graphed on a reverse-phase column (gradient elution beginning with water and ending with CH_3CN-water = 1:4). Lyophilization of the desired fractions afforded the product **28** (111 mg, 32%) as a pale yellow, fluffy solid: IR (KBr disk) 3400, 1750, 1605 cm^{-1}; UV (phosphate buffer, 0.07 M, pH 7.4) 304 nm (ϵ = 8700); ^1H NMR (D_2O) δ 1.09 (d, J = 7.2 Hz, 3 H), 3.29 (quin, J = 7.2 Hz, 1 H), 3.76-3.91 (m, 4 H), 4.08 (d, J = 14.2 Hz, 1 H), 4.21 (d, J = 14.2 Hz, 1 H), 5.81-5.85 (m, 1 H), 6.83-8.45 (m, arom, 9 H); HRMS calcd for $C_{23}H_{23}N_3O_3SNa$ $(M + 1)^+$ 444.1358, found 444.1356; HPLC purity, 94%.

Acknowledgment. We thank Sue Hill and Steve Klohr of the Analytical Research group for obtaining the high-resolution mass spectra.

Novel Benzothiophene-, Benzofuran-, and Naphthalenecarboxamidotetrazoles as Potential Antiallergy Agents[1]

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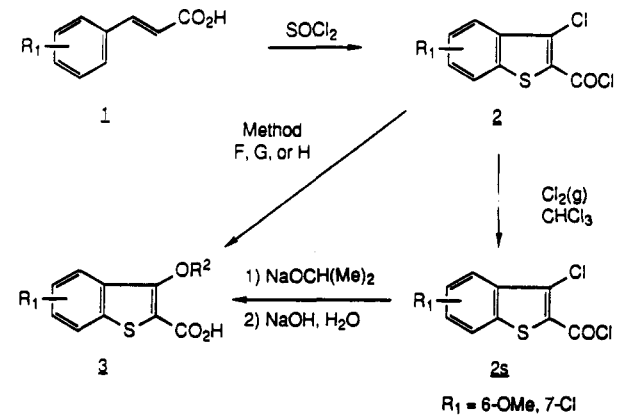
The synthesis and antiallergic activity of a series of novel benzothiophene-, benzofuran-, and naphthalenecarboxamidotetrazoles are described. A number of the compounds inhibit the release of histamine from anti-IgE stimulated basophils obtained from allergic donors. Optimal inhibition is exhibited in benzothiophenes with a 3-alkoxy substituent in combination with a 5-methoxy, 6-methoxy, or a 5,6-dimethoxy group. Compound **13c** (CI-959) also inhibited respiratory burst of human neutrophils and the release of mediators from anti-IgE-stimulated human chopped lung.

Current drug therapies for asthma have deficiencies, including, side effects, lack of compliance, lack of efficacy, lack of oral activity, and symptomatic relief without addressing the inflammatory component of the disease. For example, β-adrenergic stimulants only treat the symptoms; corticosteroids and theophylline have side effects that limit their use; and cromolyn sodium has to be taken by inhalation and is not universally effective. An orally active prophylactic agent with an antiinflammatory component would be a major advance in the therapy of asthma. The objective of our program was to discover compounds that would block the release of mediators from cells believed to play a fundamental role in the pathogenesis of allergic diseases. Mediators[2] that have been implicated in the pathogenesis of asthma or other allergic diseases include histamine, leukotrienes, platelet activating factor (PAF), and prostaglandins. Cells[3] postulated to play a key role in allergic diseases include mast cells and eosinophils, with basophils, neutrophils, and T-lymphocytes also being involved.

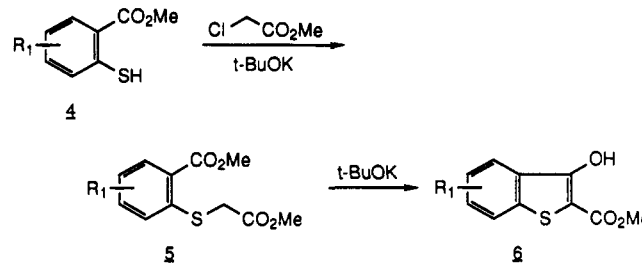
In searches for orally active cromolyn-type drugs, many potential antiasthmatic compounds[4] identified in programs using inhibition of histamine release from rat mast cells (passive cutaneous anaphylaxis test)[5] failed to show clinical efficacy.[6] The heterogeneity[7] of mast cells from different sources may be part of the reason for this failure.

To avoid these pitfalls our discovery effort focused on looking for compounds that would inhibit mediator release from a variety of human cells including mast cells and basophils. Because of their accessibility, we used human basophils for our initial screening to generate structure activity relationship (SAR) data. As a measure of mediator-release inhibition, compounds were tested for their ability to block the release of histamine from anti-IgE-stimulated human basophils. This test model, as developed by Lichtenstein and others,[8,9] has been employed in the evaluation of potential antiallergy compounds. Series of furoindoles,[10-12] indoles,[13] thiophenes, and related monocycles,[14] and triazolopyrimidines[15] have been identified previously as active in this screen.

Scheme I



Scheme II. Method B



(1) Presented, in part, at the 199th National Meeting of the American Chemical Society, Boston, MA, April 23, 1990; MEDI 81, and the 74th Annual Meeting of American Societies for Experimental Biology, Washington, DC, April 1-5, 1990; FASEBJ 4:A1123.

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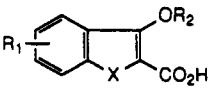
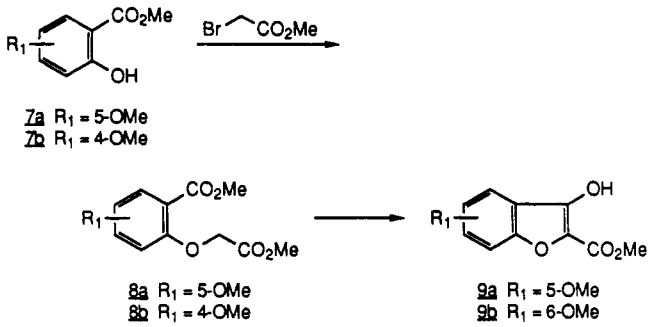
Table I. Intermediate Carboxylic Acids **3**



no.	R_1	R_2	X	method[a]	yield, %	mp, °C	cryst solvent	formula	analysis[b]
3a	5-OMe	Me	S	C	87	190 dec	MeOH	$C_{11}H_{10}O_4S$	C,H,S
b	5-OMe	Et	S	C	58	162–163 dec	CH_3CN	$C_{12}H_{12}O_4S$	C,H,S
c	5-OMe	$CHMe_2$	S	D,E	65,92	132–134	CH_3CN	$C_{13}H_{14}O_4S$	C,H,S
d	5-OMe	CMe_3	S	E	36	145–147	CH_3CN	$C_{14}H_{16}O_4S$	C,H,S
e	5-OMe	Ph	S	F	81	197	EtAc/Hx	$C_{16}H_{12}O_4S$	C,H,S
f	5-OMe	CH_2Ph	S	F	47	152–154	Toluene	$C_{17}H_{14}O_4S$	C,H,S
g	6-OMe	$CHMe_2$	S	E	86	159–160	CH_3CN	$C_{13}H_{14}O_4S$	C,H,S
h[c]	7-OMe	$CHMe_2$	S	D	22	162–163	CH_3CN	$C_{13}H_{14}O_4S$	C,H,S
j[d]	5-Cl	$CHMe_2$	S	E	79	193–195	CH_3CN	$C_{12}H_{11}ClO_3S$	C,H,S
k[e]	5-NO_2	$CHMe_2$	S	E	92	228–230 dec	THF/MeCN	$C_{12}H_{11}NO_5S$	C,H,S
l	5-Me	$CHMe_2$	S	E	77	161–162	CH_3CN	$C_{13}H_{14}O_3S$	C,H,S
m[c]	H	$CHMe_2$	S	E	82	135–137	Et_2O/CH_3CN	$C_{12}H_{12}O_3S$	C,H,S
n	5-OPh	$CHMe_2$	S	G	14	191–192 dec	EtAc	$C_{18}H_{16}O_4S$	C,H,S
o	5-OCH_2Ph	$CHMe_2$	S	G	36	160–161	EtAc/Hx	$C_{19}H_{18}O_4S$	C,H,S
p	5,6-diOMe	$CHMe_2$	S	G	41	169–170 dec	EtOH	$C_{14}H_{16}O_5S$	C,H
q	5,6-diOMe	Ph	S	F,H	31	216–217 dec	CH_3CN	$C_{17}H_{14}O_5S$	C,H
r	5,6-diOMe	CH_2Ph	S	G	38	188 dec	iPrOH	$C_{18}H_{16}O_5S$	C,H,S
s	6-OMe, 7-Cl	$CHMe_2$	S	G	74	191–192 dec		$C_{13}H_{13}ClO_4S$	C,H,Cl
t	5-OMe	$CHMe_2$	O	D	86	136–138	$MeOH/H_2O$	$C_{13}H_{14}O_5 \cdot {}^1/_2H_2O$	C,H
u	6-OMe	$CHMe_2$	O	D	64	128 dec	EtAc/Hx	$C_{13}H_{14}O_5$	C,H
v	6-OMe	$CHMe_2$	CH=CH	D	64	141–143	EtAc/Hx	$C_{15}H_{16}O_4$	C,H
w	7-OMe	$CHMe_2$	CH=CH	D	74	106–109	Et_2O/Hx	$C_{15}H_{16}O_4$	C,H

[a] See general methods C–H in the Experimental Section. [b] The elemental analysis of the carboxylic acids were within 0.4% of calculated values. [c] See ref 20 for starting material. [d] See ref 19 for starting material. [e] See ref 21 for starting material.

Scheme III



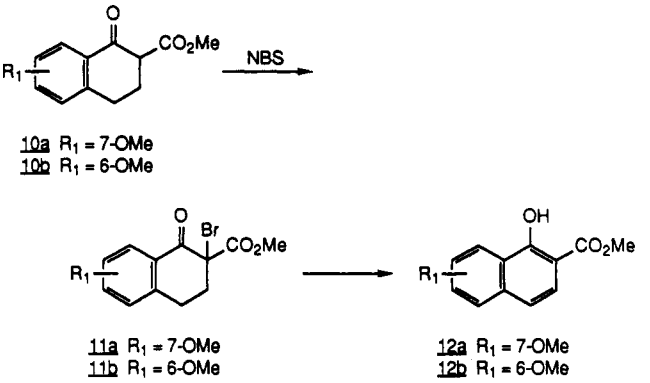
7a R_1 = 5-OMe
7b R_1 = 4-OMe

8a R_1 = 5-OMe
8b R_1 = 4-OMe

9a R_1 = 5-OMe
9b R_1 = 6-OMe

In this paper we describe series of benzothiophenes, benzofurans, and naphthalenes, which are potent inhibitors of histamine release in the basophil model.

Scheme IV

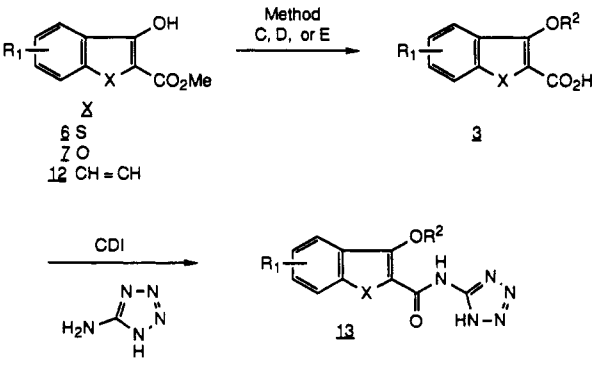


10a R_1 = 7-OMe
10b R_1 = 6-OMe

11a R_1 = 7-OMe
11b R_1 = 6-OMe

12a R_1 = 7-OMe
12b R_1 = 6-OMe

Scheme V



X
6 S
7 O
12 CH = CH

3

13

For further characterization, active compounds were

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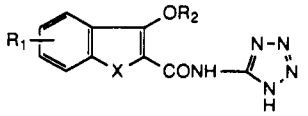
Table II. Carboxamidotetrazoles



no.	R_1	R_2	X	yield, %	mp, °C	cryst solvent	formula	analysis[a]
13a	5-OMe	Me	S	48	213–215 dec	MeOH/MeCN	$C_{12}H_{11}N_5O_3S$	C,H,N
b	5-OMe	Et	S	97	225–227 dec	MeOH	$C_{13}H_{13}N_5O_3S$	C,H,N
c	5-OMe	$CHMe_2$	S	71	214–216 dec	MeOH	$C_{14}H_{15}N_5O_3S$	C,H,N
d	5-OMe	CMe_3	S	23	246–248 dec	MeOH	$C_{15}H_{17}N_5O_3S$	C,H,N
e	5-OMe	Ph	S	78	251–252 dec	2-methoxyethanol	$C_{17}H_{13}N_5O_3S$	C,H,N
f	5-OMe	CH_2Ph	S	40	206–207	2-methoxyethanol	$C_{18}H_{15}N_5O_3S$	C,H,N
g	6-OMe	$CHMe_2$	S	89	237–239 dec	MeOH	$C_{14}H_{15}N_5O_3S$	C,H,N
h	7-OMe	$CHMe_2$	S	43	228–230	MeOH	$C_{14}H_{15}N_5O_3S$	C,H,N
i	5-OH	$CHMe_2$	S	60	254 dec	MeOH	$C_{13}H_{13}N_5O_3S$	C,H,N
j	5-Cl	$CHMe_2$	S	73	238–240	MeOH	$C_{13}H_{12}ClN_5O_2S$	C,H,N,Cl
k	5-NO_2	$CHMe_2$	S	82	211–213 dec	DMF/MeOH	$C_{13}H_{12}N_6O_4S$	C,H,N
l	5-Me	$CHMe_2$	S	80	247–278	MeOH	$C_{14}H_{15}N_5O_2S$	C,H,N
m[b]	H	$CHMe_2$	S	70	171–172	MeOH/THF	$C_{13}H_{13}N_5O_2S \cdot C_3H_4N_2$	C,H,N
n	5-OPh	$CHMe_2$	S	55	219 dec	MeOH	$C_{19}H_{17}N_5O_3S$	C,H,N
o	5-OCH_2Ph	$CHMe_2$	S	61	225–226	MeCN	$C_{20}H_{19}N_5O_3S$	C,H,N
p	5,6-diOMe	$CHMe_2$	S	27	247–248 dec	MeOH	$C_{15}H_{17}N_5O_4S$	C,H,N
q	5,6-diOMe	Ph	S	67	272 dec	DMF	$C_{18}H_{15}N_5O_4S$	C,H,N
r	5,6-diOMe	CH_2Ph	S	65	232 dec	DMF	$C_{19}H_{17}N_5O_4S$	C,H,N
s	6-OMe, 7-Cl	$CHMe_2$	S	49	251 dec	DMF	$C_{14}H_{14}N_5O_3SCl$	C,H,N,Cl
t	5-OMe	$CHMe_2$	O	82	241–245	MeCN/H_2O	$C_{14}H_{15}N_5O_4$	C,H,N
u	6-OMe	$CHMe_2$	O	70	231 dec	MeCN/DMF	$C_{14}H_{15}N_5O_4$	C,H,N
v	6-OMe	$CHMe_2$	CH=CH	81	265 dec	2-methoxyethanol DMF/H_2O	$C_{16}H_{17}N_5O_3$	C,H,N
w	7-OMe	$CHMe_2$	CH=CH	65	264 dec	DMF/H_2O	$C_{16}H_{17}N_5O_3$	C,H,N

[a] The elemental analysis for the carboxamidotetrazoles were within 0.4% of calculated values. [b] Isolated as the imidazole salt.

tested for their ability to inhibit respiratory burst in human neutrophils. Key compounds were also evaluated in human mast cell and eosinophil screens. Compounds with a broad spectrum of activity were selected for in vivo evaluation. Using this strategy, a series of potent inhibitors of cell activation was discovered.

Chemistry

The alkoxybenzothiophenecarboxylic acids **3** (Table I) were synthesized by two methods. Treatment of cinnamic acids **1** with thionyl chloride (Higa reaction)[16] generated acid chlorides **2** (method A), which were treated with alkoxides or phenoxide followed by saponification of the esters to give the alkoxy carboxylic acids (Scheme I).

Alternatively, cyclization of thioacetic ester intermediates **5**, prepared from thiols **4**, gave benzothiophenes **6** (method B, Scheme II). The esters **6** were alkylated and hydrolyzed to give key intermediate benzothiophenecarboxylic acids **3** (methods C–H, Scheme V, Table I). The 7-chloro compound **3s** was prepared by reacting the 6-methoxy compound **3g** with chlorine. The 5-OH benzothiophene **13i** was prepared by catalytic hydrogenolysis of the corresponding benzyloxy **3o** compound. Methyl 3-hydroxybenzofuran-2-carboxylates **9** were prepared by a route (Scheme III) analogous to that used for preparation of the corresponding benzothiophenes. Bromination of keto esters **10** with *N*-bromosuccinimide followed by dehydrobromination gave key methyl 1-hydroxynaphthalene-2-carboxylates **12** (Scheme IV). The alkoxycarboxylic acids were converted to the corresponding carboxamidotetrazoles (Table II) by treatment with 1,1′-carbonyldiimidazole, 5-aminotetrazole, and triethylamine in acetonitrile or THF (Scheme V).

Structure–Activity Relationships

Previous studies on a series of indole-2-carboxamidotetrazoles showed them to be potent inhibitors of mediator release from human basophils stimulated with anti-IgE.[13]

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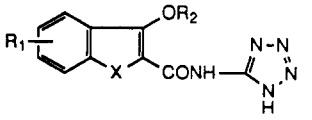
Table III. Inhibition of Histamine Release from Human Basophils and Inhibition of Superoxide Anion Release from Human Neutrophils



no.	R_1	R_2	X	histamine release % inhibition[a] 33 μM	histamine release % inhibition[a] 10 μM	inhibition of O_2^-:[b] IC_{50}, μM
13a	5-OMe	Me	S	97.3 ± 1.1 (4)	59.8 ± 3.3 (4)	>100 (2)
b	5-OMe	Et	S	98 ± 1 (2)	92.5 ± 0.5 (2)	>100 (2)
c	5-OMe	$CHMe_2$	S	97.3 ± 0.9 (6)	94.7 ± 2 (6)	14.5 (5)
d	5-OMe	CMe_3	S	100 (1)	62 (1)	>100 (2)
e	5-OMe	Ph	S	91.3 ± 0.9 (3)	96.3 ± 0.9 (3)	10.1 (2)
f	5-OMe	CH_2Ph	S	84.5 ± 7.0 (4)	80.8 ± 7.6 (4)	23.4 (2)
g	6-OMe	$CHMe_2$	S	88.6 ± 4.1 (10)	92 ± 2.3 (10)	37.0 (2)
h	7-OMe	$CHMe_2$	S	in.	in.	>100 (2)
i	5-OH	$CHMe_2$	S	86 ± 5.3 (3)	in.	47.8 (2)
j	5-Cl	$CHMe_2$	S	92 ± 3.5 (2)	73 ± 0 (2)	>100 (2)
k	5-NO_2	$CHMe_2$	S	53 (1)	in.	in. (2)
l	5-Me	$CHMe_2$	S	in.	in.	in. (2)
m	H	$CHMe_2$	S	65.8 ± 8.5 (4)	27.5 ± 8.1 (4)	>100 (2)
n	5-OPh	$CHMe_2$	S	55 ± 6 (2)	in.	>100 (2)
o	5-OCH_2Ph	$CHMe_2$	S	41.6 ± 4.9 (3)	in.	>100 (2)
p	5,6-diOMe	$CHMe_2$	S	81.7 ± 9.8 (3)	80 ± 10.5 (3)	17.7 (4)
q	5,6-diOMe	Ph	S	93.6 ± 3.6 (3)	96 ± 2.1 (3)	5.7 (2)
r	5,6-diOMe	CH_2Ph	S	90.7 ± 6.5 (3)	90.3 ± 2.8 (3)	40.0 (2)
s	6-OMe, 7-Cl	$CHMe_2$	S	in.	in.	>100 (2)
t	5-OMe	$CHMe_2$	O	43.3 ± 9	in.	>100 (2)
u	6-OMe	$CHMe_2$	O	99.5 ± 0.5	77 ± 16.2	42.5 (4)
v	6-OMe	$CHMe_2$	CH=CH	72.7 ± 5.6	31.3 ± 6.3	>100 (2)
w	7-OMe	$CHMe_2$	CH=CH	90.5 ± 3.5	51 ± 4	in. (2)
x	5-OMe	$CHMe_2$	NPh	82 ± 2 (45)	46 ± 3 (43)	>100 (5)
nedocromil				in.	in.	

[a] Percent inhibition ± standard error of the mean of basophil histamine release stimulated by anti-IgE. The number of experiments run is indicated in parentheses (*n*). Inactive (in.) is defined as <25% inhibition at the screening concentration. [b] Concentration of compound inhibiting O_2^- release from neutrophils by 50%. Inactive (in.) is defined as <5% at 100 μM. The number of experiments run is indicated in parentheses (*n*).

A combination of a 5-methoxy group with 3-alkoxy or 3-alkylthio substituents gave the most potent activity. The present work describes an extension of these studies to benzothiophenes, naphthalenes, and benzofurans and also investigates the effect of ring substitution and substitution on the oxygen in the 3-position of the benzothiophene.

The benzothiophenes, benzofurans, and naphthalenes corresponding to the potent indoles all showed activity in the basophil model. The benzothiophene series was the most potent (compare **13c**, **13t**, **13w**, and **13x**) (Table III) and was studied in detail. Both the 5- and 6-methoxy compounds, in the benzothiophene series and the 7-methoxy- and 6-methoxynaphthalenes were potent. In the benzofuran series 6-methoxy was more potent than the 5-methoxy.

In the benzothiophene series keeping the 5-OMe constant and varying the 3-alkoxy group, gave a series of potent inhibitors. The methoxy (**13a**) and *tert*-butoxy (**13d**) were less potent than the other members of the series. The 3-$OCHMe_2$ (**13g**), 3-OPh (**13e**), and 3-OCH_2Ph (**13f**) were more potent than 3-OMe (**13a**), indicating a tolerance of bulky groups in this position and showing that lipophilicity increases potency.

The 3-isopropoxy was kept constant and ring substitution was varied. The 5-methoxy compound (**13c**) was more active than the phenoxy (**13n**) or benzyloxy (**13o**) compounds, indicating a bulk limitation at this position in contrast to the 3-position. Also the unsubstituted (**13m**), 5-hydroxy (**13i**), and 5-nitro (**13k**) compounds were less potent and 5-methyl (**13l**) was inactive. The 6-methoxy (**13g**) and 5,6-dimethoxy (**13p**) show similar potency to **13c**. The 7-methoxy (**13h**) was inactive, indicating a possible spacial problem of fitting groups into this position, and a similar effect was shown for the 4-position in the indole series.[13] This effect is also evident from the lack of activity shown by the 6-methoxy-7-chloro compound **13s**. Molecular modeling[17] of all these series including furoindoles showed that 7-substituted compounds should fit in the active volume. An alternative explanation for the inactivity of 7-substituted compounds is alteration of the pattern of the electrostatic potential required for recognition by the biological ligand. Thus for optimum activity, a 5-methoxy, 6-methoxy, or 5,6-dimethoxy ring pattern combined with a 3-isopropoxy, phenoxy or benzyloxy is required.

Benzothiophenes **13c**, **13e**, **13p**, and **13g** also inhibited respiratory burst of human neutrophils (Table III). This activity distinguishes the benzothiophenes from the corresponding benzofurans, naphthalenes, and indoles; com-

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Table IV. Inhibition of Mediator Release from Human Chopped Lung (IC_{50} (μM))[a]

	histamine	LTC_4/D_4	TxB_2
13c	2.3	0.3	0.3
13e	3.5	1.1	4.9
13g	0.9	0.4	0.3
13p	4.5	0.3	<0.75
13q	4.9	9.7	<0.75
13r	2.5	1.3	<0.74
13x	11	12	12

[a] Concentrations of compound inhibiting anti-IgE-stimulated release of mediators by 50% of control value.

Table V. Secondary in Vitro Data for Cl-959[32]

human cell type	stimulus	mediator release	IC_{50}, μM[a]
basophil	anti-IgE	histamine	1.1
		LTC_4/D_4	0.2
		TxB_2	0.2
neutrophil	serum-opsonized zymosan	LTB_4	2.2
		TxB_2	4.5
		O_2^-	14.5
		myeloperoxidase	7.5
eosinophil	serum-opsonized zymosan	O_2^-	5.5
		eosinophil peroxidase	in.[b]

[a] Concentration of compound inhibiting release of mediators by 50% of control value. [b] Inactive (in.) is defined as <20% inhibition at 100 μM.

pare **13c** with **13t**, **13w**, and **13x**. In the benzothiophene series a 5-OMe or 5,6-diOMe combined with a OPh or $OCHMe_2$ in the 3-position gives the most potent compounds. Several benzothiophenes, **13c**, **13e**, **13g**, **13p**, **13q**, and **13r** and indole, **13x**, which were potent inhibitors in the basophil screen, were evaluated in a human chopped lung screen (Table IV). All the compounds were potent inhibitors of histamine, leukotrienes, and thromboxane release from anti-IgE-stimulated human mast cells, with the benzothiophenes being more potent than the indole.

Compound **13c** was further evaluated for its ability to block the release of other mediators from basophils, neutrophils, and eosinophils. The data (Tables IV and V) indicate that **13c** (CI-959) is a broad-spectrum inhibitor of activation of proinflammatory cells, and thus has the potential to be a therapeutic agent for diseases in which these cells and mediators play a role.

Experimental Section

Melting points were determined on a Mel-Temp or Electrothermal capillary apparatus and are uncorrected. The ^1H NMR spectra were determined at 90 MHz on a Varian EM-390, at 100 MHz on an IBM WP100SY, or at 200 MHz on a Varian XL-200 spectrometer with tetramethylsilane as an internal standard. The infrared spectra were recorded on a Digilab FTS-14 or a Nicolet FT-IRMS-1 spectrophotometer. Elemental analyses were provided by the Analytical Chemistry staff of this department. All new compounds yielded spectral data consistent with the proposed structure and microanalyses within ±0.4% of the theoretical values unless indicated otherwise.

3-[3-(Phenylmethoxy)phenyl]-2-propenoic Acid (1o). A stirred suspension of 5.0 g (30 mmol) of 3-hydroxycinnamic acid in 100 mL of ethanol was treated with 62 mL of aqueous 1 N NaOH and stirred for 5 min. The reaction was treated with 3.7 mL (31 mmol) of benzyl bromide, stirred for 16 h, and concentrated in vacuo. The resulting residue was stirred into 500 mL of water and acidified with concentrated HCl. The mixture was filtered, and the solid was rinsed with water and dried to afford 7.1 g (93%) of the product **1o**. Recrystallization of a sample from ethanol gave the pure product: mp 151–153 °C; IR(KBr) 1694, 1631, 1578, 1264 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.15 (s, 2 H, CH_2Ph), 6.56 (d, J = 16 Hz, 1 H, olefinic), 7.06 (d, J = 7 Hz, 1 H, ArH), 7.24–7.48 (m, 7 H, ArH), 7.56 (d, J = 16 Hz, 1 H, olefinic), 12.40 (br s, 1 H, OH). Anal. ($C_{16}H_{14}O_3$) C, H.

Method A. 3-Chloro-5-phenoxybenzo[*b*]thiophene-2-carbonyl Chloride (2n). A mixture of 4.4 g (18 mmol) of 3-phenoxycinnamic acid (**1n**),[22] 0.14 g (1.7 mmol) of pyridine, 1.3 mL (17 mmol) of *N*,*N*-dimethylformamide, and 25 mL of chlorobenzene was stirred at room temperature and treated dropwise with 10.9 g (92 mmol) of thionyl chloride. The mixture was heated at reflux for 24 h, allowed to cool, and concentrated in vacuo to leave a crystalline residue. Recrystallization from methyl *tert*-butyl ether gave 2.3 g (40%) of the pure product **2n**: mp 117–119 °C; IR (KBr) 1748, 1592, 1483 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.00–7.53 (m, 7 H, ArH), 8.10 (d, J = 8 Hz, 1 H, ArH). Anal. ($C_{15}H_8Cl_2O_2S$) C, H, Cl, S.

3-Chloro-5-(phenylmethoxy)benzo[*b*]thiophene-2-carbonyl Chloride (2o). Following method A, 4.0 g (16 mmol) of **1o** was converted to 1.5 g (48%) of **2o**: mp 139–142 °C (toluene); IR (KBr) 1741, 1602, 1487 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.24 (s, 2 H, CH_2Ph), 7.32–7.53 (m, 7 H, ArH), 7.99 (d, J = 7 Hz, 1 H, ArH). Anal. ($C_{16}H_{10}Cl_2O_2S$) C, H, S, Cl.

3,7-Dichloro-6-methoxybenzo[*b*]thiophene-2-carbonyl Chloride (2s). Chlorine (g) was bubbled through a stirred suspension of 7.9 g (30 mmol) of compound **2g**[16] in 100 mL of chloroform at room temperature for 30 min. The mixture was stirred for an additional 45 min and concentrated in vacuo. The resulting residue was triturated in 25–30 mL of methyl *tert*-butyl ether, filtered, washed with additional solvent, and dried to yield 6.1 g (71%) of the product **2s**. A sample recrystallized from tetrahydrofuran: mp 169–171 °C; IR (KBr) 1735, 1595, 1509 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.02 (s, 3 H, OCH_3), 7.52 (d, J = 9 Hz, 1 H, ArH), 7.90 (d, J = 9 Hz, 1 H, ArH). Anal. ($C_{10}H_5Cl_3O_2S$) C, H, Cl, S.

Method B. Methyl 3-Hydroxy-5-methoxybenzo[*b*]-thiophene-2-carboxylate (6a). Potassium *tert*-butoxide (231.6 g, 2.06 mol) was added in one portion to a solution of methyl 5-methoxythiosalicylate[23] (**4a**) cooled to the temperature of an ice bath. The reaction temperature rapidly rose to 38 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 25 min. Methyl chloroacetate (212.6 g, 1.96 mol) was added dropwise to the ca. 20 °C reaction mixture over 15 min, and the reaction was stirred for an additional 10 min and then heated on a steam bath for 35 min. The reaction was cooled to 40 °C and treated with an additional portion of potassium *tert*-butoxide (231.6 g, 2.06 mol) and heated on a steam bath for 15.25 h. The reaction was cooled, poured onto ice water, and carefully acidified with concentrated HCl, while maintaining the reaction temperature below 15 °C. The precipitate was isolated by filtration, washed with water, dissolved in CH_2Cl_2, and dried over Na_2SO_4. The solution was filtered through a bed of super cell (Hyflo), concentrated to 3 L, and cooled. The solid product was isolated by filtration and washed with cold methanol to give 405.1 g (87%) of a crystalline solid: mp 133–134 °C; IR (KBr) 3200, 1655, 1598, 1538, 1436, 1229, 1025 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.83 (s, 6 H, OCH_3/CO_2CH_3), 7.20 (dd, $J_{6,7}$ = 8 Hz, $J_{4,6}$ = 3 Hz, 1 H, H-6), 7.40 (d, $J_{4,6}$ = 3 Hz, 1 H, H-4), 7.83 (d, $J_{6,7}$ = 8 Hz, 1 H, H-7), 11.00 (br s, 1 H, OH). Anal. ($C_{11}H_{10}O_4S$) C, H, S.

Methyl 3-Hydroxy-6-methoxybenzo[*b*]thiophene-2-carboxylate (6g). Following method B, 76.4 g (0.39 mol) of methyl 4-methoxythiosalicylate[24] (**4g**) was converted to 75 g (82%) of **6q**: mp 124–125 °C (CH_2Cl_2–methanol); IR (KBr) 3300, 3000, 1675, 1617, 1586, 1534, 1444, 1362, 1235, 1151, 1057, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 7.00 (dd, $J_{4,5}$ = 9 Hz, $J_{5,7}$ = 2 Hz, 1 H, H-5), 7.14 (d, $J_{6,7}$ = 2 Hz, 1 H, H-7), 7.80 (d, $J_{4,5}$ = 9 Hz, 1 H, H-4), 10.16 (br s, 1 H, OH). Anal. ($C_{11}H_{10}O_4S$) C, H, S.

Methyl 3-Hydroxy-5-methylbenzo[*b*]thiophene-2-carboxylate (6l). Following method B, 105.6 g (0.58 mol) of methyl 5-methylthiosalicylate[25] was converted to 91.6 g (71%)

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of **6l**: mp 93–94 °C (methanol); IR (KBr) 3325, 2954, 1683, 1566, 1536, 1442, 1311, 1178, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 7.34 (dd, $J_{6,7}$ = 9 Hz, $J_{4,5}$ = 2 Hz, 1 H, H-6), 7.60 (d, $J_{6,7}$ = 9 Hz, 1 H, H-7), 7.69 (d, $J_{4,6}$ = 2 Hz, 1 H, H-4), 10.10 (s, 1 H, OH). Anal. ($C_{11}H_{10}O_3S$) C, H, S.

Method C. 3,5-Dimethoxybenzo[*b*]thiophene-2-carboxylic Acid (3a). Step 1. A mixture of 7.8 g (0.033 mol) of **6a**, 4.7 g (0.037 mol) of dimethyl sulfate, and 4.5 g (0.033 mol) of potassium bicarbonate in acetone (1 L) was heated at reflux for 15.5 h. The reaction was cooled and filtered, and filtrate was concentrated in vacuo. The residue was partitioned between ether and water. The ethereal layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo to yield 7.8 g of a solid. Recrystallization from CH_2Cl_2–methanol gave 7.5 g (93%) of methyl 3,5-dimethoxybenzo[*b*]thiophene-2-carboxylate as a white solid: mp 102–103 °C; IR (KBr) 1711, 1606, 1568, 1530, 1435, 1308, 1223 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.80 (s, 6 H, OCH_3 and CO_2CH_3), 4.10 (s, 3 H, OCH_3), 7.20 (dd, $J_{6,7}$ = 9 Hz, $J_{4,6}$ = 3 Hz, 1 H, H-6), 7.40 (d, $J_{4,6}$ = 3 Hz, 1 H, H-4), 7.85 (d, $J_{6,7}$ = 9 Hz, 1 H, H-7). Anal. ($C_{12}H_{12}O_4S$) C, H, S.

Step 2. Following the procedure described in step 2 of method E, the ester (6.76 g, 0.027 mol) prepared in step 1 was converted to 5.55 g (87%) of **3a** after recrystallization from methanol: mp 190 °C dec; IR (KBr) 1690, 1657, 1606, 1570, 1530, 1329, 1223, 1068 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.80 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 7.20 (dd, $J_{6,7}$ = 8 Hz, $J_{4,6}$ = 3 Hz, 1 H, H-6), 7.30 (d, $J_{4,6}$ = 3 Hz, 1 H, H-4), 7.80 (d, $J_{6,7}$ = 8 Hz, 1 H, H-7), 13.5 (br s, 1 H, CO_2H). Anal. ($C_{11}H_{10}O_4S$) C, H, S.

Method D. 5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid (3c). Step 1. A solution of 10.0 g (0.04 mol) of **6a**, 11.3 g (0.09 mol) of 2-bromopropane, and 5.4 g (0.048 mol) of potassium *tert*-butoxide in DMSO (150 mL) was heated at 100 °C for 7 h. The reaction mixture was cooled, poured into ice water, and extracted with ether. The organic layer was washed with aqueous potassium carbonate and water, dried over Na_2SO_4, and concentrated in vacuo to give 10.4 g (88%) of the product as an oil. The material was sufficiently pure for use in the subsequent reaction.

Step 2. Following the procedure is described in step 2 of method E, the above ester (10.4 g, 0.037 mol) was converted to 7.2 g (74%) of **3c**: mp 133–134 °C; IR (KBr) 1685, 1605, 1565, 1515, 1314, 1255, 1067 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (d, 6 H, $CH(CH_3)_2$), 3.90 (s, 3 H, OCH_3), 4.80 (heptet, 1 H, $CH(CH_3)_2$), 7.15–7.80 (m, 3 H, ArH), 13.25 (brs, 1 H, CO_2H). Anal. ($C_{13}H_{14}O_4S$) C, H, S.

Method E. 5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid (3c). Step 1. A mixture of 200.0 g (0.84 mol) methyl 3-hydroxy-5-methoxybenzo[*b*]thiophene-2-carboxylate (**6a**) and 635 g (3.4 mol) triisopropylisourea in acetonitrile was heated at reflux with stirring under a nitrogen atmosphere for 23.5 h. The reaction was cooled, filtered, and washed with cold acetonitrile. The filtrate was concentrated in vacuo and passed through a plug of SiO_2 (750 g, CH_2Cl_2 eluant) to give 229.8 g (98%) of methyl 5-methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylate as a viscous oil. The material was used directly in the subsequent reaction.

Step 2. A mixture of the 229.8 g (0.82 mol) of the ester, 100 g (1.8 mol) of KOH, and methanol (1.6 L) was heated at reflux on a steam bath for 3 h under a nitrogen atmosphere. The methanol was removed, and the resulting residue was dissolved in hot water (3 L) and decolorized with activated charcoal (Darko G-60). The solution was cooled, acidified with concentrated HCl, maintaining the temperature below 15 °C, and extracted with ether. The organic layer was washed with cold water, dried over Na_2SO_4, and concentrated to give 206.1 g (92%) of the acid **3c**, as a white solid: mp 133–134 °C. The product was identical with that described in method D.

Method F. 5,6-Dimethoxy-3-phenoxybenzo[*b*]thiophene-2-carboxylic Acid (3q). Step 1. A solution of 19.4 g (206 mmol) of phenol in 70 mL of *o*-dichlorobenzene was added dropwise to a stirred suspension of 8.2 g (205 mmol) of sodium hydride (60% dispersion in mineral oil) in 100 mL of *o*-dichlorobenzene, while maintaining the reaction temperature ≤15 °C. The reaction was stirred for 30 min at room temperature, and a solution of 20.0 g (69 mmol) of 3-chloro-5,6-dimethoxybenzo[*b*]thiophene-2-carbonyl chloride (**2p**)[18] in 120 mL of *o*-dichlorobenzene and 100 mL of tetrahydrofuran was slowly added. The mixture was heated at reflux for 2 h, treated with 2.3 mL (7 mmol) of tris[2(2-methoxyethoxy)ethyl]amine, and heated at reflux for 22 h. The mixture was allowed to cool, diluted with 800 mL of chloroform, and extracted with 500 mL of aqueous 1 N NaOH. The aqueous layer was further diluted with 200 mL of water and extracted with chloroform (2 × 200 mL). The combined extracts were washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo to give 13.7 g (49%) of phenyl 5,6-dimethoxy-3-phenoxybenzo[*b*]thiophene-2-carboxylate. A sample was recrystallized from ethyl acetate: mp 140–142 °C; IR (KBr) 1703, 1522, 1492 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.70 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.83–7.53 (m, 11 H, ArH), 7.72 (s, 1 H, ArH). Anal. ($C_{23}H_{18}O_5S$) C, H.

Step 2. A mixture of 1.9 g (5 mmol) of the above ester in 10 mL of methanol and 20 mL of aqueous 1 N NaOH was heated at reflux for 5 h. The mixture was stirred into 200 mL of water, and water was added until a solution was obtained. The aqueous solution was extracted with ether (2 × 100 mL), acidified with concentrated aqueous HCl, filtered, rinsed with water, and dried to afford 1.3 g (84%) of the acid (**3q**). A sample was recrystallized from acetonitrile: mp 216–217 °C; IR (KBr) 1684, 1666, 1515, 1490 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.67 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.87–7.03 (m, 3 H, ArH), 7.12 (t, J = 7 Hz, 1 H, ArH), 7.30–7.43 (m, 2 H, ArH), 7.68 (s, 1 H, ArH). Anal. ($C_{17}H_{14}O_5S$) C, H.

Method G. 6-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic Acid (3g). A solution of 3.5 mL (46 mmol) of 2-propanol in 20 mL of tetrahydrofuran was added dropwise to a stirred suspension of 1.7 g (43 mmol) of sodium hydride (60% dispersion in mineral oil) in 20 mL of tetrahydrofuran at room temperature and stirred for 1.5 h. A solution of 4.0 g (15 mmol) of 6-methoxy-3-chlorobenzo[*b*]thiophene-2-carbonyl chloride (**2g**)[16b] in 30 mL of tetrahydrofuran was added and the mixture heated to reflux for 17 h. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was partitioned between 250 mL of water and 250 mL of hexane, and the layers were separated. The aqueous phase was extracted with hexane, and the combined extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was stirred in a mixture of 2 mL of methanol and 7 mL of aqueous 1 N NaOH and heated to reflux for 7 h. The mixture was allowed to cool, diluted with water (100 mL), and extracted with 75 mL of ether. The aqueous solution was acidified with concentrated aqueous HCl, filtered, rinsed with water, and dried to afford 0.9 g (23%) of the acid **3g**. Recrystallization of a sample from ethanol gave the pure product: mp 162–163 °C; IR (KBr) 1684, 1654, 1605, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 3.91 (s, 3 H, OCH_3), 4.95 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 7.04 (dd, $J_{4,5}$ = 2 Hz, $J_{5,7}$ = 9 Hz, 1 H, ArH), 7.21 (d, $J_{4,5}$ = 2 Hz, 1 H, ArH), 7.74 (d, $J_{5,7}$ = 9 Hz, 1 H, ArH). Anal. ($C_{13}H_4O_4S$) C, H, S.

Method H. Phenyl 5,6-Dimethoxy-3-phenoxybenzo[*b*]thiophene-2-carboxylate. Step 1. A stirred suspension of 10.0 g (34 mmol) of the carbonyl chloride **2p**[18] in 125 mL of acetone under N_2 atmosphere was treated sequentially with 3.5 g (34 mmol) of triethylamine and 3.2 g (34 mmol) of phenol. The mixture was heated at reflux for 3 h. The reaction was cooled, poured into 700 mL of water, and filtered. The solid was washed with aqueous 0.5 N HCl, aqueous 0.5 M K_2CO_3, and water (3×) to give 11.5 g (96%) of phenyl 3-chloro-5,6-dimethoxybenzo[*b*]thiophene-2-carboxylate after drying. A sample was recrystallized from 1,2-dichloroethane: mp 235–236 °C; IR (KBr) 1728, 1704, 1607, 1512, 1488 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.91 (s, 6 H, OCH_3), 7.30–7.37 (m, 4 H, ArH), 7.46–7.54 (m, 2 H, ArH), 7.75 (s, 1 H, ArH). Anal. ($C_{17}H_{13}ClO_4S$) C, H.

Step 2. A solution of 3.3 g (25 mmol) of potassium phenoxide[26]

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in 70 mL of dimethyl sulfoxide under an argon atmosphere was treated in one portion with 7.0 g (20 mmol) of the above ester. The reaction was heated at 75 °C for 4 h. The mixture was cooled, poured into 500 mL of aqueous 0.25 M K_2CO_3, stirred for 2 h, and filtered. The solid was washed with water (3×) and dried to afford 7.5 g (92%) of the desired product (mp 140–142 °C), identical with material prepared in step 1 of method F. The material was saponified to **3q** as described in step 2 of method F.

Methyl 5-Methoxy-2-(2-methoxy-2-oxoethoxy)benzoate (8a). A mixture of 50.0 g (0.27 mol) of methyl 2-hydroxy-5-methoxybenzoate (**7a**), 88.0 g (0.64 mol) of anhydrous K_2CO_3, and 46.4 g (0.30 mol) of methyl bromoacetate in 300 mL of DMF was stirred at room temperature for 24 h. The reaction mixture was added to 1.0 L of ice water and stirred for 1 h. The precipitate was filtered, washed with H_2O, and recrystallized from MeOH to yield 54.7 g (78%) of diester **8a**: mp 82–85 °C; IR (KBr) 1768, 1736, 1510, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 6 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.62 (s, 2 H, CH_2), 6.72–7.09 (m, 2 H, ArH), 7.28 (m, 1 H, ArH). Anal. ($C_{12}H_{14}O_6$) C, H.

Methyl 4-Methoxy-2-(2-methoxy-2-oxoethoxy)benzoate (8b). Following the procedure for the preparation of **8a**, 27.7 g (0.15 mol) of hydroxy ester **7b** was converted to 36.0 g (93%) of diester **8b**. A sample was recrystallized from EtOAc–hexane: mp 74–77 °C (lit.[27,28] reported as an oil). Anal. ($C_{12}H_{14}O_6$) C, H.

Methyl 3-Hydroxy-5-methoxy-2-benzofurancarboxylate (9a). A solution of NaOMe, generated from 3.5 g (0.15 mol) of sodium metal in 250 mL of MeOH, was maintained in a cold H_2O bath and treated over 45 min with 27.4 g (0.11 mol) of diester **8a**. The mixture was stirred at reflux for 90 min, cooled, concentrated 50% by evaporation, and added to 500 g of ice and H_2O. The mixture was acidified with HOAc, and the product was filtered, washed with H_2O, and dried to give 21.1 g (88%) of benzofuran **9a**: mp 177–180 °C. A sample was recrystallized from MeOH–DMF–H_2O: mp 181–184 °C; IR (KBr) 3360, 1669, 1589, 1021 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.80 (s, 6 H, OCH_3), 7.08 (dd, $J_{6,7}$ = 9.0 Hz, $J_{4,6}$ = 2.5 Hz, 1 H, H-6), 7.33 (d, $J_{4,6}$ = 2.5 Hz, 1 H, H-4), 7.43 (d, $J_{6,7}$ = 9.0 Hz, 1 H, H-7), 10.60 (s, 1 H, OH). Anal. ($C_{11}H_{10}O_5$) C, H.

Methyl 3-Hydroxy-6-methoxy-2-benzofurancarboxylate (9b). A solution of 7.6 g (0.030 mol) of diester **8b** in 50 mL of THF was added dropwise to a mixture of 5.0 g (0.045 mol) of *t*-BuOK in 100 mL of THF maintained in a cold H_2O bath. The mixture was stirred at room temperature for 24 h, and the precipitated potassium salt of the product was filtered and dissolved in 200 mL of H_2O. Acidification with aqueous 6.0 N HCl precipitated the product, which was filtered and washed with H_2O to give 4.7 g (70%) of furan **9b**, mp 80–86 °C. A sample was recrystallized from MeOH–H_2O: mp 86–89 °C (lit.[27] mp 80–85 °C). Anal. ($C_{11}H_{10}O_5$) C, H.

Methyl 1,2,3,4-Tetrahydro-7-methoxy-1-oxo-2-naphthalenecarboxylate (10a). This compound was prepared by the method of Johnson et al.[28] for the analogous 5-methoxy compound. From 10.0 g (0.057 mol) of 7-methoxytetralone, there was obtained 10.5 g (79%) of ester **10a** as a yellow oil (lit.[29] mp 57.5 °C) after Kugelrohr distillation (125 °C, 0.2 Torr). Anal. ($C_{13}H_{14}O_4$) C, H.

Methyl 1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthalenecarboxylate (10b). Following the procedure for the preparation of **10a**, 29.7 g (0.17 mol) of 6-methoxytetralone was converted to 37.9 g (96%) of ester **10b**. The crude product was used directly in subsequent steps. A sample was purified by Kugelrohr distillation: mp 82–84 °C (lit.[30] mp 88–89.5 °C). Anal. ($C_{13}H_{14}O_4$) C, H.

Methyl 1,2,3,4-Tetrahydro-2-bromo-7-methoxy-1-oxo-2-naphthalenecarboxylate (11a). A solution of 2.5 g (0.011 mol) of ester **10a** in 25 mL of $CHCl_3$ was treated portionwise with 2.2 g (0.012 mol) of *N*-bromosuccinimide, followed by 12 mg (0.07 mmol) of α,α-azobisisobutyronitrile. The mixture was stirred at reflux for 1 h, cooled in ice, and diluted with 25 mL of hexane. The byproduct succinimide was filtered and discarded, and the filtrate was evaporated. Recrystallization of the residue from EtOAc–hexane yielded 2.5 g (75%) of bromo ester **11a**: mp 83–85 °C; IR (KBr) 1757, 1687, 1497, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49–3.17 (m, 4 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 7.09–7.27 (m, 2 H, ArH), 7.54 (d, $J_{6,8}$ = 2.6 Hz, 1 H, H-8). Anal. ($C_{13}H_{13}BrO_4$) C, H, Br.

Methyl 1,2,3,4-Tetrahydro-2-bromo-6-methoxy-1-oxo-2-naphthalenecarboxylate (11b). Following the procedure for the preparation of **11a**, 30.7 g (0.13 mol) of ester **10b** was brominated to yield 30.7 g (75%) of bromo ester **11b**. A sample was recrystallized from Et_2O–hexane: mp 99–101 °C; IR (KBr) 1730, 1660, 1597, 1229 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50–3.25 (m, 4 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.71 (d, $J_{5,7}$ = 2 Hz, 1 H, H-5), 6.87 (dd, $J_{5,7}$ = 2 Hz, $J_{7,8}$ = 9 Hz, 1 H, H-7), 8.05 (d, $J_{7,8}$ = 9 Hz, 1 H, H-8); ^{13}C NMR ($CDCl_3$) δ 35.85, 55.54, 76.60, 77.02, 77.44, 112.28, 114.00, 122.46, 131.39, 144.79, 164.15, 167.81, 186.02. Anal. ($C_{13}H_{13}BrO_4$) C, H, Br.

Methyl 1-Hydroxy-7-methoxy-2-naphthalenecarboxylate (12a). Following the procedure for the preparation of **12b**, 90.8 g (0.29 mol) of bromo ester **11a** was converted to 34 g (54%) of naphthol **12a**. A sample was recrystallized from EtOH: mp 79–81 °C (lit.[31] mp 81–82 °C). Anal. ($C_{13}H_{12}O_4$) C, H.

Methyl 1-Hydroxy-6-methoxy-2-naphthalenecarboxylate (12b). A solution of 10.2 g (0.067 mol) of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in 20 mL of THF was added over 15 min under nitrogen to 10.2 g (0.033 mol) of bromo ester **11b** in 100 mL of THF. The mixture was stirred at room temperature for 18 h and then poured into 500 g of ice and H_2O. After the mixture was acidified with aqueous 6.0 N HCl, the precipitated solid was filtered, washed with water and recrystallized from MeOH–H_2O to yield 5.1 g (67%) of naphthol **12b**: mp 109–111 °C; IR (KBr) 1660, 1609, 1444, 1198 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 6.97–7.30 (m, 3 H, ArH), 7.73 (d, $J_{3,4}$ = 10.0 Hz, 1 H, H-3), 8.30 (d, $J_{7,8}$ = 10.0 Hz, 1 H, H-8), 11.94 (s, 1 H, OH). Anal. ($C_{13}H_{12}O_4$) C, H.

Method I. 6-Methoxy-3-(1-methylethoxy)-*N*-1*H*-tetrazol-5-yl-benzo[*b*]thiophene-2-carboxamide (13g). A mixture of 7.5 g (28 mmol) of the acid **3g**, 4.9 g (30 mmol) of *N,N'*-carbonyldiimidazole, and 100 mL of tetrahydrofuran was stirred and heated to reflux. After 75 min, 2.4 g (28 mmol) of 5-aminotetrazole was added and the reaction heated at reflux for 3 h. The mixture was allowed to cool, stirred into 500 mL of water, acidified with concentrated HCl, and filtered. The solid was rinsed with water and dried to afford 8.3 g (89%) of the pure product: mp 237 °C dec; IR (KBr) 1667, 1603, 1407, 1224 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.41 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 3.88 (s, 3 H, OCH_3), 4.89 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 7.13 (dd, $J_{4,5}$ = 9 Hz, $J_{5,7}$ = 2 Hz, 1 H, H-5), 7.65 (d, $J_{5,7}$ = 2 Hz, 1 H, H-7), 7.88 (d, $J_{4,5}$ = 9 Hz, 1 H, H-4), 11.01 (s, 1 H, CONH). Anal. ($C_{14}H_{15}N_5O_3S$) C, H, N.

5-Hydroxy-3-(1-methylethoxy)-*N*-1*H*-tetrazol-5-yl-benzo[*b*]thiophene-2-carboxamide (13i). A mixture of 15.2 g (37 mmol) of compound **13o** and 2.0 g of 20% palladium on carbon in 1600 mL of acetic acid was sealed under hydrogen in a Parr apparatus and shaken under 40–50 psi at 40 °C for 36 h. The resulting slurry was warmed to 60 °C and filtered. The solid was washed with hot acetic acid, and the washings and filtrate were stripped of solvent by rotary evaporator. The residue was recrystallized from methanol (charcoal) to afford, in two crops, 7.1 g (60%) of pure compound **13i**: mp 254 °C dec; IR (KBr) 3243, 1659, 1600, 1533, 1512 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 4.8 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 7.11 (dd, $J_{6,7}$ = 2 Hz, $J_{4,6}$ = 9 Hz, 1 H, ArH), 7.25 (d, $J_{4,6}$ = 2 Hz,

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1 H, ArH), 7.86 (d, $J_{6,7}$ = 9 Hz, 1 H, ArH), 9.88 (br s, 1 H, OH), 11.02 (s, 1 H, CONH). Anal. ($C_{13}H_{13}N_5O_3S$) C, H, N.

Biological Methods. Human Basophil Test. The basophil procedure has been previously described.[8,33] In brief, whole human blood was obtained from well-characterized allergic donors. After sedimentation of the red cells, the leukocytes were removed, washed, and suspended in buffer solution. Cells were preincubated with the test compound, then challenged with anti-IgE. The released histamine was quantitated by using an automated fluorometric assay. The percent inhibition of histamine release was calculated by comparison of the values from the test drug treated cells with that of nondrug controls similarly challenged with anti-IgE. As a minimum, each test compound was screened in triplicate at drug concentrations of 33 and 10 μM. An inhibition of ≤25% at 33 μM was arbitrarily defined as inactive. Where an IC_{50} value was determined, additional experiments were conducted with 3-fold concentrations for 1–100 μM.

Human Chopped Lung Test. Portions of grossly normal-appearing human lung obtained during lobectomy for carcinoma were placed in Tyrode's buffer, dissected free of larger bronchioles and blood vessels, and then chopped with scissors into 25–75-mg fragments. The fragments were washed and then stored overnight in Tyrode's buffer at room temperature. Before use the next day, the tissue was again washed with buffer. Portions of lung tissue (about 400 mg) were placed in each of a series of vials containing buffer at 37 °C. After a 10-min incubation in Tyrode's buffer, test drug or vehicle was added, and 10 min later, the tissue was incubated with anti-IgE in a final dilution of 3:1000. After another 30-min incubation, samples of the supernatant were removed for assay. Histamine was assayed as described above in the guinea pig chopped lung test. Assays of leukotrienes and thromboxane were performed with commercially available RIA kits as described previously.[33]

Human Neutrophil and Eosinophil Protocols. These test were carried out as described by Wright.[34]

Human polymorphonuclear leukocyte preparations isolated from anticoagulant-treated venous blood by Ficol-Hypaque density gradient centrifugation consisted of approximately 98% neutrophils and 2% eosinophils. The eosinophils were further prepared to a purity of greater than 95% by discontinuous Percoll gradient centrifugation.

The respiratory burst of human neutrophils and eosinophils was measured as superoxide anion mediated reduction of cytochrome C. Lysosomal enzyme release was evaluated as release of myeloperoxidase and eosinophil peroxidase from neutrophils and eosinophils, respectively. Release of arachidonic acid metabolites was evaluated by radioimmunoassay.

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