and stirring continued overnight. The resulting solid was collected by filtration, and the filtrate was stirred at room temperature overnight. The precipitated solids were removed by filtration, combined with those collected previously, and recrystallized from ethyl acetate/methanol to provide 16.6 g (53%) of analytically pure **63**: mp 184–187 °C. Further recrystallization of the mother liquor provided additional crops of 4.3 g (14%) and 2.1 g (7%) of **63**: ^1H NMR (DMSO-d_6) δ 1.29 (d, J = 6 Hz, 3H), 1.44 (d, J = 6 Hz, 3H), 3.89 (s, 3H), 5.52 (heptet, J = 6 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 7.27 (dd, J = 8.5, 2.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 13.55 (br s, 1H). Anal. ($C_{13}H_{14}O_5S$) C, H.

Alternate Preparation of 5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide 1-Oxide (44). Sodium hydride (326 mg of a 60% dispersion of sodium hydride in oil, washed free of oil with pentane, 8.15 mmol) was added to a room temperature solution of **63** (2.30 g, 8.1 mmol) in 25 mL of dimethylformamide and 75 mL of tetrahydrofuran. After stirring at room temperature for 1.5 h the thick suspension was cooled to −10 °C and thionyl chloride (713 μL, 9.78 mmol) was added. After 2 h the solution was cooled to −78 °C resulting in the formation of a suspension. Ammonia gas was passed through the reaction mixture for one min. After 10 min the reaction mixture was poured into a mixture of 6 N HCl and brine. The organic phase was washed with additional acidic brine, followed by saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was recrystallized from ethyl acetate/hexane to provide 1.44 g (63%) of **44**: mp 168.5–169.5 °C.

5-Methoxy-3-(1-methylethoxy)-*N*-(phenylmethyl)-benzo[*b*]thiophene-2-carboxamide 1-Oxide (64). To a solution of **63** (200 mg, 0.71 mmol) in 2.5 mL of dimethylformamide and 7.5 mL of tetrahydrofuran was added a suspension of sodium hydride (28 mg of a 60% oil dispersion of sodium hydride washed free of oil with pentane, 0.71 mmol) in pentane. The reaction was stirred for 1.5 h resulting in a thick colorless precipitate. The reaction mixture was cooled to −10 °C, and thionyl chloride (62 μL, 0.85 mmol) was added. The reaction mixture was stirred for 1.5 h and then cooled to −78 °C, and benzylamine (388 μL, 3.55 mmol) was added. After 30 min the reaction was partitioned between ethyl acetate and 1 N HCl/brine. The organic phase was washed with brine and twice with saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography eluting with 3:7 ethyl acetate/dichloromethane to give 137 mg (52%) of **64** as a yellow gum: ^1H NMR (DMSO-d_6) δ 1.15 (d, J = 6 Hz, 3H), 1.27 (d, J = 6 Hz, 3H), 3.87 (s, 3H), 4.40 (dAB q, J = 15, 6 Hz, 1H), 4.51 (dAB q, J = 15, 6 Hz, 1H), 4.97 (heptet, J = 6 Hz, 1H), 7.08 (d, J = 2 Hz, 1H), 7.15–7.37 (m, 7H), 7.90 (d, J = 8 Hz, 1H), 9.08 (t, J = 6 Hz, 1H). Anal. ($C_{20}H_{21}NO_4S$) C, H, N.

5-Methoxy-3-(1-methylethoxy)-*N*-phenylbenzo[*b*]-thiophene-2-carboxamide 1-Oxide (65). Sodium hydride (28 mg of a 60% oil dispersion of sodium hydride, 0.71 mmol) was washed free of oil with pentane and added to a room temperature solution of **63** (200 mg, 0.71 mmol) in 2.5 mL of dimethylformamide and 7.5 mL of tetrahydrofuran. After stirring at room temperature for 1 h the thick suspension was cooled to −10 °C and thionyl chloride (62 μL, 0.85 mmol) was added. After 1.5 h aniline (323 μL, 3.5 mmol) was added and stirring was continued for 45 min. The reaction mixture was poured into 6 N HCl and brine and extracted with ethyl acetate. The organic phase was washed with acidic brine and saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was chromatographed eluting with 1:1 hexane/ethyl acetate. Recrystallization from ethyl acetate/hexane provided 180 mg (71%) of **65**: mp 132–133.5 °C; ^1H NMR (DMSO-d_6) δ 1.28 (d, J = 6 Hz, 3H), 1.40 (d, J = 6 Hz, 3H), 3.90 (s, 3H), 5.00 (heptet, J = 6 Hz, 1H), 7.1–7.2 (m, 2H), 7.23 (dd, J = 8.5, 2 Hz, 1H), 7.37 (t, J = 8 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8 Hz, 1H), 10.7 (s, 1H). Anal. ($C_{19}H_{19}NO_4S$) C, H, N.

5-Methoxy-*N*-methyl-3-(1-methylethoxy)benzo[*b*]-thiophene-2-carboxamide 1-Oxide (66). To a solution of **17** (200 mg, 0.72 mmol) and 30% aqueous hydrogen peroxide (570 μL, 5.7 mmol) in 8 mL of methanol was added selenium dioxide (32 mg, 0.29 mmol). The reaction mixture was stirred overnight, then diluted with ethyl acetate, and washed with 1 N HCl, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by chromatography eluting with a gradient of 1:9 to 1:1 ethyl acetate/dichloromethane followed by ethyl acetate. The product was recrystallized from ethyl acetate/hexane to give 65 mg (30%) of **66**: mp 123–124 °C; ^1H NMR (DMSO-d_6) δ 1.26 (d, J = 6 Hz, 3H), 1.38 (d, J = 6 Hz, 3H), 2.77 (d, J = 5.5 Hz, 3H), 3.88 (s, 3H), 5.04 (heptet, J = 6 Hz, 1H), 7.08 (d, J = 2 Hz, 1H), 7.19 (dd, J = 8, 2 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 8.4–8.5 (m, 1H). Anal. ($C_{14}H_{17}NO_4S$) C, H, N.

***N*-Ethyl-5-methoxy-3-(1-methylethoxy)benzo[*b*]-thiophene-2-carboxamide 1-Oxide (67).** Selenium dioxide (29 mg, 0.26 mmol) was added to a room temperature solution of **18** (195 mg, 0.66 mmol) in 8 mL of methanol containing 530 μL of 30% aqueous hydrogen peroxide. The reaction mixture was stirred overnight at room temperature and then poured into ethyl acetate and saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous $NaHCO_3$, 1 N HCl, and brine, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was chromatographed, eluting with a gradient of 1:9 to 1:1 ethyl acetate/methylene chloride to provide 96 mg (47%) of **67**: mp 88–90 °C; ^1H NMR (DMSO-d_6) δ 1.11 (t, J = 7 Hz, 3H), 1.26 (d, J = 6 Hz, 3H), 1.39 (d, J = 6 Hz, 3H), 3.1–3.4 (m, 2H), 3.88 (s, 3H), 5.06 (heptet, J = 6 Hz, 1H), 7.08 (d, J = 2 Hz, 1H), 7.19 (dd, J = 8, 2 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 8.57 (t, J = 5.5 Hz, 1H). Anal. ($C_{15}H_{19}NO_4S$) C, H, N.

5-Methoxy-3-(1-methylethoxy)-*N*-(1-methylethyl)-benzo[*b*]thiophene-2-carboxamide 1-Oxide (68). Following a procedure analogous to example **67**, 200 mg of **19** was oxidized to provide 111 mg (53%) of **68** as a colorless oil: ^1H NMR (DMSO-d_6) δ 1.0–1.2 (m, 6H), 1.26 (d, J = 6 Hz, 3H), 1.39 (d, J = 6 Hz, 3H), 3.88 (s, 3H), 3.8–4.2 (m, 1H), 4.9–5.2 (m, 1H), 7.18 (d, J = 2 Hz, 1H), 7.18 (dd, J = 8, 2 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 8.47 (d, J = 8 Hz, 1H). Anal. ($C_{16}H_{21}NO_4S$) C, H, N.

3-(1-Methylethoxy)benzo[*b*]thiophene-2-carboxamide 1-Oxide (69). Following a procedure analogous to example **67**, 120 mg of 4 was oxidized to provide 61 mg (33%) of **69**: mp 162–163 °C dec; ^1H NMR (DMSO-d_6) δ 1.32 (d, J = 6 Hz, 3H), 1.39 (d, J = 6 Hz, 3H), 5.20 (heptet, J = 6 Hz, 1H), 7.65–8.06 (m, 6H). Anal. ($C_{12}H_{13}NO_3S$) C, H, N.

3,5-Dimethoxybenzo[*b*]thiophene-2-carboxamide 1-Oxide (70). To a stirred solution of 14 (500 mg, 2.1 mmol) in acetone (45 mL) at room temperature was added (±)-*trans*-2-

(phenylsulfonyl)-3-phenyloxaziridine (700 mg, 2.7 mmol). After 30 h the precipitate was filtered off and washed with acetone. Additional oxaziridine (400 mg, 1.5 mmol) was added to the filtrate and stirring was continued for 4 days. The resulting precipitate was filtered off, washed with acetone, and combined with the material obtained previously. Two recrystallizations from acetonitrile gave 100 mg (19%) of **70**: mp 204−205 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 4.16 (s, 3H), 7.15 (d, J = 2 Hz, 1H), 7.20 (dd, J = 8.5, 2 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H). Anal. ($C_{11}H_{11}NO_4S$) C, H, N.

5-Methoxy-3-phenoxybenzo[*b*]thiophene-2-carboxamide 1-Oxide (71). Following a procedure analogous to example **63**, 500 mg of 5-methoxy-3-phenoxybenzo[*b*]thiophene-2-carboxylic acid[17] gave 108 mg (21%) of 5-methoxy-3-phenoxybenzo[*b*]thiophene-2-carboxylic acid 1-oxide: mp 204−206 °C; ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 3H), 6.77 (d, J = 2 Hz, 1H), 7.18−7.32 (m, 4H), 7.38−7.45 (m, 2H), 7.99 (d, J = 9.5 Hz, 1H). Anal. ($C_{16}H_{12}O_5S{\cdot}0.25H_2O$) C, H.

To a solution of this acid (200 mg, 0.63 mmol) in 20 mL of dimethylformamide and 7 mL of tetrahydrofuran was added a suspension of sodium hydride (25 mg of a 60% oil dispersion of sodium hydride washed free of oil with pentane, 0.63 mmol) in pentane. After 1 h, the resultant thick precipitate was cooled to −10 °C, and thionyl chloride (55 μL, 0.76 mmol) was added. The reaction was stirred for 1.5 h and then cooled to −78 °C, and ammonia gas was blown into the reaction mixture. After 10 min the reaction was partitioned between ethyl acetate and 1 N HCl/brine. The organic phase was washed with brine, twice with saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate/methanol/hexane to give 116 mg (58%) of **71**: mp 191−193 °C; ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H), 6.56 (d, J = 2 Hz, 1H), 7.16−7.26 (m, 4H), 7.38−7.46 (m, 2H), 7.52 (br s, 1H), 7.71 (br s, 1H), 7.97 (d, J = 9.5 Hz, 1H). Anal. ($C_{16}H_{13}NO_4S{\cdot}0.1H_2O$) C, H, N.

5-Hydroxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide 1,1′-Dioxide (72). Selenium dioxide (50 mg, 0.5 mmol) was added to a room temperature solution of **10** (300 mg, 1.2 mmol) in 12 mL of methanol containing 1 mL of 30% aqueous hydrogen peroxide. After 22 h an additional 1 mL of 30% aqueous hydrogen peroxide was added. After a total of 48 h the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was recrystallized from methyl *tert*-butyl ether, to provide 70 mg (21%) of **72**: mp 183−184 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, J = 6 Hz, 6H), 5.18 (heptet, J = 6 Hz, 1H), 7.02−7.05 (m, 2H), 7.55 (s, 1H), 7.71 (d, J = 9 Hz, 1H), 7.97 (s, 1H), 10.80 (s, 1H). Anal. ($C_{12}H_{13}NO_5S$) C, H, N.

5-Hydroxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide 1-Oxide (73). (±)-*trans*-2-(Phenylsulfonyl)-3-phenyloxaziridine (400 mg, 1.5 mmol) was added to a solution of **10** (300 mg, 1.2 mmol) in 15 mL of acetone. After stirring at room temperature for 48 h, the reaction mixture was filtered and the precipitate washed with cold acetone to give 200 mg (62%) of **73**: mp 190 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.29 (d, J = 6 Hz, 3H), 1.38 (d, J = 6 Hz, 3H), 5.16 (heptet, J = 6 Hz, 1H), 6.95−7.05 (m, 2H), 7.65−7.85 (m, 3H), 10.41 (s, 1H). Anal. ($C_{12}H_{13}NO_4S$) C, H, N.

(*S*)-5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid 1-Oxide (*R*)-α-Methylbenzylamine Salt (74). To a suspension of 2.00 g (7.08 mmol) of **63** in 15 mL of methanol was added 0.91 mL (7.08 mmol) of (*R*)-α-methylbenzylamine and the resulting solution was warmed to a gentle reflux during the addition of 500 mL of ethyl acetate and 5 mL of methanol. The solution was cooled and 810 mg (28%) of colorless crystals of **74** were collected: mp 173−174 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6 Hz, 3H), 1.32 (d, J = 6 Hz, 3H), 1.64 (d, J = 7 Hz, 3H), 3.88 (s, 3H), 4.46 (q, J = 7 Hz, 1H), 5.91 (heptet, J = 6 Hz, 1H), 6.98 (dd, J = 8, 2 Hz, 1H), 7.04 (d, J = 2 Hz, 1H), 7.1−7.3 (m, 3H), 7.47 (d, J = 7 Hz, 2H), 7.61 (d, J = 8 Hz, 1H); $[\alpha]^{20}$ = −187.9° (5 mg/mL, $CHCl_3$), optical purity (98% ee) determined by HPLC [CHIRALCEL OD-R, a DAICEL chiral column from Chiral Technologies, Inc. (cellulose tris(3,5-dimethylphenylcarbamate) on a 10 μm silica gel substrate), 4.6 × 250 mm column; solvent, acetonitrile/0.5 N perchlorate buffer (pH 2.5) (1:1); flow rate, 1.0 mL/min; t_R 3.83 min]. Anal. ($C_{21}H_{25}NO_5S$) C, H, N.

Single-Crystal X-ray Analysis of 74 and 75. Crystallographic data were collected on Enraf-Nonius CAD4 diffractometer with Cu K radiation and a graphite crystal monochromoter. Data were collected at room temperature using the Ω scan technique. Lorentz and polarization corrections were applied to the data and the structure was solved by direct methods. All calculations were performed on a VAX computer using MolEN. Both **74** and **75** had similar cell dimensions and angles and belonged to the monoclinic space group P21. The actual cell dimensions of **74** were a = 11.852, b = 6.214, c = 15.638. Both structures refined to an R-factor of greater than 5%.

(*S*)-5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid 1-Oxide (63*S*). A solution of 720 mg (1.78 mmol) of **74** in 200 mL of ethyl acetate was washed twice with a minimal amount of 1 N HCl and twice with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to provide 459 mg (91%), of **63*S***: mp 170−171 °C; $[\alpha]^{20}$ = −352.1° (5 mg/mL, $CHCl_3$), optical purity (98% ee) determined by HPLC [CHIRALCEL OD-R, a DAICEL chiral column from Chiral Technologies, Inc. (cellulose tris(3,5-dimethylphenylcarbamate) on a 10 μm silica gel substrate), 4.6 × 250 mm column; solvent, acetonitrile/0.5 N perchlorate buffer (pH 2.5) (1:1); flow rate, 1.0 mL/min; t_R 3.84 min]. Anal. ($C_{13}H_{14}O_5S$) C, H.

(*S*)-5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide 1-Oxide (44*S*). To a solution of 410 mg (1.45 mmol) of **63*S*** in 15 mL of tetrahydrofuran and 3 mL of dimethylformamide was added a suspension of sodium hydride (64 mg of a 60% oil dispersion of sodium hydride washed free of oil with pentane, 1.59 mmol) in pentane. The reaction mixture was stirred at room temperature for 1 h and then cooled to −10 °C. Thionyl chloride (0.13 mL, 1.74 mmol) was added, and the reaction solution was cooled to −78 °C. Ammonia gas was blown into the reaction for 15 s and repeated after 1 min. After stirring at −78 °C for 10 min the reaction mixture was partitioned between ethyl acetate and a minimal amount of 6 N HCl and brine. The organic phase was washed twice with an aqueous acid/brine solution, once with a minimal amount of saturated aqueous $NaHCO_3$, and once with brine. The organic phase was dried over $MgSO_4$, filtered, concentrated, and chromatographed eluting with 3:2 to 4:1 ethyl acetate/dichloromethane to yield 210 mg of a colorless powder. Recrystallization from ethyl acetate/methanol provided analytically pure **44*S***: mp 154−155 °C; $[\alpha]^{20}$ = −294.4° (5 mg/mL, $CHCl_3$), optical purity (98% ee) determined by HPLC [CHIRALCEL OD-R, a DAICEL chiral column from Chiral Technologies, Inc. (cellulose tris(3,5-dimethylphenylcarbamate) on a 10 μm silica gel substrate), 4.6 × 250 mm column; solvent, acetonitrile/0.5 N perchlorate buffer (pH 2.5) (1:3); flow rate, 1.0 mL/min; t_R 6.66 min]. Anal. ($C_{13}H_{15}NO_4S$) C, H, N.

(*R*)-5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid 1-Oxide (*S*)-α-Methylbenzylamine Salt (75). To a suspension of 770 mg (2.73 mmol) of enantiomerically enriched **63** (retrieved from the mother liquor of the preparation of **74**) in 15 mL of methanol was added 350 μL (2.73 mmol) of (*S*)-α-methylbenzylamine. The resulting solution was warmed to gentle reflux with the addition of 500 mL of ethyl acetate. The solution was cooled and the resulting precipitate filtered to give 490 mg (45%) of **75**: mp 176−177 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6 Hz, 3H), 1.32 (d, J = 6 Hz, 3H), 1.64 (d, J = 7 Hz, 3H), 3.88 (s, 3H), 4.46 (q, J = 7 Hz, 1H), 5.91 (heptet, J = 6 Hz, 1H), 6.98 (dd, J = 8, 2 Hz, 1H), 7.04 (d, J = 2 Hz, 1H), 7.1−7.3 (m, 3H), 7.47 (d, J = 7 Hz, 2H), 7.61 (d, J = 8 Hz, 1H); $[\alpha]^{20}$ = +196.5° (5 mg/mL, $CHCl_3$), optical purity (98% ee) determined by HPLC [CHIRALCEL OD-R, a DAICEL chiral column from Chiral Technologies, Inc. (cellulose tris(3,5-dimethylphenylcarbamate) on a 10 μm silica gel substrate), 4.6 × 250 mm column; solvent, acetonitrile/0.5 N perchlorate buffer (pH 2.5) (1:1); flow rate, 1.0 mL/min; t_R 4.64 min]. Anal. ($C_{21}H_{25}NO_5S$) C, H, N.

(*R*)-5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid 1-Oxide (63*R*). A solution of 400 mg (0.99 mmol) of **75** in 200 mL of ethyl acetate was washed twice with a minimal amount of 1 N HCl and twice with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to provide 288 mg (100%) of **63*R***: mp 175–176 °C; $[\alpha]^{20}$ = +365.8° (5 mg/mL, $CHCl_3$), optical purity (98% ee) determined by HPLC [CHIRALCEL OD-R, a DAICEL chiral column from Chiral Technologies, Inc. (cellulose tris(3,5-dimethylphenylcarbamate) on a 10 μm silica gel substrate), 4.6 × 250 mm column; solvent, acetonitrile/0.5 N perchlorate buffer (pH 2.5) (1:1); flow rate, 1.0 mL/min; t_R 4.58 min]. Anal. ($C_{13}H_{14}O_5S$) C, H.

(*R*)-5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamide 1-Oxide (44*R*). To a solution of 800 mg (2.83 mmol) of **63*R*** in 25 mL of tetrahydrofuran and 6 mL of dimethylformamide was added was added a suspension of sodium hydride (125 mg of a 60% oil dispersion of sodium hydride washed free of oil with pentane, 3.12 mmol) in pentane. The reaction mixture was stirred at room temperature for 1 h and then cooled to −10 °C. Thionyl chloride (0.25 mL, 3.40 mmol) was added, and the reaction solution was cooled to −78 °C. Ammonia gas was blown into the reaction for 15 s and repeated after 1 min. After stirring at −78 °C for 10 min, the reaction mixture was partitioned between ethyl acetate and 6 N HCl and brine. The organic phase was washed twice with aqueous acid/brine and then with a minimal amount of saturated aqueous $NaHCO_3$, followed by brine. The organic phase was dried over $MgSO_4$, filtered, concentrated, and recrystallized from ethyl acetate/methanol. Additional recrystallization from ethyl acetate/methanol yielded 400 mg of **44*R***: mp 156–158 °C; $[\alpha]^{20}$ = +331.7° (5 mg/mL, $CHCl_3$), optical purity (98% ee) determined by HPLC [CHIRALCEL OD-R, a DAICEL chiral column from Chiral Technologies, Inc. (cellulose tris(3,5-dimethylphenylcarbamate) on a 10 μm silica gel substrate), 4.6 × 250 mm column; solvent, acetonitrile/0.5 N perchlorate buffer (pH 2.5) (1:3); flow rate, 1.0 mL/min; t_R 9.11 min]. Anal. ($C_{13}H_{15}NO_4S$) C, H, N.

Assay for the Inhibition of Human Umbilical Vein Endothelial Cell (HUVEC) Activation ($Na^{51}CrO_4$-Labeled Neutrophil Adhesion Assay). Endothelial Cell Culture. Second passage HUVECs (Clonetics Corporation, San Diego, CA) were seeded into Falcon 24 well cell culture plates (Becton Dickinson, Lincoln Park, NJ) at approximately 2 × 10^4 cells per well. The cells were grown to confluent monolayers in endothelial basal medium (EBM, Clonetics) supplemented with 5% fetal calf serum (Hyclone Laboratories, Logan, UT), 10 ng/mL EGF, 1 μg/mL hydrocortisone, 0.4% bovine brain extract (Clonetics) in 5% CO_2 at 37 °C.

Human neutrophils were isolated from anticoagulant-treated venous blood obtained from healthy volunteers. The preparation was kept cold (4 °C) with slight agitation in Ca^{2+}-free Hanks' (pH 7.4) buffer to avoid neutrophil activation. Neutrophils (30 × 10^6) were labeled for 60 min at 37 °C with 100 μCi $Na^{51}CrO_4$ (ICN Biomedicals, Costa Mesa, CA) in 2.0 mL of Ca^{2+}- and Mg^{2+}-free Hanks' balanced salt solution (HBSS, GIBCO Laboratories, Grand Island, NY). The cells were washed two times in HBSS and suspended in unsupplemented EBM.

Test compounds were prepared as 10 mL stock solutions at a concentration of 1.0 mmol. The compounds were initially solubilized in 0.1 mL of DMSO followed by the addition of 9.9 mL of supplemented EBM. The drug preparations were then diluted in one step to a concentration of 200 μmol.

Stimulation of HUVECs with human tumor necrosis factor-α (TNF-α, 200 U/mL, Genzyme, Boston, MA) in the presence or absence of 100 μmol test compound was initiated 4 h prior to the addition of neutrophils. Unstimulated (vehicle control) and TNF-stimulated without test compound treatments were also run in each plate. Immediately prior to addition of ^{51}Cr-labeled neutrophils to the HUVEC monolayers, the cultures were washed with 1 mL of unsupplemented EBM to remove stimulus and or drug. Neutrophils (5 × 10^5) were then added to the HUVECs in 0.5 mL of unsupplemented media and incubated at 37 °C for 30 min. Nonadherent neutrophils were removed by aspiration. Following an additional wash, adherent neutrophils were lysed with 0.5 mL of 1 N NH_4OH overnight at 37 °C. Lysates were collected and the radioactivity in each well was determined by γ-ray spectroscopy.

The assay was considered valid if the TNF stimulation of the HUVECs resulted in at least a 300% increase in neutrophil adherence over adherence to unstimulated HUVEC. Results were expressed as means of percent inhibition of TNF-stimulated adherence. Some compounds which exhibited inhibitory activity of greater than 70% at 100 μM were retested at concentrations of 33.3, 10.0, 3.3, and 1.0 μM to determine IC_{50} values. Linear regression analysis of the means of the inhibition values were used to determine the IC_{50}.

Assay for the Inhibition of Human Umbilical Vein Endothelial Cell (HUVEC) Activation (Calcein AM-Labeled Neutrophil Adhesion Assay). Endothelial Cell Culture. Second passage HUVEC (Clonetics Corporation, San Diego, CA, CC-2617) were seeded into Corning (Corning glass works, Corning, NY) 96 well cell culture plates at approximately 5 × 10^3 cells/well and grown to confluency in supplemented endothelial basal medium (EBM, MCDB-131, Clonetics, 10 ng/mL EGF, 1 μg/mL hydrocortisone, 0.4% bovine brain extract, 5% fetal bovine serum). One day prior to running the assay, typically 3 days postseeding, the cultures were refed with 0.2 mL/well supplemented EBM (S-EBM).

Test compounds were prepared as 10 mL stock solutions at a concentration of 1.0 mM. The compounds were initially solubilized in 0.1 mL of DMSO followed by the addition of 9.9 mL of S-EBM. The drug preparations were then diluted in one step to a concentration of 66.6 μM. Solubilizations and dilutions were performed in polystyrene containers.

Human neutrophils were isolated from anticoagulant-treated venous blood obtained from healthy volunteers. The cell preparations consisted of greater than 98% neutrophils. The preparation was kept cold (4 °C) with slight agitation in Ca^{2+}-free Hanks' (pH 7.4) buffer to avoid neutrophil activation.

Recombinant human tumor necrosis factor-α (TNF, Genzyme, Boston, MA, code TNF-H) was prepared at 400 U/mL in S-EBM. Stock TNF was prepared to 20 000 U/mL in Delbecco's phosphate-buffered saline (PBS, Gibco, Grand Island, NY) plus 0.1% BSA and stored at −70 °C. HUVEC were washed one time with 0.2 mL of warm unsupplemented EBM and then stimulated for 4 h at 37 °C with 200 U/mL TNF in the presence of 33.3 μM test compound. This was accomplished by adding 0.1 mL of 400 U/mL TNF and 0.1 mL of 66.6 μM test compound. These additions were done slowly as to not disrupt the HUVEC monolayer. Each compound was tested in six wells. Unstimulated (vehicle control) and TNF-stimulated without test compound treatments were also run in each plate.

One hour prior to adding the neutrophils to the HUVEC, neutrophils (5 × 10^6/mL) were labeled for 30 min at 37 °C with 5 μM calcein-AM (Molecular Probes, Eugene, OR) in Hanks' balanced salt solution plus 0.45% BSA. Stock calcein was prepared to 5 mM in anhydrous DMSO and stored desiccated at −20 °C. At the end of the incubation the cells were washed two times in cold HBSS and resuspended to a final concentration of 1 × 10^6 cells/mL in unsupplemented EBM.

At the end of the 4 h stimulation and immediately prior to the addition of the neutrophils to the HUVEC monolayer, the plates were washed with 0.2 mL of warm unsupplemented EBM to remove TNF and drug. Neutrophils (1 × 10^5 cells) were slowly added to each of the treated wells and incubated for 30 min at 37 °C. At the end of the incubation the plates were washed two times with 0.2 mL of warm unsupplemented EBM followed by a final addition of 0.1 mL for plate scanning.

The relative fluorescence was determined using a Millipore Cytofluor 2300 system (excitation = 480, emission = 530, sensitivity = 4). The assay was considered valid if the TNF stimulation of the HUVEC resulted in a 300% increase in neutrophil adherence over adherence to unstimulated HUVEC. Results were expressed as means of percent inhibition of TNF-stimulated adherence. Compounds which exhibited inhibitory activity of 50% or greater at 33.3 μM were retested at concentrations of 33.3, 10.0, 3.3, and 1.0 μM to determine IC_{50}

values. Linear regression analysis of the means of the inhibition values were used to determine the IC_{50}.

Intercellular Adhesion Molecule-1 and E-Selectin HUVEC Surface Expression Assay (ICAMH and ESELH). Cell Culture and Cytokine Stimulation. Human umbilical cord endothelial cells (HUVECs) (Clonetics Corporation, San Diego, CA) were harvested with 0.025% trypsin/0.01% EDTA and then resuspended in fresh endothelial basal media [Clonetics containing hydrocortisone (2 mg/L), epidermal growth factor (0.05 ug/L), bovine brain extract (12 mg/L), and heat inactivated fetal calf serum (6%) from Hyclone]. The cells were seeded into 96 well tissue culture plates and allowed to grow until confluent. The cells were stimulated with tumor necrosis factor-α (TNFα) (Genzyme) to obtain a final media concentration of 140 U/mL and incubated at 37 °C for 4 h. The cells were washed 3 times with calcium- and magnesium-free phosphate-buffered saline. The monocultures were fixed by adding 10% buffered formalin to the wells for 15 min. The cells were washed 3 times with Dulbecco's Modified Eagle Media (Gibco) containing 2% bovine serum albumin (DMEM/2% BSA) and refrigerated overnight.

Murine monoclonal antihuman ICAM-1 (R & D Systems, cat no. BBA-4) or murine monoclonal antihuman E-selectin (R & D, cat no. BBA-2) dissolved in DMEM/2% BSA were added to each well at 0.5 ug/mL and allowed to incubate at 37 °C for 2 h. HUVEC monocultures were washed 4 times with DMEM/2% BSA. A peroxidase-conjugated sheep antimouse IgG (Cappel) was added (1:3000 dilution) and allowed to incubate 1 h at 37 °C. The cells were then washed 4 times with DMEM. A color reagent (Biorad) was added to the fixed cells and incubated 15 min at room temperature. The reaction was stopped with a 2% oxalic acid solution and the absorbence read at 414 nm.

Compounds were dissolved in DMSO at a concentration of 30 mmol and diluted with media to obtain final testing concentrations. HUVECs received compound dissolved in media 30 min before the TNF-α challenge. The absorbance of nonstimulated HUVECs was subtracted from the absorbance values of TNF-α stimulated cells. Percent inhibition was determined by comparing the absorbance of vehicle treated cells with drug treated cells. IC_{50}s were determined using linear regression analysis.

Assay for the Inhibition of Human Aortic Endothelial Cell (HAEC) Activation (Monocyte Adhesion Assay). Protocol was essentially run as previously reported.[28]

Vascular Cell Adhesion Molecule-1 and Intercellular Cell Adhesion Molecule-1 HAEC Surface Expression Assay (VCAMA and ICAMA). Cell Culture and Cytokine Stimulation. Human aortic endothelial cells (HAECs) (Cell System, Kirkland, WA) were seeded at 100 000 cells/mL/well in 24 well cluster plates and placed in a 5% CO_2 to 95% O_2 humidified incubator at 37 °C. At confluence (typically after 24 h) the cells were incubated with TNF-α (250 U/mL) (Genzyme) in the presence or absence of compound(s) at indicated concentrations (dissolved in DMSO, 0.005% final DMSO concentration) for 18 h. After this incubation, media was removed, and the cells were washed three times with PBS and fixed for 15 min with 10% buffered formalin at room temperature. After removal of formalin, cells were washed three times with Dulbecco's Modified Eagle Media (Gibco) containing 2% bovine serum albumin (DMEM/2% BSA) and then processed separately for VCAM-1 or ICAM-1 cell surface detection.

VCAM-1. The cells were incubated with anti-VCAM-1 monoclonal antibody (BBA#6, R&D Systems) for 2 h at 37 °C. The unbound antibody was aspirated, and cells were washed three times with DMEM/2% BSA and incubated with biotin conjugated goat antimouse IgG+IgM, F(ab)2 fragments (#115-066-068, Jackson Immuno Research Lab) (1:1000 dilution) for 1 h at 37 °C. The second antibody was then aspirated, and the cells were washed three times. [^{125}I]Streptavidin (Amersham) (1:60 dilution) was added, and the cells were incubated for 15 min at 4 °C. Cells were washed four times and digested overnight with the addition of 500 μL of 1 N NaOH and the radioactivity contained in the digests was counted. Cell surface VCAM-1 expression is shown as radioactivity bound to the cell and is the average of assays performed in duplicate or triplicate.

ICAM-1. Anti-ICAM-1 monoclonal antibody (BBA#3, R&D Systems) was added to the cells and incubated for 2 h at 37 °C. The media was aspirated, and the cells were washed 3 times with DMEM/2% BSA. The second antibody (sheep antimouse IgG (#55558, Cappel; 1:3000 dilution) was added and the cells were incubated for 1 h at 37 °C. After removal of the unbound second antibody the cells were washed three times with DMEM and then incubated with a color reagent (HRP kit, BioRad) for 15 min at 37 °C in the dark. Fifty microliters from each well was transferred to 96 well plates and the absorbance read at 414 nm on a Titertek ELISA reader. ICAM-1 expression is presented as OD414 and is the average of assays performed in duplicate or triplicate.

Thioglycollate-Induced Peritonitis (THIOPMN). Female Balb/c inbred mice were orally dosed with vehicle (0.5% hydroxypropyl methyl cellulose with 0.2% Tween 80) or compound dissolved or suspended in vehicle. One hour after dose administration, the mice were anesthetized by diethyl ether inhalation and intraperitoneally injected with 1.0 mL of 3% thioglycollate medium in saline. Two hours post thioglycollate injection, the animals were euthanized by carbon dioxide asphyxiation and injected with 6 mL of Dulbecco's phosphate-buffered saline containing 10 U/mL sodium heparin and 0.1% bovine serum albumin. The peritoneal cavity was massaged and an incision was made into the cavity to allow fluid to be collected into 15 mL centrifuge tubes. An aliquot was removed and the total number of cells counted using a Coulter counter. A second aliquot was removed for microscopy using the Cytospin 2 and subsequent staining with modified Wright's stain was performed. Hematologic differentials were performed to determine the percentage of neutrophils which had extravasated into the peritoneal cavity.

Reverse Passive Arthus Pleurisy Assay (RPA). Male outbred Wistar rats (220–245 gms, Charles River Labs) were fasted for 16–18 h. Vehicle (0.5% hydroxy propyl methylcellulose/0.2% Tween 80) or compound suspended in vehicle were administered orally. One hour later the animals were lightly anesthetized with ether and given an intravenous injection of 2.5 mg of bovine serum albumin (BSA) in saline. Immediately following the intravenous injection a small incision was made in between the ribs and 0.2 mL of a rabbit IgG fraction anti-BSA (10 mg/mL in PBS) in PBS was injected into the pleural cavity using a 20 gauge oral dosing needle. The incision was then closed with a 9 mm stainless steel wound clip. Four hours later the animals were euthanized with carbon dioxide and the pleural cavity flushed with 2 mL of a 0.325% phenol red solution in PBS. The exudate–buffer were removed from the pleural cavity for analysis. White blood cells (>90% neutrophils) were counted by using a Coulter counter. The pleural exudate volume was measured by a dye dilution method (Carter, G. W., et al. *J. Pharm. Pharmacol.* **1982**, *34*, 66–67). Drug treatment groups were compared to a vehicle treated group and statistical significance determined using Student's *t* test.

Mycobacterium-Induced Footpad Edema (MFE) and Adjuvant Arthritis (AIP). Protocols were run as previously reported.[32]

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