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; (±)-**6**, 119878-55-6; (±)-**7**, 119878-11-4; (±)-**8**, 119878-12-5; (±)-**9**, 119878-13-6; (±)-**10**, 119878-14-7; (±)-**11**, 119878-15-8; (±)-**12**, 119878-16-9; (±)-**13**, 119878-17-0; (±)-**14**, 119878-18-1; (±)-**14**·HCl, 119878-39-6; (±)-**15**, 119878-19-2; (±)-**15**·HCl, 119878-40-9; (±)-**16**, 119878-20-5; (±)-**16**·HCl, 119878-41-0; (±)-**17**, 119878-21-6; (±)-**17**·HCl, 119878-42-1; (±)-**18**, 119878-22-7; (±)-**18**·$C_4H_4O_4$, 119878-43-2; (±)-**19**, 119878-23-8; (±)-**19**·HCl, 119878-44-3; (±)-**20**, 119878-38-5; (±)-**20**·$C_4H_4O_4$, 119907-54-9; (±)-**21**, 119878-24-9; (±)-**22**, 119878-25-0; (±)-**22**·HCl, 119878-45-4; (±)-**23**, 119878-26-1; (±)-**23**·$C_4H_4O_4$, 119878-46-5; (±)-**24**, 119878-27-2; (±)-**24**·$C_2H_2O_4$, 119907-55-0; (±)-**25**, 119878-28-3; (±)-**25**·HCl, 119878-47-6; (±)-**26**, 119878-29-4; (±)-**26**·$C_4H_4O_4$, 119878-48-7; (±)**27**, 119878-30-7; (±)-**27**·HCl, 119878-49-8; (±)-**28**, 119878-31-8; (±)-**28**·$C_4H_4O_4$, 119878-50-1; (±)-**29**, 119878-32-9; (±)-**29**·$C_4H_4O_4$, 119878-51-2; (±)-**30**, 119878-33-0; (±)-**30**·HCl, 119878-52-3; (±)-**31**, 119878-34-1; (±)-**31**·HCl, 119878-53-4; (±)-**32**, 119878-35-2; (±)-**33**, 119878-36-3; (±)-**33**·$C_4H_4O_4$, 119878-54-5; (±)-**33**(R_1 = H), 119878-10-3; (±)-**34**, 119878-37-4; (±)-**34** (R_1 = H), 119907-53-8; (±)-**35**, 21797-84-2; **36**, 119878-56-7; 2-BrC_6H_4COCl, 7154-66-7; 3-BrC_6H_4COCl, 1711-09-7; 4-BrC_6H_4COCl, 586-75-4; 4-ClC_6H_4COCl, 122-01-0; 4-FC_6H_4COCl, 403-43-0; 4-$MeOC_6H_4COCl$, 100-07-2; 3,4-$Cl_2C_6H_3COCl$, 3024-72-4; 3,4-$Cl_2C_6H_3CH_2CO_2H$, 5807-30-7; 4-$BrC_6H_4CH_2CO_2H$, 1878-68-8; $C_6H_5(CH_2)_2COCl$, 645-45-4; 4-$BrC_6H_4SO_2Cl$, 98-58-8; 4-$CH_3C_6H_4COCl$, 874-60-2; 4-$CF_3C_6H_4COCl$, 329-15-7; 3,4-$Br_2C_6H_3COCl$, 21900-35-6; 2-Cl, 4-BrC_6H_3COCl, 21900-55-0; 2-CH_3, 4-BrC_6H_3COCl, 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

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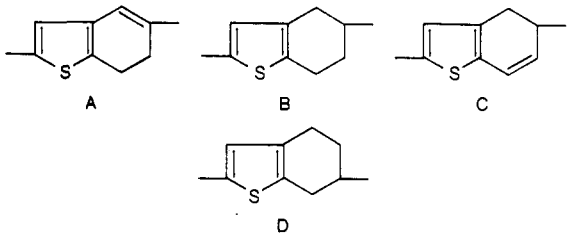
1-Imidazolylalkyl-substituted di- or tetrahydrobenzo[*b*]thiophenecarboxylic acid derivatives and related compounds were synthesized from tetrahydrobenzo[*b*]thiophene derivatives (1 or 4) in order to study the structure–activity relationships of the inhibition of thromboxane A_2 synthetase in vitro. 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 A_2 synthetase inhibition.

In recent years, the interesting biological properties of thromboxane A_2 (TXA_2) 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, Needleman[3] discovered that imidazole inhibited thromboxane synthetase, the enzyme that converts prostaglandin H_2 to the potent vasoconstrictor and platelet aggregating agent TXA_2. 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 TXA_2 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 TXA_2 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 ($NaBH_4$) reduction of **2** followed by

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‡ Biological Research Laboratories.

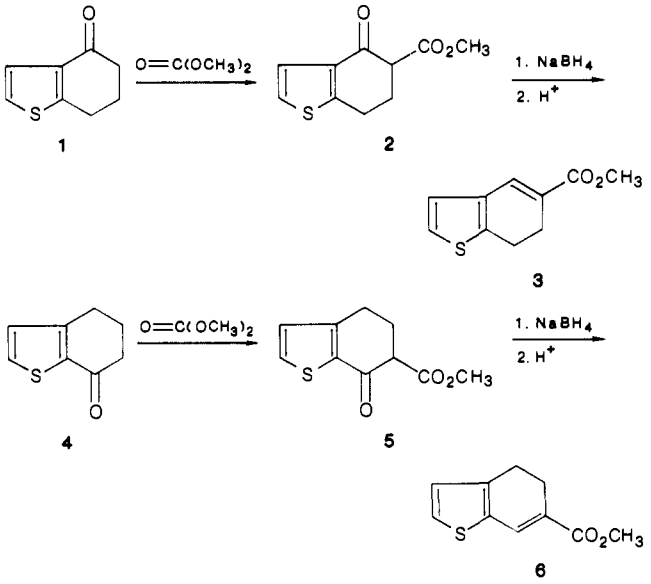
(1) (a) Yoshimoto, Y.; Yamamoto, S.; Hayaishi, O. *Prostaglandins* **1978**, *16*, 529. (b) Iizuka, K.; Akahana, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. *J. Med. Chem.* **1981**, *24*, 1139. (c) Tanouchi, T.; Kawamura, M.; Ohyama, 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.; Schneck, 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.

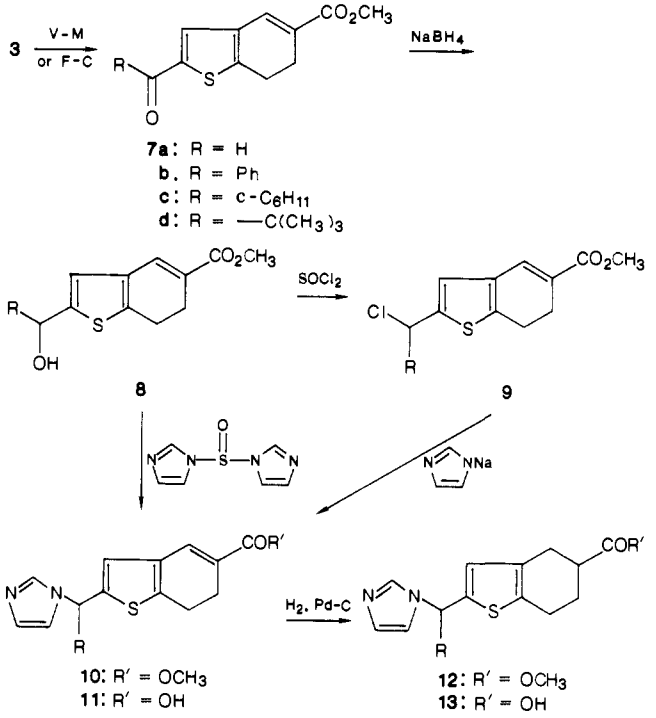
(3) Needleman, P.; Ferrendelli, J. A.; Minkes, M. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 1716.

0022-2623/89/1832-1265$01.50/0

Scheme I



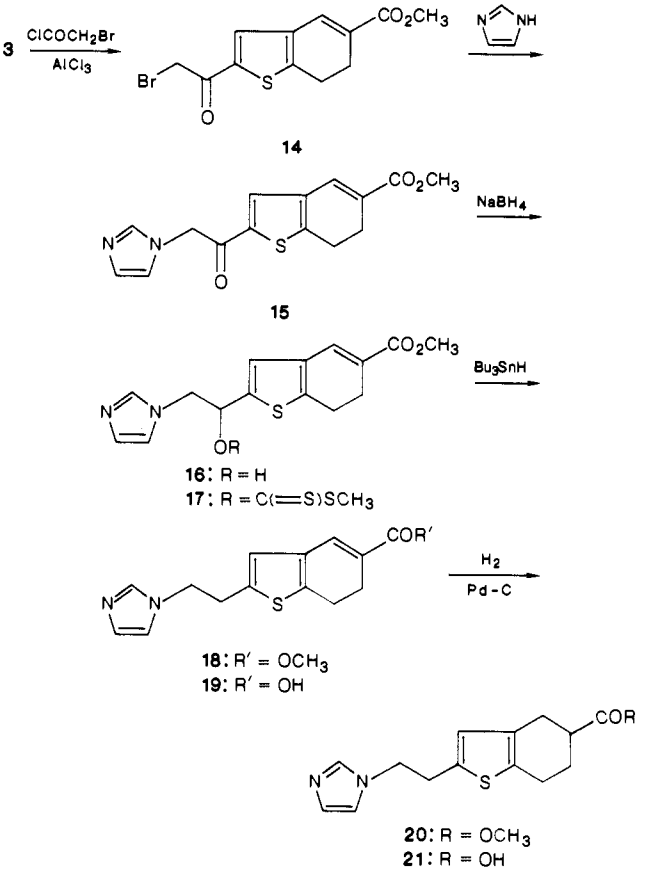
Scheme II[a]



[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 CH_3OCHCl_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**.

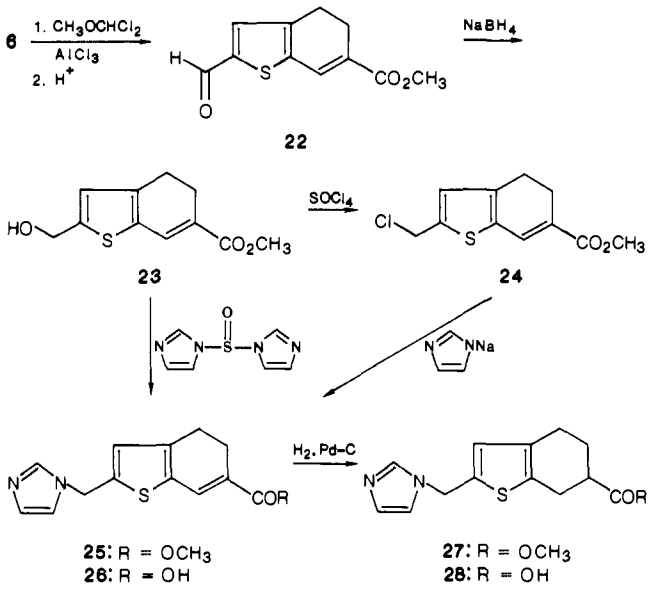
Sodium borohydride reduction of **7** followed by chlorination with $SOCl_2$ gave **9**. Reaction of **9** with imidazole sodium salt in DMF afforded the desired imidazolylmethyl-substituted benzo[*b*]thiophenes (**10**), which in turn were converted to acids **11** by acidic or basic hydrolysis. Compounds **10a–d** could also be obtained directly from alcohols **8a–d** by their reaction with *N,N'*-thionyldiimidazole. This novel transformation of benzyl alcohols by *N,N'*-thionyldiimidazole 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.

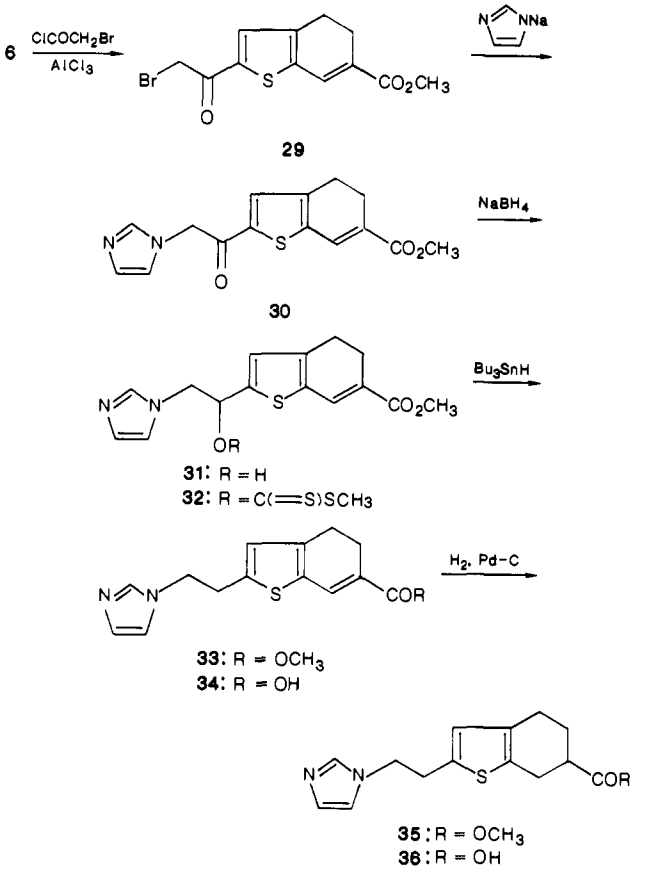
The imidazolylethyl-substituted compounds (**19** and **21**) were prepared as shown in Scheme III. The bromoacetyl derivative **14**, which was obtained by Friedel–Crafts reaction of **3** with $ClCOCH_2Br$, was allowed to react with imidazole in the presence of $NaHCO_3$ to give **15**. Reduction of **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 hydrogena-

(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.; Ingerman, C. M.; Smith, J. B. *Science* **1974**, *183*, 1085.

Scheme IV



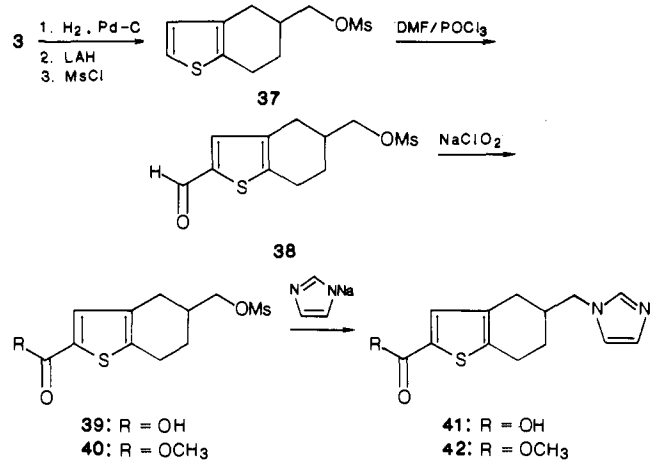
Scheme V



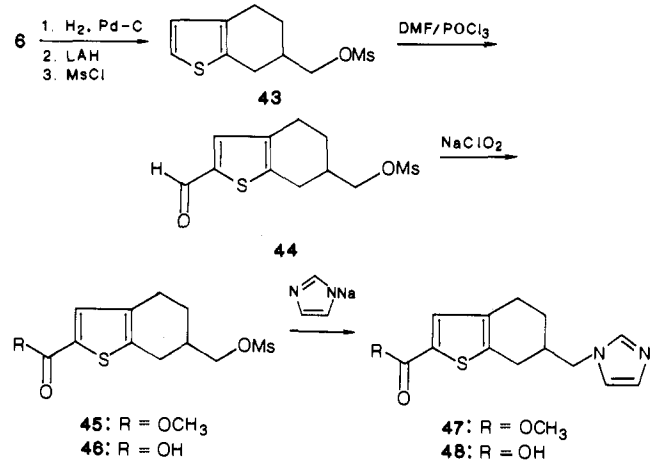
tion of 18 gave the corresponding tetrahydrobenzo[b]-thiophene (20). This material was hydrolyzed to give the carboxylic acid (21).

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 $NaBH_4$ reduction gave alcohol 23. Treatment of 23 with $SOCl_2$ 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'-thionyldiimidazole. 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.

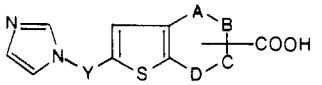
Next, the isomeric benzo[b]thiophene derivatives having a 2-carboxylic acid function were synthesized in order to compare their biological activity with that of the compounds having a 5- or 6-carboxylic acid function. Catalytic hydrogenation, LAH reduction and subsequent mesylation of 3 gave 37 (Scheme VI). Vilsmeier–Haack reaction of 37 with DMF–$POCl_3$ 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.

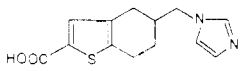
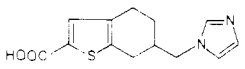
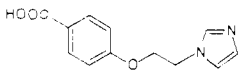
Results and Discussion

The TXA_2 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 TXA_2 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	$-CH_2-$	$-CH=CH-$	$-CH_2CH_2-$	5	>260	$C_{13}H_{11}N_2OSNa\cdot{}^1/_2H_2O$	0.093
11b	$-CH(Ph)-$	$-CH=CH-$	$-CH_2CH_2-$	5	180–184	$C_{19}H_{15}N_2O_2SNa$	0.114
11c	$-CH(c\text{-}C_6H_{11})-$	$-CH=CH-$	$-CH_2CH_2-$	5	214–219	$C_{19}H_{21}N_2O_2SNa\cdot{}^3/_2H_2O$	>10
11d	$-CH(^tBu)-$	$-CH=CH-$	$-CH_2CH_2-$	5	235–237	$C_{17}H_{19}N_2O_2SNa\cdot{}^3/_2H_2O$	>10
19	$-CH_2CH_2-$	$-CH=CH-$	$-CH_2CH_2-$	5	180–183	$C_{14}H_{13}N_2O_2SNa$	0.10
13a	$-CH_2-$	$-CH_2CH_2-$	$-CH_2CH_2-$	5	213–215	$C_{13}H_{14}N_2O_2S\cdot HCl\cdot{}^1/_4H_2O$	0.086
21	$-CH_2CH_2-$	$-CH_2CH_2-$	$-CH_2CH_2-$	5	144–151	$C_{14}H_{16}N_2O_2S\cdot HCl$	1.02
26	$-CH_2-$	$-CH_2CH_2-$	$-CH=CH-$	6	>260	$C_{13}H_{11}N_2O_2SNa$	0.013
28	$-CH_2-$	$-CH_2CH_2-$	$-CH_2CH_2-$	6	197–198	$C_{13}H_{14}N_2O_2S\cdot HCl$	0.026
34	$-CH_2CH_2-$	$-CH_2CH_2-$	$-CH=CH-$	6	>260	$C_{14}H_{13}N_2O_2SNa$	>10
36	$-CH_2CH_2-$	$-CH_2CH_2-$	$-CH_2CH_2-$	6	>260	$C_{14}H_{16}N_2O_2S\cdot HCl$	1.85
42					138–140	$C_{13}H_{14}N_2O_2S\cdot HCl$	0.114
48					223–228	$C_{13}H_{14}N_2O_2S\cdot HCl$	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 imidazolylmethyl 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 TXA_2 synthetase. It is interesting that the 5-imidazolylmethyl-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 TXA_2 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 TXA_2 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. TXA_2 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 TXB_2 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, PGI_2 synthetase, or 15- and 5-lipoxygenase at 10^2 μM.

In conclusion, we have shown that several compounds of di- or tetrahydrobenzo[*b*]thiophenecarboxylic acids with imidazolylalkyl substituents were potent TXA_2 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 ^{1}H NMR ($CDCl_3$ or D_2O) spectra. The IR spectra were recorded on a JASCO IRA-2 or IRA-302 spectrophotometer, and the ^{1}H 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 μg/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 (Packerd 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*-TsOH·H_2O (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%). ^{1}H 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. ($C_{10}H_{10}O_2S$) 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%; ^{1}H 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. ($C_{10}H_{10}O_2S$) 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 $CHCl_2OCH_3$ (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; ^{1}H 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. ($C_{11}H_{10}O_3S$) 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%; ^{1}H 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. ($C_{17}H_{14}O_3S$) 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%. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H, ^{t}Bu), 3.82 (s, 3 H, $COOCH_3$), 7.52 (s, 1 H, H-4), 7.62 (s, 1 H, H-3). Anal. ($C_{15}H_{18}O_3S$) 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): ^{1}H 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 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. ^{1}H 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. ($C_{13}H_{11}N_2O_2SNa \cdot {}^1/_2H_2O$) 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; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3 H, $COOCH_3$), 4.48 (d, J = 11 Hz, 1 H, C*H*OH), 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%; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 9 H, ^{t}Bu), 3.74 (s, 3 H, $COOCH_3$), 4.48 (br s, 1 H, C*H*OH), 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%. ^{1}H 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%. ^{1}H 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%. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9 H, ^{t}Bu), 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. ($C_{19}H_{21}N_2O_2SNa \cdot {}^3/_2H_2O$) 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. ($C_{17}H_{19}N_2O_2SNa \cdot {}^3/_2H_2O$) 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%); ^{1}H 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%; ^{1}H 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%; ^{1}H 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 recyrstallized from EtOH/ether, giving colorless leaflets 0.92 g (70%): mp 213.0–215.0 °C. Anal. ($C_{13}H_{14}N_2O_2S \cdot HCl \cdot {}^1/_4H_2O$) 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%). ^{1}H 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]oxy]ethyl]-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%). ^{1}H 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%). ^{1}H 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%; ^{1}H 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). 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. ($C_{14}H_{16}N_2O_2S$·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). ^{1}H 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: ^{1}H 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**; ^{1}H 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%); ^{1}H 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; ^{1}H NMR (270 MHz, D_2O, TMS as external standard) δ 2.2–2.5 (m, 4 H, H-4 × 2, H-5 × 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%; ^{1}H 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; ^{1}H 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. ($C_{13}H_{14}N_2O_2$-S·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%; ^{1}H 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]oxy]ethyl]-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%; ^{1}H 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. ($C_{17}H_{18}N_2O_3S_3$) 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%; ^{1}H NMR ($CDCl_3$) δ 3.22 (t, J = 6.5 Hz, 2 H, H-2′ × 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%; ^{1}H NMR ($CDCl_3$) δ 3.13 (t, J = 7.0 Hz, 2 H, H-2′ × 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. ($C_{14}H_{16}N_2O_2S$·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%); ^{1}H 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·$10H_2O$ (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%); ^{1}H 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%; ^{1}H 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 successivly 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 N_2 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 Na_2SO_4, 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%); ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H, $COOCH_3$), 3.95 (d, J = 6.0 Hz, 2 H, CH_2N), 6.85–7.6 (4 H, 3-H and imidazole). Anal. ($C_{14}H_{16}N_2O_2S$) 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. ($C_{13}H_{14}N_2O_2S$·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%; ^{1}H NMR ($CDCl_3$) δ 2.98 (s, 3 H, OSO_2CH_3), 4.17 (d, J = 6.0 Hz, 2 H, CH_2O), 6.88 (AB q, 2 H, H-2 and H-3).

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%; ^{1}H NMR ($CDCl_3$) δ 3.05 (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 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; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3 H, OSO_2CH_3), 3.86 (s, 3 H, $COOCH_3$), 4.20 (d, J = 5.0 Hz, 2 H, CH_2O), 7.48 (s, 1 H, H-3). Anal. ($C_{12}H_{16}O_5S_2$) 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%; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3 H, $COOCH_3$), 3.96 (d, J = 6.0 Hz, 2 H, CH_2N), 6.9–7.6 (4 H, H-3 and imidazole). Anal. ($C_{14}H_{16}N_2O_2S$) 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. ($C_{13}H_{14}N_2O_2S$·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; $CHCl_2OCH_3$, 4885-02-3; $ClCOCH_2Br$, 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

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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 amastogote 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 clomipramine[2] as well as the structurally related neuroleptic phenothiazines[3] demonstrate potent cytotoxic effects against both the extracellular

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