$\omega/2\theta$ scans. Unit cell parameters were obtained from least-squares fitting of the diffractometer angles of 25 centered reflections ($40° < 2\theta < 50°$). No decay was observed in the four standard reflections or in the crystal itself during data collection. Intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction was applied, with Ψ scan intensity data. A total of 1742 reflections were measured, of which 1671 were considered observed [$I > 2\sigma(I)$].

X-ray Structure Analysis of 4b. The structure was solved by direct methods using the 246 highest E values with the program system MULTAN 80.[19] Refinement by full-matrix least squares was based on $|F_o|$ with 1671 data [$I > 2\sigma(I)$] with all the non-H atoms assigned anisotropic thermal parameters. Hydrogen atoms bonded to the C atoms on the adenine ring system were given fixed geometry (C–H 1.08 Å), and only their thermal parameters were refined. The remaining hydrogen atoms were assigned isotropic thermal parameters according to the type of atom to which they are bonded; their positions and thermal parameters were refined. In the final refinement cycle the two CH_3, the vinyl $=CH_2$, the OH, and the NH_2 groups were allowed to move as rigid bodies, to obtain a well-defined structure. The weighting scheme used was $w^{-1} = \sigma^2|F_o| + 0.0004|F_o|^2$. Scattering factors for C, N, and O were those of Cromer and Mann.[20] The scattering factor used for H was that for a spherical bonded H atom.[21] The structure converged to a final residuals $R = 0.052$ and $wR = 0.051$ for 231 parameters. Least-squares refinement and geometric calculations were performed with SHELX76.[22] The final difference Fourier map showed no distinct features (maximum +0.28 e/Å^3, and minimum −0.41 e/Å^3). The molecular structure and atomic numbering scheme of the molecule is shown in Figure 1. The bond lengths and angles are comparable to those in an X-ray structure of the parent compound, 2′,3′-*O*-isopropylideneadenosine.[23] Structure factor data, coordinates, and thermal parameters have been deposited with the British Library.

Enzyme Studies. Assay of M-2 and M-T activity and determination of inhibition constants were carried out as detailed previously.[1] The type of double-reciprocal plots so obtained have been illustrated previously.[7]

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Supplementary Material Available: Table I listing final fractional atomic coordinates and temperature factors, Table II listing interatomic distances and angles (2 pages); Table III listing structure factor data (7 pages). Ordering information is given on any current masthead page.

(19) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; DeClercq, J.-P.; Woolfson, M. M. MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data; University of York: York, England, 1980.
(20) Cromer, D. T.; Mann, J. B. *Acta Crystallogr.* **1968**, *A24*, 321.
(21) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
(22) Sheldrick, G. M. SHELX-76. A Program for Crystal Structure Determination; University of Cambridge: Cambridge, England, 1976.
(23) Sprang, S.; Rohrer, D. C.; Sundaralingam, M. *Acta Crystallogr.* **1978**, *B34*, 2803.

[(1*H*-Imidazol-1-yl)methyl]- and [(3-Pyridinyl)methyl]pyrroles as Thromboxane Synthetase Inhibitors[1]

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Several [(1*H*-imidazol-1-yl)methyl]- and [(3-pyridinyl)methyl]pyrroles were prepared and evaluated in vitro as thromboxane synthetase inhibitors in human platelet aggregation studies. A number of structures, e.g. **10b,f,g,i** (respective IC_{50} values: 1 μM, 50 nM, 42 nM, 44 nM) showed superior in vitro inhibition of TXA_2 synthetase when compared to the standard dazoxiben (**1**). However, it was found that in vitro potency did not translate into nor correlate with in vivo activity when these compounds were evaluated in mice in a collagen–epinephrine-induced pulmonary thromboembolism model. (*E*)-1-Methyl-2-[(1*H*-imidazol-1-yl)methyl]-5-(2-carboxyprop-1-enyl)pyrrole (**10b**) was found to offer protection against collagen–epinephrine-induced mortality in mice, thereby demonstrating that oral administration is an effective route for absorption of this drug. Additional evidence for the oral effectiveness of **10b** in lowering serum TXB_2 levels was obtained by performing ex vivo radioimmunoassay experiments with rats. A 13-week study of **10b** in rats with reduced renal mass was conducted in order to evaluate the role of TXA_2 production in hypertension and renal dysfunction. Although serum and urinary TXB_2 levels in rats were found to be lowered during this study by **10b**, the levels of urinary protein excretion remained comparable to that of the control group.

Thromboxane A_2 (TXA_2), a potent and labile mediator of platelet aggregation and vasoconstriction, is endogenously generated mainly by blood platelets by the enzyme TXA_2 synthetase from the endoperoxide PGH_2. Prostacyclin (PGI_2) is similarly produced from this endoperoxide by an enzyme located primarily in endothelial cells of the arteries and blood vessels, and is a potent inhibitor of platelet aggregation and a vasodilator. The symbiotic relationship between the effects of PGI_2 and TXA_2 has been suggested as one of the natural balancing mechanisms for physiological hemodynamics.[2] The imbalanced overproduction of TXA_2 has been suggested in numerous pathological events.[3-7]

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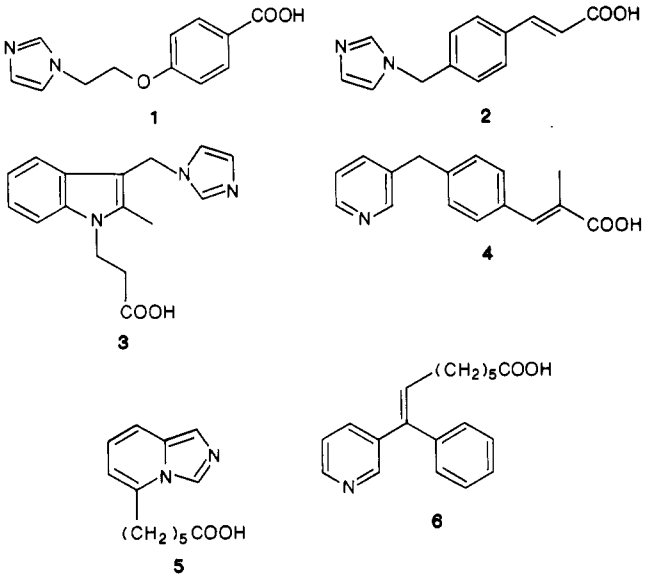
(1) Contribution No. 749 from the Institute of Organic Chemistry.
(2) (a) Moncada, S.; Vane, J. R. *Pharmacol. Rev.* **1979**, *30*, 293. (b) Nicolau, K. C. *Annu. Rep. Med. Chem.* **1979**, *14*, 178. (c) Hamberg, M.; Svensson, J.; Wakabayski, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 345.
(3) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994.

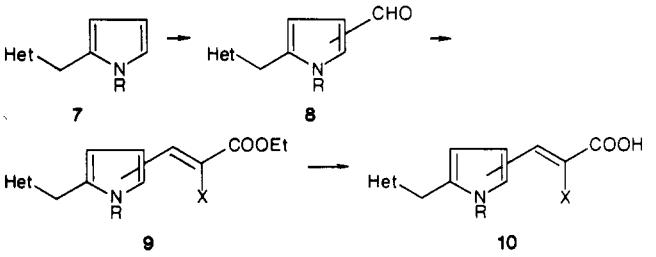
0022-2623/89/1832-0890$01.50/0

Although nonsteroidal antiinflammatory agents limit TXA_2 production through blockage of the cyclooxygenase enzyme in the arachidonic acid cascade, this early inhibition may limit the later production of other prostaglandins beneficial to cardiovascular maintenance. A more desirable situation might be a selective inhibition of the TXA_2 synthetase enzyme, therefore allowing the later synthesis of beneficial prostaglandin products, e.g. PGI_2. Although inhibition of TXA_2 synthesis will result in increased levels of endoperoxide PGH_2, which is both proaggregative and vasoconstrictive in vitro, it was believed that endogenous enzymes, i.e. PGI_2 synthetase, would ultimately utilize and redirect the endoperoxide into an increased production of PGI_2.[8]

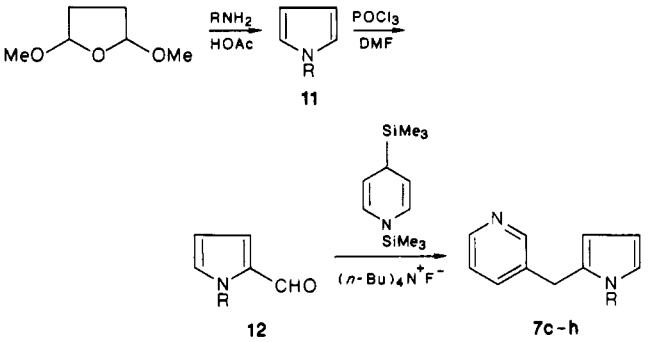
Several reports have recently appeared describing potent selective inhibitors of TXA_2 synthetase, exemplified by structures **1–6**.[9-14] Investigation of the structural parameters required for an effective TXA_2 inhibitor has been in progress by several research groups over the past several years. A survey of successful TXA_2 synthetase inhibitors quickly reveals the common features associated with these selective inhibitors: (1) a sterically hindered nitrogen-containing heterocyclic base with an approximate conjugate acidity of pK_a = 5–7, e.g. 1-substituted imidazole, 3-substituted pyridine, imidazopyridine, and (2) a carboxylic acid terminus located 8–10 Å from the basic heterocyclic nitrogen atom. The distance of separation between the heterocyclic and carboxylate termini necessary for optimal activity is coincidently similar to the approximate 8.5-Å separation between the reactive bridged endoperoxide oxygen atoms and the side chain carboxylate terminus of PGH_2.



Scheme I



Scheme II

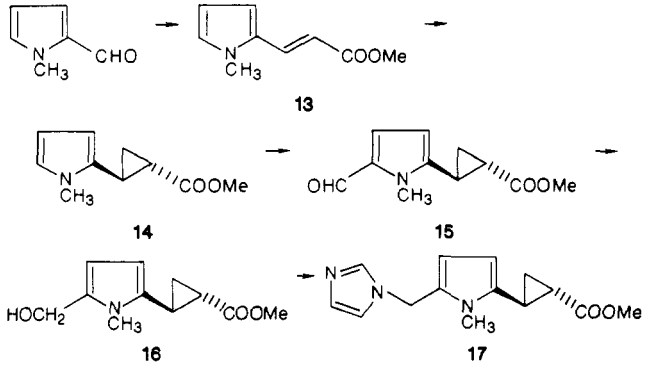


At the onset of our research, little description of the enzyme involved with the transformation of PGH_2 to TXA_2 was available in the literature. This structural rearrangement is mechanistically plausible[15] via a cationic or radical-like intermediate, suggesting that an oxidative electron transfer step may be involved in the overall enzymatic process. Alkylimidazoles and -pyridines have been reported to inhibit the oxidative processes of cytochrome P-450 enzymes by presumed binding of these substrates to the heme iron.[16] The nature of the rearrangement of PGH_2 to TXA_2, as well as the types of substrates that inhibited this enzymatic process, supported an early premise that a cytochrome P-450 enzyme was likely to be involved. This early contention was given credence by the report of Ullrich and Haurand that the cytochrome P-450 enzyme fraction of human blood platelets possessed the enzymatic TXA_2 synthetase activity, and its binding affinity was quantitatively correlated with several known TXA_2 synthetase inhibitors.[17]

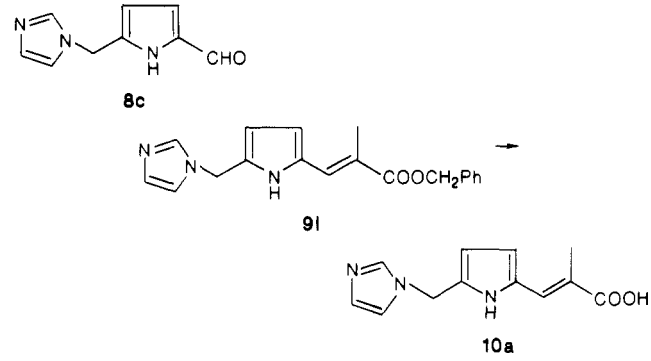
Since the cytochrome P-450 enzymes are associated with numerous other biological processes, the need to separate the desired inhibition of the TXA_2 synthetase enzyme from other cytochrome P-450 processes was immediately obvious. Dickinson et al. have demonstrated that intro-

(4) (a) Neri Serneri, G. G. *Cardiovascular Pharmacol. Prostaglandins*; Herman, A. G., Vanhoutte, P. M., Devolin, H., Goossens, A., Eds.; Raven Press: New York, 1982; pp 361–374. (b) Pitt, B.; Shea, M. J.; Romson, J. L.; Lucchessi, B. R. *Ann. Int. Med.* **1983**, *99*, 83.
(5) (a) Myers, A.; Penhos, J.; Ramey, E.; Ramwell, P. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 369. (b) Lefer, A. M.; Okamatsu, S.; Smith, E. F., III; Smith, J. B. *Thromb. Res.* **1981**, *23*, 265.
(6) (a) Stuart, M. J. *Arteriosclerosis* **1982**, *7*, 203. (b) Mehta, J. *J. Am. Med. Assoc.* **1983**, *249*, 2818.
(7) Verstraete, M. *Br. J. Clin. Pharmacol.* **1983**, *15*, 75.
(8) (a) Nijkamp, F. P.; Moncada, S.; White, H. L.; Vane, J. R. *Eur. J. Pharmacol.* **1979**, *44*, 179. (b) Needleman, P.; Wyche, A.; Raz, A. J. *J. Clin. Invest.* **1979**, *63*, 345.
(9) (a) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J *J. Med. Chem.* **1985**, *28*, 1427. (b) Sneddon, J. *Drugs Future* **1981**, *6*(11), 693.
(10) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M. *J. Med. Chem.* **1981**, *24*, 1139.
(11) (a) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1986**, *29*, 342. (b) Fischer, S.; Strappler, M.; Bohlig, B.; Bernutz, C.; Wober, W.; Weber, P. C. *Circulation* **1983**, *68*, 821.
(12) Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Miyamoto, T.; Taniguchi, K.; Hayashi, *J. Med. Chem.* **1981**, *24*, 1149.
(13) Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. *J. Med. Chem.* **1985**, *28*, 164.
(14) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. *J. Med. Chem.* **1985**, *28*, 287.
(15) Porter, N. A.; Mebane, R. C. *Tetrahedron Lett.* **1982**, *23*, 2289.
(16) (a) Leibman, K. C.; Ortiz, E. *Drug. Metab. Dispos.* **1973**, *1*, 184. (b) *Ibid.* **1973**, *1*, 775.
(17) Ullrich, V.; Haurand, M. *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Samulesson, B., Paoletti, R., Ramwell, P., Eds.; Raven Press: New York, 1983; Vol. 11, pp 105–110.

Scheme III



Scheme IV



duction of a carboxylic acid group with a TXA_2 synthetase inhibitor not only increased potency but also decreased its activity against adrenal steroid 11β-hydroxylase.[18] It was believed that further differentiation between these processes may be accomplished through diversification of the molecular framework separating the requisite carboxylic acid and heterocyclic termini.

In this paper we present our effort to synthesize novel compounds as selective inhibitors of TXA_2 synthetase. Several [(1*H*-imidazol-1-yl)methyl]- and [(3-pyridinyl)-methyl]pyrroles were prepared and evaluated as TXA_2 synthetase inhibitors in in vitro blood platelet aggregation studies as well as ex vivo and in vivo animal models.

Chemistry

A majority of the compounds investigated were prepared as shown in Scheme I. Vilsmeier–Haack formylation of pyrrole **7** afforded carboxaldehyde **8**. In most cases, the formylation step provided a separable mixture of the 4- and 5-formyl isomers. Wittig reaction of carboxaldehydes **8** and saponification of the resulting esters **9** afforded carboxylic acids **10**.

Preparation of the requisite 2-[(3-pyridinyl)methyl]-pyrroles **7c–h** employed in Scheme I is described in Scheme II. 1-Phenyl- and 1-ethylpyrrole were obtained commercially while other pyrroles were prepared by condensation of an appropriate amine with 2,5-dimethoxytetrahydrofuran in glacial acetic acid. Vilsmeier–Haack formylation of pyrroles **11** afforded carboxaldehydes **12**. Condensation of aldehydes **12** with 1,4-bis(trimethylsilyl)-1,4-dihydropyridine and tetra-*n*-butylammonium fluoride furnished 2-[(3-pyridinyl)methyl]pyrroles **7c–h**.[19]

Introduction of the cyclopropyl group of compound **17** required a different synthetic strategy outlined in Scheme III. Wittig reaction of 1-methyl-2-pyrrolecarboxaldehyde with methyl (triphenylphosphoranylidene)acetate and cyclopropanation of the resulting acrylate ester **13** under the conditions described by Vorbrüggen[20] (ethereal $CH_2N_2/Pd(OAc)_2$) afforded cyclopropane **14**. Vilsmeier–Haack formylation of **14** gave exclusively the α-formylated pyrrole **15** and reduction of this aldehyde with sodium borohydride in methanol furnished alcohol **16**. Compound **17** was obtained by treatment of alcohol **16** with freshly prepared thionylbis(imidazole).

Scheme IV shows the preparation of compound **10a**, which circumvented a problem of ester hydrolysis in Scheme I. Although ester **9a** could be prepared, hydrolysis using base only resulted in elimination of the imidazole due to the lack of substitution at the pyrrole nitrogen. The acid lability of pyrroles excluded the possibility of acid-catalyzed ester hydrolysis; therefore a nonhydrolytic method was employed for the preparation of compound **10a**. Wittig reaction of aldehyde **8c** with benzyl (triphenylphosphoranylidene)propionate[21] and hydrogenolysis of the resulting benzyl ester **9l** afforded carboxylic acid **10a**.

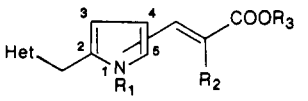
Results and Discussion

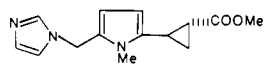
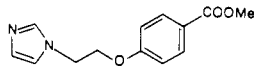
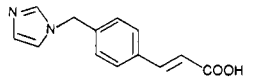
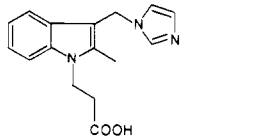
In platelet-rich plasma (PRP), the medium used for most platelet aggregation studies with thromboxane synthetase inhibitors, there are no enzymes for conversion of PGH_2 to prostacyclin. Serum albumin, which is present in PRP, catalyzes the conversion of PGH_2 to both PGE_2 and PGD_2. It has been shown by Crist-Hazelhoff[22] that albumin from different species causes conversion of PGH_2 to a species-dependent ratio of PGE_2 and PGD_2 and human albumin favors the production of PGE_2. PGD_2 is a potent stimulator of adenylate cyclase in the human platelet, although at the concentrations likely to be formed in PRP, PGE_2 is a promoter of the second phase of aggregation in human PRP[23] and therefore may outweigh the benefits of PGD_2 production. The presence of an exogenous enzyme that would utilize the buildup of proaggregatory PGH_2 to produce additional antiaggregatory prostaglandins may shift the balance toward inhibition of platelet aggregation.

As a preliminary screen of biological activity, the compounds listed in Table I were each tested at several concentrations with human PRP in the presence of a pig aortic microsomes (PAM) with ADP as an aggregation inducer. An IC_{50} value was calculated from the resulting dose–response curve. PAM was used as an exogenous source of PGI_2 synthetase in order to convert the buildup of proaggregative endoperoxides, which result from TXA_2 synthetase inhibition, into PGI_2. In this in vitro system, the results of testing in the presence or absence of PAM is indicative of the mechanism by which inhibition of blood platelets may be occurring. Inhibitors of TXA_2 will only show an inhibition of platelet aggregation while in the presence of the endoperoxide convering enzyme (PAM) while inhibition in its absence would be evidence of an alternative pathway of action, e.g. cyclooxygenase or phosphodiesterase inhibition. As final corroboration of the mechanism by which these compounds inhibited blood platelet aggregation, radioimmunoassay (RIA) with **10b** in rats has shown a concomitant increased production of

(18) Cross, P. E.; Dickinson, R. P. *Second SCI–RSC Medicinal Chemistry Symposium*; Emmett, J. C., Ed.; Special Publication Royal Society of Chemistry No. 50, 1984; pp 268–285.
(19) Tsuge, O.; Kanemasa, S.; Naritomi, T.; Tanaka, J. *Chem. Lett.* **1984**, 1255.
(20) Mende, U.; Radüchel, B.; Skuballa, W.; Vorbrüggen, H. *Tetrahedron Lett.* **1975**, 629.
(21) Gossauer, A.; Kühne, G. *Justus Liebigs Ann. Chem.* **1977**, 664.
(22) Crist-Hazelhof, E.; Nugteren, D. H.; Van Dorp, D. A. *Biochim. Biophys. Acta* **1976**, *450*, 450.
(23) (a) Shio, H.; Ramwell, P. W.; Jessup, S. J. *Prostaglandins* **1972**, *1*, 29. (b) MacIntyre, D. E.; Gordon, J. L. *Nature (London)* **1975**, *258*, 337.

Table I. In Vitro Biological Activity of TXA_2 Synthetase Inhibitors



no.	Het[a]	R_1	R_2	R_3	position of side chain	yield, %	mp, °C	recryst solvent	formula	anal.[b]	IC_{50},[c] μM	relative potency[d]
9a	I	H	CH_3	C_2H_5	5	52	163–164	EtOAc	$C_{14}H_{17}N_3O_2$	C,H,N	8.1	0.31
9b	I	CH_3	CH_3	C_2H_5	5	62	80–83	EtOAc/MeOH	$C_{15}H_{19}N_3O_2$	C,H,N	26	0.08
9c	I	CH_3	CH_3	C_2H_5	4	32	oil		$C_{15}H_{19}N_3O_2$	C,H,N	1.8	1.1
9d	I	CH_3	H	C_2H_5	5	98	82–84	EtOAc/MeOH	$C_{14}H_{17}N_3O_2$	C,H,N	8.9	0.25
9e	I	CH_3	H	C_2H_5	4	70	105–107	EtOAc	$C_{14}H_{17}N_3O_2$	C,H,N	1.8	1.2
9f	P	CH_3	CH_3	C_2H_5	5	51	112–113	EtOAc/hexane	$C_{17}H_{20}N_2O_2$	C,H,N	49%	
9g	P	C_2H_5	CH_3	C_2H_5	5	50	oil		$C_{18}H_{22}N_2O_2$	C,H,N	14	0.14
9h	P	$CH(CH_3)_2$	CH_3	C_2H_5	5	70	oil		$C_{19}H_{24}N_2O_2$	C,H,N	32	0.06
9i	P	$C(CH_3)_3$	CH_3	C_2H_5	4	87	oil		$C_{20}H_{26}N_2O_2$	C,H;N[e]	3.2	0.59
9j	P	$CH_2C(CH_3)_3$	CH_3	C_2H_5	5	83	oil		$C_{21}H_{28}N_2O_2$	C,N;H[f]	57	0.03
9k	P	C_6H_5	CH_3	C_2H_5	5	92	oil		$C_{22}H_{22}N_2O_2$	C,H,N	180	0.01
9l	I	H	CH_3	$CH_2C_6H_5$	5	75	149–150	EtOH	$C_{19}H_{19}N_3O_2$	C,H,N	20	0.11
10a	I	H	CH_3	H	5	84	168–170	EtOH	$C_{12}H_{13}N_3O_2$	C,H,N	9.1	0.24
10b	I	CH_3	CH_3	H	5	90	183–185	EtOH	$C_{13}H_{15}N_3O_2$	C,H,N	1.0	2.2
10c	I	CH_3	CH_3	H	4	88	190–193	MeOH/EtOAc	$C_{13}H_{15}N_3O_2$	C,H,N	1.6	1.3
10d	I	CH_3	H	H	5	90	163–165	MeOH/EtOAc	$C_{12}H_{13}N_3O_2$	C,H,N	3.8	0.75
10e	I	CH_3	H	H	4	85	180–185	$MeOH/CH_2Cl_2$	$C_{12}H_{13}N_3O_2$	C,H,N	4.6	0.62
10f	P	CH_3	CH_3	H	5	82	183–185	EtOAc/MeOH	$C_{15}H_{16}N_2O_2$	C,H,N	0.05	46
10g	P	C_2H_5	CH_3	H	5	86	145–147	acetone/hexane	$C_{16}H_{18}N_2O_2$	C,H,N	0.042	45
10h	P	$CH(CH_3)_2$	CH_3	H	5	75	gum		$C_{17}H_{20}N_2O_2$	H,N;C[g]	2.1	0.9
10i	P	$C(CH_3)_3$	CH_3	H	4	64	172–174	EtOAc	$C_{18}H_{22}N_2O_2$	C,H,N	0.044	43
10j	P	$CH_2C(CH_3)_3$	CH_3	H	5	95	78–80	EtOH	$C_{19}H_{24}N_2O_2$	C,H,N	78	0.24
10k	P	C_6H_5	CH_3	H	5	92	144–146	EtOH	$C_{20}H_{18}N_2O_2$	C,H,N	24	0.08
17						79	oil		$C_{14}H_{17}N_3O_2$	C,H,N	9.1	0.22
1							132–134[i]		$C_{12}H_{12}N_2O_3 \cdot HCl$		2.28 ± 0.48[h]	
2							228–232[j]		$C_{13}H_{12}N_2O_2 \cdot HCl \cdot H_2O$		1.4	1.7
3							189–191[k]		$C_{16}H_{17}N_3O_2 \cdot 0.25H_2O$		1.9	1.0

[a] I = 1*H*-imidazol-1-yl; P = 3-pyridinyl. [b] Elemental analyses were within 0.4% of theoretical values unless otherwise noted. [c] IC_{50}'s are screening values for in vitro inhibition of ADP-induced aggregation of human PRP in the presence of pig aortal microsomes. Each IC_{50} value is a one-time determination generated from a dose–response curve. The curve was derived from several (n = 3–5) points of drug concentration, each point being an average of measurements (n = 1–3). For weakly active compounds, percentage values indicate degree of inhibition observed when tested at the maximum concentration of 5×10^{-5} M. [d] Relative activity of TXA_2 synthetase inhibitor compared to the activity of dazoxiben (1) in the same experiment. [e] N: calcd, 8.58; found, 9.34. [f] H: calcd, 8.29; found, 8.91. [g] C: calcd, 71.81; found, 72.40. [h] Average value ± standard deviation over all determinations (n = 55). [i] Reported mp 138–139.5 °C.[9b] [j] Reported mp 214–217 °C.[10] [k] Reported mp 195–197 °C.[11a]

6-keto-$PGF_{1\alpha}$ at the expense of TXB_2 formation which is characteristic[8] of specific TXA_2 synthetase inhibition.

The in vitro activity of the prepared series of compounds does not depend significantly nor consistently with the position of the carboxylate containing side chain. Whereas the 4-substituted pyrrole derivative **9c** and **9e** appear to have increased in vitro activity when compared to their 5-substituted congeners **9b** and **9d**, the corresponding carboxylic acids **10c** and **10e** display an inversed and diminished affect when compared respectively with carboxylic acids **10b** and **10d**. Replacement of the imidazole with 3-pyridinyl appears to offer enhancement of in vitro activity when comparing **10b** with **10f,gi**. The effect of pyrrole nitrogen substitution upon in vitro activity was also explored. Nitrogen substitution by a group as large as *tert*-butyl was well tolerated but may require the repositioning of the carboxylic side chain to the more remote 4-position on the pyrrole ring in order to maintain activity. The absence of pyrrole nitrogen substitution appears to diminish in vitro activity. Isosteric replacement of the acrylate side chain with a cyclopropanecarboxylate side chain did not effect any discernible difference in biological activity.

In most cases, the carboxylic acids are more potent inhibitors of TXA_2 synthetase than their corresponding ester congeners. This observation may be due to the esters acting as poor substrates of this enzyme and the lack of the necessary hydrolytic enzymes for their transformation to active substrates in vivo. A number of prepared compounds show a greater efficacy in in vitro inhibition of TXA_2 synthetase than several compounds previously described in the literature, e.g. dazoxiben (1), OKY-046 (2), and dazmegrel (3). Compounds **10b**, **10f**, **10g**, and **10i** were the most active of the prepared series.

Compounds that displayed superior in vitro screening values were further evaluated for bioavailability and effectiveness in several in vivo models. A collagen–epinephrine-induced pulmonary thromboembolism model[24]

Table II. Protection by TXA_2 Synthetase Inhibitors against Mortality in a Pulmonary Thromboembolism Model in Mice[a]

test material administered	dose,[c] mg/kg iv	no. of animals tested	time of test material administration, h	% of animals surviving[d]
positive control[b]		10	−3	10
dazoxiben (1)	10	10	−1	30
	25	9	−3	67[e]
10b	6.25	10	−3	70[e]
	12.5	10	−3	70[e]
	25	10	−3	90[e]
10f	10	10	−3	0
	20	10	−3	30
10g	10	10	−3	10
	20	10	−3	10
10i	10	10	−3	30

[a] Mortality induced by injection of collagen extract and epinephrine (see the Experimental Section). [b] (Carboxymethyl)cellulose (CMC), the test material vehicle, was tested alone as a positive control. [c] Dose of TXA_2 synthetase inhibitor. [d] Survival 24 h after collagen extract and epinephrine administration. [e] $p < 0.05$.

Table III. Protection by TXA_2 Synthetase Inhibitors against Mortality in a Pulmonary Thromboembolism Model in Mice following Oral Administration[a]

test material administered	dose,[c] mg/kg po	no. of animals per group	% of animals surviving 24 h; hour of dosing: −1	−3	−5	−7	−18
positive control[b]		10	10	20	10	10	10
dazoxiben (1)	10	10	50[d]	40	20	20	10
10b	10	10	50[d]	40	40	30	10
dazmegrel (3)	10	10	20	11[e]	20	0	10

[a] Mortality induced by injection of collagen and epinephrine (see the Experimental Section). [b] (Carboxymethyl)cellulose (CMC), the test material vehicle, was tested alone as a positive control. [c] Dose of TXA_2 synthetase inhibitor. [d] $p < 0.1$. [e] Nine animals tested.

using mice was studied with several compounds where it was presumed that TXA_2 production may play a major role in the dissemination of intravascular coagulation. The compounds were evaluated for effectiveness at a single time point iv dosage (Table II) followed by examination of their duration of action and bioavailability (Table III) in a po multi time point study. In this model it was empirically discovered that the most consistent protection against mortality was realized when the animals were dosed intravenously with a TXA_2 inhibitor 3 h before administration of the collagen–epinephrine and that **10b** was the most efficacious compound of the prepared series.

Several points are evident by the results presented in Tables I–III. It is obvious that in vitro activity does not translate into nor correlate very well with in vivo activity. Although **10i** is 20 times more potent than **10b** against in vitro blood platelet aggregation, the latter appears to be more effective in vivo against pulmonary thromboembolism. Two other compounds, **10f** and **10g**, with IC_{50} values (Table I) comparable to that of **10i** also proved to be only marginally active (≤30% survival rate @ ≤20 mg/kg @ −3 h administration of drug) when adminsitered by an intravenous route. Further discrimination of biological activity is apparent when comparing the results of intravenous versus oral administration of these test materials. Oral absorption of **10b** was demonstrated by its protective effect against collagen–epinephrine-induced pulmonary thromboembolism, as well as ex vivo inhibition of blood platelet aggregation and radioimmunoassay in rats (vide infra). The protection against thrombosis offered by **10b** and dazoxiben (1) were equivalent and superior to the protection offered by dazmegrel (3). Curiously, Dickinson et al. have observed a reverse order of potency and duration of action between dazoxiben and dazmegrel in lowering serum prostanoid formation in human subjects.[11]

Several reports[25] have indicated that TXA_2 may play a role in the etiology of certain types of inflammation. A reported study[25b] of rats implanted with carrageenan-impregnated sponges and dosed orally at 5–10 mg/kg with a selective TXA_2 synthetase inhibitor, dazoxiben (1) or CGS 13080 (5), has shown that harvested polymorphonuclear leukocytes had a reduced capability to synthesize TXB_2, PGE_2, and LTB_4. Further evaluation of the effectiveness of TXA_2 synthetase inhibition upon inflammation was studied with **10b** in the following models: 12-*O*-tetradecanoylphorbol acetate (TPA) induced ear edema in mice[26a] (0.5 mg/mouse, topical); rat adjuvant-induced arthritis[26b] (4.25 mg/rat po); phenylquinone-induced writhing in mice[26b] (3 mg/mouse, po); arachidonic acid induced ear edema in mice[26c] (2 mg/mouse, topical); oxazolone-induced delayed hypersensitivity ear edema in mice[26d] (25 mg/kg, po); carrageenan-induced rat paw edema[26b] (10 mg/rat, po). In all of the above cases, **10b** was found to be ineffective.

The effect of **10b** on systolic blood pressure and proteinuria was studied with a 5/6 renal ablated rat as a model of progressive renal injury. The renal injury that results from 5/6 renal ablation leads to hypertension, proteinuria, and glomerular sclerosis.[27] The factors responsible for this progressive kidney disease are not completely understood. Previous studies have indicated that substances, such as heparin, which inhibit blood coagulation, retard the development and progression of renal failure and hypertension in rats with severe renal ablation.[28] Furthermore, other studies have implicated a connection between an enhanced level of glomerular TXA_2 production and renal dysfunction.[30] Purkerson et al.[29] have suggested the possibility that platelet aggregation and intraglomerular thrombosis may play a key role in the level of glomerulosclerosis present in the renal ablated rat model. It has also been found that renal production of TXA_2 is increased in rats with ablated kidneys as compared to normal rats[29] and that treatment with a TXA_2 synthetase inhibitor, OKY 1581 (4), increases renal blood flow and glomerular filtration as well as decreases urinary excretion of protein and thromboxane B_2. The purpose of our study was to determine whether selective inhibition of thromboxane

(24) Di Minno, G.; Silver, M. J. *J. Pharmacol. Exp. Ther.* **1983**, *225*, 57.

(25) (a) Higgs, G. A.; Moncada, S.; Salmon, J. A.; Seager, K. *Br. J. Pharmacol.* **1983**, *79*, 863. (b) Robson, R. D.; Liauw, L.; Tjan, J.; Sakane, Y.; Eu, E. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1984**, *43*(4), 1038, Abstract No. 4409.

(26) (a) Young, J. M.; Wagner, B. M.; Spires, D. A. *J. Invest. Dermatol.* **1983**, *80*, 48. (b) Rooks, W. H., II; Tomolonis, A. J.; Maloney, P. J.; Roszkowski, A.; Wallach, M. B. *Agents Actions* **1980**, *10*, 266. (c) Young, J. M.; Spires, D. A.; Bedford, C. J.; Wagner, B.; Ballaron, S. J.; De Young, L. M. *J. Invest. Dermatol.* **1984**, *82*, 367. (d) Young, J. M.; Wagner, B. M.; Fisk, R. A. *Br. J. Dermatol.* **1978**, *99*, 665.

(27) Anderson, S.; Meyer, T. W.; Rennke, H. G.; Brenner, B. M. *J. Clin. Invest.* **1985**, *76*, 612.

(28) (a) Purkerson, M. L.; Hoffsten, P. E.; Klahr, S. *Kidney Int.* **1976**, *9*, 407. (b) Purkerson, M. L.; Joist, J. H.; Greenberg, D.; Kay, D.; Hoffsten, P. E.; Klahr, S. *Thromb. Res.* **1982**, *26*, 227.

(29) Purkerson, M. L.; Joist, J. H.; Yates, J.; Valdes, A.; Morrison, A.; Klahr, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 193.

(30) (a) Remuzzi, G.; Iberti, L.; Rossini, M.; Morelli, C.; Carminati, C.; Cattaneo, G. M.; Bertani, T. *J. Clin. Invest.* **1985**, *75*, 94. (b) Uderman, H. D.; Jackson, E. K.; Puet, D.; Workman, R. J. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 969. (c) Groene, H. J.; Dunn, M. J. *Clin. Res.* **1983**, *31*, 749A.

Table IV. Results of TXB_2 RIA on Urine and Serum Samples from Rats with 5/6 Nephrectomy with and without **10b**

sample group	$\bar{X}$ ± SEM TXB_2 in urine, ng/day	% inhibn thromboxane from control	$\bar{X}$ ± SEM TXB_2 in serum, ng/day	% inhibn thromboxane from control
normal, intact, untreated rats	122 ± 6.4 (n = 3)			
control[a]	199 ± 74.1 (n = 6)[b]	0	498 ± 61.8 (n = 5)[c]	0
68 mg/kg per day **10b**	42 ± 11.3 (n = 4)[b,d,e]	78.9		
205 mg/kg per day **10b**	45 ± 10.2 (n = 5)[b,d,e]	77.4	10 ± 2.1 (n = 4)[f,g]	98.0
410 mg/kg per day **10b**[h]	59 ± 4.5 (n = 4)[d,e,i]	70.4	36 ± 15.5 (n = 4)[j,g]	92.8

[a] 5/6 renal ablated rats that received water. [b] Urine was collected 8 weeks after surgery. [c] Blood was collected (3 mL) on the 12th week following surgery. [d] $p < 0.01$ comparison versus normal, intact rats. [e] Due to the large standard of error in the control group, none of the values for thromboxane levels in urine in the treated groups were considered significantly lower. [f] Blood was collected (3 mL) on the 10th week following surgery. [g] $p < 0.01$. [h] Drug dose was increased from 68 mg/kg per day to 410 mg/kg per day on the 10th week after surgery. [i] Urine was collected on the 11th week following surgery. [j] Blood was collected (3 mL) on the 13th week following surgery.

Table V. Histology of Excised Rat Kidneys after 10–13 Weeks Dosing with **10b**

sample group	total glomeruli with lesions:[a] $\bar{X}$ ± SEM
control (n = 6) 11 ± 3	11 ± 3
205 mg/kg per day (n = 4)	13 ± 4
410 mg/kg per day (n = 4)[b]	8 ± 3

[a] The types of lesions identified included glomerular mesangial proliferation, tubular hyaline casts, cortical interstitial inflammation, and hydronephrosis. [b] Rats dosed at 68 mg/kg per day for 9 weeks followed by dosing at 410 mg/kg per day for 4 weeks.

synthesis by oral administration of **10b** could alter the progression of kidney disease in the 5/6 renal ablated rat model.

The results of this study using **10b** are illustrated in Tables IV and V. Although a progressive increase of proteinurea was noted during this study in both the control and treated groups, no significnt decreases in systolic blood pressure or urinary protein excretion were observed in the treated groups as compared to the control group (data not shown). The measured thromboxane levels in urine were lower in the treated group as compared to normal (intact, untreated) rats, but due to the large standard error in the control group values, the urinary TXB_2 levels in the treated group were not considered significantly lower. However, TXB_2 levels in the serum of the treated group were significantly lower than those of the control group.

Throughout the duration of the study no significant differences in the growth rate between the control and treated groups were noticed (data not shown). Finally, a histological examination of the rat kidneys, performed after the drug treatment was discontinued, found no significant differences between the control and treated groups in the production of glomerular lesions.

Although the above study demonstrates that **10b** is systematically available by oral administration, it raises several questions concerning the accuracy by which the 5/6 renal ablated rat may describe the renal disease state or the role by which TXA_2 is involved in its pathology. The radical injury presented by the ablation model may be unrepresentative of the actual insidious process of hypertension and eventual renal failure.[31] The urine and serum TXB_2 level measurements in the above study are only indirect evidence of the effect of thromboxane synthetase inhibition. A simultaneous direct measurement of glomerular filtration rates and renal TXA_2 levels in rats treated with **10b** might be a more conclusive indication of the role which TXA_2 plays in hypertension and renal failure in the above ablation model.

Angiotensin II and thromboxane A_2 are known to be potent vasoconstrictors in the renal system, but recent studies have indicated that the former may play a more important role in hypertension and renal dysfunction. Anderson et al.[27] have shown that treatment of 5/6 renal ablated rats with an angiotension coverting enzyme (ACE) inhibitor, enalapril, can reduce the severity of glomerular damage as well as reverse the increased systolic blood pressure and attenuate proteinuria induced by ablation. Rosenkranz and Hayashi[32] have recently reported that treatment of 5/6 renal ablated rats with a combination of enalapril, at a threshold effective dose (4 mg/kg per day, po), and **10b** (60 mg/kg per day, po) does not afford additional benefits beyond that offered by administration of enalapril (4 mg/kg per day, po) alone. This latter observation seems to minimize the role of TXA_2 in this model, although experiments with other TXA_2 synthetase inhibitors, TXA_2 antagonists, and renal failure models should be conducted to make this conclusive.

Experimental Section

Biology. (a) In Vitro Thromboxane Synthetase Inhibition. Human blood was collected into siliconized vacutainers (15 mL) containing 0.5 mL of 11.25% sodium citrate per container (final concentration 0.38% sodium citrate). Platelet-rich plasma (PRP) was obtaied from centrifugation of the collected blood at 200g at room temperature. Pig aortal microsomes (PAM) were prepared by the method of Moncada and Neichi et al.[33] Aggregation experiments were followed by the turbidimetric methods of Born[34] using Payton dual-channel aggregometers. The thromboxane synthetase inhibitor (10 μL of drug concentration being tested) was added to 1.0 mL of PRP and incubated at 37 °C with stirring (500 rpm) for 2 min. The appropriate amount of PAM was added and incubated for an additional 3 min. The amount of PAM used was that determined initially to maximize PGI_2 production in the presence of the standard dazoxiben, which gave an IC_{50} of 2.5×10^{-6} M (subsequently the amount of PAM employed was that giving a similar IC_{50} for the standard). Platelet aggregation was induced by the addition of ADP (10 μL, 5×10^{-4} M, 5 μM final concentration) and the result recorded. An IC_{50} value was determined from a dose–reponse curve derived by testing at several drug concentrations, ranging from 5×10^{-4} to 1×10^{-8} M.

(b) Collagen–Epinephrine-Induced Pulmonary Thromboembolism.[24] Male Swiss–Webster mice (Hilltop Lab Animals) weighing 22–26 g were employed in this assay. At times and by routes indicated in Tables II and III, test materials were administered in 0.2 mL of solution in CMC ((carboxymethyl)cellulose)). At hour 0, collagen-induced pulmonary thromboembolism was induced by administering 600–1000 μg/kg of collagen extract[35] (Hormon-Chemie, München, GMBH) and 80 μg/kg epinephrine hydrochloride intravenously in 0.2 mL of 0.9% saline via the tail

(31) Fine, L. G. *Kidney Int.* **1988**, *33*, 116.
(32) Rosenkranz, R. P.; Hayashi, C. M. *Proc. Western Pharmacol. Soc.* **1988**, *31*, 81.
(33) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663. (b) Neichi, T.; Tomisawa, S.; Kubodera, N.; Uchida, Y. *Prostaglandins* **1980**, *19*(4), 577.
(34) Born, G. V. R. *J. Physiol.* **1962**, *162*, 67P.
(35) The exact amount of collagen extract administration varied for each sample obtained from the supplier. An assay of the requisite amount was accomplished by determining the minimum amount necessary to produce 90–100% mortality when coadministered with 80 μg/kg epinephrine hydrochloride in mice, which served as a positive control group.

vein. The animals were observed for approximately 24 h after collagen administration, and mortality was noted.

(c) Renal Ablated Rat Model. Male rats (Munich Wistar) weighing 200–270 g were anesthetized with 50 mg/kg brevital sodium, ip. A midline abdominal incision was made and 5/6 renal ablation was achieved by right nephrectomy and ligation of the arterial branches supplying blood to two-thirds of the left kidney. The animals were allowed to recover. One week following surgery, the rats were separated into three groups: group I received water; group II received drug at a concentration of 500 mg/L in drinking water, which was equivalent to 68 mg/kg per day; group III received drug at a concentration of 1500 mg/L in drinking water, which was equivalent to 205 mg/kg per day. Following 9 weeks of dosing, the drug concentration for the rats from group II was increased to 3000 mg/L (drug dose equivalent to 410 mg/kg per day). The animals in group II received this higher dose for 4 additional weeks.

Conscious systolic blood pressures were monitored weekly by using the tail cuff method. Urinary protein excretion during a 24-h period was measured every 2 weeks by using the sulfosalicylic acid method. For some of the animals, radioimmunoassays measuring TXB_2 levels were performed on both urine (8–11 weeks postsurgery) and serum (10–13 weeks postsurgery) samples from both control and treated groups. At the end of the 10th week of dosing, the kidneys from the rats in group III were perfused with a tissue fixative for morphological studies. The kidneys from the rats in group I and II were perfused similarly at the end of the 13th week.

Chemistry. All melting points are uncorrected and obtained on a Thomas-Hoover capillary melting point apparatus. The structures of all compounds were confirmed by their IR and ^1H NMR spectra. The IR spectra were recorded on a Sargent-Welch 3-200 spectrophotometer and the ^1H NMR spectra were obtained on a Varian EM390 or Bruker WM300 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed in house by Syntex Analytical Research Services or Atlantic Micro Lab, Atlanta, GA, and found to be within 0.4% of theoretical values unless otherwise noted.

Pyrroles and pyrrolecarboxaldehydes employed in syntheses were obtained either from a commercial source or by methods previously described in the chemical literature. All reactions were performed under a dry nitrogen atmosphere unless noted otherwise.

2-[(1*H*-Imidazol-1-yl)methyl]pyrrole (7a). A solution of 2-[(*N*,*N*-dimethylamino)methyl]pyrrole (8.69 g, 70.0 mmol) and imidazole (4.78 g, 70.0 mmol) in xylene (50 mL) was heated at reflux for 6 h. The solvent was removed under reduced pressure and the resulting dark oil (10.9 g) was purified by column chromatography on silica with $MeOH/CH_2Cl_2$ (5:95) as an eluent to obtain **7a** as a brown solid (6.45 g, 63%): mp 89–91 °C (toluene/hexane); ^1H NMR ($CDCl_3$) δ 4.97 (s, 2 H, CH_2), 6.17 (m, 2 H, pyrrole H-3,4), 6.83 (m, 2 H, pyrrole H-5 and imidazole H-5), 6.97 (t, 1 H, J = 1.0 Hz, imidazole H-4), 7.03 (br s, 1 H, imidazole H-2).

1-Methyl-2-[(1*H*-imidazol-1-yl)methyl]pyrrole (7b). A 50% dispersion of sodium hydride in mineral oil (0.96 g, 20.0 mmol) was added to a solution of **7a** (2.94 g, 20.0 mmol) in dry DMF (20 mL). After hydrogen evolution had ceased (15–20 min), methyl iodide (2.84 g, 20.0 mmol) was added and the solution stirred for 18 h. The reaction was diluted with water (200 mL) and extracted with methylene chloride (2 × 100 mL), dried (Na_2SO_4), and evaporated to an oil. Purification by column chromatography on silica gel using acetone/CH_2Cl_2 (1:3) as the eluent afforded **7b** (2.14 g, 66%) as an oil: ^1H NMR ($CDCl_3$) δ 3.37 (s, 3 H, NCH_3), 5.06 (s, 2 H, CH_2), 6.10 (t, 1 H, J = 3.4, pyrrole H-3), 6.20 (m, 1 H, pyrrole H-4), 6.63 (t, 1 H, J = 2.3 Hz, pyrrole H-5), 6.87 (t, J = 1.0 Hz, imidazole H-5), 7.07 (t, 1 H, J = 1.0 Hz, imidazole H-4), 7.45 (br s, 1 H, imidazole H-2).

1-Methyl-2-[(3-pyridinyl)methyl]pyrrole (7c). A solution of 1-methyl-2-pyrrolecarboxaldehyde (2.00 g, 18.3 mmol) and 1,4-bis(trimethylsilyl)-1,4-dihydropyridine (4.13 g, 18.3 mmol) in tetrahydrofuran (37 mL) was treated with a solution of tetra-*n*-butylammonium fluoride (1.83 mL, 1 M in THF, 1.83 mmol). The reaction was stirred under a dry nitrogen atmosphere at ambient temperature for 24 h. The reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 × 75 mL), and the extracts were dried (Na_2SO_4). The extract was concentrated to an oil and chromatographed on a column of silica gel with $MeOH/CH_2Cl_2$ (2.5:97.5) as the eluent to afford **7c** (2.70 g, 86%) as an oil: ^1H NMR ($CDCl_3$) δ 3.50 (s, 3 H, NCH_3), 4.00 (s, 2 H, CH_2), 5.97 (m, 1 H, pyrrole H-3), 6.13 (t, 1 H, J = 3.0 Hz, pyrrole H-4), 6.67 (t, 1 H, J = 2.3 Hz, pyrrole H-5), 7.32 (dd, 1 H, J = 7.5, 2.3 Hz, pyridine H-4), 7.53 (dt, J = 7.5, 2.3 Hz, pyridine H-4), 8.65 (s, 2 H, pyridine H-2,6).

The following 2-[(3-pyridinyl)methyl]pyrroles were prepared similarly. 1-Ethyl-2-[(3-pyridinyl)methyl]pyrrole (**7d**): 43% yield. 1-Prop-2-yl-2-[(3-pyridinyl)methyl]pyrrole (**7e**): 40% yield. 1-(1,1-Dimethylethyl)-2-[(3-pyridinyl)methyl]pyrrole (**7f**): 46% yield. 1-(2,2-Dimethylpropyl)-2-[(3-pyridinyl)methyl]pyrrole (**7g**): 21% yield. 1-Phenyl-2-[(3-pyridinyl)methyl]pyrrole (**7h**): 55% yield.

1-Methyl-2-[(1*H*-imidazol-1-yl)methyl]-5-formylpyrrole (8a) and 1-Methyl-2-[(1*H*-imidazol-1-yl)methyl]-4-formylpyrrole (8b). Phosphorus oxychloride (2.63 g, 17.1 mmol) was added dropwise to dimethylformamide (1.33 mL, 1.25 g, 17.1 mmol) while the temperature was maintained between 10 and 20 °C with an ice bath. After the addition was complete, the reaction was warmed to ambient temperature for 30 min and then cooled to 5 °C with an ice-salt cooling bath. A solution of **7b** (1.84 g, 11.4 mmol) in DMF (10 mL) was added at a rate that maintained the reaction temperature between 12 and 15 °C. The cooling bath was removed and the reaction mixture warmed to ambient temperature before being heated to 80 °C for 30 min. The reaction mixture was cooled to ambient temperature, and a solution of sodium acetate trihydrate (12.0 g, 88.1 mmol) in water (15 mL) was added cautiously at first and then as rapidly as possible. The mixture was cautiously neutralized with solid potassium carbonate (2.40 g, 17.4 mmol) and the solvent was removed under vacuum. The residue was extracted with acetone (3 × 50 mL) and filtered, and the filtrate was concentrated to an oil. The last traces of DMF were removed by heating the oil under high vacuum. The residue was chromatographed on silica gel with $CHCl_3$/hexane/MeOH (45:45:8) as an eluant to afford **8a** (1.59 g, 74%) as an oil: ^1H NMR ($CDCl_3$) δ 3.88 (s, 3 H, NCH_3), 5.17 (s, 2 H, CH_2), 6.19 (d, 1 H, J = 3.7 Hz, pyrrole H-3), 6.85 (br s, 1 H, imidazole H-5), 6.92 (d, 1 H, J = 3.7 Hz, pyrrole H-4), 7.13 (br s, 1 H, imidazole H-4), 7.54 (br s, 1 H, imidazole H-2), 9.65 (s, 1 H, CHO).

Further elution afforded **8b** (0.35 g, 16%) as an oil: ^1H NMR ($CDCl_3$) δ 3.53 (s, 3 H, NCH_3), 5.13 (s, 2 H, CH_2), 6.73 (d, 1 H, J = 1.5 Hz, pyrrole H-3), 6.91 (br s, 1 H, imidazole H-5), 7.12 (br s, 1 H, imidazole H-4), 7.33 (d, 1 H, J = 1.5 Hz, pyrrole H-5), 7.53 (br s, 1 H, imidazole H-2), 9.75 (s, 1 H, CHO).

The following 4-formyl- and 5-formylpyrroles were prepared similarly. 2-[(1*H*-Imidazol-1-yl)methyl]-5-formylpyrrole (**8c**): 85% yield. 1-Methyl-2-[(3-pyridinyl)methyl]-5-formylpyrrole (**8d**): 70% yield. 1-Ethyl-2-[(3-pyridinyl)methyl]-5-formylpyrrole (**8e**): 45% yield. 1-Prop-2-yl-2-[(3-pyridinyl)methyl]-5-formylpyrrole (**8f**): 27% yield. 1-(1,1-Dimethylethyl)-2-[(3-pyridinyl)methyl]-4-formylpyrrole (**8g**): 74% yield. 1-(2,2-Dimethylpropyl)-2-[(3-pyridinyl)methyl-5-formylpyrrole (**8h**): 63% yield. 1-Phenyl-2-[(3-pyridinyl)methyl]-5-formylpyrrole (**8i**): 70% yield.

(*E*)-1-Methyl-2-[2-(methoxycarbonyl)ethenyl]pyrrole (13). A suspension of (carbomethoxymethyl)triphenylphosphonium bromide (18.6 g, 44.8 mmol), sodium methoxide (2.42 g, 44.8 mmol), and 1-methyl-2-formylpyrrole (2.45 g, 22.4 mmol) in acetonitrile (40 mL) was heated at reflux for 18 h. The solvent was removed under reduced pressure and the residue partitioned between ether and water. The ethereal extract was dried (Na_2SO_4), concentrated to an oil, and chromatographed on a column of silica gel with EtOAc/hexane (1:9) as the eluent to afford **13** as an oil (3.6 g, 97%): ^1H NMR ($CDCl_3$) δ 3.52 (s, 3 H, NMe), 3.60 (s, 3 H, OCH_3), 6.02 (d, 1 H, J = 15.8 Hz, acrylate α-H), 6.03 (dd, 1 H, J = 4.5, 4.1 Hz, pyrrole H-4), 6.60 (m, 2 H, pyrrole H-3, 5), 7.53 (d, 1 H, J = 15.8 Hz, acrylate β-H).

***trans*-1-Methyl-2-[2-(methoxycarbonyl)cycloprop-1-yl]pyrrole (14).** A solution of **13** (6.00 g, 36.0 mmol) in ether (50 mL) was treated with ethereal diazomethane (120 mL) in the presence of palladium(II) acetate (60.0 mg, 0.27 mmol) as described by Vorbrüggen.[20] The resulting solution was filtered through a pad of Celite and concentrated to an oil. Analysis by gas chromatography indicated that the reaction was only 60–75% com-

plete. The crude product thus obtained was resubjected to the above reaction conditions until a conversion of >95% had been realized. Chromatographic purification of the crude product (6.75 g) on a column of silica gel using EtOAc/hexane (1:9) as the eluent afforded **14** as an oil (6.21 g, 96%): ^{1}H NMR ($CDCl_3$) δ 1.15–1.92 (m, 3 H, cyclopropyl-H), 2.38 (m, 1 H, CHCOOR), 3.63 (s, 3 H, NCH_3), 3.75 s, 3 H, OCH_3), 5.83 (m, 1 H, pyrrole H-3) 6.02 (t, 1 H, J = 3.4 Hz), 6.58 (t, 1 H, J = 3.4 Hz).

***trans*-1-Methyl-2-[2-(methoxycarbonyl)cycloprop-1-yl]-5-formylpyrrole (15).** Vilsmeier–Haack formylation of **14** by the procedure described for the preparation of **8a** gave **15** (75%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.17–2.03 (series of unresolved multiplets, 3 H, cyclopropyl-H), 2.38 (m, 1 H, CHCOOR), 3.77 (s, 3 H, NCH_3), 3.99 (s, 3 H, OCH_3), 6.00 (d, 1 H, J = 4.5 Hz, pyrrole H-3), 6.89 (d, 1 H, J = 4.5 Hz, pyrrole H-4), 9.58 (s, 1 H, CHO).

***trans*-1-Methyl-2-[(1*H*-imidazol-1-yl)methyl]-5-[2-(methoxycarbonyl)cycloprop-1-yl]pyrrole (17).** A solution of **15** (1.92 g, 93.0 mmol) in methanol (25 mL) was cooled to 0 °C and treated with sodium borohydride (350 mg, 9.20 mmol). After the reaction was stirred for 2.5 h, TLC indicated that the reduction was not complete. An additional amount of sodium borohydride (0.10 g, 2.63 mmol) was added and the reaction stirred for an additional hour. The solvent was evaporated and the residue dissolved in ether (75 mL). The ethereal extract was washed with water (3 × 25 mL), dried (Na_2SO_4), and evaporated to provide alcohol **16** (1.91 g) as an oil pure enough for further use: ^{1}H NMR ($CDCl_3$) δ 1.15–1.90 (m, 3 H, cyclopropyl-H), 2.35 (m, 1 H, CHCOOR), 3.65 (s, 3 H, NCH_3), 3.75 (s, 3 H, OCH_3), 4.55 (s, 2 H, CH_2), 5.77 (d, 1 H, J = 3.8 Hz, pyrrole H-3), 6.02 (d, 1 H, J = 3.8 Hz, pyrrole H-4).

The above alcohol was added as a solution in THF (50 mL) to a cooled (0 °C) solution of thionylbis(imidazole) (prepared previously by reaction of imidazole (3.74 g, 54.9 mmol) with thionyl chloride (1.64 g, 13.8 mmol) in 50 mL of THF and removal of the precipitated imidazole hydrochloride). After the reaction mixture was stirred at ambient temperature for 2 h, the solvent was evaporated and the residue dissolved in CH_2Cl_2 (100 mL). The extract was washed with water (4 × 25 mL), dried (Na_2SO_4), and evaporated to an oil. The crude product was purified by chromatography on silica gel with MeOH/CH_2Cl_2 (5:95) as the eluent to afford **17** (1.93 g, 79%) as an oil.

(*E*)-2-[(1*H*-Imidazol-1-yl)methyl]-5-[2-(ethoxycarbonyl)prop-1-enyl]pyrrole (9a). A solution of **8c** (880 mg, 5.02 mmol) and ethyl 2-(triphenylphosphoranylidene)propionate (1.88 g, 5.19 mmol) in acetonitrile (7 mL) was heated at reflux for 18 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with MeOH/CH_2Cl_2 (5:95) as the eluent to afford **9a** (1.03 g). Recrystallization from ethyl acetate gave a crystalline solid (0.75 g, 52%).

Compounds **9b,c,f–k** were prepared similarly by using the above procedure.

Compounds **9d** and **9e** were prepared similarly by using the above procedure except ethyl (triphenylphosphoranylidene)acetate was employed as the Wittig reagent.

Compound **9l** was prepared similarly by using the above procedure except benzyl 2-(triphenylphosphoranylidene)propionate[21] was employed as the Wittig reagent.

(*E*)-2-[(1*H*-Imidazol-1-yl)methyl]-5-(2-carboxyprop-1-enyl)pyrrole (10a). A solution of **9l** (1.00 g, 3.11 mmol) in ethanol (20 mL) was hydrogenated at atmospheric pressure over 10% palladium on carbon (750 mg). The hydrogenation was discontinued upon reaching theoretical uptake of hydrogen and the reaction was filtered. Evaporation of the solvent and recrystallization of the resulting solid from ethanol afforded **10a** (600 mg, 84%).

(*E*)-1-Methyl-2-[(1*H*-imidazol-1-yl)methyl]-5-(2-carboxyprop-1-enyl)pyrrole (10b). A solution of **9b** (2.79 g, 10.0 mmol) and potassium hydroxide (1.15 g, 17.4 mmol) in absolute ethanol (12 mL) was heated at 70 °C for 2 h. The solvent was removed under reduced pressure, the residue dissolved in water (10 mL), and the pH adjusted to 7 with 1 N HCl. The solid that precipitated from the aqueous solution was filtered, washed with cold water, and air-dried to give **10b** (1.82 g, 73%) as a fine powder, mp 183–185 °C. Additional material could be isolated by evaporation of the above filtrate under reduced pressure and extraction of the residue with MeOH/CH_2Cl_2 (1:1). The extract was filtered and evaporated to afford an orange oil (660 mg), which was chromatographed on silica gel with MeOH/CH_2Cl_2 (containing 1% v/v acetic acid) as the eluent in a gradient from 6:94 to 10:90. The chromatographed material was dissolved in MeOH/CH_2Cl_2 (1:1), decolorized with charcoal, and filtered. Evaporation of the filtrated afforded **10b** (420 mg, 17%), identical in all respects with the earlier isolated material.

Carboxylic acids **10c–k** were similarly prepared by using the above procedure.

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Registry No. 1, 78218-09-4; 1·HCl, 74226-22-5; 2, 82571-53-7; 2·HCl, 78712-43-3; 3, 76894-77-4; 7a, 76660-67-8; 7b, 118896-40-5; 7c, 118896-41-6; 7d, 118896-42-7; 7e, 118896-43-8; 7f, 118896-44-9; 7g, 118896-45-0; 7h, 118896-46-1; 8a, 118896-33-6; 8b, 118896-47-2; 8c, 118896-48-3; 8d, 118896-49-4; 8e, 118896-50-7; 8f, 118896-51-8; 8g, 118896-52-9; 8h, 118896-53-0; 8i, 118896-54-1; 9a, 118896-34-7; 9b, 118896-55-2; 9c, 118896-56-3; 9d, 118896-57-4; 9e, 118896-58-5; 9f, 118896-59-6; 9g, 118896-60-9; 9h, 118896-61-0; 9i, 118896-62-1; 9j, 118896-63-2; 9k, 118896-75-6; 9l, 118896-76-7; 10a, 118896-35-8; 10b, 118896-64-3; 10c, 118896-65-4; 10d, 118896-66-5; 10e, 118896-67-6; 10f, 118896-68-7; 10g, 118896-69-8; 10h, 118896-70-1; 10i, 118896-71-2; 10j, 118896-72-3; 10k, 118896-73-4; 13, 69917-84-6; 14, 118896-36-9; 15, 118896-37-0; 16, 118896-38-1; 17, 118896-39-2; imidazole, 288-32-4; 2-[(*N*,*N*-dimethylamino)methyl]pyrrole, 14745-84-7; 1-methyl-2-pyrrolecarboxaldehyde, 1192-58-1; 1,4-bis(trimethylsilyl)-1,4-dihydropyridine, 29173-25-9; 1-ethyl-2-pyrrolecarboxaldehyde, 2167-14-8; 1-prop-2-yl-2-pyrrolecarboxaldehyde, 23373-77-5; 1-(1,1-dimethylethyl)-2-pyrrolecarboxaldehyde, 23373-78-6; 1-(2,2-dimethylpropyl)-2-pyrrolecarboxaldehyde, 118896-74-5; 1-phenyl-2-pyrrolecarboxaldehyde, 30186-39-1; (carbomethoxymethyl)triphenylphosphonium bromide, 1779-58-4; 1-methyl-2-formylpyrrole, 1192-58-1; thionylbis(imidazole), 3005-50-3; ethyl 2-(triphenylphosphoranylidene)propionate, 5717-37-3; ethyl (triphenylphosphoranylidene)acetate, 1099-45-2; benzyl 2-(triphenylphosphoranylidene)propionate, 63613-50-3; thromboxane synthetase, 61276-89-9.