

Acknowledgment. We express our thanks to G. Robertson and R. Oeckinghaus for performing elemental analyses, to N. Cahoon and M. Hatolski for running IR spectra, and to M. Brzechffa for mass spectra. The in vivo analgesic evaluations were carried out by F. Ambrose and W. Autry. We also express our thanks to G. Rihs and H. Walter at Ciba-Geigy Central Research in Basel, Switzerland, for the X-ray crystal structure determination.

Registry No. 4, 2038-57-5; 5, 119907-56-1; (\pm)-6, 119878-55-6; (\pm)-7, 119878-11-4; (\pm)-8, 119878-12-5; (\pm)-9, 119878-13-6; (\pm)-10, 119878-14-7; (\pm)-11, 119878-15-8; (\pm)-12, 119878-16-9; (\pm)-13, 119878-17-0; (\pm)-14, 119878-18-1; (\pm)-14-HCl, 119878-39-6; (\pm)-15, 119878-19-2; (\pm)-15-HCl, 119878-40-9; (\pm)-16, 119878-20-5; (\pm)-16-HCl, 119878-41-0; (\pm)-17, 119878-21-6; (\pm)-17-HCl, 119878-42-1; (\pm)-18, 119878-22-7; (\pm)-18-C₄H₄O₄, 119878-43-2; (\pm)-19, 119878-23-8; (\pm)-19-HCl, 119878-44-3; (\pm)-20, 119878-38-5; (\pm)-20-C₄H₄O₄, 119907-54-9; (\pm)-21, 119878-24-9; (\pm)-22, 119878-25-0; (\pm)-22-HCl, 119878-45-4; (\pm)-23, 119878-26-1; (\pm)-23-C₄H₄O₄, 119878-46-5; (\pm)-24, 119878-27-2; (\pm)-24-C₂H₂O₄, 119907-55-0; (\pm)-25, 119878-28-3; (\pm)-25-HCl, 119878-47-6; (\pm)-26,

119878-29-4; (\pm)-26-C₄H₄O₄, 119878-48-7; (\pm)-27, 119878-30-7; (\pm)-27-HCl, 119878-49-8; (\pm)-28, 119878-31-8; (\pm)-28-C₄H₄O₄, 119878-50-1; (\pm)-29, 119878-32-9; (\pm)-29-C₄H₄O₄, 119878-51-2; (\pm)-30, 119878-33-0; (\pm)-30-HCl, 119878-52-3; (\pm)-31, 119878-34-1; (\pm)-31-HCl, 119878-53-4; (\pm)-32, 119878-35-2; (\pm)-33, 119878-36-3; (\pm)-33-C₄H₄O₄, 119878-54-5; (\pm)-33(R₁ = H), 119878-10-3; (\pm)-34, 119878-37-4; (\pm)-34 (R₁ = H), 119907-53-8; (\pm)-35, 21797-84-2; 36, 119878-56-7; 2-BrC₆H₄COCl, 7154-66-7; 3-BrC₆H₄COCl, 1711-09-7; 4-BrC₆H₄COCl, 586-75-4; 4-ClC₆H₄COCl, 122-01-0; 4-FC₆H₄COCl, 403-43-0; 4-MeOC₆H₄COCl, 100-07-2; 3,4-Cl₂C₆H₃COCl, 3024-72-4; 3,4-Cl₂C₆H₃CH₂CO₂H, 5807-30-7; 4-BrC₆H₄CH₂CO₂H, 1878-68-8; C₆H₅(CH₂)₂COCl, 645-45-4; 4-BrC₆H₄SO₂Cl, 98-58-8; 4-CH₃C₆H₄COCl, 874-60-2; 4-CF₃C₆H₄COCl, 329-15-7; 3,4-Br₂C₆H₃COCl, 21900-35-6; 2-Cl, 4-BrC₆H₃COCl, 21900-55-0; 2-CH₃, 4-BrC₆H₃COCl, 21900-45-8; benzyl chloroformate, 501-53-1; ethyl chloroformate, 541-41-3.

Supplementary Material Available: Tables listing bond distances, bond angles, positional parameters for hydrogen and non-hydrogen atoms, and general displacement parameter expressions (5 pages). Ordering information is given on any current masthead page.

Synthesis and Thromboxane Synthetase Inhibitory Activity of Di- or Tetrahydrobenzo[*b*]thiophenecarboxylic Acid Derivatives

Yoshiya Amemiya, Atsuke Terada,* Kazuyuki Wachi, Hachio Miyazawa, Naoko Hatakeyama, Keiichi Matsuda,[†] and Takeshi Oshima[†]

Medicinal Chemistry Research Laboratories, New Lead Research Laboratories, and Biological Research Laboratories, Sankyo Co., Ltd., Hiromachi, Shinagawa-ku Tokyo 140, Japan. Received May 16, 1988

1-Imidazolylalkyl-substituted di- or tetrahydrobenzo[*b*]thiophenecarboxylic acid derivatives and related compounds were synthesized from tetrahydrobenzo[*b*]thiophene derivatives (1 or 4) in order to study the structure-activity relationships of the inhibition of thromboxane A₂ synthetase in vitro. Sodium 2-(1-imidazolylmethyl)-4,5-dihydrobenzo[*b*]thiophene-6-carboxylate (26) and 2-(1-imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-carboxylic acid hydrochloride (28) showed the most potent and specific activity in vitro and in vivo for thromboxane A₂ synthetase inhibition.

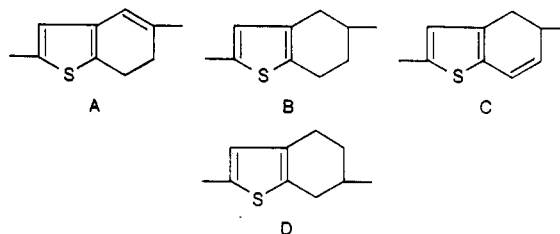
In recent years, the interesting biological properties of thromboxane A₂ (TXA₂) synthetase inhibitors have been described.¹ Furthermore, such inhibitors have been found to be useful in the treatment or prevention of cardio- and cerebrovascular diseases.²

In 1977, Needleman³ discovered that imidazole inhibited thromboxane synthetase, the enzyme that converts prostaglandin H₂ to the potent vasoconstrictor and platelet aggregating agent TXA₂. After this discovery, many compounds^{1,4} having the imidazole (or pyridine) moiety were synthesized in the expectation of obtaining potent inhibitors. In many cases, the structural requirements for TXA₂ synthetase inhibitors possessing a high degree of selectivity are the presence of a carboxylic acid group and an imidazole moiety in a molecule. Furthermore, the distance between the imidazole and carboxylic acid groups has been found to be especially important for optimal potency.^{1b,d}

On the basis of this knowledge, we turned our attention to the development of new TXA₂ synthetase inhibitors and to the synthesis of relatively rigid bicyclic compounds such as the dihydro- and tetrahydrobenzo[*b*]thiophenes (A-D).

Chemistry

The dihydrobenzo[*b*]thiophene derivatives possessing a carboxylic acid group at either the 5- or 6-position were synthesized as shown in Scheme I. Reaction of 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (1)⁵ with dimethyl



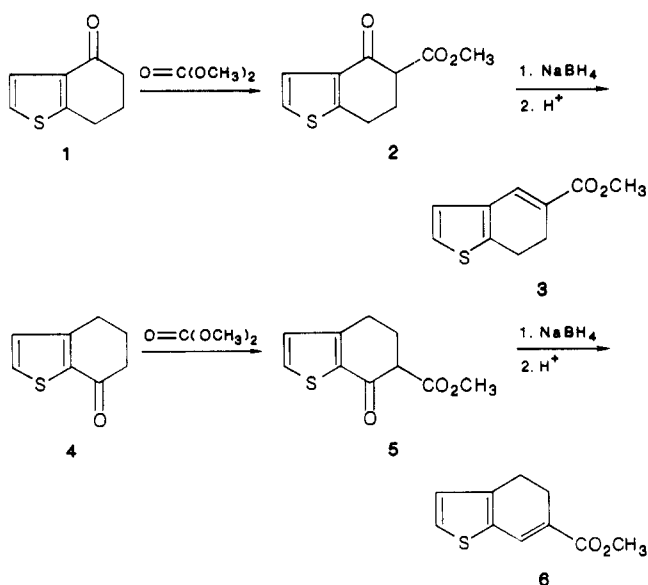
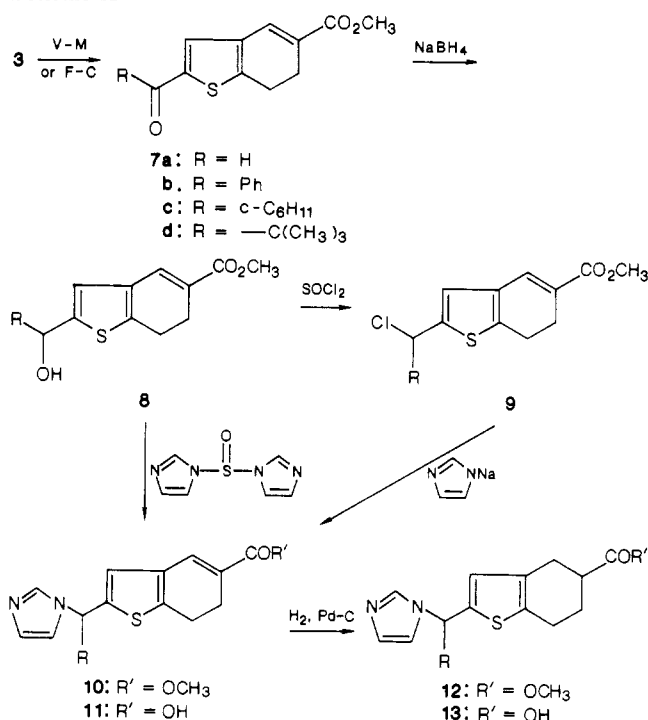
carbonate in the presence of NaH gave carboxylate 2. Sodium borohydride (NaBH₄) reduction of 2 followed by

- (1) (a) Yoshimoto, Y.; Yamamoto, S.; Hayaishi, O. *Prostaglandins* 1978, 16, 529. (b) Iizuka, K.; Akahana, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohya, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. *J. Med. Chem.* 1981, 24, 1139. (c) Tanouchi, T.; Kawamura, M.; Ohya, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Iizuka, K.; Nakazawa, M. *J. Med. Chem.* 1981, 24, 1149. (d) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* 1985, 28, 1427. (e) Parry, M. J.; Randall, M. J.; Hawkeswood, E.; Cross, P. E.; Dickinson, R. P. *Br. J. Pharmacol.* 1982, 77, 547.
- (2) (a) Nijkamp, F. P.; Moncada, S.; White, H. L.; Vane, I. R. *Eur. J. Pharmacol.* 1977, 44, 179. (b) Reuben, S. R.; Kuan, P.; Cairns, J.; Gyde, O. H. *Br. J. Clin. Pharmacol.* 1983, 15, 83s. (c) Luderer, J. R.; Nicholas, G. G.; Neumyer, M. M.; Riley, D. L.; Vary, J. E.; Garcia, G.; Schneek, D. W. *Clin. Pharmacol. Ther.* 1984, 36, 105. (d) Tani, E.; Maeda, Y.; Fukumori, T.; Nakao, M.; Kochi, N.; Morimura, T.; Yokota, M.; Matsumoto, T. *J. Neurosurg.* 1984, 61, 24. (e) Reilly, I. A. G.; Doran, J.; Smith, B.; Fitzgerald, G. A. *Clin. Res.* 1985, 33, 287A.
- (3) Needleman, P.; Ferrendelli, J. A.; Minkes, M. *Proc. Natl. Acad. Sci. U.S.A.* 1977, 74, 1716.

[†] New Lead Research Laboratories.

[†] Biological Research Laboratories.

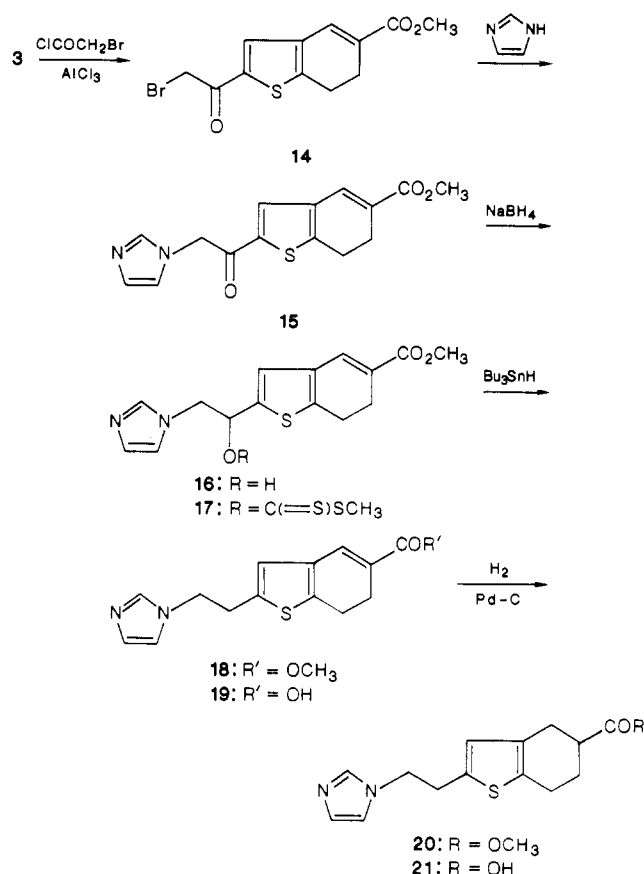
Scheme I

Scheme II^a

^a V-M = Vilsmeier-Haack reaction, F-C = Friedel-Crafts reaction.

dehydration gave methyl 6,7-dihydrobenzo[b]thiophene-5-carboxylate (3). Likewise, the 6-carboxylate (6) isomer was prepared from 7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (4)⁶ via the intermediate 5.

Scheme III



Carrying out the Vilsmeier-Haack reaction of 3 with DMF-POCl_3 gave aldehyde 7a (Scheme II). Compound 7a was also obtained by the reaction of 3 with $\text{CH}_3\text{OCHCl}_2$ in the presence of AlCl_3 under Friedel-Crafts reaction conditions followed by acidic hydrolysis. Similarly, Friedel-Crafts reaction of 3 with acyl halides afforded acyl compounds 7b-d.

Sodium borohydride reduction of 7 followed by chlorination with SOCl_2 gave 9. Reaction of 9 with imidazole sodium salt in DMF afforded the desired imidazolylmethyl-substituted benzo[b]thiophenes (10), which in turn were converted to acids 11 by acidic or basic hydrolysis. Compounds 10a-d could also be obtained directly from alcohols 8a-d by their reaction with N,N' -thionyl-diimidazole. This novel transformation of benzyl alcohols by N,N' -thionyl-diimidazole into the corresponding N -benzylimidazoles was found in the course of the study for the formation of the imidazole compounds. We are now investigating the scope and limitation of this reaction.

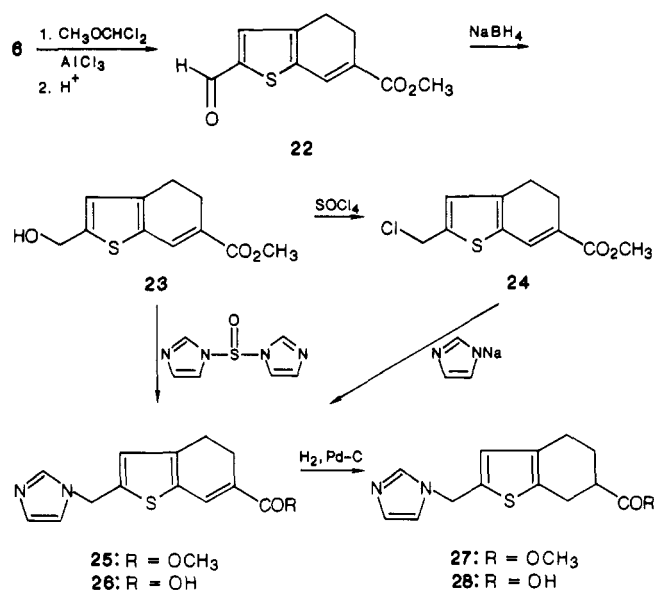
To examine the biological role of the Δ^4 double bond, catalytic hydrogenation of compounds 10a-d was carried out to give the corresponding tetrahydrobenzo[b]thiophene (13) derivatives.

The imidazolylethyl-substituted compounds (19 and 21) were prepared as shown in Scheme III. The bromoacetyl derivative 14, which was obtained by Friedel-Crafts reaction of 3 with ClCOCH_2Br , was allowed to react with imidazole in the presence of NaHCO_3 to give 15. Reduction of 15 with NaBH_4 gave alcohol 16. The xanthate ester (17) of 16 was reduced with tin hydride to afford the imidazolylethyl-substituted ester (18), which in turn was converted to acid 19 by hydrolysis. Catalytic hydrogenation

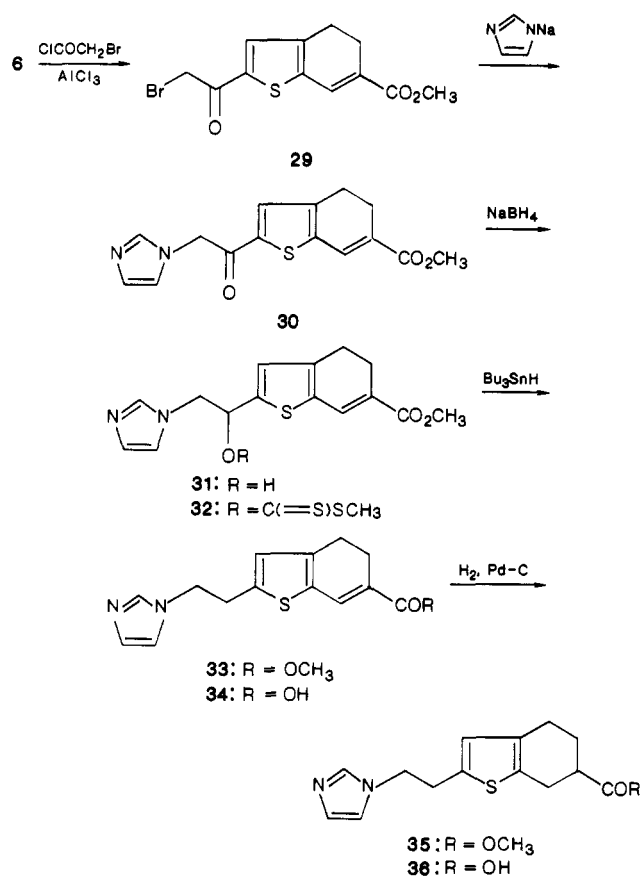
- (4) (a) Burke, S. E.; DiCola, G.; Lefer, M. A. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 842. (b) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1986**, *29*, 1637. (c) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1986**, *29*, 1643. (d) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. *J. Med. Chem.* **1985**, *28*, 287.
 (5) Fieser, L. F.; Kennelly, R. G. *J. Am. Chem. Soc.* **1935**, *57*, 1611.
 (6) MacDowell, D. W. H.; Greenwood, T. D. *J. Heterocycl. Chem.* **1965**, *2*, 44.
 (7) Needleman, P.; Moncada, S.; Bunting, S.; Vane, J. R.; Hamberg, M.; Samuelsson, B. *Nature* **1976**, *261*, 558.

- (8) Silver, M. J.; Hoch, W.; Kocsis, J. J.; Ingeman, C. M.; Smith, J. B. *Science* **1974**, *183*, 1085.

Scheme IV



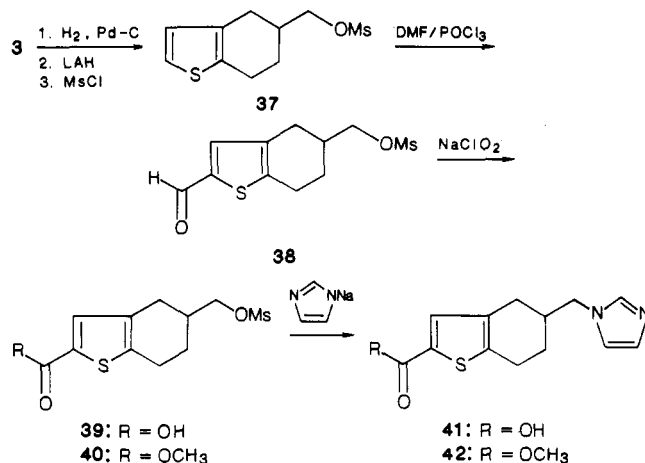
Scheme V



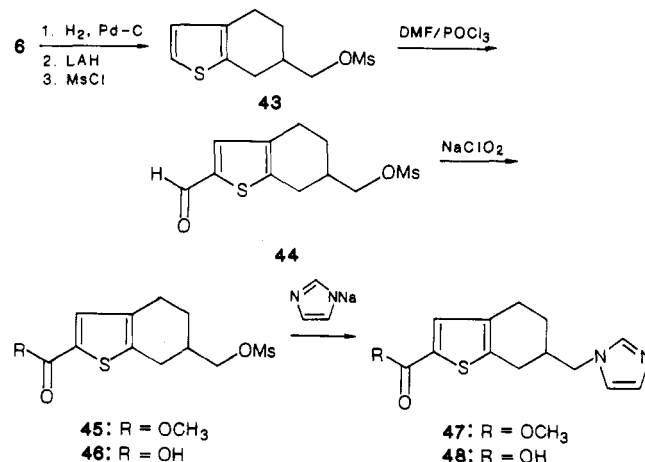
tion of 18 gave the corresponding tetrahydrobenzo[b]thiophene (20). This material was hydrolyzed to give the carboxylic acid (21).

On the other hand, the 6-carboxylic acid congeners were prepared through the sequence of reactions outlined in Schemes IV and V. Formylation of 6 under Friedel-Crafts reaction conditions as described for 7 followed by NaBH₄ reduction gave alcohol 23. Treatment of 23 with SOCl₂ followed by imidazole sodium salt gave the product 25. Catalytic hydrogenation of 25 gave the corresponding tetrahydrobenzo[b]thiophene (27). Compound 25 was also obtained directly through the reaction of alcohol 23 with *N,N'*-thionyl-diimidazole. In a way similar to that shown

Scheme VI



Scheme VII



in Scheme III, imidazolylethyl 6-carboxylic acid 35 was derived from 6 via 32.

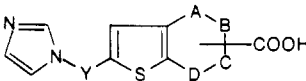
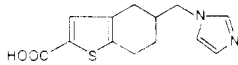
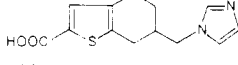
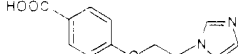
Next, the isomeric benzo[b]thiophene derivatives having a 2-carboxylic acid function were synthesized in order to compare their biological activity with that of the compounds having a 5- or 6-carboxylic acid function. Catalytic hydrogenation, LAH reduction and subsequent mesylation of 3 gave 37 (Scheme VI). Vilsmeier-Haack reaction of 37 with DMF-POCl₃ afforded the 2-formylated compound 38. Oxidation of 38 with sodium chlorite followed by esterification (MeOH/H⁺) gave 40. Condensation of 40 with imidazole sodium salt followed by acidic hydrolysis gave the desired 5-imidazolylmethyl-substituted 2-carboxylic acid derivative 42. Likewise, the 6-imidazolylmethyl-substituted 2-carboxylic acid derivative 48 was prepared from 6 via 46 as shown in Scheme VII.

Results and Discussion

The TXA₂ synthetase inhibitory activity of the compounds obtained in this study are summarized in Table I. Some of the compounds (e.g., 11a, 11b, 19, 13a, 13b, 21, 26, 28, 36, and 42) in this series were far more active than dazoxiben.

In the series of benzo[b]thiophene-5-carboxylic acids, the introduction of a cyclohexyl (11c) or a *tert*-butyl (11d) group into the imidazolylmethyl side chain markedly decreased potency, while the introduction of a phenyl group (11b) showed only a 1/2-fold decrease when compared with the parent compound 11a. The imidazolylethyl-substituted compound 19 showed the same level of activity against TXA₂ synthetase as the imidazolylmethyl compound 11a.

Table I. Imidazolyl-Substituted Di- or Tetrahydrobenzo[*b*]thiophenecarboxylic Acid Derivatives

							
no.	Y	A-B	C-D	position of COOH	mp, °C	formula	TXA ₂ synthetase IC ₅₀ , ^a μM
11a	-CH ₂ -	-CH=CH-	-CH ₂ CH ₂ -	5	>260	C ₁₃ H ₁₁ N ₂ O ₂ Na ¹ /2H ₂ O	0.093
11b	-CH(Ph)-	-CH=CH-	-CH ₂ CH ₂ -	5	180-184	C ₁₉ H ₁₅ N ₂ O ₂ Na	0.114
11c	-CH(c-C ₆ H ₁₁)-	-CH=CH-	-CH ₂ CH ₂ -	5	214-219	C ₁₉ H ₂₁ N ₂ O ₂ Na ³ /2H ₂ O	>10
11d	-CH(^t Bu)-	-CH=CH-	-CH ₂ CH ₂ -	5	235-237	C ₁₇ H ₁₉ N ₂ O ₂ Na ³ /2H ₂ O	>10
19	-CH ₂ CH ₂ -	-CH=CH-	-CH ₂ CH ₂ -	5	180-183	C ₁₄ H ₁₃ N ₂ O ₂ Na	0.10
13a	-CH ₂ -	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	5	213-215	C ₁₃ H ₁₄ N ₂ O ₂ S·HCl ¹ /4H ₂ O	0.086
21	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	5	144-151	C ₁₄ H ₁₆ N ₂ O ₂ S·HCl	1.02
26	-CH ₂ -	-CH ₂ CH ₂ -	-CH=CH-	6	>260	C ₁₃ H ₁₁ N ₂ O ₂ Na	0.013
28	-CH ₂ -	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	6	197-198	C ₁₃ H ₁₄ N ₂ O ₂ S·HCl	0.026
34	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	-CH=CH-	6	>260	C ₁₄ H ₁₃ N ₂ O ₂ Na	>10
36	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	6	>260	C ₁₄ H ₁₆ N ₂ O ₂ S·HCl	1.85
42					138-140	C ₁₃ H ₁₄ N ₂ O ₂ S·HCl	0.114
48					223-228	C ₁₃ H ₁₄ N ₂ O ₂ S·HCl	2.68
dazoxiben							0.106

^a Each result represents the mean of three determinations.

Compound 13, the saturated analogue of 11a, exhibited almost the same activity as the parent compound (11a). The benzo[*b*]thiophene-6-carboxylic acids 26 and 28 exhibited significantly greater potency than the 5-carboxylic acid derivatives.

In general, for the optimal potency of the analogues related to dazoxiben,^{1b,d} the optimum distance between N-1 of the imidazole and the carboxylic acid was found to be 8.5-9.0 Å. According to Dreiding model studies, the distance between the imidazole and the carboxylic acid moieties of 26 and 28 was close to this range. The imidazolylethyl-substituted compounds (34 and 36) showed a dramatic decrease in activity in comparison with the corresponding imidazolymethyl compounds (26 and 28). In this case, the distance between the imidazole and the carboxylic acid group is probably too great.

The benzo[*b*]thiophene-2-carboxylic acids 42 and 48 also showed inhibitory activity against TXA₂ synthetase. It is interesting that the 5-imidazolymethyl-substituted compound 42 had almost the same activity as 13a, but the 6-substituted compound 48 possessed a much lower activity in comparison with 28, in spite of the same distance between the imidazole and the carboxylic acid of 42 and 13a and 48 and 28.

In order to compare the inhibitory activity against TXA₂ synthetase of 4,5- or 6,7-dihydrobenzo[*b*]thiophene-2-carboxylic acids, we attempted to prepare these compounds, but the syntheses were unsuccessful because of the instability of the intermediates.

On the basis of the above preliminary data, 26 and 28 were selected for additional evaluation.

As shown in Table II, compound 26 was found to be 100-fold more active in inhibiting human microsomal TXA₂ synthetase than dazoxiben.

Table III gives the results of the ex vivo assay when 26 and 28 were administered orally to the rat. It was found that 28 was most potent.

Furthermore, these compounds were evaluated in a thrombosis model induced by sodium arachidonate injection in rabbit and their results are shown in Table IV.

In this in vivo assay, 26 was found to be the most potent compound, being at least 7 times as active as dazoxiben.

Table II. Inhibitory Effects of 26 and 28 on Human and Rabbit Platelet Microsomal TXA Synthetase

compd	IC ₅₀ , ^a nM; enzyme source:	
	human	rabbit
26	6	13
28	20	26
dazoxiben	620	106

^a Each result represents the mean of three determinations.**Table III.** TXA₂ Synthetase Inhibitory Activity of 26 and 28 in ex Vivo Test System

compd	ID ₅₀ , ^a μM/kg (95% confidence limits)	n ^b
26	0.064 (0.043-0.099)	5
28	0.027 (0.013-0.050)	5
dazoxiben	0.468 (0.101-0.209)	5

^a Inhibition of rat serum TXB₂ production (2 h after oral administration). ^b n = number of animals used for each dose.**Table IV.** Protection against Sodium Arachidonate Induced Sudden Death

compd	ED ₅₀ , ^a μM/kg, po (95% confidence limits)	n ^b
26	0.43 (0.25-0.71)	5
28	0.90 (0.47-1.67)	5
dazoxiben	3.17 (1.30-7.44)	6

^a Rabbit, 1 h after administration. ^b n = number of animals used for each dose.

Compounds 26 and 28 did not show any significant inhibitory effects on other enzymes involved in arachidonic acid metabolism, such as PG cyclooxygenase, PGI₂ synthetase, or 15- and 5-lipoxygenase at 10² μM.

In conclusion, we have shown that several compounds of di- or tetrahydrobenzo[*b*]thiophenecarboxylic acids with imidazolylalkyl substituents were potent TXA₂ synthetase inhibitors. Among them, sodium 2-(1-imidazolylmethyl)-4,5-dihydrobenzo[*b*]thiophene-6-carboxylate (26) and 2-(1-imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-carboxylic acid hydrochloride (28) exhibited

particularly potent activity in ex vivo and in vivo assays.

Experimental Section

All melting points were determined on a Büchi melting point apparatus and are uncorrected. The structures of all compounds were confirmed by their IR (KBr or Nujol) and ^1H NMR (CDCl_3 or D_2O) spectra. The IR spectra were recorded on a JASCO IRA-2 or IRA-302 spectrophotometer, and the ^1H NMR spectra were obtained on a Varian EM-360 or -390 or Nihondenshi GX-270 spectrometer using TMS as an internal standard unless otherwise stated. Abbreviations used are TEA = triethylamine, IPA = isopropyl alcohol, and DMAP = 4-(dimethylamino)pyridine.

Pharmacology. Assay for Inhibition of Thromboxane A_2 Synthetase in Vitro. Human and rabbit platelet microsomes were prepared according to the method of Needleman et al.⁷ as a source of TXA_2 synthetase. Reaction mixtures (total volume 200 μL) consisting of human or rabbit platelet microsomes, 1 mM epinephrine, 20 $\mu\text{g}/\text{mL}$ of hemoglobin, and a test compound (dissolved in 4 μL of EtOH) were preincubated in 100 mM Tris-HCl buffer (pH 7.6) at 37 °C for 5 min. The reaction was started by adding 3.2 nmol of [^{14}C]arachidonic acid (0.17 μCi , dissolved in 5 μL of EtOH), and performed at 37 °C for 15 min. The reaction mixture was acidified to pH 3.0 with 0.2 N citric acid, and the products were extracted with EtOAc. The extracts were dried under an N_2 gas stream, dissolved in methanol, spotted on a thin-layer plate (Merck, Kieselgel 60F), and chromatographed in a solvent system of the organic phase of EtOAc/AcOH/isooctane/ H_2O (11/2/5/10). The radioactive zones on the plate were detected by autoradiography and the areas corresponding to TXB_2 were scraped off and counted in a liquid scintillation counter (Packard Co. Ltd.). The counts for TXB_2 of the compound treated assay were compared with those of the control assay. The IC_{50} values were determined graphically and all the determination were performed in triplicate.

Ex Vivo Experiments. Male Wistar rats weighing 200–220 g were fasted for 20 h and test compounds or the vehicle were given orally. Blood (2 mL) was withdrawn from the abdominal aorta under anesthesia with ether 2 h after the oral administration and allowed to clot at 37 °C for 90 min. The serum was then separated for the radioimmunoassay of TXB_2 .

Antithrombotic Activity. The experiments were performed according to a modification of the method described by Silver et al.⁸ Conscious male Japanese White rabbits were fasted for 20 h and given an intravenous injection of 1.4 mg/kg sodium arachidonate (AA, Sigma A6523) dissolved in physiological saline into the marginal ear vein over 30 s. Test compounds were administered orally by means of a rubber stomach tube 1 h before the AA injection. Unmedicated rabbits died within a couple of minutes due to mainly pulmonary thrombosis or thromboembolism and myocardial ischemia. The number of surviving rabbits during the test period (60 min) was recorded. The ED_{50} value were determined by the probit method.

Chemistry. Methyl 6,7-Dihydrobenzo[b]thiophene-5-carboxylate (3). To a stirred suspension of a 55% dispersion of NaH in mineral oil (6.31 g, 0.115 mol) in dry DMF (100 mL) was added dropwise a solution of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (20 g, 0.131 mol) in dry DMF (50 mL) at room temperature over 30 min under dry N_2 . After stirring of the reaction mixture for 10 min, dimethyl carbonate (33 mL) was added at 5 °C over 20 min. The solution was stirred at room temperature for 90 min and then poured into water. Extraction with EtOAc and evaporation of solvent gave methyl 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate as a solid. The solid, thus obtained, was dissolved in a mixture of MeOH and THF (each 100 mL) and the solution was cooled to –15 °C. To the above solution was added NaBH_4 (4.98 g, 0.132 mol) over 1 h. The mixture was stirred at this temperature for 30 min, and then an excess of crushed solid CO_2 was added. The excess of CO_2 was allowed to evaporate, and the mixture was concentrated in vacuo. The residue was dissolved in EtOAc and the solution was washed with brine, dried over Na_2SO_4 , and evaporated to give an oil. The oil, thus obtained, was dissolved in toluene and refluxed with $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (2.5 g, 13 mmol) azeotropically for 30 min. After that, the reaction solution was poured into water and extracted with EtOAc. The organic layer was washed successively with NaHCO_3 solution and brine, dried over Na_2SO_4 ,

and evaporated. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (1:1 v/v) gave the product 3 as an oil: yield 20.1 g (79%). ^1H NMR (CDCl_3) δ 3.79 (s, 3 H, COOCH_3), 7.00 (AB q, 2 H, H-2 and H-3), 7.53 (br s, 1 H, H-4). Anal. ($\text{C}_{10}\text{H}_{10}\text{O}_3$) C, H, S.

Methyl 4,5-Dihydrobenzo[b]thiophene-6-carboxylate (6). The title compound was similarly prepared as an oil from 7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene as described above: yield 81%; ^1H NMR (CDCl_3) δ 3.80 (s, 3 H, COOCH_3), 7.08 (AB q, 2 H, H-2 and H-3), 7.54 (s, 1 H, H-7). Anal. ($\text{C}_{10}\text{H}_{10}\text{O}_3$) C, H, S.

Methyl 2-Formyl-6,7-dihydrobenzo[b]thiophene-5-carboxylate (7a). Method A. To a stirred suspension of AlCl_3 (10.3 g, 77 mmol) in dry CH_2Cl_2 (50 mL) was added a solution of 3 (7.50 g, 39 mmol) in dry CH_2Cl_2 (30 mL) at –10 °C under N_2 . After 10 min, a solution of $\text{CHCl}_2\text{OCH}_3$ (5.24 mL, 58 mmol) in dry CH_2Cl_2 (30 mL) was added at –10 °C over 1 h. The reaction mixture was stirred at –10 °C for 1 h and poured into water containing crushed ice and concentrated HCl (10 mL) and vigorously stirred for 30 min. The formylated compound 7a was extracted with CH_2Cl_2 , and the combined extracts were washed successively with NaHCO_3 solution and brine and dried over Na_2SO_4 . Evaporation of the solvent and recrystallization of the residue from EtOAc–hexane gave 7a as colorless needles: yield 8.21 g (94%); mp 125.0–127.0 °C; ^1H NMR (CDCl_3) δ 3.82 (s, 3 H, COOCH_3), 7.51 (br s, 1 H, H-4), 7.61 (s, 1 H, H-3), 9.89 (s, 1 H, CHO). Anal. ($\text{C}_{11}\text{H}_{10}\text{O}_5$) C, H, S.

Method B. To a solution of dry DMF (71.0 mL) and dry CH_2Cl_2 (70 mL) was added dropwise phosphorus oxychloride (69.0 mL) between 35 and 40 °C. After stirring of the reaction mixture for 30 min, a solution of 3 (70.1 g, 0.369 mol) in DMF (110 mL) and CH_2Cl_2 (35 mL) was added dropwise into above solution at room temperature. The reaction mixture was refluxed for 2.5 h and poured into water. A solution of Na_2CO_3 (157 g) in H_2O (700 mL) was added with stirring. The precipitate, thus formed, was collected, washed with H_2O , and dried in vacuo. Recrystallization from EtOAc–hexane gave colorless needles (mp 125.0–127.0 °C): yield 72.6 g (88%).

Methyl 2-Benzoyl-6,7-dihydrobenzo[b]thiophene-5-carboxylate (7b). The title compound 7b was similarly prepared by method A as described above from 3 and benzoyl chloride as an oil: yield 81%; ^1H NMR (CDCl_3) δ 3.75 (s, 3 H, COOCH_3), 7.2–7.9 (m, 7 H, H-3, H-4, and Ph). Anal. ($\text{C}_{17}\text{H}_{14}\text{O}_3$) C, H, S.

Methyl 2-(2,2-Dimethyl-1-oxopropyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (7d). The title compound 7d was similarly prepared by method A as described above from 3 and pivaloyl chloride as an oil: yield 33%. ^1H NMR (CDCl_3) δ 1.40 (s, 9 H, ^tBu), 3.82 (s, 3 H, COOCH_3), 7.52 (s, 1 H, H-4), 7.62 (s, 1 H, H-3). Anal. ($\text{C}_{15}\text{H}_{18}\text{O}_5$) C, H, S.

Methyl 2-(Hydroxymethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (8a). To a solution of 7a (0.95 g, 4.27 mmol) in 90% (v/v) THF (10 mL) was added portion to portion NaBH_4 (0.17 g, 4.49 mmol) at 5 °C. After 30 min, an excess of crushed solid CO_2 was added. The excess of CO_2 was allowed to evaporate and the mixture was concentrated in vacuo. The residue was dissolved in EtOAc and the solution was washed with brine, dried over Na_2SO_4 , and evaporated, giving quantitatively the product as an oil (0.96 g): ^1H NMR (CDCl_3) δ 3.75 (s, 3 H, COOCH_3), 4.66 (br s, 2 H, CH_2OH), 6.72 (br s, 1 H, H-3), 7.32 (br s, 1 H, H-4).

Methyl 2-(1-Imidazolylmethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (10a). To a stirred solution of imidazole (2.91 g, 42.7 mmol) and 4-DMAP (0.05 g, 4.1 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise a solution of SOCl_2 (0.78 mL, 11.9 mmol) in dry CH_2Cl_2 (4 mL) at room temperature under dry N_2 . After 30 min, a solution of 8a (0.96 g, 4.28 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise at room temperature and stirring was continued for 15 h at ambient temperature. Organic solvent was evaporated in vacuo. The residue was dissolved in EtOAc and the solution was washed with NaHCO_3 solution and brine, successively. The extracts, after being dried over Na_2SO_4 , were evaporated, and the residue was chromatographed on silica gel. Elution with EtOAc/TEA/EtOH (20/1/1 v/v) gave 10a: yield 0.76 g (65%), which was recrystallized from acetone/hexane, giving colorless needles: mp 87.0–89.0 °C. ^1H NMR (CDCl_3) δ 3.78 (s, 3 H, COOCH_3), 5.19 (s, 2 H, CH_2N), 6.85 (br s, 1 H, H-3), 6.98, 7.07, and 7.56 (each br s, each 1 H, imidazole), 7.42 (br s,

1 H, H-4). Anal. ($C_{14}H_{14}N_2O_2S$) C, H, N, S.

Sodium 2-(1-Imidazolylmethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (11a). Compound 10a (0.13 g) was hydrolyzed in the usual manner. Recrystallization from MeOH/acetone gave 0.10 g of 11a as colorless needles (as a half-hydrate): mp >260 °C. Anal. ($C_{13}H_{11}N_2O_2SNa \cdot 1/2 H_2O$) C, H, N, S.

Methyl 2-(Phenylhydroxymethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (8b). The title compound 8b was prepared similarly as described above from 7b as an oil: yield 95%.

Methyl 2-(Cyclohexylhydroxymethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (8c). The title compound 8c was prepared similarly as described above from 7c as an oil: yield quantitative; 1H NMR ($CDCl_3$) δ 3.76 (s, 3 H, $COOCH_3$), 4.48 (d, $J = 11$ Hz, 1 H, $CHOH$), 6.70 (s, 1 H, H-3), 7.39 (br s, 1 H, H-4).

Methyl 2-(2,2-Dimethyl-1-hydroxypropyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (8d). The title compound 8d was prepared similarly as described above from 7d as an oil: yield 98%; 1H NMR ($CDCl_3$) δ 0.98 (s, 9 H, tBu), 3.74 (s, 3 H, $COOCH_3$), 4.48 (br s, 1 H, $CHOH$), 6.69 (s, 1 H, H-3), 7.37 (br s, 1 H, H-4).

Methyl 2-(1-Imidazolylphenylmethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (10b). The title compound 10b was prepared similarly as described above from 8b as an oil: yield, 65%. 1H NMR ($CDCl_3$) δ 3.77 (s, 3 H, $COOCH_3$), 6.64 and 6.70 (each s, each 1 H, H-2' and H-3), 6.9–7.6 (m, 9 H, H-4, imidazole and Ph). Anal. ($C_{20}H_{18}N_2O_2S$) C, H, N, S.

Methyl 2-(Cyclohexyl-1-imidazolylmethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (10c). The title compound 10c was prepared similarly as described above from 8c as an oil: yield 25%. 1H NMR ($CDCl_3$) δ 3.78 (s, 3 H, $COOCH_3$), 4.89 (d, $J = 15.5$ Hz, 1 H, H-2'), 6.8–7.6 (5 H, H-3, H-4, and imidazole). Anal. ($C_{20}H_{24}N_2O_2S$) C, H, N, S.

Methyl 2-[1-(1-Imidazolyl)-2,2-dimethylpropyl]-6,7-dihydrobenzo[b]thiophene-5-carboxylate (10d). The title compound was prepared similarly as described above from 8d as an oil: yield 78%. 1H NMR ($CDCl_3$) δ 1.06 (s, 9 H, tBu), 3.80 (s, 3 H, $COOCH_3$), 5.11 (s, 1 H, H-2'), 6.91 (s, 1 H, H-3), 7.06, 7.14, 7.45, and 7.64 (each br s, each 1 H, H-4 and imidazole). Anal. ($C_{18}H_{22}N_2O_2S$) C, H, N, S.

Sodium 2-(1-Imidazolylphenylmethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (11b). The title compound 11b was prepared similarly as described above from 10b as colorless needles from EtOH-ether: yield 54%; mp 180.0–184.0 °C. Anal. ($C_{19}H_{15}N_2O_2SNa$) C, H, N, S.

Sodium 2-(Cyclohexyl-1-imidazolylmethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate (11c). The title compound 11c was prepared similarly as described above from 10c as colorless needles from MeOH-ether: yield 56%; mp 214.0–219.0 °C. Anal. ($C_{19}H_{21}N_2O_2SNa \cdot 3/2 H_2O$) C, H, N, S.

Sodium 2-[1-(1-Imidazolyl)-2,2-dimethylpropyl]-6,7-dihydrobenzo[b]thiophene-5-carboxylate (11d). The title compound 11d was prepared similarly as described above from 10d as colorless needles from MeOH-ether: yield 68%; mp 235.0–237.0 °C. Anal. ($C_{17}H_{19}N_2O_2SNa \cdot 3/2 H_2O$) C, H, N, S.

Methyl 2-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate (12a). A mixture of 10a (0.30 g, 1.09 mmol), 10% Pd-C (1.0 g), and 1 N HCl (1.15 mL) was hydrogenated under dry H_2 in the usual manner. The catalyst was filtered off and the filtrate was concentrated to give 12a: yield 0.27 g (73%); 1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, $COOCH_3$), 5.14 (s, 2 H, CH_2N), 6.65 (s, 1 H, H-3), 6.97, 7.06, and 7.55 (each br s, each 1 H, imidazole).

Methyl 2-(1-Imidazolylphenylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate (12b). The title compound 12b was prepared similarly as described above from 10b as an oil: yield 52%; 1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, $COOCH_3$).

Methyl 2-(Cyclohexyl-1-imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate (12c). The title compound 12c was prepared similarly as described above from 10c as an oil: yield 73%; 1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, $COOCH_3$), 4.85 (d, $J = 10$ Hz, 1 H, H-2'), 6.63 (s, 1 H, H-3), 7.00 and 7.53 (each s, 2 H and 1 H, imidazole).

2-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylic Acid Hydrochloride (13a). A solution

of 12a (1.20 g, 4.34 mmol) in concentrated HCl (3 mL) and glacial acetic acid (3 mL) was refluxed for 4 h and then evaporated in vacuo. The residual solid, thus obtained, was recrystallized from EtOH/ether, giving colorless leaflets 0.92 g (70%): mp 213.0–215.0 °C. Anal. ($C_{13}H_{14}N_2O_2S \cdot HCl \cdot 1/4 H_2O$) C, H, N, S, Cl.

2-(1-Imidazolylphenylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylic Acid Hydrochloride (13b). The title compound 13b was prepared similarly as described above from 12b as a colorless amorphous powder from EtOH/ether: yield 63%. Anal. ($C_{19}H_{24}N_2O_2S \cdot HCl \cdot H_2O$) C, H, N, S, Cl.

2-(Cyclohexyl-1-imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylic Acid Hydrochloride (13c). The title compound 13c was prepared similarly as described above from 12c as colorless needles from MeOH/ether: yield 55%; mp 202.0–204.0 °C. Anal. ($C_{19}H_{24}N_2O_2S \cdot HCl \cdot H_2O$) C, H, N, S, Cl.

2-[1-(1-Imidazolyl)-2,2-dimethylpropyl]-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylic Acid Hydrochloride (13d). The title compound 13d was prepared similarly as described above from 12d as a colorless amorphous powder from EtOH-ether: yield 63%. Anal. ($C_{17}H_{22}N_2O_2S \cdot HCl$) C, H, N, S, Cl.

Methyl 2-[2-(1-Imidazolyl)-1-oxoethyl]-6,7-dihydrobenzo[b]thiophene-5-carboxylate (15). Compound 3 (1.85 g, 9.72 mmol) and bromoacetyl chloride (1.10 mL) was subjected to Friedel-Crafts reaction conditions as described in the preparation of 7a (method A), giving 14 (methyl 2-(2-bromo-1-oxoethyl)-6,7-dihydrobenzo[b]thiophene-5-carboxylate), as a solid. Crude 14, thus obtained, and imidazole (2.45 g, 36.0 mmol) were dissolved in MeOH (40 mL) and THF (20 mL), and the solution was refluxed for 2 h and then evaporated. The residue was chromatographed on silica gel. Elution with EtOAc/TEA/EtOH (40/1/1 v/v) gave 15 as an oil: yield 2.65 g (90%). 1H NMR ($CDCl_3$) δ 3.81 (s, 3 H, $COOCH_3$), 5.21 (s, 2 H, CH_2CO), 6.9–7.6 (4 H, H-4 and imidazole). Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N, S.

Methyl 2-[2-(1-Imidazolyl)-1-[(methylthio)thiocarbonyl]oxyethyl]-6,7-dihydrobenzo[b]thiophene-5-carboxylate (17). Compound 15 (0.32 g, 1.06 mmol) was reduced under the conditions described in the preparation of 8a, giving the alcohol derivative 16 in quantitative yield. To a stirred solution of 16 in dry THF (6 mL) was added a 55% dispersion of NaH in mineral oil (92 mg, 2.11 mmol) under dry N_2 . After 2 h, CS_2 (0.32 mL, 5.32 mmol) was added at room temperature and the mixture stirred for 15 min, and then MeI (0.33 mL, 5.30 mmol) was added at room temperature. After 30 min, the reaction mixture was poured into water and extracted with EtOAc. Extracts were washed with brine, dried over Na_2SO_4 , and evaporated. The residue was chromatographed on silica gel. Elution with EtOAc/EtOH/TEA (10/1/1 v/v) gave 17 as an oil: yield 0.18 g (43%). 1H NMR ($CDCl_3$) δ 2.43 (s, 3 H, SCH_3), 3.77 (s, 3 H, $COOCH_3$), 5.12 (dd, $J = 6.0$ and 8.0 Hz, 1 H, $CH_2CHOCSSCH_3$). Anal. ($C_{17}H_{18}N_2O_3S_3$) C, H, N, S.

Methyl 2-[2-(1-Imidazolyl)ethyl]-6,7-dihydrobenzo[b]thiophene-5-carboxylate (18). A solution of 17 (0.18 g, 0.456 mmol), tributyltin hydride (0.24 mL, 0.905 mmol), and catalytic amounts of azobisisobutyronitrile in THF (3 mL) was refluxed for 3 h under dry N_2 and evaporated. The residue was dissolved in CH_3CN and the solution was washed several times with hexane. Evaporation of CH_3CN gave an oil which was chromatographed on silica gel. Elution with EtOAc/TEA/EtOH (20/1/1 v/v) gave 18 as an oil: yield 80 mg (61%). 1H NMR ($CDCl_3$) δ 3.17 (t, $J = 7.0$ Hz, 2 H, CH_2CH_2N), 3.78 (s, 3 H, $COOCH_3$), 4.16 (t, $J = 7.0$ Hz, 2 H, CH_2N), 6.51 (s, 1 H, H-3), 6.86, 7.03, and 7.37 (4 H in total, H-4 and imidazole). Anal. ($C_{15}H_{16}N_2O_2S$) C, H, N, S.

Sodium 2-[2-(1-Imidazolyl)ethyl]-6,7-dihydrobenzo[b]thiophene-5-carboxylate (19). The title compound 19 was prepared similarly as described for the preparation of 11a from 18 as colorless needles from EtOH/ether: yield 60%; mp 180.0–183.0 °C dec. Anal. ($C_{14}H_{13}N_2O_2SNa$) C, H, N, S.

Methyl 2-[2-(1-Imidazolyl)ethyl]-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate (20). The title compound 20 was prepared similarly as described for the preparation of 12a from 18 as an oil: yield 68%; 1H NMR ($CDCl_3$) δ 3.14 (t, $J = 7.0$ Hz, 2 H, CH_2CH_2N), 3.72 (s, 3 H, $COOCH_3$), 4.15 (t, $J = 7.0$ Hz, 2 H, CH_2N), 6.34 (s, 1 H, H-3), 6.88, 7.03, and 7.38 (each s, each 1 H, imidazole).

2-[2-(1-Imidazolyl)ethyl]-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylic Acid Hydrochloride (21). A solution

thiophene-5-carboxylic Acid Hydrochloride (21). The title compound 21 was prepared similarly as described above for the preparation of 13a from 20 as colorless needles from IPA/ether: yield 58%; mp 144.0–151.0 °C. Anal. ($C_{14}H_{16}N_2O_2S \cdot HCl$) C, H, N, S, Cl.

Methyl 2-Formyl-4,5-dihydrobenzo[b]thiophene-6-carboxylate (22). The title compound 22 was prepared similarly according to the method B described for the preparation of 7a from 6: yield 87%; mp 88.0–89.0 °C (from IPA). 1H NMR ($CDCl_3$) δ 3.83 (s, 3 H, $COOCH_3$), 7.50 (br s, 1 H, H-7), 7.57 (s, 1 H, H-3), 9.86 (s, 1 H, CHO). Anal. ($C_{11}H_{10}O_2S$) C, H, S.

Methyl 2-(Hydroxymethyl)-4,5-dihydrobenzo[b]thiophene-6-carboxylate (23). The title compound 23 was prepared similarly as described for the preparation of 8a from 22 in quantitative yield as an oil: 1H NMR ($CDCl_3$) δ 3.80 (s, 3 H, $COOCH_3$), 4.70 (s, 2 H, CH_2OH), 6.77 (s, 1 H, H-3), 7.43 (s, 1 H, H-7).

Methyl 2-(Chloromethyl)-4,5-dihydrobenzo[b]thiophene-6-carboxylate (24). To a stirred solution of 23 (6.80 g, obtained from 22 (6.74 g, 30.3 mmol) as described above) and dry pyridine (2.5 mL, 30.1 mmol) in dry CH_2Cl_2 (100 mL) was added a solution of $SOCl_2$ (8.3 mL, 114 mmol) in dry CH_2Cl_2 (40 mL) at room temperature over 1 h. Then the reaction mixture was poured into H_2O containing $NaHCO_3$ (21 g) and extracted with CH_2Cl_2 . Combined extracts were washed with brine, dried over Na_2SO_4 , and evaporated to give crude 24 as a solid: yield 7.26 g (99%) from 22; 1H NMR ($CDCl_3$) δ 3.81 (s, 3 H, $COOCH_3$), 4.72 (s, 2 H, CH_2Cl), 6.87 (s, 1 H, H-3), 7.44 (s, 1 H, H-7).

Methyl 2-(1-Imidazolylmethyl)-4,5-dihydrobenzo[b]thiophene-6-carboxylate (25). To a stirred suspension of a 55% dispersion of NaH in mineral oil (1.37 g, 31.4 mmol) in dry DMF (70 mL) was added a solution of imidazole (2.55 g, 35.5 mmol) in dry DMF (45 mL) dropwise at 5 °C under dry N_2 over 15 min, giving a clear solution. After 30 min, a solution of 24 (7.26 g, 29.9 mmol) in dry DMF (20 mL) was added into the above solution over 15 min. After 15 min, the reaction mixture was poured into H_2O and extracted with EtOAc. Extracts were washed several times with brine, dried over Na_2SO_4 , and evaporated. The residue was chromatographed on silica gel. Elution with EtOAc/TEA/EtOH (50/1/1 v/v) gave the product 25 as an oil: yield 7.36 g (89%); 1H NMR ($CDCl_3$) δ 3.80 (s, 3 H, $COOCH_3$), 5.23 (s, 2 H, CH_2N), 7.01, 7.12, 7.45, and 7.58 (each s, each 1 H, H-7 and imidazole). Anal. ($C_{14}H_{14}N_2O_2S$) C, H, N, S.

Sodium 2-(1-Imidazolylmethyl)-4,5-dihydrobenzo[b]thiophene-6-carboxylate (26). The title compound 26 was prepared similarly as described above for the preparation of 11a from 25 as colorless needles from 80% MeOH/acetone: yield 78%; mp >260 °C; 1H NMR (270 MHz, D_2O , TMS as external standard) δ 2.2–2.5 (m, 4 H, H-4 \times 2, H-5 \times 2), 5.04 (s, 2 H, CH_2N), 6.63, 6.77, 6.90, and 7.50 (each s, 5 H in total, H-3, H-7, and imidazole). Anal. ($C_{13}H_{11}N_2O_2SNa$) C, H, N, S.

Methyl 2-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylate (27). The title compound 27 was prepared similarly as described above for the preparation of 12a from 25 as an oil: yield 80%; 1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, $COOCH_3$), 5.13 (s, 2 H, CH_2N), 6.62, 6.95, 7.04, and 7.53 (each s, each 1 H, H-3 and imidazole). Anal. ($C_{14}H_{16}N_2O_2S$) C, H, N, S.

2-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylic Acid Hydrochloride (28). The title compound 28 was prepared similarly as described above for the preparation of 13 from 27 as colorless needles from EtOH/acetone: yield 82%; mp 197.0–198.0 °C; 1H NMR (90 MHz, D_2O , TMS as external standard) δ 5.97 (s, 2 H, CH_2N), 7.41, 7.96, and 9.28 (each s, 4 H in total, H-3 and imidazole). Anal. ($C_{13}H_{14}N_2O_2S \cdot HCl$) C, H, N, S, Cl.

Methyl 2-[2-(1-Imidazolyl)-1-oxoethyl]-4,5-dihydrobenzo[b]thiophene-6-carboxylate (30). The title compound 30 was prepared similarly as described above for the preparation of 15 from 6 via 29 as an oil: yield 85%; 1H NMR ($CDCl_3$) δ 3.81 (s, 3 H, $COOCH_3$), 5.22 (s, 2 H, CH_2N), 7.0–7.6 (5 H in total, H-3, H-7, and imidazole). Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N, S.

Methyl 2-[2-(1-Imidazolyl)-1-[(methylthio)thiocarbonyl]oxyethyl]-4,5-dihydrobenzo[b]thiophene-6-carboxylate (32). The title compound 32 was prepared similarly as described for the preparation of 17 from 30 via 31 as an oil:

yield 40%; 1H NMR ($CDCl_3$) δ 2.45 (s, 3 H, SCH_3), 3.79 (s, 3 H, $COOCH_3$), 5.17 (dd, $J = 5.0$ and 7.8 Hz, 1 H, $CHOCSSCH_3$). Anal. ($C_{17}H_{18}N_2O_3S_2$) C, H, N, S.

Methyl 2-[2-(1-Imidazolyl)ethyl]-4,5-dihydrobenzo[b]thiophene-6-carboxylate (33). The title compound 33 was prepared similarly as described for the preparation of 18 from 32 as an oil: yield 70%; 1H NMR ($CDCl_3$) δ 3.22 (t, $J = 6.5$ Hz, 2 H, H-2' \times 2), 3.79 (s, 3 H, $COOCH_3$), 4.19 (t, $J = 6.5$ Hz, 2 H, CH_2N), 6.54 (s, 1 H, H-3), 6.9–7.5 (4 H, H-7 and imidazole). Anal. ($C_{15}H_{16}N_2O_2S$) C, H, N, S.

Sodium 2-[2-(1-Imidazolyl)ethyl]-4,5-dihydrobenzo[b]thiophene-6-carboxylate (34). The title compound 34 was prepared similarly as described above for the preparation of 19 from 33 as colorless needles from MeOH/ether: yield 80%; mp >260 °C. Anal. ($C_{14}H_{13}N_2O_2SNa$) C, H, N, S.

Methyl 2-[2-(1-Imidazolyl)ethyl]-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylate (35). The title compound 35 was prepared similarly as described above for the preparation of 12a from 33 as an oil: yield 72%; 1H NMR ($CDCl_3$) δ 3.13 (t, $J = 7.0$ Hz, 2 H, H-2' \times 2), 3.71 (s, 3 H, $COOCH_3$), 4.14 (t, $J = 7.0$ Hz, 2 H, CH_2N), 6.35 (s, 1 H, H-3), 6.90, 7.04, and 7.40 (each br s, each 1 H, imidazole). Anal. ($C_{15}H_{18}N_2O_2S$) C, H, N, S.

2-[2-(1-Imidazolyl)ethyl]-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylic Acid Hydrochloride (36). The title compound 36 was prepared similarly as described above for the preparation of 13a from 35 as a colorless amorphous powder from EtOH/ether: yield 71%. Anal. ($C_{14}H_{16}N_2O_2S \cdot HCl$) C, H, N, S, Cl.

5-[[[(Methylsulfonyl)oxy]methyl]-4,5,6,7-tetrahydrobenzo[b]thiophene (37). A mixture of 3 (5.03 g, 25.9 mmol) and 10% Pd-C (3.5 g) was hydrogenated under dry H_2 in the usual manner. The catalyst was filtered off and the filtrate was concentrated to give methyl 4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate as an oil: yield 3.20 g (63%); 1H NMR ($CDCl_3$) δ 3.74 (s, 3 H, $COOCH_3$), 6.94 (AB q, H-2 and H-3). The saturated compound (3.20 g, 16.3 mmol) thus obtained was dissolved in ether (35 mL), and LAH (0.62 g, 16.3 mmol) was added at 5 °C. After 30 min, the reaction mixture was quenched with $Na_2SO_4 \cdot 10H_2O$ (6.0 g, 18.6 mmol) and filtered. The filtrate was evaporated, giving 5-(hydroxymethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene (2.73 g, quantitative yield) as an oil. To a solution of the above alcohol derivative (2.73 g, 16.2 mmol) and TEA (6.8 mL, 48.8 mmol) in CH_2Cl_2 (50 mL) was added a solution of mesyl chloride (2.5 mL, 32.3 mmol) in CH_2Cl_2 (20 mL) dropwise at 5 °C. After 1 h, the reaction mixture was poured into water and extracted with EtOAc. Extracts were washed successively with $NaHCO_3$ solution and brine and dried over Na_2SO_4 . Evaporation of the solvent gave 37 as an oil: yield 3.08 g (77%); 1H NMR ($CDCl_3$) δ 2.98 (s, 3 H, OSO_2CH_3), 4.16 (d, $J = 5.0$ Hz, 2 H, CH_2O), 6.89 (AB q, H-2 and H-3).

2-Formyl-5-[[[(methylsulfonyl)oxy]methyl]-4,5,6,7-tetrahydrobenzo[b]thiophene (38). The title compound 38 was prepared similarly as described above for the preparation of 7a (method B) from 37 as an oil: yield 65%; 1H NMR ($CDCl_3$) δ 3.06 (s, 3 H, OSO_2CH_3), 4.24 (d, $J = 5.0$ Hz, 2 H, CH_2O), 7.46 (s, 1 H, H-3), 9.85 (s, 1 H, CHO). Anal. ($C_{11}H_{14}O_4S_2$) C, H, S.

Methyl 5-[[[(Methylsulfonyl)oxy]methyl]-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylate (40). To a stirred solution of 38 (2.01 g, 7.32 mmol) and sulfamic acid (4.44 g, 45.7 mmol) in aqueous dioxane (48 mL, 1/5 v/v) was added dropwise a solution of sodium chlorite (0.99 g, 10.9 mmol) in H_2O (5 mL) at room temperature over 10 min. After 30 min the organic solvent was evaporated. The residue was extracted with EtOAc, and the combined extracts were washed with brine. The extracts, after being dried over Na_2SO_4 , were evaporated, giving the carboxylic acid derivative. A solution of carboxylic acid derivative thus obtained and a catalytic amount of H_2SO_4 in MeOH (20 mL) was refluxed for 3 h and evaporated. The residue was dissolved in EtOAc and the solution was washed successively with H_2O , $NaHCO_3$ solution, and brine, dried over Na_2SO_4 , and evaporated. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (3/2 v/v) gave the product 40 as an oil: yield 2.11 g (95%).

Methyl 5-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylate (41). To a stirred suspension of a 55% dispersion of NaH in mineral oil (0.12 g, 2.75 mmol) in

dry DMF (10 mL) was added dropwise a solution of imidazole (0.35 g, 5.14 mmol) in dry DMF (10 mL) at room temperature under dry N₂ and the mixture stirred for 30 min. Then, a solution of 40 (0.78 g, 2.56 mmol) in dry DMF (20 mL) was added dropwise at room temperature and the mixture then heated at 50 °C for 2 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine for several times, dried over Na₂SO₄, and evaporated. The residue was chromatographed on silica gel. Elution with EtOAc/TEA/EtOH (20/1/1 v/v) gave the product as an oil: yield 0.52 g (73%); ¹H NMR (CDCl₃) δ 3.85 (s, 3 H, COOCH₃), 3.95 (d, *J* = 6.0 Hz, 2 H, CH₂N), 6.85–7.6 (4 H, H-3 and imidazole). Anal. (C₁₄H₁₆N₂O₂S) C, H, N, S.

5-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylic Acid Hydrochloride (42). The title compound 42 was prepared similarly as described above for the preparation of 13a from 41 as colorless needles from IPA/ether: yield 92%; mp 138.0–140.0 °C. Anal. (C₁₃H₁₄N₂O₂S·HCl) C, H, N, S, Cl.

6-[(Methylsulfonyl)oxy]methyl]-4,5,6,7-tetrahydrobenzo[*b*]thiophene (43). The title compound 43 was prepared similarly as described above for the preparation of 37 from 6 as an oil: yield 78%; ¹H NMR (CDCl₃) δ 2.98 (s, 3 H, OSO₂CH₃), 4.17 (d, *J* = 6.0 Hz, 2 H, CH₂O), 6.88 (AB q, 2 H, H-2 and H-3), 4.24 (d, *J* = 5.0 Hz, 2 H, CH₂O), 7.46 s, 1 H, H-3), 9.85 (s, 1 H, CHO). Anal. (C₁₁H₁₄O₄S₂) C, H, S.

2-Formyl-6-[(methylsulfonyl)oxy]methyl]-4,5,6,7-tetrahydrobenzo[*b*]thiophene (44). The title compound 44 was prepared similarly as described above for the preparation of 38 from 43 as an oil: yield 64%; ¹H NMR (CDCl₃) δ 3.05 (s, 3 H, OSO₂CH₃), 4.24 (d, *J* = 5.0 Hz, 2 H, CH₂O), 7.46 s, 1 H, H-3), 9.85 (s, 1 H, CHO). Anal. (C₁₁H₁₄O₄S₂) C, H, S.

Methyl 6-[(Methylsulfonyl)oxy]methyl]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (46). The title compound was prepared similarly as described above for the preparation of 40 from 44 as colorless needles from EtOAc/hexane: yield 85%; mp 188.0–191.0 °C; ¹H NMR (CDCl₃) δ 3.05 (s, 3 H, OSO₂CH₃), 3.86 (s, 3 H, COOCH₃), 4.20 (d, *J* = 5.0 Hz, 2 H, CH₂O), 7.48 (s, 1 H, H-3). Anal. (C₁₂H₁₆O₅S₂) C, H, S.

Methyl 4-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (47). The title compound 47 was

prepared similarly as described above for the preparation of 41 from 46 as a colorless amorphous powder: yield 96%; ¹H NMR (CDCl₃) δ 3.83 (s, 3 H, COOCH₃), 3.96 (d, *J* = 6.0 Hz, 2 H, CH₂N), 6.9–7.6 (4 H, H-3 and imidazole). Anal. (C₁₄H₁₆N₂O₂S) C, H, N, S.

6-(1-Imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylic Acid Hydrochloride (48). The title compound 48 was prepared similarly as described above for the preparation of 13a from 47 as a colorless amorphous powder from IPA/ether: yield 64%. Anal. (C₁₃H₁₄N₂O₂S·HCl) C, H, N, S, Cl.

Registry No. 1, 13414-95-4; 2, 112101-60-7; 3, 112101-59-4; 3 (4,5,6,7-tetrahydro), 112101-66-3; 4, 1468-84-4; 5, 114686-05-4; 6, 114686-04-3; 7a, 112101-55-0; 7b, 112101-62-9; 7c, 112101-70-9; 7d, 112135-62-3; 8a, 112101-53-8; 8b, 112101-54-9; 8c, 112101-72-1; 8d, 114685-81-3; 10a, 112101-36-7; 10b, 112101-40-3; 10c, 112101-49-2; 10d, 112101-47-0; 11, 3005-50-3; 11a, 114686-23-6; 11a-Na, 112101-37-8; 11b, 114686-01-0; 11b-Na, 112101-41-4; 11c, 119971-54-9; 11c-Na, 112101-50-5; 11d, 119971-55-0; 11d-Na, 112101-48-1; 12a, 112101-38-9; 12b, 119971-61-8; 12c, 112101-51-6; 12d, 119971-62-9; 13a, 114686-21-4; 13a·HCl, 112101-39-0; 13b·HCl, 119971-59-4; 13c·HCl, 112101-52-7; 13d·HCl, 119971-60-7; 14, 119971-43-6; 15, 119971-44-7; 16, 119971-45-8; 17, 119971-46-9; 18, 112135-60-1; 19, 114686-02-1; 19-Na, 112101-44-7; 20, 119971-47-0; 21, 119971-48-1; 21·HCl, 119971-56-1; 22, 114685-92-6; 23, 114707-26-5; 24, 119971-49-2; 25, 114685-83-5; 26, 114685-12-3; 26-Na, 113817-57-5; 27, 114685-91-5; 28, 114686-11-2; 28·HCl, 114685-78-8; 29, 114686-86-8; 30, 114685-85-7; 31, 114685-88-0; 32, 114685-87-9; 33, 114685-89-1; 34, 114686-19-0; 34-Na, 114685-90-4; 35, 114685-69-7; 36, 114686-14-5; 36·HCl, 114685-70-0; 37, 114685-57-3; 37 alcohol, 114685-56-2; 38, 114685-58-4; 39, 119971-50-5; 40, 114685-59-5; 41, 114685-45-9; 42, 114686-03-2; 42·HCl, 114685-46-0; 43, 114685-34-6; 44, 114685-35-7; 45, 119971-51-6; 46, 114685-36-8; 47, 114685-49-3; 48, 119971-53-8; 48·HCl, 114685-50-6; CHCl₂OCH₃, 4885-02-3; ClCOCH₂Br, 22118-09-8; cyclohexanecarbonyl chloride, 2719-27-9; pivaloyl chloride, 3282-30-2; 1*H*-imidazole, 288-32-4; thromboxane synthetase, 61276-89-9.

Hybrid Molecules: Growth Inhibition of *Leishmania donovani* Promastigotes by Thiosemicarbazones of 3-Carboxy-β-carbolines

Robert H. Dodd,* Catherine Ouannès, Malka Robert-Géro, and Pierre Potier

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91190 Gif-sur-Yvette, France.
Received July 27, 1988

The thiosemicarbazones of β-carboline-3-carboxaldehyde (compound 2) and 3-acetyl-β-carboline (compound 3) were found to effectively inhibit the in vitro growth of the promastigote form of *Leishmania donovani*, 50% inhibition being obtained at concentrations of 5.0 and 2.5 μM, respectively, while irreversible growth inhibition was achieved at 40 (compound 2) and 17.5 μM (compound 3). The thiosemicarbazone of pyridine-2-carboxaldehyde (compound 4) was considerably less active while both methyl β-carboline-3-carboxylate (compound 1) and the thiosemicarbazone of ethyl 5-formyl-6-azaindole-2-carboxylate (compound 5) were inactive at the highest concentrations tested. At concentrations provoking approximately 50% growth inhibition of promastigotes, compound 2 was observed to preferentially block DNA rather than RNA synthesis, but for compound 3, the reverse was true. Compound 3, the most active analogue studied, may thus act, at least partly, via a novel, though as yet unelucidated, mechanism.

Human leishmaniasis is a major and often fatal tropical parasitic disease for which few efficacious and easily administered treatments are known at present.¹ The causative agents of leishmaniasis are various species of the protozoa *Leishmania* belonging to the family Trypanosomatidae. One of these, *Leishmania donovani*, infects macrophages of reticuloendothelial organs in its amastigote form, giving rise to visceral leishmaniasis. Recently,

it has been shown that certain compounds known to interact with the mammalian central nervous system also exhibit leishmanicidal properties. Thus, both tricyclic antidepressants such as clomipramine² as well as the structurally related neuroleptic phenothiazines³ demonstrate potent cytotoxic effects against both the extracellular

(1) D'Arcy, P. F.; Harron, D. W. G. *Pharm. Internat.* 1983, 238.

(2) Zilberstein, D.; Dwyer, D. M. *Science* 1984, 226, 977.

(3) Pearson, R. D.; Manian, A. A.; Hareus, J. L.; Hall, D.; Hewlett, E. L. *Science* 1982, 217, 369.