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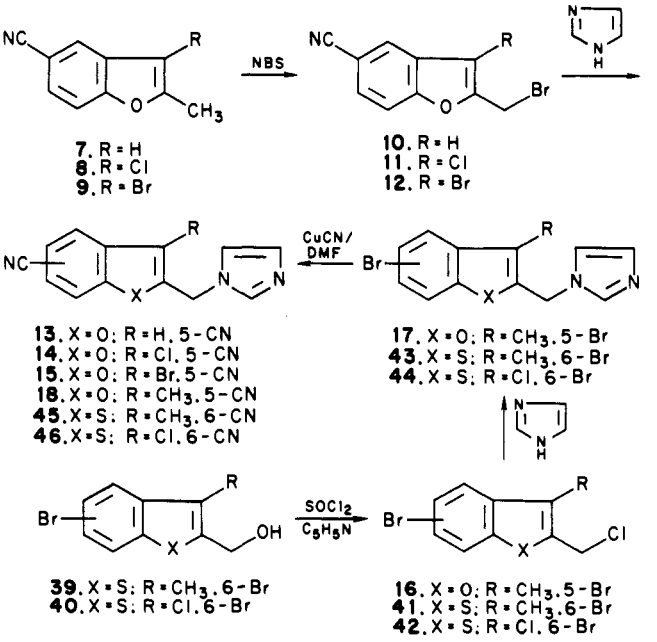
Pfizer Central Research, Sandwich, Kent CT13 9NJ, U.K. *Received November 25, 1985*

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



(1) Randall, M. J.; Parry, M. J.; Hawkeswood, E.; Cross, P. E.; Dickinson, R. P. *Thromb. Res.* **1981**, *23*, 145.
(2) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1985**, *28*, 1427.
(3) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1986**, *29*, 342.
(4) Lewis, P.; Tyler, H. M. *Br. J. Clin. Pharmacol. Suppl. 1* **1983**, *15*, 15–140S.
(5) Cross, P. E.; Dickinson, R. P. German Patent 3 001 762, 1980; *Chem. Abstr.* **1980**, *93*, 239415*w*.
(6) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. *J. Med. Chem.* **1981**, *24*, 1139.
(7) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.*, preceding paper in this issue.

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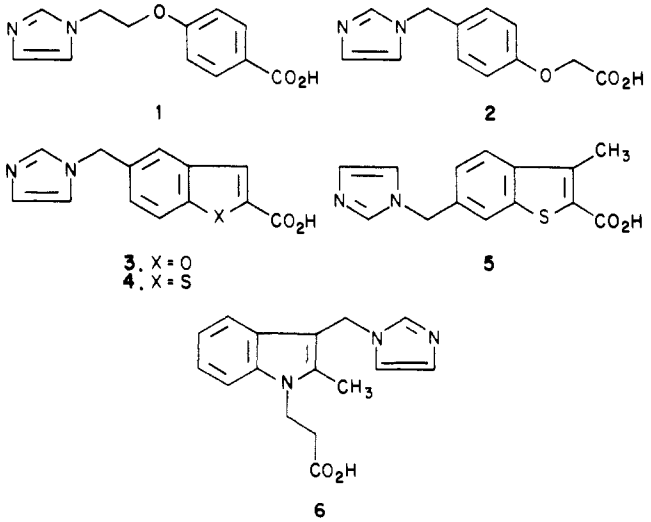


pounds were found to have the same level of activity as 2 against TxA_2 synthetase in vitro. Compound 5 was found to have a similar profile to 1 when evaluated in conscious dogs[7] but was less potent in vivo than 6 (dazmegrel).[3]

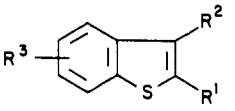
This paper describes the preparation and inhibitory activity of a related series of 1*H*-imidazol-1-ylmethyl-substituted benzo[*b*]furans, benzo[*b*]thiophenes, indoles, and naphthalenes similarly based on structure 1.

Chemistry. All 1*H*-imidazol-1-ylmethyl-substituted carboxylic acids were prepared by either acidic or basic hydrolysis of a nitrile or ester. The specific procedures used are summarized in Table I.

Benzo[*b*]furan-5-carboxylic acids were all prepared by hydrolysis of a carbonitrile. 2-Methylbenzo[*b*]furan-5-carbonitrile 7 was used as the precursor to 13–15 (Scheme I). Chlorination of 7 (SO_2Cl_2) or bromination (Br_2) gave the 3-halo derivatives 8 and 9. Reaction of 7–9 with NBS gave the bromomethyl derivatives 10–12, which were treated with an excess of imidazole and $NaHCO_3$ in acetone to give 13–15, respectively. The carbonitrile 18 was prepared from the chloromethyl compound 16[8] by treatment with imidazole followed by reaction of the product 17 with CuCN in DMF.

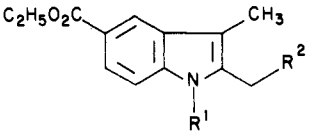
Benzo[*b*]thiophene-5-carboxylic acids were all obtained by hydrolysis of ester precursors prepared according to Scheme II. The esters 27–29 were prepared in several steps from 21, which was chlorinated (SO_2Cl_2) or brominated (Br_2) to give the 3-halo derivatives 22 and 23. Bromination of 21–23 with NBS gave the bromomethyl compounds 24–26, which were treated with imidazole as before to give 27–29. Chloromethylation of the esters 30 and 31 gave 32 and 33, respectively. Treatment of 32 with imidazole sodium salt in DMF gave 34, while 35 was prepared from 33 as before using imidazole and $NaHCO_3$ in acetone. The novel starting ester 21 was prepared from 5-bromo-2-methylbenzo[*b*]thiophene (19), which was converted via the Grignard reagent to the acid 20, which was then esterified. The ester 31 was prepared from 3,5-dibromobenzo[*b*]thiophene (36), which was treated with *n*-BuLi and dimethyl disulfide to give 37. This was converted via the Grignard reagent to the acid 38, which was esterified to give 31.

The benzo[*b*]thiophene-6-carboxylic acids 73 and 75 (Table I) were obtained from nitrile precursors 45 and 46 prepared according to Scheme I. Treatment of the alcohols 39 and 40 with $SOCl_2$ gave the chloromethyl compounds 41 and 42, respectively. Reaction of 41 and 42 with imidazole and $NaHCO_3$ gave 43 and 44, which were converted to the nitriles 45 and 46, respectively, with CuCN in DMF. The alcohol starting material 39 was prepared from 2,6-dibromo-3-methylbenzo[*b*]thiophene (47) by treatment with *n*-BuLi followed by paraformaldehyde. The chloro analogue 40 was prepared from 4-bromocinnamic acid, which was converted to 3-chlorobenzo[*b*]thiophene-2-carboxylic acid chloride 48 by treatment with $SOCl_2$ and pyridine using the method of Wright and Brabander.[9] Reduction of 48 with $LiAlH_4$ gave the alcohol 40.



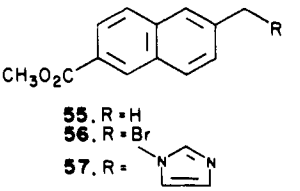
19. $R^1 = CH_3$; $R^2 = H$; $R^3 = 5\text{-Br}$
20. $R^1 = CH_3$; $R^2 = H$; $R^3 = 5\text{-}CO_2H$
36. $R^1 = H$; $R^2 = Br$; $R^3 = 5\text{-Br}$
37. $R^1 = H$; $R^2 = SCH_3$; $R^3 = 5\text{-Br}$
38. $R^1 = H$; $R^2 = SCH_3$; $R^3 = 5\text{-}CO_2H$
47. $R^1 = Br$; $R^2 = CH_3$; $R^3 = 6\text{-Br}$
48. $R^1 = COCl$; $R^2 = Cl$; $R^3 = 6\text{-Br}$

The indole esters 53 and 54 were prepared from the 2,3-dimethylindole ester 49, which was N-acetylated (NaH/CH_3COCl) to give 50. Treatment of 50 with Br_2 gave an unstable product assigned the structure 51 by analogy with the bromination of 1-acetyl-2,3-dimethylindole.[10] Reaction of 51 with imidazole and $NaHCO_3$ gave 52, which was deacetylated with ethanolic NH_3 to give the ester 53. A 16.5% NOE enhancement of the signal for H-4 was observed in the NMR spectrum on irradiation of the methyl resonance in 53, but there was no effect on H-4 on irradiation of the CH_2 resonance. This provides indirect evidence for the correctness of the structural assignment of the bromination product 51. Methylation of 53 by treatment with NaH followed by Me_2SO_4 gave the ester 54.



49. $R^1 = R^2 = H$
50. $R^1 = COCH_3$; $R^2 = H$
51. $R^1 = COCH_3$; $R^2 = Br$
52. $R^1 = COCH_3$
53. $R^1 = H$
54. $R^1 = CH_3$
} $R^2 =$

The naphthalene ester 57 was prepared from 2-methylnaphthalene-6-carboxylic acid ethyl ester 55 by treatment with NBS and reaction of the product 56 with imidazole and $NaHCO_3$. The naphthalene acids 81 and



55. R = H
56. R = Br
57. R =

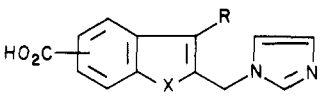
82 were prepared by hydrolysis of the nitriles 65 and 66 for which the α-tetralone derivative 58 was a precursor

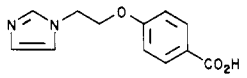
(8) Dann, O.; Volz, G.; Demant, E.; Pfeifer, W.; Bergen, G.; Fick, H.; Walkenhorst, E. *Annalen* 1973, 1112.

(9) Wright, W. B.; Brabander, H. J. *J. Heterocycl. Chem.* 1971, *8*, 711.

(10) Dmitrienko, G. I. *Heterocycles* 1979, *12*, 1141.

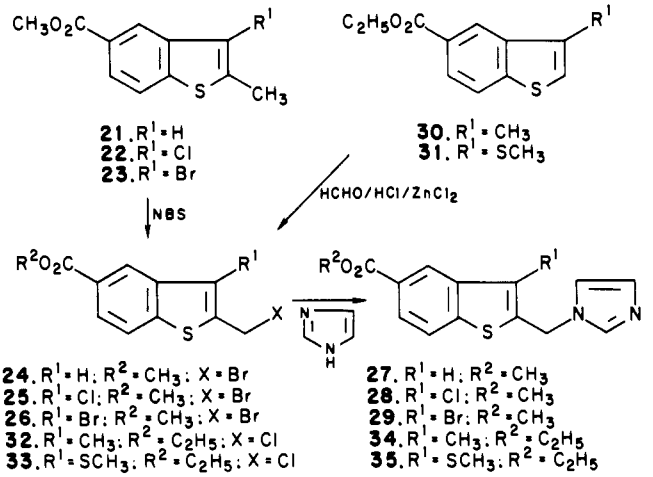
Table I. 2-(1*H*-Imidazol-1-ylmethyl)-Substituted Carboxylic Acids



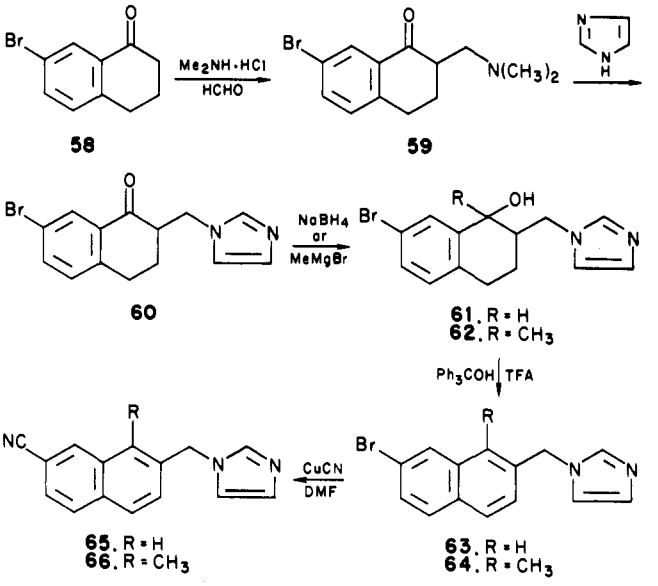
no.	X	R	posn of CO_2H	mp, °C	yield, %	method	formula[b]	IC_{50},[a] M: TxA_2 synthetase	PGI_2 synthetase	cyclo-oxygenase	11β-hydroxylase
67	O	H	5	283–285	74	C	$C_{13}H_{10}N_2O_3$	1.2×10^{-8}			
68	O	CH_3	5	246–248[c]	81	C	$C_{14}H_{12}N_2O_3$	3.4×10^{-8}	$>10^{-4}$	$>2 \times 10^{-4}$	1.0×10^{-4}
69	O	Cl	5	248–250	53	D	$C_{13}H_9ClN_2O_3$	3.1×10^{-8}	$>10^{-4}$	$>2 \times 10^{-4}$	$>10^{-4}$
70	O	Br	5	249–251	40	D	$C_{13}H_9BrN_2O_3$	3.0×10^{-8}			
71	S	H	5	280–282	92	E	$C_{13}H_{10}N_2O_2S$	1.5×10^{-8}	$>10^{-4}$	$>2 \times 10^{-4}$	$>10^{-4}$
72	S	CH_3	5	298–299[d]	70	F	$C_{14}H_{12}N_2O_2S \cdot HCl$	1.7×10^{-8}	$>10^{-4}$	$>2 \times 10^{-4}$	$>10^{-4}$
73	S	CH_3	6	254–255	81	C	$C_{14}H_{12}N_2O_2S$	1.8×10^{-8}	$>10^{-4}$	$>2 \times 10^{-4}$	
74	S	Cl	5	265–267	87.5	E	$C_{13}H_9ClN_2O_2S$	2.2×10^{-8}		$>2 \times 10^{-4}$	
75	S	Cl	6	256–257	75	D	$C_{13}H_9ClN_2O_2S$	4.0×10^{-8}	$>10^{-4}$	$>2 \times 10^{-4}$	
76	S	Br	5	245–246	74	E	$C_{13}H_9BrN_2O_2S$	2.7×10^{-8}			$>10^{-4}$
77	S	SCH_3	5	256–258	93	E	$C_{14}H_{12}N_2O_2S_2$	4.3×10^{-8}			
78	NH	CH_3	5	268–269	66	E[e]	$C_{14}H_{13}N_3O_2$	3.7×10^{-8}			
79	NCH_3	CH_3	5	283–284	86	E	$C_{15}H_{15}N_3O_2$	3.2×10^{-8}		$>2 \times 10^{-4}$	
80	CH=CH	H	6[f]	275–278	49	E	$C_{15}H_{12}N_2O_2$	3.4×10^{-8}			
81	CH=CH	H	7[f]	270–272	72	C	$C_{15}H_{12}N_2 \cdot O_2$	7.1×10^{-8}			
82	CH=CH	CH_3	7[f]	>300	62	C	$C_{16}H_{14}N_2O_2$	2.5×10^{-8}		$>2 \times 10^{-4}$	$>10^{-4}$
1								3.0×10^{-9}	$>10^{-4}$	$>10^{-4}$[g]	$>10^{-4}$

[a] Each result represents the mean of two determinations. [b] All compounds gave C, H, and N analyses within 0.4% of the theoretical values. [c] Crystallized from MeOH. [d] Crystallized from EtOH/Et_2O. [e] Compound **52** used as starting material. [f] Naphthalene numbering. [g] Determined by using ram seminal vesicle microsomes (ref 1 and 2).

Scheme II



Scheme III



(Scheme III). Mannich reaction on **58** with formaldehyde and dimethylamine gave **59**, which was treated with imidazole in refluxing xylene to give **60**. The latter was either reduced to **61** with $NaBH_4$ or treated with MeMgBr to give **62**. Dehydration and dehydrogenation to **63** and **64**, respectively, was carried out in one step by prolonged treatment with triphenylmethyl trifluoroacetate.[11] The nitriles **65** and **66** were obtained by treatment of **63** and **64** with CuCN in DMF.

Results and Discussion

The results in Table I show that all compounds have similar potency against TxA_2 synthetase in vitro. This is not surprising, since, in these relatively rigid bicyclic systems, the distance between the imidazole and carboxylic acid groups will be essentially constant. This distance has been found to be important for optimal potency with analogues related to **1**[2,6] and with the heterocyclic carboxylic acid analogues in the preceding paper.[7] Compounds **67–82** have similar overall dimensions to the most potent of the heterocyclic analogues reported previously, such as **3–5**.[7]

In the cases examined, compounds had negligible activity against PGI_2 synthetase and cyclooxygenase. As a measure of the potential for causing undesirable side effects through inhibition of other cytochrome P-450 enzymes, several of the compounds were evaluated for inhibition of adrenal steroid 11β-hydroxylase. Of the compounds tested, only **68** showed significant activity at 10^{-4} M, but it is still highly selective for TxA_2 synthetase.

Several of the compounds showed a high level of activity in vivo when evaluated in anesthetized rabbits[12] or in

(11) Fu, P. P.; Harvey, R. G. *Tetrahedron Lett.* 1974, 3217.

(12) Parry, M. J.; Randall, M. J., unpublished results, procedure as described in ref 3.

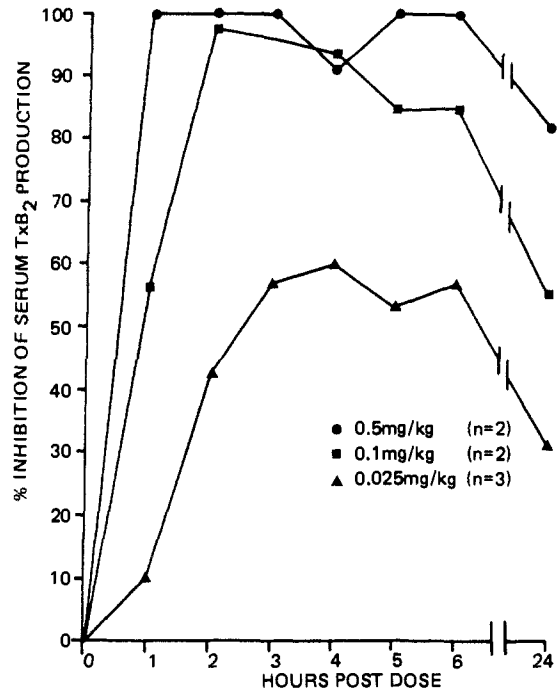


Figure 1. Inhibition of TxB_2 production in whole blood from dogs following a single oral dose of **73**.

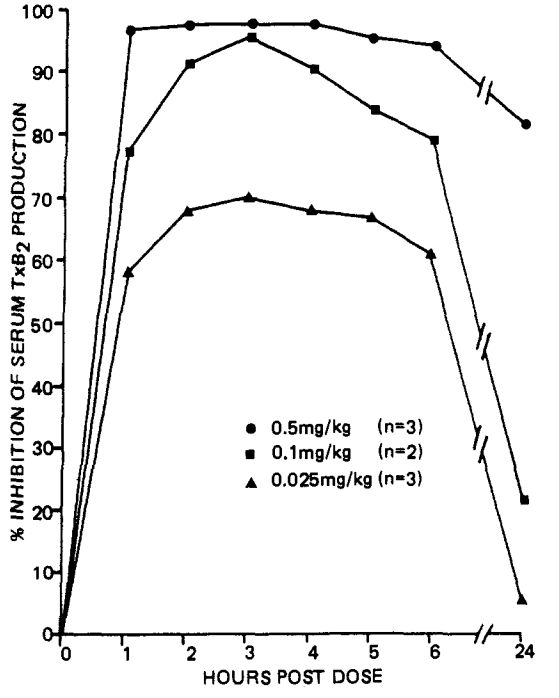


Figure 2. Inhibition of TxB_2 production in whole blood from dogs following a single oral dose of **75**.

conscious dogs. For example, oral administration of 0.5 mg/kg of the benzo[*b*]thiophene **73** to conscious dogs caused almost complete inhibition of thromboxane synthesis for 6 h (Figure 1). A dose of 0.1 mg/kg was only slightly less effective, and a significant level of inhibition was produced by a dose as low as 0.025 mg/kg. The compound had a long duration of action and, 24 h after the 0.5 mg/kg dose, inhibition was still greater than 80%. A similar picture was seen with the chloro analogue **75** (Figure 2). By contrast, a 0.5 mg/kg dose of **6** gave a slightly lower maximal level of inhibition, and after 15 h the level of inhibition was below 40%.[3]

In general, benzo[*b*]thiophenes were more potent in vivo

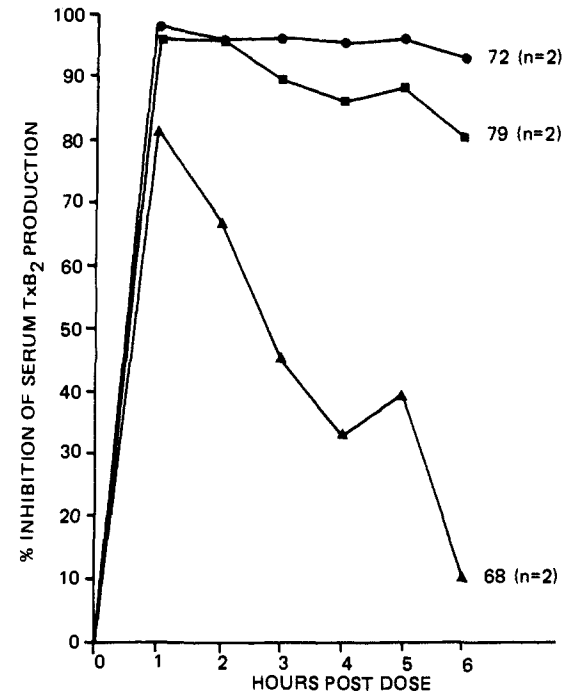


Figure 3. Inhibition of TxB_2 production in whole blood from dogs following single oral doses of 0.5 mg/kg of **68**, **72**, and **79**.

Table II. Ionization Constants of 1*H*-Imidazol-1-ylmethyl-Substituted Carboxylic Acids[a]

no.	pK_a (acid)	pK_a (base)	no.	pK_a (acid)	pK_a (base)
3	2.38	7.17	71	3.90	6.34
4	2.74	6.77	72	3.82	6.58
5	3.34	6.35	73	3.59	6.04
68	3.91	6.08	79	4.08	6.32

[a] In H_2O at 25 °C.

than the corresponding benzo[*b*]furan analogues. Figure 3 shows a comparison of the activities of the benzo[*b*]-thiophene **72** with the same dose of the benzo[*b*]furan analogue **68**. The former compound showed similar potency to **73** and **75**, but **68** was less potent and had a much shorter duration of activity. The *N*-methylindole analogue **79** was almost as potent as **72**, but the indole **78** showed only weak activity in anesthetized rabbits and was not investigated in dogs.

The naphthalene analogues have not been investigated as fully in vivo, but preliminary evaluation of **82** in anesthetized rabbits suggests that it has similar potency to **72**.[12]

Thus, in general, the compounds described here have markedly superior potency in vivo to the related analogues in the preceding paper.[7] The similarity in in vitro potency indicates that this superiority in vivo does not result from a difference in intrinsic activity, but is more likely to be due to differences in distribution, metabolism, or rate of excretion. Physicochemical properties such as the degree of ionization might be expected to influence the pharmacokinetic profile of the compounds, and the representative pK_a values in Table II show that compounds **68**, **72**, **73**, and **79** are less acidic and also slightly less basic than the previously reported[7] benzo[*b*]furan- and benzo[*b*]-thiophene-2-carboxylic acid analogues **3** and **4**. Compound **5**, the most potent analogue of the previous series in vivo, is also less acidic and less basic than **3** and **4**. No clear correlation appears to exist between pK_a and in vivo potency for the remaining compounds in Table II, and other factors are probably responsible for the greater in vivo

potency of, for example, **72** and **79** over **68**.

In summary, we have shown that several 2-(1*H*-imidazol-1-ylmethyl) carboxylic acids of benzo[*b*]furan, benzo[*b*]thiophene, indole, and naphthalene are potent and, in the cases examined, selective inhibitors of TxA_2 synthetase. Evaluation of the compounds in vivo showed that the benzo[*b*]thiophenes were generally the most potent, and three compounds, **72**, **73**, and **75**, showed a high level of activity after oral administration of doses as low as 0.1 mg/kg to conscious dogs. Compounds **73** and **75** were also found to have a long duration of action.

Experimental Section

Biology. Methods for the determination of inhibitory activity against TxA_2 synthetase, PGI_2 synthetase, and adrenal steroid 11β-hydroxylase in vitro have been described previously.[2]

Activity against cyclooxygenase was determined by using rat basophilic leukemia (RBL-1) cells grown according to the method of Jakschik et al.[13] This system also produces 5-hydroxyeicosatetraenoic acid (5-HETE) and so, in addition, gives a measure of activity against the 5-lipoxygenase enzyme. The cells were washed once with RPMI 1640 (Grand Island Biological Co., Grand Island, NY) and resuspended in RPMI 1640 at a cell density of 2×10^6 cells/mL. Aliquots (0.5 mL) of cell suspension were preincubated for 10 min at 30 °C with a 1-μL solution of compound in Me_2SO. The incubation was started by simultaneous addition of 5 μL of [^{14}C]arachidonic acid (AA) (specific radioactivity ~50 mCi/mmol) in EtOH and 2 μL of A-23187 in Me_2SO to give final concentrations of 5 and 3 μM, respectively. The incubation was terminated after 5 min by the addition of 0.27 mL of CH_3CN/AcOH (100:3), chilled for 1 h to permit protein precipitation and then clarified by centrifugation. Product analysis was performed by HPLC. The clarified sample (100 μL) was injected onto an RP-18, OD 032 column (2.6 mm I.D., Brownlee) and developed by using a mobile phase of CH_3CN/H_2O/AcOH over a linear gradient from 35–65% CH_3CN for 1 min at a flow rate of 2 mL/min. The developing solvent was continued at 65% CH_3CN for a total of 4 min before being recycled to the original conditions. Detection of product radioactivity was performed with a Berthold 504 radioactivity moniter equipped with a 500-μL flow cell mixing 2.4 mL/min Omnifluor (New England Nuclear) with column effluent. Integration of peak areas was performed with a SP-400 computing integrator (Spectra Physics). Radiolabeled products were eluted in the order prostaglandin D_2 (PGD_2), dihydroxy fatty acids, 5-HETE, and AA. The area under the curve for each product was compared with the average value for non-compound-treated samples. The activity of compounds against cyclooxygenase as measured by inhibition of PGD_2 formation is summarized in Table I. None of the compounds tested had significant activity against 5-lipoxygenase.

The procedure for the determination of oral activity in conscious dogs was described in the previous paper.[7]

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

2-Methylbenzo[*b*]thiophene-5-carboxylic Acid (20). A solution of 5-bromo-2-methylbenzo[*b*]thiophene (**19**) (33.0 g, 0.145 mol) and iodomethane (103.2 g, 0.73 mol) in dry ether (250 mL) was added dropwise to a stirred mixture of Mg (17.7 g) and dry ether (50 mL) at such a rate that gentle reflux was maintained. The mixture was heated under reflux for 30 min, cooled, and poured onto crushed solid CO_2. When the CO_2 had evaporated, the residue was shaken with ether and dilute HCl and the mixture was filtered. The organic layer was extracted several times with dilute NaOH solution, and the combined extracts were acidified with concentrated HCl. The solid was filtered off and crystallized from EtOH/H_2O to give **20**, yield 17.4 g (62.5%): mp 220–222 °C. Anal. ($C_{10}H_8O_2S$) H. Calcd C, 62.48. Found C, 62.06.

2-Methylbenzo[*b*]thiophene-5-carboxylic Acid Methyl Ester (21). A suspension of **20** (17.4 g, 0.0906 mol) in MeOH (250 mL) was saturated with HCl gas and then heated under reflux for 30 min. The solution was cooled, and the solid was filtered off to give **21**, yield 16.7 g (89.5%): mp 97–98 °C. Anal. ($C_{11}H_{10}O_2S$) C, H.

3-Chloro-2-methylbenzo[*b*]furan-5-carbonitrile (8). A solution of 2-methylbenzo[*b*]furan-5-carbonitrile (**7**) (1.52 g, 0.01 mol) and SO_2Cl_2 (1.49 g, 0.011 mol) in $CHCl_3$ (25 mL) was heated under reflux for 9 h and cooled. The solution was washed successively with H_2O, dilute NaOH solution, and H_2O and dried (Na_2SO_4). Evaporation of the $CHCl_3$ gave a solid, which was crystallized twice from MeOH to give **8**, yield 0.45 g (24%): mp 131.5–133.5 °C. Anal. ($C_{10}H_6ClNO$) C, H, N.

3-Chloro-2-methylbenzo[*b*]thiophene-5-carboxylic acid methyl ester (22) was prepared similarly by treatment of **21** with SO_2Cl_2; yield 50%; mp 85–86 °C. Anal. ($C_{11}H_9ClO_2S$) C, H.

3-Bromo-2-methylbenzo[*b*]furan-5-carbonitrile (9). Br_2 (3.20 g, 0.02 mol) was added dropwise to a stirred mixture of **7** (3.04 g, 0.02 mol) and anhydrous sodium acetate (2.0 g) in AcOH (30 mL). The mixture was stirred at room temperature for 1 h and then poured into H_2O (ca. 200 mL). The mixture was extracted several times with $CHCl_3$, and the combined extracts were washed successively with H_2O, dilute NaOH solution, and H_2O and dried (Na_2SO_4). Evaporation of the $CHCl_3$ gave a gummy solid, which was triturated with MeOH and filtered to give **9**, yield 3.44 g (73%): mp 163–165 °C, raised to 164–166 °C on crystallization from IPA/PE (bp 60–80 °C). Anal. ($C_{10}H_6BrNO$) C, H, N.

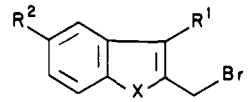
3-Bromo-2-methylbenzo[*b*]thiophene-5-carboxylic Acid Methyl Ester (23). Br_2 (2.08 g, 0.013 mol) was added dropwise to a stirred mixture of **21** (2.40 g, 0.012 mol) and anhydrous sodium acetate (2.40 g) in $CHCl_3$ (50 mL). The mixture was stirred for 2 h and then washed successively with H_2O and $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the $CHCl_3$ gave a solid, which was crystallized from MeOH/H_2O to give **23**, yield 2.00 g (58%): mp 84–85 °C. Anal. ($C_{11}H_9BrO_2S$) C, H.

2-(Bromomethyl)benzo[*b*]furan-5-carbonitrile (10). A mixture of **7** (1.57 g, 0.01 mol), *N*-bromosuccinimide (1.78 g, 0.01 mol), and azobisisobutyronitrile (0.1 g) in CCl_4 (25 mL) was heated under reflux for 3 h. The mixture was cooled, washed with H_2O, and dried (Na_2SO_4). Evaporation of the solvent gave a solid, which was crystallized from EtOAc/PE (bp 60–80 °C) to give **10**, yield 1.20 g (51%): mp 106–109 °C. Anal. ($C_{10}H_6BrNO$) C, H.

Bromomethyl compounds prepared similarly are listed in Table III.

6-Bromo-3-methylbenzo[*b*]thiophene-2-methanol (39). A 1.55 M solution of *n*-BuLi in hexane (15.5 mL, 0.024 mol) was added dropwise to a stirred solution of 2,6-dibromo-3-methyl-

Table III. Bromomethyl-Substituted Intermediates



no.	X	R^1	R^2	mp,[a] °C	yield, %	formula[b]
10	O	H	CN	106–109	51	$C_{10}H_6BrNO$
11	O	Cl	CN	124–127	62	$C_{10}H_5BrClNO$
12	O	Br	CN	129–131	79	$C_{10}H_5Br_2NO$
24	S	H	CO_2CH_3	106–107	46	$C_{11}H_9BrO_2S$[c]
25	S	Cl	CO_2CH_3	144–145	39	$C_{11}H_8BrClO_2S$
26	S	Br	CO_2CH_3	173–174	49	$C_{11}H_8Br_2O_2S$
56	CH=CH	H	CO_2CH_3	103–106[d]	69	$C_{13}H_{11}BrO_2$[e]

[a] Compounds were crystallized from EtOAc/PE (bp 60–80 °C) unless otherwise indicated. [b] All compounds gave C and H analyses within 0.4% of the theoretical value unless otherwise stated. [c] C: calcd, 46.33; found, 45.89 [d] Crystallized from $CHCl_3$/PE (bp 60–80 °C). [e] C: calcd, 55.93; found, 55.45.

(13) Jakschik, B. A.; Lee, L. H.; Shuffer, G.; Parker, C. W. *Prostaglandins* **1978**, *16*, 733.

(14) Cross, P. E.; Dickinson, R. P. *Heterocycles* **1985**, *23*, 2391.

benzo[*b*]thiophene (**47**)[14] (6.60 g, 0.022 mol) in dry ether (150 mL) at 0 °C under dry N_2, and the mixture was stirred at 0 °C for 30 min. Paraformaldehyde (0.71 g, 0.024 mol) was then added portionwise, and the mixture was stirred at 0 °C for 3 h. H_2O was then added, and the layers were separated. The ether layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on silica gel. Elution with $CHCl_3$ first gave some impurity followed by a solid, which was crystallized from EtOAc/PE (bp 60–80 °C) to give **39**, yield 3.20 g (59%): mp 95–96 °C. Anal. ($C_{10}H_9BrOS$) C, H.

6-Bromo-3-chlorobenzo[*b*]thiophene-2-carboxylic Acid Chloride (48). A mixture of 4-bromocinnamic acid (49.95 g, 0.22 mol), $SOCl_2$ (79.80 mL, 1.10 mol), pyridine (1.77 mL), and chlorobenzene (220 mL) was heated under reflux for 72 h and then cooled and filtered. The filtrate was evaporated, and the residue was triturated with PE (bp 60–80 °C) and filtered. The solid was cyrstallized from toluene/PE (bp 60–80 °C) to give **48**, yield 26.60 g (39%): mp 126–127 °C. Anal. ($C_9H_3BrCl_2OS$) C, H.

6-Bromo-3-chlorobenzo[*b*]thiophene-2-methanol (40). A solution of **48** (6.20 g, 0.02 mol) in dry ether (50 mL) and dry THF (50 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.58 g, 0.015 mol) in dry ether (250 mL) at 0 °C under dry N_2. The mixture was stirred at room temperature for 30 min, heated under reflux for 2.5 h, and then cooled and allowed to stand for 18 h. It was then cooled to 0 °C, and the excess of $LiAlH_4$ was destroyed by the successive addition of H_2O (1.0 mL), 5 N NaOH (1.0 mL), and water (2.0 mL) with vigorous stirring. The mixture was filtered, and the filtrate was evaporated to give a solid, which was chromatographed on silica gel. Elution with $CHCl_3$ first gave some impurity followed by a solid, which was crystallized from $CHCl_3$ to give **40**, yield 2.22 g (40%); mp 117–118 °C. Anal. ($C_9H_6BrClOS$) C, H.

6-Bromo-2-(chloromethyl)-3-methylbenzo[*b*]thiophene (41). $SOCl_2$ (2.0 mL) was added dropwise to a stirred solution of **39** (3.60 g, 0.0147 mol) and pyridine (3 drops) in $CHCl_3$ (80 mL). The solution was stirred at room temperature for 1 h, then washed with H_2O and $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the solvent gave a quantitative yield of **41**. A sample crystallized from PE (bp 40–60 °C) had mp 92–93 °C. Anal. ($C_{10}H_8BrClS$) C, H.

6-Bromo-3-chloro-2-(chloromethyl)benzo[*b*]thiophene (42) was prepared similarly by treatment of **40** with $SOCl_2$ and pyridine, yield 87%: mp 97–98 °C (from PE, bp 40–60 °C). Anal. ($C_9H_5BrCl_2S$) C, H.

5-Bromo-3-(methylthio)benzo[*b*]thiophene (37). A 1.55 M solution of *n*-BuLi in hexane (35.0 mL, 0.054 mol) was added dropwise to a stirred solution of 3,5-dibromobenzo[*b*]thiophene (**36**) (14.60 g, 0.05 mol) in dry ether (600 mL) at −70 °C under dry N_2. The mixture was stirred at −70 °C for 30 min, and then a solution of dimethyl disulfide (4.90 g, 0.052 mol) in dry ether (10 mL) was added with stirring over 5 min. The mixture was stirred at −70 °C for 4 h and then allowed to warm up to room temperature. H_2O (50 mL) was added, and the organic layer was separated, washed with H_2O, and dried (Na_2SO_4). Evaporation of the ether gave an oil, which was chromatographed on silica gel. Elution with PE (bp 40–60 °C) gave a small amount of impurity followed by the product as an oil. Distillation of the oil gave **37**, yield 10.36 g (80%): bp 140–144 °C 0.6 mm; mp 56–57 °C. Anal. ($C_9H_7BrS_2$) C, H.

3-(Methylthio)benzo[*b*]thiophene-5-carboxylic Acid (38). Successive treatment of **37** with Mg and CO_2 as described for the preparation of **20** gave **38**, yield 55%: mp 205–207 °C (from EtOH/H_2O). Anal. ($C_{10}H_8O_2S_2$) C, H.

3-(Methylthio)benzo[*b*]thiophene-5-carboxylic Acid Ethyl Ester (31). A mixture of **38** (5.62 g, 0.025 mol) and $POCl_3$ (2 mL) in EtOH (200 mL) was heated under reflux for 18 h and then evaporated. The residue was dissolved in ether, and the solution was washed with $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). Evaporation of the solvent gave a solid, which was crystallized from EtOH to give **31**, yield 5.84 g (93%): mp 67–69 °C. Anal. ($C_{12}H_{12}O_2S_2$) C, H.

2-(Chloromethyl)-3-(methylthio)benzo[*b*]thiophene-5-carboxylic Acid Ethyl Ester (33). HCl gas was passed for 2 h through a mixture of **31** (1.0 g, 0.004 mol), paraformaldehyde (0.24 g, 0.008 mol), and anhydrous $ZnCl_2$ (0.20 g) in $CHCl_3$ (30 mL) at 0 °C. The resulting mixture was stirred at room temperature for 18 h and then washed with H_2O. The organic layer was separated, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on silica gel. Elution with toluene gave a solid, which was crystallized from PE (bp 60–80 °C) to give **33**, yield 0.42 g (35%): mp 95–96 °C. Anal. ($C_{13}H_{13}ClO_2S_2$) C, H.

2-(Chloromethyl)-3-methylbenzo[*b*]thiophene-5-carboxylic acid ethyl ester (32) was prepared similarly from 3-methylbenzo[*b*]thiophene-5-carboxylic acid ethyl ester (**30**), yield 45%; mp 63–64 °C (from PE, bp 40–60 °C). Anal. ($C_{13}H_{13}ClO_2S$) C, H.

1-Acetyl-2,3-dimethylindole-5-carboxylic Acid Ethyl Ester (50). NaH (0.80 g of 50% dispersion in mineral oil, 0.0167 mol) was added portionwise to a stirred solution of 2,3-dimethylindole-5-carboxylic acid ethyl ester (**49**) (3.50 g, 0.016 mol) in dry DMF (25 mL). The mixture was stirred at room temperature for 30 min and then cooled to 0 °C. A solution of acetyl chloride (1.27 g, 0.016 mol) in dry DMF (2.5 mL) was added dropwise with stirring over 2 min. The resulting mixture was stirred at room temperature for 3 h and then poured into H_2O. The mixture was extracted several times with EtOAc, and the combined extracts were washed well with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was chromatographed on silica gel. Elution with $CHCl_3$ first gave mineral oil followed by a solid, which was crystallized from EtOAc/PE (bp 60–80 °C) to give **50**, yield 1.22 g (32%): mp 98–101 °C. Anal. ($C_{15}H_{17}NO_3$) C, H.

1-Acetyl-2-(bromomethyl)-3-methylindole-5-carboxylic Acid Ethyl Ester (51). Br_2 (0.45 g, 0.0028 mol) was added dropwise over 1 min to a stirred solution of **50** (0.65 g, 0.0028 mol) in AcOH (1.3 mL). After a few minutes a precipitate formed. The mixture was diluted with 5 mL of ether, and the solid was filtered off, washed with ether, and dried to give crude **51**, yield 0.38 g (45%): mp 125–130 °C. The product was unstable and was used immediately.

7-Bromo-2-[(dimethylamino)methyl]-3,4-dihydro-1(2*H*)-naphthalenone (59). A mixture of 7-bromo-3,4-dihydro-1(2*H*)naphthalenone (**58**) (2.20 g, 0.01 mol), dimethylamine hydrochloride (1.06 g, 0.013 mol), paraformaldehyde (0.40 g, 0.0132 mol), EtOH (3 mL), and concentrated HCl (2 drops) was heated under reflux for 2 h and cooled. The mixture was diluted with a little acetone, and the solid was filtered off, washed with acetone, and crystallized from MeOH/EtOAc to give **59** hydrochloride, yield 1.91 g (60%): mp 176–178 °C. Anal. ($C_{13}H_{16}BrNO\cdot HCl$) C, H, N.

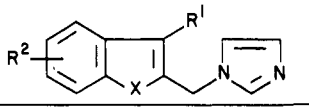
The hydrochloride salt was converted to the free base by dissolving in H_2O and adding an excess of $NaHCO_3$ solution. Ether extraction gave the base as an oil.

7-Bromo-3,4-dihydro-2-(1*H*-imidazol-1-ylmethyl)-1(2*H*)-naphthalenone (60). A solution of **59** free base (6.0 g, 0.021 mol) and imidazole (2.50 g, 0.037 mol) in xylene (30 mL) was heated under reflux for 1.5 h and then evaporated. The residue was dissolved in Et_2O, and the solution was washed with dilute HCl. The acid extract was basified with dilute NaOH, and the mixture was extracted with $CHCl_3$. The combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was crystallized from EtOAc to give **60**, yield 4.55 g (71%): mp 129–131 °C. Anal. ($C_{14}H_{13}BrN_2O$) C, H, N.

7-Bromo-2-(1*H*-imidazol-1-ylmethyl)naphthalene (63). A solution of **60** (1.80 g, 0.0059 mol) and $NaBH_4$ (0.27 g, 0.0071 mol) in EtOH (20 mL) was heated under reflux for 1.5 h and then evaporated. The residue was partitioned between EtOAc and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc, and the organic layers were combined, washed with H_2O, and dried (Na_2SO_4). Evaporation of the solvent gave a quantitative yield of **61** as an amorphous solid, which was used directly. A mixture of **61** (1.01 g, 0.0033 mol) and triphenylmethanol (1.71 g, 0.0066 mol) in TFA (20 mL) was heated under reflux for 7 days and then cooled and poured into H_2O. The mixture was basified with dilute KOH solution and extracted several times with EtOAc. The combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on silica gel. Elution with $CHCl_3$ first gave byproducts followed by a solid, which was crystallized from EtOAc/PE (bp 60–80 °C) to give **63**, yield 0.73 g (77%): mp 133–135 °C. Anal. ($C_{14}H_{11}BrN_2$) C, H, N.

7-Bromo-1-methyl-2-(1*H*-imidazol-1-ylmethyl)naphthalene (64). A 3 M solution of MeMgBr in THF (20 mL, 0.06 mol) was

Table IV. 1*H*-Imidazol-1-ylmethyl-Substituted Intermediates[a]



no.	X	R^1	R^2	mp,[b] °C	method	yield, %	formula[c]
13	O	H	5-CN	106–107	A	73	$C_{13}H_9N_3O$[d]
14	O	Cl	5-CN	131–133	A	74	$C_{13}H_8ClN_3O$
15	O	Br	5-CN	119–122	A	66	$C_{13}H_8BrN_3O$
17	O	CH_3	5-Br	104–105	A	57	$C_{13}H_{11}BrN_2O$
18	O	CH_3	5-CN	146–149	B	41	$C_{14}H_{11}N_3O$
27	S	H	5-CO_2CH_3	127–128	A	50	$C_{14}H_{12}N_2O_2S$
28	S	Cl	5-CO_2CH_3	138–139	A	74	$C_{14}H_{11}ClN_2O_2S$
29	S	Br	5-CO_2CH_3	146–147	A	39	$C_{14}H_{11}BrN_2O_2S$
35	S	SCH_3	5-$CO_2C_2H_5$	105–107	A	82	$C_{16}H_{16}N_2O_2S_2$
43	S	CH_3	6-Br	138–139	A	52	$C_{13}H_{11}BrN_2S$
44	S	Cl	6-Br	123–124	A	75	$C_{12}H_8BrClN_2S$
45	S	CH_3	6-CN	154–155	B	69.5	$C_{14}H_{11}N_3S$
46	S	Cl	6-CN	158–159	B	54	$C_{13}H_8ClN_3S$[e]
52	$NCOCH_3$	CH_3	5-$CO_2C_2H_5$	114–116	A[f]	87	$C_{18}H_{19}N_3O_3$
56	CH=CH	H	6-CO_2CH_3[g]	148–149	A	42	$C_{16}H_{14}N_2O_2$
65	CH=CH	H	7-CN[g]	128–130	B	56	$C_{15}H_{11}N_3$
66	CH=CH	CH_3	7-CN[g]	145.5–146.5	B	51	$C_{16}H_{13}N_3$

[a] Other intermediates prepared by individual methods are described in the Experimental Section. [b] Compounds were crystallized from EtOAc/PE. [c] All compounds gave C, H, and N analyses within 0.4% of the theoretical value unless otherwise stated. [d] C: calcd, 69.94; found, 69.46. [e] C: calcd, 57.04; found, 56.63. [f] Reaction carried out at room temperature for 18 h. [g] Naphthalene numbering.

added dropwise with stirring to a solution of **60** (2.5 g, 0.0082 mol) in dry THF (50 mL). The mixture was stirred at room temperature for 15 min, heated under reflux for 3.5 h, and then allowed to stand at room temperature for 18 h. A saturated solution of NH_4Cl (90 mL) was added cautiously with stirring, and the layers were separated. The aqueous layer was extracted with EtOAc, and the organic layers were combined, washed with H_2O, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was chromatographed on silica gel. Elution with $CHCl_3$ gave a small amount of impurity and starting material. Further elution with $CHCl_3$/MeOH (20:1) gave **62** as an oil (2.0 g, 76%), which was used directly.

Treatment of **62** with triphenylmethanol and TFA as described for **63** above gave **64** (75%): mp 112–113 °C (from EtOAc/PE, bp 60–80 °C). Anal. ($C_{15}H_{13}BrN_2$) C, H, N.

2-(1*H*-Imidazol-1-ylmethyl)benzo[*b*]furan-5-carbonitrile (13) (Method A). A mixture of **10** (0.96 g, 0.004 mol), imidazole (2.72 g, 0.04 mol), and $NaHCO_3$ (1.0 g) in acetone (50 mL) was heated under reflux for 4 h and then evaporated. The residue was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. Elution with $CHCl_3$ first gave some impurity followed by a solid, which was crystallized from EtOAc/PE (bp 60–80 °C) to give **13**, yield 0.65 g (73%): mp 106–107 °C. Anal. ($C_{13}H_9N_3O$) C, H, N.

Other 1*H*-imidazol-1-ylmethyl-substituted compounds prepared similarly are listed in Table IV.

2-(1*H*-Imidazol-1-ylmethyl)-3-methylbenzo[*b*]thiophene-5-carboxylic Acid Ethyl Ester (34). NaH (0.50 g of a 50% dispersion in mineral oil, 0.0104 mol) was added portionwise to a stirred solution of imidazole (0.68 g, 0.01 mol) in dry DMF (30 mL), and the mixture was stirred at room temperature for 30 min. A solution of **32** (2.70 g, 0.01 mol) in dry DMF (5 mL) was added over 2 min, and the resulting mixture was stirred for 2 h and then evaporated. The residue was dissolved in EtOAc, and the solution was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was chromatographed on silica gel. Elution with $CHCl_3$/PE (bp 40–60 °C) first gave some impurity followed by a solid, which was crystallized from EtOAc/PE (bp 60–80 °C) to give **34**, yield 1.40 g (47%): mp 126–127 °C. Anal. ($C_{16}H_{16}N_2O_2S$) C, H, N.

2-(1*H*-Imidazol-1-ylmethyl)-3-methylbenzo[*b*]thiophene-6-carbonitrile (45) (Method B). A mixture of **43** (1.01 g, 0.0033 mol) and CuCN (1.80 g, 0.02 mol) in DMF (20 mL) was heated under reflux for 22 h, then cooled and poured into H_2O. The solid was filtered off, washed with H_2O, and then suspended in a mixture of concentrated NH_3 solution (100 mL) and EtOAc (150 mL). The mixture was stirred until no solid remained, and the organic layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was crystallized from EtOAc/PE (bp, 60–80 °C) to give **45**, yield 0.58 g (69.5%): mp 154–155 °C. Anal. ($C_{14}H_{11}N_3S$) C, H, N.

Compounds prepared by this method are listed in Table IV.

2-(1*H*-Imidazol-1-ylmethyl)-3-methylindole-5-carboxylic Acid Ethyl Ester (53). A solution of **52** (4.0 g, 0.0123 mol) in 10% ethanolic NH_3 (100 mL) was allowed to stand for 18 h and then evaporated. Crystallization of the residue from EtOAc gave **53**, yield 2.30 g (66%): mp 201–202 °C; 250 MHz ^1H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 2.44 (s, 3 H, CH_3), 4.40 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 5.18 (s, 2 H, CH_2), 6.83 (br s, 1 H, imidazole H-5), 7.04 (br s, 1 H, imidazole H-4), 7.08 (br s, 1 H, imidazole H-2), 7.35 (d, 1 H, J = 8.6 Hz, indole H-7), 7.89 (dd, 1 H, J = 8.6, 1.7 Hz, indole H-6), 8.36 (d, 1 H, J = 1.7 Hz, indole H-4). Irradiation of the methyl group gave a 16.5% NOE enhancement of the signal at 8.36. Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

2-(1*H*-Imidazol-1-ylmethyl)-1,3-dimethylindole-5-carboxylic Acid Ethyl Ester (54). NaH (0.11 g of a 50% dispersion in mineral oil, 0.0022 mol) was added portionwise to a stirred solution of **53** (0.57 g, 0.002 mol) in dry DMF (20 mL), and the mixture was stirred at room temperature for 30 min. A solution of dimethyl sulfate (0.26 g, 0.002 mol) was added dropwise, and the mixture was stirred for 18 h and then evaporated. The residue was chromatographed on silica gel. Elution with $CHCl_3$ first gave mineral oil and impurity followed by a solid, which was crystallized from EtOAc/PE (bp 60–80 °C) to give **54**, yield 0.40 g (67%): mp 109–110 °C. Anal. ($C_{17}H_{19}N_3O_2$) C, H, N.

2-(1*H*-Imidazol-1-ylmethyl)-3-methylbenzo[*b*]thiophene-6-carboxylic Acid (73) (Method C). A mixture of **45** (0.40 g, 0.0016 mol), NaOH (0.20 g, 0.005 mol), EtOH (2 mL), and H_2O (20 mL) was heated under reflux for 24 h. The solution was evaporated, the residue dissolved in H_2O, and the solution acidified with AcOH. The solid was filtered off and purified by redissolving it in diluted NaOH, filtering, and acidifying wth AcOH. The solid was filtered off, washed with H_2O, and dried to give **73**, yield 0.35 g (81%): mp 254–255 °C. Anal. ($C_{14}H_{12}N_2O_2S$) C, H, N.

3-Chloro-2-(1*H*-imidazol-1-ylmethyl)benzo[*b*]furan-5-carboxylic Acid (69) (Method D). A solution of **14** (0.35 g, 0.00136 mol) in concentrated H_2SO_4 (5 mL) and H_2O (5 mL) was heated under reflux for 1 h and then cooled, diltued with 5 mL of H_2O, and made just alkaline with 5 N NaOH solution. The solution was filtered and acidified with AcOH. The solid was filtered off, washed with water, and dried to give **69**, yield 0.20 g (53%): mp 248–250 °C. Anal. ($C_{13}H_9ClN_2O_3$) C, H, N.

2-(1*H*-Imidazol-1-ylmethyl)benzo[*b*]thiophene-5-carboxylic Acid (71) (Method E). A mixture of **27** (0.80 g,

0.0029 mol), KOH (0.40 g, 0.007 mol), MeOH (5 mL), and H_2O (5 mL) was heated under reflux for 3 h and then evaporated. Workup as for method C gave **71**, yield 0.70 g (92%): mp 280–282 °C. Anal. ($C_{13}H_{10}N_2O_2S$) C, H, N.

2-(1*H*-Imidazol-1-ylmethyl)-3-methylbenzo[*b*]thiophene-5-carboxylic Acid (72) (Method F). A mixture of **34** (1.0 g, 0.0033 mol) and 6 N HCl (80 mL) was heated on a steam bath for 6 h and then cooled. The solid was filtered off, dried, and crystallized from EtOH/Et_2O to give **72** HCl, yield 0.72 g (70%): mp 298–299 °C. Anal. ($C_{14}H_{12}N_2O_2S$·HCl) C, H, N.

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Synthesis and Opioid Antagonist Potencies of Naltrexamine Bivalent Ligands with Conformationally Restricted Spacers[1]

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Bivalent ligands 1–4 with naltrexamine pharmacophores and spacers of different lengths containing a fumaryl moiety were synthesized and evaluated for μ and κ opioid antagonist activity on the electrically stimulated guinea pig ileal longitudinal muscle (GPI). The fumaryl moiety was incorporated into the spacer in order to determine the effect of conformational restriction of the spacer on the relationship between spacer length and opioid antagonist potency. While it was found that the fumaryl and succinyl series (11) possessed a very similar structure–potency profile with respect to antagonism at μ opioid receptors, the interaction of these two series at κ receptors differed substantially from one another. This difference was manifested by the longer spacer requirement for peak κ antagonist potency in the fumaryl relative to the succinyl series. It is concluded that the conformational restriction imposed by the fumaryl group in a short spacer ($n = 0$) prevents effective interaction of both pharmacophores with vicinal recognition sites of the κ receptor system; as the spacer is lengthened ($n = 2$) and becomes more flexible, the simultaneous occupation of vicinal recognition sites occurs with greater facility.

Bivalent ligands are defined[2,3] as structures that contain two pharmacophores joined through a connecting unit (spacer). Such compounds have attracted attention as opioid receptor probes.[2-13] Of considerable interest is the use of this approach in the design of opioid antagonists that are selective for specific receptor types. In this regard, we have reported that a short spacer between β-naltrexamine pharmacophores favors κ antagonist activity.[2,4,6] It was proposed that the vicinal sites which recognize κ-selective bivalent ligands are closer to one another than those that recognize μ- or δ-selective bivalent ligands.

This paper describes studies designed to test this proposal. We have investigated the effect of conformational restriction of the spacer on κ and μ opioid receptor antagonist activity of the bivalent ligand series **1–4**. The results of these studies lend additional support to the proximity of the vicinal recognition sites for κ-selective bivalent ligands.

Table I. Physical Properties of *N,N'*-Fumaroylbis(oligoglycine)naltrexamine

compd no.	R_f	% yield	formula[a]
1	0.76[b]	55	$C_{44}H_{52}N_4O_8 \cdot 5H_2O$
2	0.26[c]	97	$C_{48}H_{58}N_6O_{10} \cdot 3H_2O$
3	0.57[d]	83	$C_{52}H_{64}N_8O_{12} \cdot 3H_2O$
4	0.86[e]	45	$C_{60}H_{76}N_{12}O_{16} \cdot 6H_2O$

[a] C, H, N analyses were within 0.4% of theory. Melting point for 1–4 was >270 °C. [b] EtOAc–MeOH–NH_4OH (80:20:1). [c] EtOAc–MeOH–NH_4OH (75:25:1). [d] EtOAc–MeOH–NH_4OH (8:8:0.2). [e] EtOAc–MeOH–H_2O–NH_4OH (8:8:8:1).

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