compounds. Serum prolactin levels were determined by the method and reagents for radioimmunoassay provided by the Hormone Distribution Program of NIAMDD, using PRL-RP-1 and PRL-S-7, and [^{125}I]-PRL purchased from New England Nuclear Co.

Registry No. 1, 31272-21-6; 8, 56877-15-7; 9, 85723-93-9; 10, 103094-23-1; 11, 103068-59-3; 12, 103068-60-6; 13 (5-*N*-Me), 103068-68-4; 13·HCl, 103068-64-0; 14, 103068-61-7; 15, 103068-62-8; 16, 103068-63-9; 17, 103068-65-1; 18, 103068-66-2; 19, 103068-97-9; 20, 103068-67-3; 21, 103068-98-0; 22, 103068-99-1; 23, 103068-69-5; 24, 103068-70-8; 25, 85747-92-8; 25·2HCl, 85723-66-6; 25·HCl, 103068-82-2; 26, 85723-00-8; 26·2HCl, 103068-74-2; 26·HCl, 85723-65-5; 27, 85723-04-2; 27·2HCl, 103068-75-3; 27·HCl, 103068-83-3; 28, 103068-71-9; 28·2HCl, 103068-76-4; 28·HCl, 103068-84-4; 29, 85723-12-2; 29·2HCl, 103068-77-5; 29·HCl, 103094-24-2; 30, 85723-17-7; 30·2HCl, 103068-78-6; 30·HCl, 103068-85-5; 31, 103068-72-0; 31·2HCl, 103068-79-7; 31·HCl, 103068-86-6; 32, 103068-73-1; 32·2HCl, 103068-80-0; 32·HCl, 103068-87-7; 33, 85723-38-2; 33·$C_4H_4O_4$, 85723-39-3; 34, 103068-88-8; 34·2$C_4H_4O_4$, 103068-90-2; 35, 85723-48-4; 35·2$C_4H_4O_4$, 85723-49-5; 36, 85723-22-4; 36·2$C_4H_4O_4$, 85723-23-5; 37, 85723-44-0; 37·2$C_4H_4O_4$, 85723-45-1; 38, 85723-20-2; 38·2$C_4H_4O_4$, 85723-21-3; 38 (bromo deriv), 63960-69-0; 39, 103068-89-9; 39·2$C_4H_4O_4$, 103068-91-3; 40, 85723-34-8; 40·2$C_4H_4O_4$, 85723-35-9; 41, 85723-32-6; 41·2$C_4H_4O_4$, 85723-33-7; 42, 85723-42-8; 42·2$C_4H_4O_4$, 85723-43-9; 43 (n = 2, R″$_2$ = N(CH(CH$_3$)$_2$)$_2$), 103068-92-4; 43 (n = 2, R″$_2$ = c-N(CH$_2$)$_5$), 103094-25-3; 43 (n = 3, R″$_2$ = N(CH$_3$)$_2$), 103068-93-5; 43 (n = 3, R″$_2$ = c-N(CH$_2$)$_5$), 103068-94-6; 43 (n = 3, R″$_2$ = c-N(CH(CH$_3$)(CH$_2$)$_4$), 85723-84-8; 43 (n = 3, N-CH$_3$, R″$_2$ = c-N(CH(CH$_3$)(CH$_2$)$_4$), 103068-95-7; 43 (n = 3, c-N(CH$_2$CH(CH$_3$)(CH$_2$)$_3$) = R″$_2$), 103068-96-8; 43 (n = 3, c-N((CH$_2$)$_2$CH(CH$_3$)(CH$_2$)$_2$) = R″$_2$), 103094-26-4; 43 (n = 3, R″$_2$ = NHC(CH$_3$)$_3$), 103094-27-5; 43 (n = 3, N-CH$_3$, R″$_2$ = c-N(CH(CH$_3$)(CH$_2$)$_4$), 103068-81-1; 2-FC$_6$H$_4$COCl, 393-52-2; 2-BrC$_6$H$_4$F, 1072-85-1; H$_2$N(CH$_2$)$_2$N(CH(CH$_3$)$_2$), 121-05-1; H$_2$N(CH$_2$)$_3$N(CH$_3$)$_2$, 109-55-7; H$_2$N(CH$_2$)$_3$NC(CH$_3$)$_3$, 52198-64-8; pyrrolidine, 123-75-1; piperidine, 110-89-4; 4-phenylpiperidine, 771-99-3; 4-(1-phenyl-1,2,3,4,5-pentahydro-4-oxopyrimid-5-yl)piperidine, 1021-25-6; 1-piperidineethanamine, 27578-60-5; 2-methyl-1-piperidinepropanamine, 25560-00-3; 3-methyl-1-piperdinepropanamine, 14156-91-3; 4-methyl-1-piperidinepropanamine, 6241-30-1; 1-piperidinepropanamine, 3529-08-6; *N*-methyl-2-methyl-1-piperidinepropanamine, 85723-73-5.

Selective Thromboxane Synthetase Inhibitors. 3. 1*H*-Imidazol-1-yl-Substituted Benzo[*b*]furan-, Benzo[*b*]thiophene-, and Indole-2- and -3-carboxylic Acids

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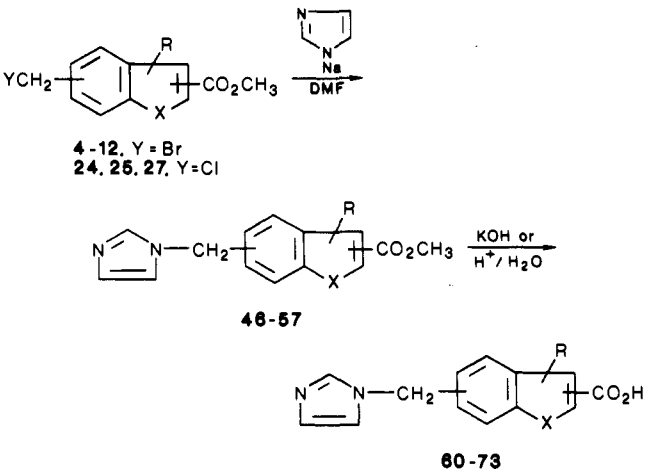
Pfizer Central Research, Sandwich, Kent CT13 9NJ, U.K. *Received November 25, 1985*

The preparation of a series of 1*H*-imidazol-1-yl-substituted benzo[*b*]furan-, benzo[*b*]thiophene-, and indolecarboxylic acids is described. Most of the compounds were potent inhibitors of TxA_2 synthetase in vitro, and the distance between the imidazole and carboxylic acid groups was found to be important for optimal potency. The most potent compound in vivo was 6-(1*H*-imidazol-1-ylmethyl)-3-methylbenzo[*b*]thiophene-2-carboxylic acid (71), which, in conscious dogs, showed a similar profile of activity to that of dazoxiben (1).

1-Substituted imidazoles are known to inhibit thromboxane synthetase, the enzyme that converts prostaglandin H_2 (PGH_2) to the potent vasoconstrictor and platelet-aggregating agent thromboxane A_2 (TxA_2).[1-7] Thus, they are potentially useful for the treatment or prevention of cardiovascular conditions where vasospasm or thrombosis may be a contributing factor.[8-11] It has been shown that, in many cases, introduction of a carboxylic acid group into the imidazole 1-substituent can increase potency against TxA_2 synthetase.[2-4,6,7] The presence of a carboxyl function has the additional advantage of reducing activity against other enzymes that are susceptible to inhibition by 1-substituted imidazoles such as liver microsomal cyto-

Scheme I



(1) Tai, H.-H.; Yuan, B. *Biochem. Biophys. Res. Commun.* **1978**, *80*, 236.
(2) Yoshimoto, Y.; Yamamoto, S.; Hayaishi, O. *Prostaglandins* **1978**, *16*, 529.
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(8) Moncada, S.; Gryglewski, R. J.; Bunting, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 715.
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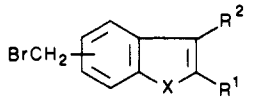
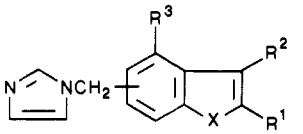
Table I. Bromomethyl-Substituted Esters



no.	X	R^1	R^2	posn of CH_2Br	mp, °C	yield, %	recryst[a] solvent	formula[b]
4	O	CO_2CH_3	H	5	106–108	48	Et_2O	$C_{11}H_9BrO_3$
5	O	CO_2CH_3	H	6	117–119	63	EtOAc/PE	$C_{11}H_9BrO_3$
6	S	CO_2CH_3	H	5	108–110	72	PE (bp 80–100 °C)	$C_{11}H_9BrO_2S$
7	S	CO_2CH_3	H	6	103.5–106	80	$MeOH/H_2O$	$C_{11}H_9BrO_2S$[c]
8	S	CO_2CH_3	H	7	95–98	36	EtOAc/PE	$C_{11}H_9BrO_2S$[d]
9	S	H	CO_2CH_3	5	133–135	55	Et_2O	$C_{11}H_9BrO_2S$
10	S	H	CO_2CH_3	6	165–167	55	EtOAc/PE	$C_{11}H_9BrO_2S$
11	S	H	CO_2CH_3	7	89–90	53	Et_2O/PE (bp 40–60 °C)	$C_{11}H_9BrO_2S$
12	S	CO_2CH_3	Cl	6	152–153	59	$CHCl_3$/PE	$C_{11}H_8BrClO_2S$
34	$NCOCH_3$	CO_2CH_3	H	5	84–86	67	EtOAc/PE (bp 40–60 °C)	$C_{13}H_{12}BrNO_3$
35	$NCOCH_3$	CO_2CH_3	H	6	93–95	78	PE	$C_{13}H_{12}BrNO_3$

[a] PE, petroleum ether, bp 60–80 °C unless otherwise stated. [b] All compounds gave C and H (**4–12**) or C, H, and N (**34**, **35**) analyses within 0.4% of the theoretical value unless otherwise stated. [c] C: calcd, 46.33; found, 46.75. [d] C: calcd, 46.33; found, 45.83.

Table II. 1*H*-Imidazol-1-ylmethyl-Substituted Esters

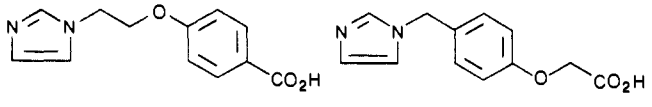


no.	X	R^1	R^2	R^3	posn of Im CH_2	mp, °C	yield, %	recryst[a] solvent	formula[b]
46	O	CO_2CH_3	H	H	5	146–147	48	EtOAc/PE	$C_{14}H_{12}N_2O_3$
47	O	CO_2CH_3	H	H	6	172–174	56	EtOAc	$C_{14}H_{12}N_2O_3$
48	S	CO_2CH_3	H	H	5	168–169	37	$MeOH/H_2O$	$C_{14}H_{12}N_2O_2S$
49	S	CO_2CH_3	H	H	6	143–144	33	IPA	$C_{14}H_{12}N_2O_2S$
50	S	CO_2CH_3	H	H	7	125–126	42	EtOAc/PE	$C_{14}H_{12}N_2O_2S$
51	S	H	CO_2CH_3	H	5	212–214	76	IPA	$C_{14}H_{12}N_2O_2S$·HCl
52	S	H	CO_2CH_3	H	6	117–118.5	65	EtOAc/PE	$C_{14}H_{12}N_2O_2S$
53	S	H	CO_2CH_3	H	7	136–138	42	EtOAc/PE	$C_{14}H_{12}N_2O_2S$
54	S	CO_2CH_3	CH_3	H	5	136–138	54	EtOAc/PE	$C_{15}H_{14}N_2O_2S$[c]
55	S	CO_2CH_3	CH_3	H	6	147–148	54	EtOAc/PE	$C_{15}H_{14}N_2O_2S$
56	S	CO_2CH_3	Cl	H	6	170–172	51	$CHCl_3$/PE	$C_{14}H_{11}ClN_2O_2S$
57	S	CO_2CH_3	H	OCH_3	6	161–162	40	EtOAc/PE	$C_{15}H_{14}N_2O_3S$

[a] PE, petroleum ether, bp 60–80 °C. [b] All compounds gave C, H, and N analyses within 0.4% of the theoretical value unless otherwise stated. [c] C: calcd, 62.91; found, 62.43.

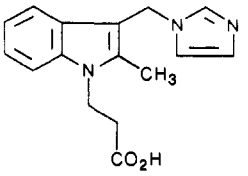
chrome P-450 and adrenal steroid 11β-hydroxylase, thereby reducing the potential for causing undesirable side effects.[6,7]

We have reported previously[6,12] that **1** (dazoxiben) is a potent and highly selective inhibitor of TxA_2 synthetase, and the compound has undergone extensive evaluation in human volunteers and patients.[13] We[14] and other workers[4] have also found that the isomeric compound **2** is a potent and selective inhibitor of TxA_2 synthetase.



1

2



3

The previous paper in this series[7] reported that **3** (UK-38,485, dazmegrel) is a more potent and longer acting TxA_2 synthetase inhibitor than **1** in both animals and man.[15] As part of our follow-up program to **1** and **3**, we were interested in examining the effect of incorporating the ether linkage of **1** and **2** into a heterocyclic ring system such as benzo[*b*]furan. This paper describes the synthesis and activity of benzo[*b*]furans, together with some benzo[*b*]-thiophene and indole analogues, based on structure **2**. The following paper[16] will describe heterocycles based on structure **1**.

Chemistry. (1*H*-Imidazol-1-ylmethyl)benzo[*b*]furan- and -benzo[*b*]thiophenecarboxylic acids (Table III) were prepared by treatment of a halomethyl-substituted carboxylic acid methyl ester with imidazole sodium salt in DMF at room temperature followed, in most cases, by basic hydrolysis of the resulting 1*H*-imidazol-1-yl-substituted ester (Scheme I). In the case of the benzo[*b*]furan ester **46**, acidic hydrolysis was used, and the hydroxybenzo[*b*]-thiophene-2-carboxylic acid **74** was prepared by treatment of the methoxy ester **57** with HBr.

The bromomethyl-substitued ester staring materials **4–12** (Table I) were prepared by NBS bromination of the corresponding methylbenzo[*b*]furan or methylbenzo[*b*]-

(12) Randall, M. J.; Parry, M. J.; Hawkeswood, E.; Cross, P. E.; Dickinson, R. P. *Thromb. Res.* **1981**, *23*, 145.
(13) Lewis, P.; Tyler, H. M. *Br. J. Clin. Pharmacol. Suppl. 1* **1983**, *15*, 15–140S.
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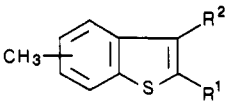
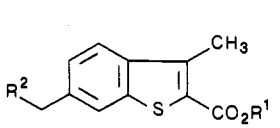
thiophene esters. Two novel benzo[*b*]thiophene esters, **13** and **14**, were prepared by standard means from the known



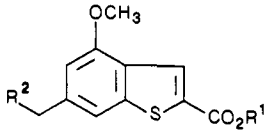
13: $R^1 = CO_2CH_3$, $R^2 = H$; 5-CH_3
14: $R^1 = CO_2CH_3$, $R^2 = H$; 6-CH_3
15: $R^1 = H$, $R^2 = CO_2CH_3$; 6-CH_3
16: $R^1 = R^2 = H$; 6-CH_3
17: $R^1 = H$, $R^2 = Br$; 6-CH_3
18: $R^1 = R^2 = Br$; 6-CH_3
19: $R^1 = H$, $R^2 = CO_2H$; 6-CH_3

acids. The novel 6-methylbenzo[*b*]thiophene-3-carboxylic acid methyl ester (**15**) was prepared in several steps from 6-methylbenzo[*b*]thiophene (**16**). The latter was converted to the 3-bromo derivative **17** by dibromination to give **18**, followed by selective removal of the 2-bromine with *n*-BuLi followed by hydrolysis. Monobromination of **16** is reported to give an almost equal mixture of 2- and 3-bromo compounds,[18] which we have confirmed. Successive treatment of **17** with *n*-BuLi and CO_2 followed by esterification of the product **19** gave the ester **15**.

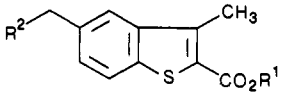
In some cases, (chloromethyl)benzo[*b*]thiophene-2-carboxylic esters were used (**24**, **25**, **27**). Compounds **24** and **25** were prepared by esterification (MeOH/HCl) of the corresponding hydroxymethyl acids **20** and **21**,[17] followed by treatment of the ester products **22** and **23** with $SOCl_2$. Esterification of the 5-hydroxymethyl acid **26**[17] under the same conditions gave the chloromethyl-substituted ester **27** directly together with smaller amounts of the methoxymethyl compound **28** and the hydroxymethyl compound **29**.



20: $R^1 = H$, $R^2 = OH$
22: $R^1 = CH_3$, $R^2 = OH$
24: $R^1 = CH_3$, $R^2 = Cl$



21: $R^1 = H$, $R^2 = OH$
23: $R^1 = CH_3$, $R^2 = OH$
25: $R^1 = CH_3$, $R^2 = Cl$

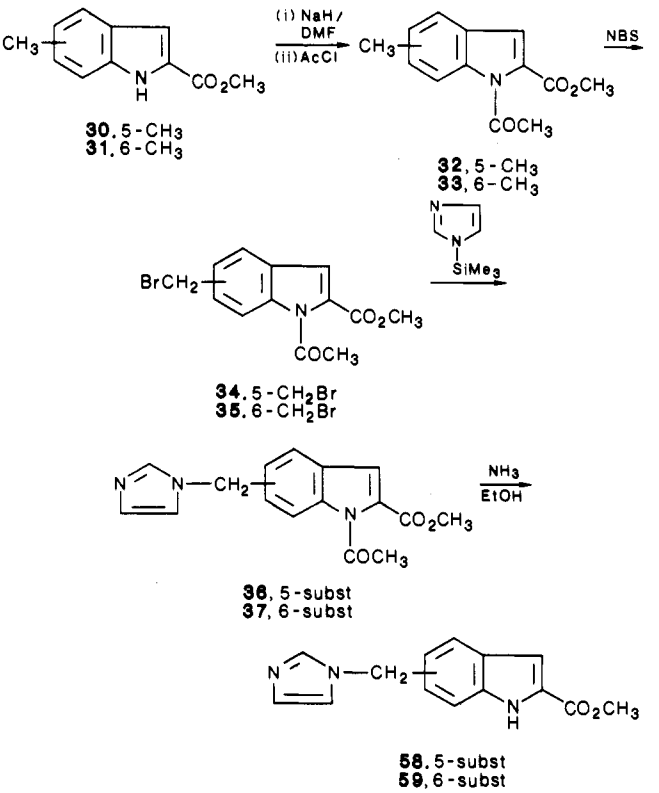


26: $R^1 = H$, $R^2 = OH$
27: $R^1 = CH_3$, $R^2 = Cl$
28: $R^1 = CH_3$, $R^2 = OCH_3$
29: $R^1 = CH_3$, $R^2 = OH$

A modified approach was used for preparation of the indole esters (Scheme II). The methylindole esters **30** and **31** were first converted to the *N*-acetyl derivatives **32** and **33**, which were then converted to the bromomethyl derivatives **34** and **35** with NBS. Attempts to brominate **30** and **31** directly led to exclusive bromination at the 3-position. Treatment of **34** with imidazole sodium salt led to complete decomposition, probably initiated by attack of the imidazole anion at the *N*-acetyl group. However, treatment of **34** and **35** with an excess of 1-(trimethylsilyl)-1*H*-imidazole in toluene gave satisfactory yields of the products **36** and **37**. Partial deacetylation occurred during workup, so the product mixtures were treated with ethanolic NH_3 to give the deprotected products **58** and **59** that were then hydrolyzed in the usual way.

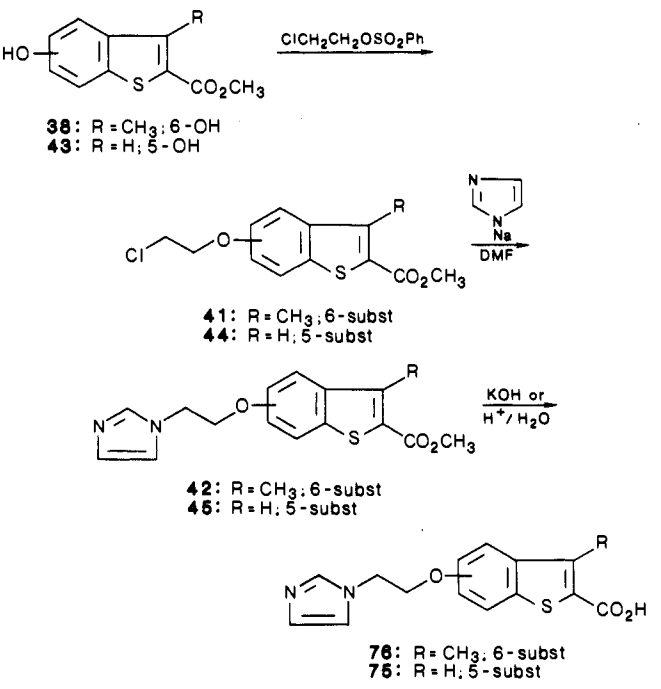
Compounds **75** and **76** with ether linking groups were prepared from hydroxybenzo[*b*]thiophene-2-carboxylic

Scheme II



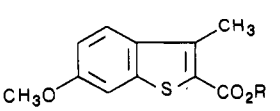
30, 5-CH_3
31, 6-CH_3
32, 5-CH_3
33, 6-CH_3
34, 5-CH_2Br
35, 6-CH_2Br
36, 5-subst
37, 6-subst
58, 5-subst
59, 6-subst

Scheme III



38: R = CH_3; 6-OH
43: R = H; 5-OH
41: R = CH_3; 6-subst
44: R = H; 5-subst
42: R = CH_3; 6-subst
45: R = H; 5-subst
76: R = CH_3; 6-subst
75: R = H; 5-subst

esters (Scheme III). The hydroxy ester **38** was prepared by esterification (MeOH/HCl) of the methoxy acid **39** followed by demethylation of the product **40** using BBr_3.

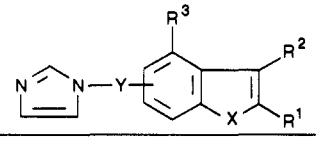


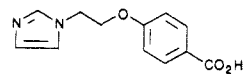
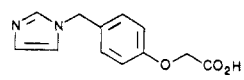
39, R = H
40, R = CH_3

Demethylation of the acid **39** using HBr led to simultaneous decarboxylation. Treatment of **38** with NaH in DMF followed by 2-[(phenylsulfonyl)oxy]ethyl chloride

(17) Cross, P. E.; Dickinson, R. P. *Heterocycles* **1985**, *23*, 2391.
(18) Clark, P. D.; Clarke, K.; Scrowston, R. M.; Sutton, T. M. *J. Chem. Res. Synop.* **1978**, 10.

Table III. 1*H*-Imidazol-1-yl-Substituted Carboxylic Acids



no.	X	Y	R^1	R^2	R^3	posn of Im Y	mp, °C	yield, %	formula[a]	TxA_2 synthetase IC_{50},[b] M
60	O	CH_2	CO_2H	H	H	5	266 dec[c]	54	$C_{13}H_{10}N_2O_3 \cdot HCl$	3.4×10^{-8}
61	O	CH_2	CO_2H	H	H	6	273–275	53	$C_{13}H_{10}N_2O_3$	2.0×10^{-8}
62	S	CH_2	CO_2H	H	H	5	270–272[d]	74	$C_{13}H_{10}N_2O_2S$	2.1×10^{-8}
63	S	CH_2	CO_2H	H	H	6	288–289[d]	53	$C_{13}H_{10}N_2O_2S$	1.8×10^{-8}
64	S	CH_2	CO_2H	H	H	7	264–266	53	$C_{13}H_{10}N_2O_2S$	1.2×10^{-7}
65	NH	CH_2	CO_2H	H	H	5	264–266	72	$C_{13}H_{11}N_3O_2$	5.0×10^{-9}
66	NH	CH_2	CO_2H	H	H	6	275–277[e]	32	$C_{13}H_{11}N_3O_2$	3.3×10^{-8}
67	S	CH_2	H	CO_2H	H	5	235–237[c]	52	$C_{13}H_{10}N_2O_2S$	1.7×10^{-6}
68	S	CH_2	H	CO_2H	H	6	280–282	84	$C_{13}H_{10}N_2O_2S$	1.9×10^{-8}
69	S	CH_2	H	CO_2H	H	7	276–277	47	$C_{13}H_{10}N_2O_2S$	3.4×10^{-8}
70	S	CH_2	CO_2H	CH_3	H	5	268–270	45	$C_{14}H_{12}N_2O_2S$	2.9×10^{-8}
71	S	CH_2	CO_2H	CH_3	H	6	277–278	84	$C_{14}H_{12}N_2O_2S$	5.2×10^{-9}
72	S	CH_2	CO_2H	Cl	H	6	255–257	78	$C_{13}H_9ClN_2O_2S$	7.4×10^{-9}
73	S	CH_2	CO_2H	H	OCH_3	6	273–274	79	$C_{14}H_{12}N_2O_3S$	5.0×10^{-9}
74	S	CH_2	CO_2H	H	OH	6	297–299	57.5	$C_{13}H_{10}N_2O_3S$[f]	5.2×10^{-8}
75	S	CH_2CH_2O	CO_2H	H	H	5	255–258[g]	59	$C_{14}H_{12}N_2O_3S \cdot HCl \cdot 0.5H_2O$	4.2×10^{-7}
76	S	CH_2CH_2O	CO_2H	CH_3	H	6	239–240	70	$C_{15}H_{14}N_2O_3S$	1.4×10^{-7}
1										3.0×10^{-9}
2										3.1×10^{-8}

[a] All compounds gave C, H, and N analyses within 0.4% of the theoretical value unless otherwise stated. [b] Each result represents the mean of two determinations. [c] Recrystallized from IPA. [d] Recrystallized from H_2O. [e] Recrystallized from $AcOH/H_2O$. [f] C: calcd, 56.92; found 56.42. [g] Recrystallized from $EtOH/Et_2O$.

gave the chloroethyl ether **41**. Reaction of **41** with imidazole sodium salt in DMF gave **42**, which was converted to the acid **76** by basic hydrolysis. The 5-hydroxy ester **43** was treated with 2-[(phenylsulfonyl)oxy]ethyl chloride in the presence of MeOH/MeONa. The resulting chloro ether **44** was converted to the imidazol-1-yl ester **45** as before while the carboxylic acid **75** was prepared by acidic hydrolysis.

Results and Discussion

The benzo[*b*]furan **60**, which incorporates the overall skeleton of **2**, has identical potency against TxA_2 synthetase but is less potent than **1** (Table III). The benzo[*b*]thiophene and indole isosteres **62** and **65** retain activity as do the 6-(1*H*-imidazol-1-ylmethyl) isomers **61**, **63**, and **66**. The 7-substituted benzo[*b*]thiophene isomer **64** is slightly less potent. Evaluation of the compounds in anesthetized rabbits showed that none was as potent as **1** although **63** showed a moderate level of activity,[19] and further analogue synthesis was based on this structure.

The 3-carboxylic acid analogues **68** and **69** show the same level of activity against TxA_2 synthetase as **63**, but there is a marked drop in potency with **67**. In the latter case, the distance between the imidazole ring and the carboxylic acid group is probably too short. This is in line with results from other series where it was found that there is an optimum distance between the imidazole and acid groups.[2-4,6] Examination of Dreiding models of **1**, **2**, and related compounds indicated that a distance of 8.5–9.0 Å between N-1 of the imidazole and the carboxyl carbon is optimal.[4] The corresponding distance in the most poent of the present compounds is close to this range.

Introduction of additional substituents into **63** either at the 3- (**71**, **72**) or 4-positions (**73**, **74**) gives potent compounds. Compound **70**, the 3-methyl analogue of **62**, has a similar level of activity.

Compounds **75** and **76**, which incorporate the 1*H*-imidazol-1-ylethoxy group present in **1** are less potent than the corresponding analogues with a methylene linkage between the rings, **62** and **71**. These results again emphasize the importance of the overall imidazole to carboxyl distance for optimal potency.

Of the compounds **67–76**, only **71** showed significantly greater potency than **63** in vivo.[19] The compound was evaluated further in conscious dogs and Figure 1 shows the effect of administration of 1 mg/kg compared with the same dose of **1**. The potency of the two compounds was virtually identical, although the decline in activity after 6 h appeared greater for **1**. By contrast, the same dose of **3** gave a higher maximal level of inhibition (92.5% after 2 h) and thromboxane production was still inhibited by more than 80% 6 h after dosing.[7] Like **1**[6,12] and **3**,[7] compound **71** was found to have no significant effect on cyclooxygenase, PGI_2 synthetase, or adrenal steroid 11β-hydroxylase at 10^{-4} M.

In conclusion, we have shown that several benzo[*b*]furan-, benzo[*b*]thiophene-, and indolecarboxylic acids with imidazole-containing substituents are potent TxA_2 synthetase inhibitors. As in other series, the distance between the imidazole and carboxyl groups appears to be important for optimal potency. Compound **71** was found to have similar potency in vivo to **1** but less than that of **3**.

Experimental Section

Enzyme Assays. Methods used for the determination of

(19) Parry, M. J.; Randall, M. J., unpublished results (procedure as described in ref 7).

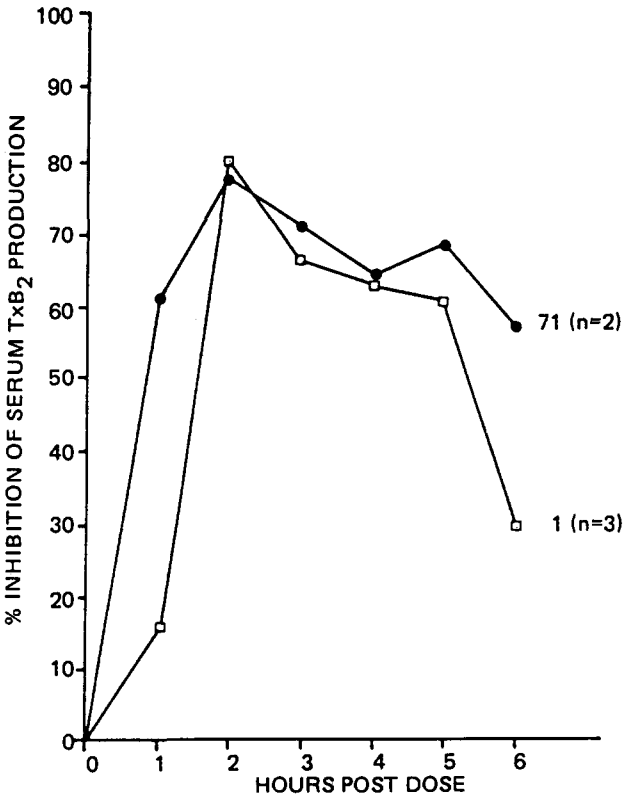


Figure 1. Inhibition of TxB_2 production in whole blood from dogs following a single oral dose of 71 (1 mg/kg) compared with the same dose of 1.

activity against TxA_2 synthetase, cyclooxygenase, and adrenal steroid 11β-hydroxylase in vitro have been described in the first paper of this series.[6]

Oral Efficacy in Dogs. Blood samples were obtained from the external jugular vein of conscious male beagles 1 h and immediately before administration of compound to establish control serum levels of TxB_2. The test compound, ground with excipient (starch/lactose) in a ratio of 1:3, was administered in loosely filled gelatin capsules. Further blood samples were then taken from each dog at hourly intervals. The blood samples (1 mL) were allowed to clot in glass tubes for 1 h at 37 °C, and the serum was obtained by centrifugation at 2000*g* for 10 min at room temperature. The protein in 100-μL samples was precipitated by addition of 500 μL of EtOH and, after thorough mixing, the precipitate was centrifuged at 10000*g* for 2 min. Aliquots (5–10 μL) of the EtOH supernatant were added to Isogel Tris buffer (1 mL), and the TxB_2 content was determined by a specific radioimmunoassay as described previously.[12] Results were calculated as the percentage reduction in serum TxB_2 levels following compound administration, relative to control levels prior to dosing.

Chemistry. All melting points are uncorrected and were obtained on an Electrothermal capillary melting point apparatus. The structures of all compounds were confirmed by their IR and ^1H NMR spectra. The IR spectra were recorded on a Perkin-Elmer 197 or 237 spectrophotometer, and the ^1H NMR spectra were obtained on a Varian XL-100-15 or a Bruker WM 250 spectrometer using Me_4Si as internal standard.

2,3-Dibromo-6-methylbenzo[*b*]thiophene (18). Bromine (15.2 g, 0.095 mol) was added over 5 min to a stirred solution of 6-methylbenzo[*b*]thiophene (**16**; 7.0 g, 0.047 mol) in $CHCl_3$ (70 mL) at room temperature, and the solution was stirred for 4 h. Evaporation of the solvent gave a solid that was crystallized from MeOH to give **18**: yield 12.4 g (86%); mp 67.5–68.5 °C. Anal. ($C_9H_6Br_2S$) C, H.

3-Bromo-6-methylbenzo[*b*]thiophene (17). A 1.6 M solution of *n*-BuLi in hexane (24.3 mL, 0.038 mol) was added over 5 min to a stirred solution of **18** (11.76 g, 0.038 mol) in dry Et_2O (150 mL) at 0 °C under dry N_2. The solution was stirred at 0 °C for 1 h, and then H_2O (50 mL) was added. The organic layer was separated, dried (Na_2SO_4), and evaporated, and the residue was distilled to give **17**: yield 5.80 g (67%); bp 112–114 °C (0.2 mm); mp 51–53 °C (from MeOH); 250-MHz ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H, CH_3), 7.20 (dd, 1 H, J = 8.3, 1.7 Hz, H-5), 7.25 (s, 1 H, H-2), 7.55 (d, 1 H, J = 1.7 Hz, H-7), 7.63 (d, 1 H, J = 8.3 Hz, H-4).

6-Methylbenzo[*b*]thiophene-3-carboxylic Acid (19). A 1.0 M solution of *n*-BuLi in hexane (15.0 mL, 0.015 mol) was added over 5 min to a stirred solution of **17** (3.0 g, 0.013 mol) in dry Et_2O (40 mL) at −78 °C under dry N_2. The mixture was stirred at this temperature for 30 min, and then an excess of freshly crushed solid CO_2 was added. The excess CO_2 was allowed to evaporate, and the mixture was extracted with H_2O followed by 2 N NaOH solution. The extracts were combined and acidified with concentrated HCl. The solid was filtered off, washed with water, dried, and crystallized from toluene to give **19**: yield 1.60 g (64%); mp 205–209 °C. Anal. ($C_{10}H_8O_2S$) C, H.

6-Methylbenzo[*b*]thiophene-3-carboxylic Acid Methyl Ester (15). A solution of **19** (1.32 g, 0.0069 mol) in methanol (20 mL) was saturated with HCl gas, heated under reflux for 3 h, and then evaporated. The residue was dissolved in Et_2O, and the solution was washed with dilute $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the Et_2O gave **15**: yield 1.31 g (92.5%); mp 82–84 °C (from PE, bp 40–60 °C). Anal. ($C_{11}H_{10}O_2S$) C, H.

The following benzo[*b*]thiophenecarboxylic acid esters were prepared similarly.

5-Methylbenzo[*b*]thiophene-2-carboxylic Acid Methyl Ester (13): 97%; mp 78–79 °C (from MeOH). Anal. ($C_{11}H_{10}O_2S$) C, H.

6-Methylbenzo[*b*]thiophene-2-carboxylic Acid Methyl Ester (14): 81%; mp 92–92.5 °C (from MeOH). Anal. ($C_{11}H_{10}O_2S$) C, H.

6-Methoxy-3-methylbenzo[*b*]thiophene-2-carboxylic Acid Methyl Ester (40): 70%; mp 118–120 °C (from MeOH). Anal. ($C_{12}H_{12}O_3S$) C, H.

1-Acetyl-6-methylindole-2-carboxylic Acid Methyl Ester (33). A 50% dispersion of NaH in mineral oil (4.70 g, 0.098 mol) was added portionwise to a stirred solution of 6-methylindole-2-carboxylic acid methyl ester (**31**; 18.0 g, 0.095 mol) in dry DMF (100 mL). The mixture was stirred for 1 h, and then acetyl chloride (8.0 g, 0.102 mol) was added dropwise with cooling. The mixture was stirred at room temperature for 5 h and poured into water. Extraction with EtOAc gave an oil that was chromatographed on silica gel with $CHCl_3$ as eluent. After elution of mineral oil, the early fractions contained pure product. The product fractions were evaporated, and the solid was crystallized from MeOH to give **33**: yield 14.4 g (66%); mp 51–53 °C. Anal. ($C_{13}H_{13}NO_3$) C, H, N.

1-Acetyl-5-methylindole-2-carboxylic acid methyl ester (32) was prepared similarly from 5-methylindole-2-carboxylic acid methyl ester (**30**): yield 74.5%; bp 160 °C (0.05 mm) (Kugelrohr). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

6-(Bromomethyl)benzo[*b*]thiophene-3-carboxylic Acid Methyl Ester (10). A mixture of **15** (1.03 g, 0.005 mol), NBS (0.89 g, 0.005 mol), and azobis(isobutyronitrile) (0.20 g) in CCl_4 (25 mL) was heated under reflux for 3 h, then cooled, and washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated, and the residue was crystallized from EtOAc/PE (bp 60–80 °C) to give **10**: yield 0.78 g (55%); mp 165–167 °C. Anal. ($C_{11}H_9BrO_2S$) C, H.

Other bromomethyl compounds prepared similarly are summarized in Table I.

6-(Hydroxymethyl)-3-methylbenzo[*b*]thiophene-2-carboxylic Acid Methyl Ester (22). A solution of **20**[17] (0.50 g, 0.00225 mol) in MeOH (25 mL) was saturated with dry HCl, heated under reflux for 2 h, and then evaporated. The residue was dissolved in ether, and the solution was washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. Elution with $CHCl_3$ first gave some impurity followed by pure **22**: yield 0.31 g (58.5%); mp 121–122 °C (from toluene/PE, bp 80–100 °C). Anal. ($C_{12}H_{12}O_3S$) C, H.

6-(Hydroxymethyl)-4-methoxybenzo[*b*]thiophene-2-carboxylic Acid Methyl Ester (23). Esterification of **21**[17] as described above gave **23**: 83%; mp 113–114 °C (from EtOAc/PE, bp 60–80 °C). Anal. ($C_{12}H_{12}O_4S$) C, H.

Esterification of 5-(Hydroxymethyl)-3-methylbenzo[*b*]thiophene-2-carboxylic Acid (26). Esterification of **26**[17] as described above gave a crude product that was chromatographed ($SiO_2/CHCl_3$) to give, in order of elution, **27–29**. 5-(Chloro-

methyl)-3-methylbenzo[b]thiophene-2-carboxylic acid methyl ester (27): 42%; mp 115–117 °C (from hexane); 250-MHz ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3 H, 3-CH_3), 3.93 (s, 3 H, CO_2CH_3), 4.74 (s, 2 H, CH_2), 7.51 (dd, 1 H, J = 8.5, 1.6 Hz, H-6), 7.82 (d, 1 H, J = 8.5 Hz, H-7), 7.84 (d, 1 H, J = 1.6 Hz, H-4). Anal. ($C_{12}H_{11}ClO_2S$) C, H. 5-(Methoxymethyl)-3-methylbenzo[b]thiophene-2-carboxylic acid methyl ester (28): 22%; mp 88–89 °C (from hexane); 250-MHz ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3 H, 3-CH_3), 3.44 (s, 3 H, OCH_3), 3.93 (s, 3 H, CO_2CH_3), 4.60 (s, 2 H, CH_2), 7.45 (dd, 1 H, J = 8.2, 1.5 Hz, H-6), 7.81 (d, 1 H, J = 1.5 Hz, H-4), 7.81 (d, 1 H, J = 8.2 Hz, H-7). Anal. ($C_{13}H_{15}O_3S$) C, H. 5-(Hydroxymethyl)-3-methylbenzo[b]thiophene-2-carboxylic acid methyl ester (29): 15%; mp 132–133 °C (from EtOAc/PE, bp 60–80 °C); 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.80 (t, 1 H, J = 5.8 Hz, OH), 2.78 (s, 3 H, 3-CH_3), 3.93 (s, 3 H, CO_2CH_3), 4.85 (d, 2 H, J = 5.8 Hz, CH_2), 7.48 (dd, 1 H, J = 8.4, 1.5 Hz, H-6), 7.82 (d, 1 H, J = 8.4 Hz, H-7), 7.84 (d, 1 H, J = 1.5 Hz, H-4). Anal. ($C_{12}H_{13}O_3S$) C, H.

6-(Chloromethyl)-3-methylbenzo[b]thiophene-2-carboxylic Acid Methyl Ester (24). $SOCl_2$ (0.75 mL) was added cautiously to a solution of **22** (0.70 g, 0.003 mol) and pyridine (3 drops) in $CHCl_3$ (7.5 mL). The solution was allowed to stand for 1 h and was then washed with H_2O and $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the solvent gave a solid that was crystallized from PE (bp 60–80 °C) to give **24**: yield 0.63 g (83%); mp 128–129 °C. Anal. ($C_{12}H_{11}ClO_2S$) C, H.

6-(Chloromethyl)-4-methoxybenzo[b]thiophene-2-carboxylic Acid Methyl Ester (25). Treatment of **23** with $SOCl_2$ and pyridine as described above gave **25**: 75%; mp 147–148 °C (from EtOAc/PE, bp 60–80 °C). Anal. ($C_{12}H_{11}ClO_3S$) C, H.

6-Hydroxy-3-methylbenzo[b]thiophene-2-carboxylic Acid Methyl Ester (38). BBr_3 (5.0 mL) was added dropwise to a stirred solution of **40** (4.70 g, 0.02 mol) in dry CH_2Cl_2 (200 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min followed by 24 h at room temperature. It was treated cautiously with MeOH to decompose excess BBr_3 and then washed with $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel using $CHCl_3$ as eluent. After elution of some impurity, pure product was obtained. The product fractions were evaporated, and the residue was crystallized from EtOAc/PE (bp 60–80 °C) to give **38**: yield 3.58 g (81%); mp 174–176 °C. Anal. ($C_{11}H_{10}O_3S$) C, H.

6-(2-Chloroethoxy)-3-methylbenzo[b]thiophene-2-carboxylic Acid Methyl Ester (41). A 50% dispersion of NaH in mineral oil (0.48 g, 0.01 mol) was added portionwise to a stirred solution of **38** (2.22 g, 0.01 mol) in dry DMF (20 mL). The mixture was stirred for 30 min and cooled to 0 °C, and 2-[(phenylsulfonyl)oxy]ethyl chloride (2.64 g, 0.012 mol) was added. Stirring was continued at room temperature for 2 h, and the mixture was then poured into water. Extraction with EtOAc gave a solid that was chromatographed on silica gel. Elution with $CHCl_3$ gave a solid that was crystallized from EtOAc/PE (bp 60–80 °C) to give **41**: yield 1.69 g (59%); mp 131–132 °C. Anal. ($C_{13}H_{13}ClO_3S$) C, H.

5-(2-Chloroethoxy)benzo[b]thiophene-2-carboxylic Acid Methyl Ester (44). Sodium (0.163 g, 0.007 mol) was dissolved in MeOH (15 mL) and 5-hydroxybenzo[b]thiophene-2-carboxylic acid methyl ester (**43**; 1.47 g, 0.007 mol) and 2-[(phenylsulfonyl)oxy]ethyl chloride (1.57 g, 0.007 mol) were added. The solution was heated under reflux for 8 h and then evaporated. The residue was dissolved in ether, and the solution was washed with water and dried (Na_2SO_4). The ether was evaporated, and the residue was chromatographed ($SiO_2/CHCl_3$) to give a solid that was crystallized from EtOAc/PE (bp 60–80 °C) to give **44**: yield 0.74 g (39%); mp 116–117 °C. Anal. ($C_{12}H_{11}ClO_3S$) C, H.

6-(1H-Imidazol-1-ylmethyl)benzo[b]thiophene-3-carboxylic Acid Methyl Ester (52). A 50% dispersion of NaH in mineral oil (0.118 g, 0.0025 mol) was added portionwise to a stirred solution of imidazole (0.167 g, 0.0025 mol) in dry DMF (5 mL). The mixture was stirred for 1 h, and then a solution of **10** (0.70 g, 0.0025 mol) in dry DMF (5 mL) was added dropwise. The mixture was stirred at room temperature for 2 h and then poured into water. Extraction with ethyl acetate gave a solid that was chromatographed on silica gel. Elution with $CHCl_3$ gave a solid that was crystallized from EtOAc/PE (bp 60–80 °C) to give **52**: yield 0.44 g (65%); mp 117–118.5 °C. Anal. ($C_{14}H_{12}N_2O_2S$) C, H, N.

Other compounds were prepared similarly from a bromomethyl or chloromethyl-substituted heterocyclic ester and are listed in Table II.

6-(1H-Imidazol-1-ylmethyl)indole-2-carboxylic Acid Methyl Ester (59). A solution of **35** (3.10 g, 0.01 mol) in toluene (25 mL) was added dropwise to a stirred solution of 1-(trimethylsilyl)-1H-imidazole (5.60 g, 0.04 mol) in toluene (25 mL) at 80 °C. The mixture was stirred at 80 °C for 2 h and then evaporated. Water was added, and the mixture was extracted with EtOAc to give an oil that was dissolved in a concentrated solution of NH_3 in EtOH (40 mL). After 2.5 h, the solution was evaporated and the residue was chromatographed on silica gel. Elution with $CHCl_3$ gave a solid that was crystallized from EtOAc to give **59**: yield 1.49 g (58%); mp 204–205 °C. Anal. ($C_{14}H_{13}N_3O_2$) C, H, N.

5-(1H-Imidazol-1-ylmethyl)indole-2-carboxylic Acid Methyl Ester (58). Treatment of **34** with 1-(trimethylsilyl)-1H-imidazole as described above gave **58**: 61%; mp 195–196.5 °C (from EtOAc/PE, bp 60–80 °C). Anal. ($C_{14}H_{13}N_3O_2$) C, H, N.

5-[2-(1H-Imidazol-1-yl)ethoxy]benzo[b]thiophene-2-carboxylic Acid Methyl Ester (45). A 50% dispersion of NaH in mineral oil (0.22 g, 0.0046 mol) was added portionwise to a stirred solution of imidazole (0.306 g, 0.0045 mol) in dry DMF (10 mL). Stirring was continued for 30 min, and then **44** (1.22 g, 0.0045 mol) was added. The solution was heated on a steam bath for 5 h and then poured into water. Extraction with EtOAc gave an oil that was chromatographed on silica gel. Elution with $CHCl_3$ initially gave some impurity followed by a solid that was crystallized from EtOAc/PE (bp 60–80 °C) to give **45**: yield 0.45 g (33%); mp 127–129 °C. Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N.

6-[2-(1H-Imidazol-1-yl)ethoxy]-3-methylbenzo[b]thiophene-2-carboxylic Acid Methyl Ester (42). Treatment of imidazole with NaH followed by **41** according to the above method gave **42**: 19%; mp 162–163 °C (from EtOAc/PE, bp 60–80 °C). Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N.

6-(1H-Imidazol-1-ylmethyl)benzo[b]thiophene-3-carboxylic Acid (68). A mixture of **52** (0.35 g, 0.0013 mol), KOH (0.1 g), MeOH (5 mL), and H_2O (2.5 mL) was heated under reflux for 2 h and then evaporated. The residue was dissolved in H_2O, and the solution was filtered and acidified with AcOH. The solid was filtered off and purified by reprecipitation from aqueous KOH with AcOH to give **68**: yield 0.28 g (84%); mp 280–282 °C. Anal. ($C_{13}H_{10}N_2O_2S$) C, H, N.

Other compounds prepared similarly are listed in Table III.

5-(1H-Imidazol-1-ylmethyl)benzo[b]furan-2-carboxylic Acid Hydrochloride (60). A solution of **46** (2.0 g, 0.0078 mol) in concentrated HCl (10 mL) and AcOH (10 mL) was heated on a steam bath for 2 h and then evaporated. The residue was crystallized from IPA to give **60**·HCl: yield 1.18 g (54%); mp 266 °C dec. Anal. ($C_{13}H_{10}N_2O_3$·HCl) C, H, N.

5-[2-(1H-Imidazol-1-yl)ethoxy]benzo[b]thiophene-2-carboxylic Acid (75). A mixture of **45** (0.35 g, 0.001 16 mol) and concentrated HCl (5 mL) was heated on a steam bath for 5 h and then evaporated. Crystallization of the residue from EtOH/Et_2O gave **75**·HCl·0.5H_2O: yield 0.23 g (59%); mp 255–258 °C. Anal. ($C_{14}H_{12}N_2O_3S$·HCl·0.5H_2O) C, H, N.

4-Hydroxy-6-(1H-imidazol-1-ylmethyl)benzo[b]thiophene-2-carboxylic Acid (74). A mixture of **57** (0.10 g, 0.000 33 mol), 48% aqueous HBr (2.0 mL), and AcOH (1.0 mL) was heated under reflux for 4 h and then evaporated. The solid was dissolved in H_2O, and the solution was made alkaline with NaOH and filtered. Acidification with AcOH gave a solid that was filtered off, washed with H_2O, and dried to give **74**: yield 0.052 g (57.5%); mp 297–299 °C. Anal. ($C_{13}H_{10}N_2O_3S$) H, N; C: calcd, 56.92; found, 56.42.

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82787-85-7; **16**, 16587-47-6; **17**, 66490-18-4; **18**, 82787-83-5; **19**, 82787-84-6; **20**, 82787-94-8; **21**, 82787-99-3; **22**, 82787-95-9; **23**, 82788-00-9; **24**, 82787-96-0; **25**, 82788-01-0; **26**, 82787-89-1; **27**, 82787-90-4; **28**, 82787-91-5; **29**, 102870-02-0; **30**, 102870-03-1; **31**, 18377-65-6; **32**, 102870-04-2; **33**, 82788-44-1; **34**, 102920-72-9; **35**, 82788-45-2; **38**, 82788-19-0; **40**, 82788-18-9; **41**, 82788-20-3; **42**, 82788-21-4; **43**, 82788-15-6; **44**, 82788-16-7; **45**, 82788-17-8; **46**, 82788-36-1; **47**, 82788-39-4; **48**, 82787-71-1; **49**, 82801-17-0; **50**, 82787-79-9; **51**, 82787-81-3; **52**, 82787-87-9; **53**, 82787-82-4; **54**, 82787-92-6; **55**, 82787-97-1; **56**, 82787-80-2; **57**, 82788-02-1; **58**, 102870-05-3; **59**, 82788-46-3; **60**, 102870-06-4; **61**, 82788-71-4; **62**, 82788-51-0; **63**, 82788-52-1; **64**, 82788-53-2; **65**, 102870-07-5; **66**, 82788-73-6; **67**, 82788-57-6; **68**, 82788-58-7; **69**, 82788-60-1; **70**, 82788-54-3; **71**, 82788-48-5; **72**, 82788-55-4; **73**, 82788-56-5; **74**, 82788-50-9; **75**, 82788-49-6; **76**, 82788-62-3; 2-[(phenylsulfonyl)oxy]ethyl chloride, 16670-48-7; imidazole, 288-32-4; 1-(trimethylsilyl)-1*H*-imidazole, 18156-74-6; methyl 5-methylbenzofuran-2-carboxylate, 82788-34-9; methyl 6-methylbenzofuran-2-carboxylate, 82788-37-2; methyl 7-methylbenzo[*b*]thiophene-2-carboxylate, 3751-50-6; methyl 5-methylbenzo[*b*]thiophene-3-carboxylate, 82787-73-3; methyl 7-methylbenzo[*b*]thiophene-3-carboxylate, 7312-03-0; methyl 3-chloro-6-methylbenzo[*b*]-thiophene-2-carboxylate, 59812-34-9; thromboxane synthetase, 61276-89-9.

Selective Thromboxane Synthetase Inhibitors. 4. 2-(1*H*-Imidazol-1-ylmethyl) Carboxylic Acids of Benzo[*b*]furan, Benzo[*b*]thiophene, Indole, and Naphthalene

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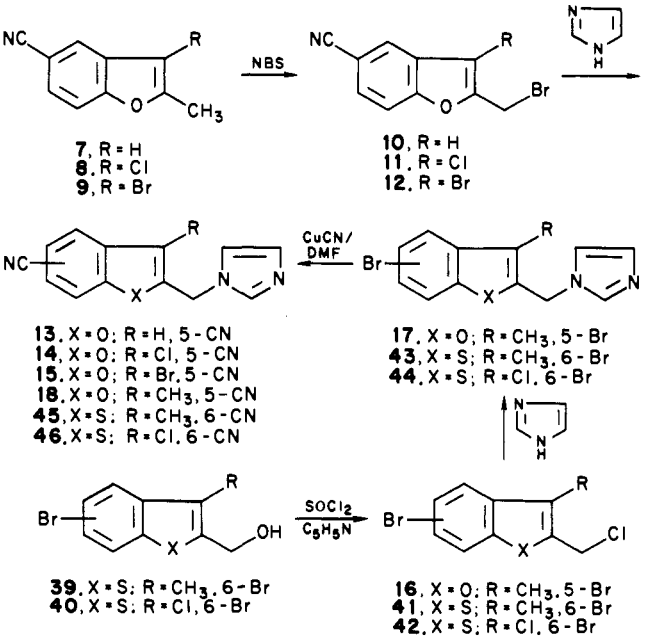
The preparation of a series of 2-(1*H*-imidazol-1-ylmethyl)-substituted carboxylic acids of benzo[*b*]furan, benzo[*b*]thiophene, indole, and naphthalene is described. All compounds showed a similar level of activity as TxA_2 synthetase inhibitors in vitro, having IC_{50} values between 1 and 7×10^{-8} M. In the cases examined, compounds had, at most, only negligible activity against PGI_2 synthetase, cyclooxygenase, and steroid 11β-hydroxylase. The benzo[*b*]thiophenes generally showed the greatest potency in vivo, and compounds **72**, **73**, and **75** caused almost complete inhibition of thromboxane production for 6 h after oral administration of 0.5 mg/kg to conscious dogs. In the case of **73** and **75**, thromboxane production was still inhibited by 80% after 24 h.

We have reported previously[1,2] that **1** (dazoxiben) is a potent inhibitor of thromboxane synthetase, which converts prostaglandin H_2 (PGH_2) to the potent vasoconstrictor and platelet aggregating agent thromboxane A_2 (TxA_2). Compound **1** is highly selective and has no significant effect against either cyclooxygenase or prostaglandin I_2 (PGI_2) synthetase, which converts PGH_2 to the potent vasodilator and antiaggregatory agent PGI_2. The presence of the carboxylic acid group in **1** and other TxA_2 synthetase inhibitors has the advantage of reducing activity against other enzymes that are normally susceptible to inhibition by 1-substituted imidazoles such as liver microsomal cytochrome P-450 and adrenal steroid 11β-hydroxylase.[2,3] Compound **1** has undergone clinical evaluation in conditions in which vasospasm or thrombosis may play a major contributory role.[4]

The isomeric compound **2** is also a potent and selective TxA_2 synthetase inhibitor,[5,6] and the preceding paper[7] described the synthesis and activity of a series of anologues in which the heteroatom linkage was incorporated into a heterocyclic ring system. Thus, the benzo[*b*]furan **3**, the benzo[*b*]thiophene analogue **4**, and several related com-

Scheme I



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