21615-34-9; 4-$ClC_6H_4COCl$, 122-01-0; 3-$BrC_6H_4COCl$, 1711-09-7; 4-$H_3COC_6H_4COCl$, 100-07-2; 2,4-dihydro-2,5-dimethyl-3*H*-pyrazol-3-one, 2749-59-9; 2-ethyl-2,4-dihydro-5-methyl-3*H*-pyrazol-3-one, 19364-68-2; 2,4-dihydro-5-methyl-2-(2-methylethyl)-3*H*-pyrazol-3-one, 934-41-8; 2,4-dihydro-5-methyl-2-propyl-3*H*-pyrazol-3-one, 42098-18-0; 2-butyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one, 65156-70-9; 5-ethyl-2,4-dihydro-2-methyl-3*H*-pyrazol-3-one, 31272-03-4; thiophenecarbonyl chloride, 5271-67-0; furancarbonyl chloride, 527-69-5; 2-naphthalenecarbonyl chloride, 2243-83-6; 1-methyl-5-pyrazolone, 10234-66-9.

# Thromboxane Synthase Inhibitors. Synthesis and Pharmacological Activity of (*R*)-, (*S*)-, and (±)-2,2-Dimethyl-6-[2-(1*H*-imidazol-1-yl)-1-[[(4-methoxyphenyl)-methoxy]methyl]ethoxy]hexanoic Acids

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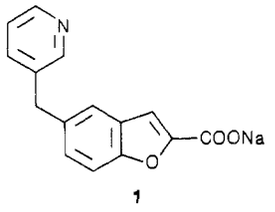
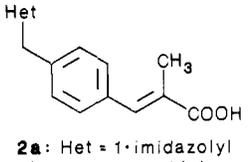
A series of substituted ω-[2-(1*H*-imidazol-1-yl)ethoxy]alkanoic acid derivatives were synthesized and evaluated for their ability to inhibit thromboxane synthase both in vitro and in vivo. Compound **13** was identified as a potent and selective competitive inhibitor of human platelet thromboxane synthase having a $K_i$ value of $9.6 \times 10^{-8}$ M. In collagen-treated human whole blood, **13** potentiated levels of 6-keto$PGF_{1\alpha}$. Enantiospecific syntheses afforded the *R* and *S* enantiomers of **13**, of which the *S* enantiomer **13b** was the more potent. Compounds **13** and **13b** were potent in vivo inhibitors of thromboxane synthase with good oral activity and duration of action.

Thromboxane $A_2$ ($TxA_2$), discovered by Hamberg et al.[1] and unequivocably characterized through synthesis by Still and co-workers,[2] is an unstable molecule derived from thromboxane synthase catalyzed rearrangement of the prostaglandin endoperoxide $PGH_2$.[3] $TxA_2$, formed by platelets and locally in tissues such as vascular smooth muscle and cardiac muscle cells, has been implicated in a variety of circulatory disorders, including unstable angina, coronary artery vasospasm, trauma- or endotoxin-induced shock, and acute myocardial infarction. Recent pharmacological data obtained with the selective $TxA_2$ synthase inhibitors furegrelate (**1**)[4] and OKY 0046/1581 (**2a,b**)[5-7] has demonstrated potential clinical utility for these compounds. Thus, when administered either alone or in combination with other agents such as cyclosporin, calcium channel blockers, and $TxA_2$ receptor antagonists, significant protection against unstable angina, allograft rejection, tumor proliferation, and coronary thrombosis has been observed in animal models.

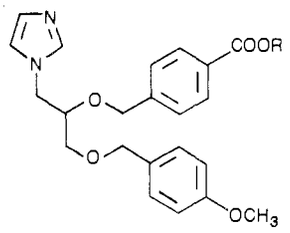



**1**

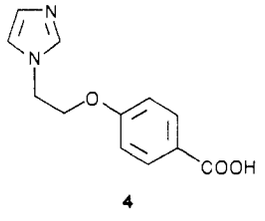



**2a**: Het = 1-imidazolyl
**b**: Het = 3-pyridyl

We recently reported on the structural requirements for a novel series of selective, imidazole-based $TxA_2$ synthase inhibitors.[8] However, on either intravenous or oral administration the lead compound from this series, **3a**, was rapidly metabolized to acid **3b** and excreted as the glucuronide. These findings prompted further structural modifications with the aim of improving the pharmacokinetic properties of the series while maintaining potent inhibitory activity against $TxA_2$ synthase in vitro and in vivo.




**3a**: R = Et
**b**: R = H




**4**

Whereas there are many examples of the glucuronidation of aryl acids, simple alkanoic acids are rarely conjugated.[9] Moreover, there is considerable precedent for the inhibition of $TxA_2$ synthase by molecules containing alkanoic and alkenoic acid groups.[10,11] Initially analogues of compounds **3a** and **3b** were prepared with incorporation of alkyl spacer groups designed to enable the molecules to adopt conformations in which the imidazole and carboxylate pharmacophores occupied similar regions of space to those in the more rigid benzoic acid derivatives (**3a,b**).

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(1) Hamberg, M.; Svensson, J.; Samuellson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994.
(2) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372.
(3) Haurand, M.; Ullrich, V. *J. Biol. Chem.* **1985**, *260*, 15059.
(4) Lefer, A. M. *Drugs Future* **1986**, *11*, 197.
(5) Ito, T.; Ogawa, K.; Watanabe, J.; Chen, L. S.; Shikano, M.; Imaizumi, T.; Shibata, Y.; Ito, Y.; Miyazaki, Y.; Satake, T. *Biomed. Biochim. Acta* **1984**, *43*, S 125.
(6) Suzuki, S.; Iwabuchi, T.; Tanaka, T.; Kanayama, S.; Ottomo, M.; Hatanaka, M.; Aihara, H. *Acta Neurochirur.* **1985**, *77*, 133.
(7) Tada, M.; Hoshida, S.; Kuzuya, T.; Inoue, M.; Minamino, T.; Abe, H. *Int. J. Cardiol.* **1985**, *8*, 301.
(8) Manley, P. W.; Allanson, N. M.; Booth, R. F. G.; Buckle, P. E.; Kuzniar, E. J.; Lad, N.; Lai, S. M. F.; Lunt, D. O.; Tuffin, D. P. *J. Med. Chem.*, in press.
(9) Caldwell, J. *Drugs Pharm. Sci.* **1980**, *10A*, 211.
(10) Kayama, N.; Sakaguchi, K.; Kaneko, S.; Kubuto, T.; Fukuzawa, T.; Kawamura, S.; Yoshimoto, T.; Yamamoto, S. *Prostaglandins* **1981**, *21*, 543.
(11) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. *J. Med. Chem.* **1981**, *24*, 1139.

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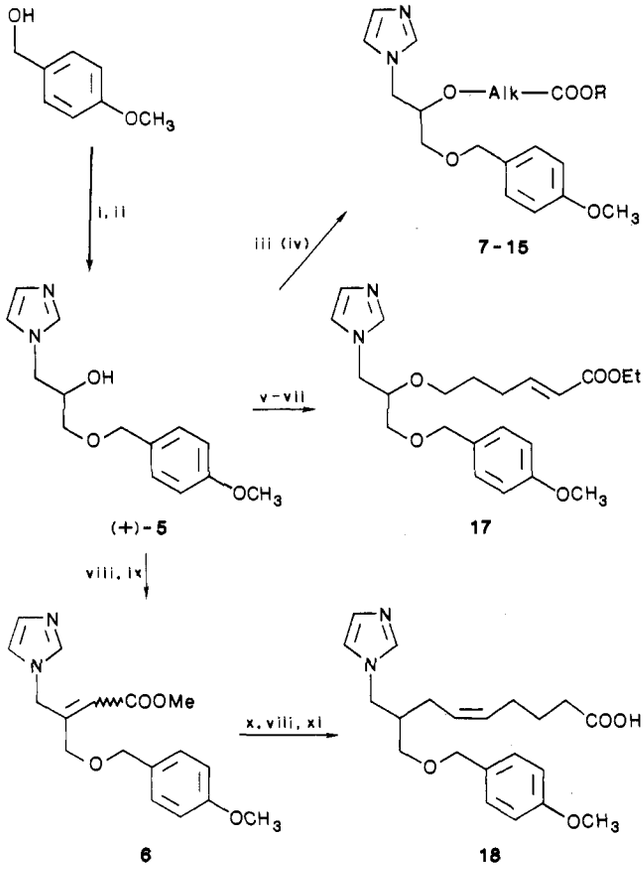
**Scheme I.** Synthetic Routes to Racemic Imidazole Derivatives[a]




[a] Reagents: (i) NaH, epibromohydrin; (ii) imidazole; (iii) KOH, DMSO, BrAlkCOOR; (iv) ClCOOEt, $Et_3N$, EtOH; (v) KOH, DMSO, $I(CH_2)_3\overline{CHO(CH_2)_2O}$; (vi) $H_2SO_4$; (vii) $Ph_3P{=}CHCOOEt$, $C_6H_6$; (viii) $(COCl)_2$, DMSO; (ix) $Ph_3P{=}CHCOOMe$, THF; (x) $LiAlH_4$; (xi) $Ph_3P^+(CH_2)_3COOH{\cdot}Br^-$, KO-*t*-Bu, THF.

In this paper we describe studies that culminated in the identification of the racemic compound **13** and in particular its *S* enantiomer **13b** as potent, selective inhibitors of $TxA_2$ synthase that possess good oral activity.

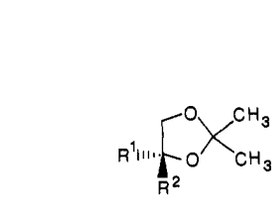
## Chemistry

The majority of the compounds prepared for this study were synthesized as racemates by using the routes outlined in Scheme I. Thus the pivotal, racemic alcohol **5** was etherified to give the alkanoic acids and esters **7–15** by KOH–DMSO alkylation (method A) with the appropriate ω-bromo ester, followed by reesterification via a mixed anhydride (method C) where necessary. The alkenoic ester **17** was prepared by etherification of **5** with 4-iodobutanal ethylene acetal,[12] followed by deprotection and Wittig olefination; the corresponding acid **16** was obtained by hydrolysis of **17**. The desoxy compounds **19–21** were obtained by esterification, or hydrogenation followed by esterification, of the acid **18**, which was prepared from **5** by Swern oxidation with subsequent homologation of the resulting ketone, via **6**, followed by Wittig olefination.

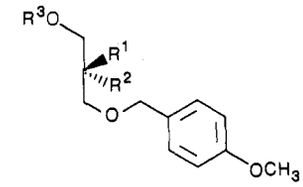
Compounds **16** and **17** were assigned the *E* configuration from the olefinic proton couplings in their NMR spectra ($J$ = 15.6 and 15.8 Hz, respectively); compound **18** was confirmed as having the *Z* configuration from its olefinic coupling constant ($J$ = 11.5 Hz) revealed on decoupling the allylic protons by irradiation at 510 Hz.

(12) Pleshakov, M. G.; Vaxilev, A. E.; Sarycheva, I. K.; Preobrazhenski, N. A. *Zh. Obshch. Khim.* **1961**, *31*, 1545; *Chem. Abstr.* **1961**, *55*, 23339*d*.

Enantiospecific synthesis of the *R* and *S* enantiomers, **13a** ($[\alpha]^{25}_D$ −38.1°) and **13b** ($[\alpha]^{25}_D$ +38.7°), of compound **13** was achieved via alkylation of the corresponding enantiomers (**5a** and **5b**) of the alcohol **5**, available from commercially available starting materials. Thus benzylation of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol gave the *S* ketal **22a**, acid hydrolysis of which afforded the *R* diol **23a**. Sulfonylation of the less hindered primary hydroxyl group of **23a** with triisopropylbenzenesulfonyl chloride gave the *S* alcohol **24a**, which on reaction with imidazole gave **5a**. The corresponding *S* enantiomer **5b** was prepared in a similar fashion from (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol.




**22a**: $R^1$ = H, $R^2$ = 4-$CH_2OCH_2C_6H_4OCH_3$
**b**: $R^1$ = 4-$CH_2OCH_2C_6H_4OCH_3$, $R^2$ = H




**23a**: $R^1$ = OH, $R^2$ = H, $R^3$ = H
**b**: $R^1$ = H, $R^2$ = OH, $R^3$ = H
**24a**: $R^1$ = OH, $R^2$ = H, $R^3$ = $SO_2Ar$
**b**: $R^1$ = H, $R^2$ = OH, $R^3$ = $SO_2Ar$
Ar = 2,4,6-*i*-$Pr_3C_6H_2$

## Biology

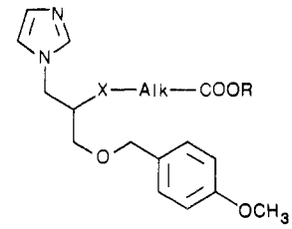
Inhibition of collagen-stimulated $TxA_2$ synthesis in human platelet-rich plasma was evaluated by measurement of supernatant levels of the stable metabolic product $TxB_2$ by radioimmunoassay. The inhibitory activities of compounds against $TxA_2$ synthase were derived by computer analysis of the data using a logit transformation and weighted linear regression, and are expressed as $IC_{50}$ values with dazoxiben being included as a standard. Data was excluded from experiments where the logit error was greater than 3, and the activities in Table I are mean values taken from a minimum of three determinations in duplicate. Active compounds were subsequently evaluated for their mean (four animals) percentage inhibition of collagen-induced $TxB_2$ generation in guinea pig whole blood ex vivo 1 h after oral dosing (Table II). The dose-related effect of selected compounds was also investigated 1 h after oral administration and expressed as $ED_{50}$ values (Table II).

## Discussion

The inhibitory activities of the compounds studied, expressed as $IC_{50}$ values, are shown in Table I. The results show that in general, for this series of compounds, the ethyl esters have similar in vitro activities to their corresponding acid derivatives. The relatively weak activity of the ester **14**, compared to its parent acid **13**, is probably due to the inability of the platelet esterases to cleave the sterically hindered ester group to the free acid pharmacophore. Conversely, the increased potency of the ester **10**, compared to its parent acid **9**, probably reflects the greater platelet permeability of the more lipophilic ester prior to intraplatelet deesterification. These observations are in accordance with those made previously for a related series of compounds.[8] In both cases no difference in activity was observed on oral administration to guinea pigs (Table II) or rhesus monkeys (data not shown) presumably due to the operation of different metabolic deesterification mechanisms prior to the compounds entering the platelet.

Molecular modeling suggested that due to the conformational flexibility of **3a**/**3b**, the distance between the

**Table I.** Physicochemical Data and Inhibitory Activity of Imidazole Derivatives vs. $TxB_2$ Generation in Intact Human Platelets




| compd | X | Alk | R | method[a] | yield,[b] % | mp, °C | formula[c] | $IC_{50}$ ($\mu$M)[d] vs. $TxB_2$ |
|---|---|---|---|---|---|---|---|---|
| dazoxiben | | | | | | | | 1.29 (±0.17) |
| **3a** | O | 4-$CH_2C_6H_4$ | H | | | | | 0.54 (±0.07) |
| **7** | O | $(CH_2)_4$ | H | A | 10 | oil | $C_{19}H_{26}N_2O_5 \cdot 0.1H_2O$ | 0.73 (±0.34) |
| **8** | O | $(CH_2)_4$ | Et | C | 62 | oil | $C_{21}H_{30}N_2O_5 \cdot 0.3H_2O$ | 0.75 (±0.09) |
| **9** | O | $(CH_2)_5$ | H | A | 64 | oil | $C_{20}H_{28}N_2O_5$ | 0.56 (±0.20) |
| **10** | O | $(CH_2)_5$ | Et | C | 58 | oil | $C_{22}H_{32}N_2O_5 \cdot 0.1H_2O$ | 0.12 (±0.05) |
| **11** | O | $(CH_2)_6$ | H | A | 48 | oil | $C_{21}H_{30}N_2O_5$ | 1.89 (±1.50) |
| **12** | O | $(CH_2)_6$ | Et | C | 32 | oil | $C_{23}H_{34}N_2O_5 \cdot 0.3H_2O$ | 4.00 (±2.45) |
| **13** | (±)-O | $(CH_2)_4CMe_2$ | H | A | 31 | 69–70 | $C_{22}H_{32}N_2O_5$ | 0.12 (±0.02) |
| **13a** | (*R*)-O | $(CH_2)_4CMe_2$ | H | A | 35 | oil | $C_{22}H_{32}N_2O_5$ | 0.42 (±0.11) |
| **13b** | (*S*)-O | $(CH_2)_4CMe_2$ | H | A | 55 | oil | $C_{22}H_{32}N_2O_5 \cdot 0.2H_2O$ | 0.036 (±0.01) |
| **14** | O | $(CH_2)_4CMe_2$ | Et | | 14 | oil | $C_{24}H_{36}N_2O_5$ | 17.6 (±1.9) |
| **15** | O | $(CH_2)_6CMe_2$ | H | A | 47 | 63–64[e] | $C_{24}H_{36}N_2O_5$ | >20 |
| **16** | O | (*E*)-$(CH_2)_3CH{=}CH$ | H | | 57 | oil | $C_{20}H_{26}N_2O_5 \cdot 0.5H_2O$ | 8.33 (±5.10) |
| **17** | O | (*E*)-$(CH_2)_3CH{=}CH$ | Et | | 39 | oil | $C_{22}H_{30}N_2O_5$ | 10.0 (±2.6) |
| **19** | $CH_2$ | (*Z*)-$CH{=}CH(CH_2)_3$ | Et | C | 30 | oil | $C_{23}H_{32}N_2O_4$ | 0.39 (±0.35) |
| **20** | $CH_2$ | $(CH_2)_5$ | H | | 85 | 79–80 | $C_{21}H_{30}N_2O_4$ | 1.43 (±0.62) |
| **21** | $CH_2$ | $(CH_2)_5$ | Et | C | 34 | oil | $C_{23}H_{34}N_2O_4$ | 1.00 (±0.02) |

[a] See Experimental Section for detailed procedures. [b] Yields were not optimized. [c] C, H, N analyses were within ±0.4% of calculated values. [d] $IC_{50}$ = mean (±SEM) (≥3 experiments) molar concentration of test compound required to reduce the amount of $TxB_2$ formed by collagen-stimulated human PRP. [e] Recrystallized from $Et_2O$–hexane.

**Table II.** Effect of Test Compounds on Collagen-Induced $TxB_2$ Generation in Guinea Pig Whole Blood ex Vivo at 1 h Post Oral Dose

| | | $TxB_2$ pg/0.1 mL/500 × $10^3$ platelet | | | |
|---|---|---|---|---|---|
| compound | dose, mg/kg | control | test | % inhibn[a] | $ED_{50}$,[b] mg/kg |
| indomethacin | 10 | 2012 ± 339 | 27 ± 16 | 99 | <10 |
| dazoxiben | 30 | 1949 ± 141 | 674 ± 105 | 54 | 9.3 |
| **3a** | 30 | 714 ± 270 | 742 ± 177 | −4 | |
| **7** | 30 | 1823 ± 587 | 1047 ± 110 | 43 | |
| **8** | 30 | 1823 ± 587 | 2018 ± 303 | −11 | |
| **9** | 30 | 710 ± 270 | 130 ± 30 | 82 | 10.5 |
| **10** | 30 | 2040 ± 120 | 750 ± 250 | 63 | 13.5 |
| **11** | 30 | 1228 ± 224 | 923 ± 159 | 25 | |
| **12** | 30 | 4050 ± 1032 | 2720 ± 1053 | 33 | |
| **13** | 30 | 1192 ± 127 | 153 ± 36 | 87 | 3.4 |
| **13a** | 30 | 1985 ± 235 | 572 ± 250 | 71 | 12.0 |
| **13b** | 10 | 1211 ± 208 | 61.9 ± 123 | 95 | 1.4 |
| **14** | 30 | 1840 ± 320 | 55 ± 11 | 97 | 6.7 |
| **16** | 30 | 1371 ± 137 | 1302 ± 433 | 4 | |
| **19** | 30 | 1648 ± 194 | 1265 ± 157 | 23 | |
| **20** | 30 | 1371 ± 137 | 1620 ± 139 | −18 | |
| **21** | 30 | 1454 ± 240 | 683 ± 327 | 53 | |

[a] Mean (≥4 animals) percentage inhibition of the production of serum $TxB_2$ 1 h after oral administration of test compound to guinea pigs. [b] Oral dose causing 50% inhibition ($p < 0.05$). Minimum of four animals per dose and at least four dose points on the dose–response curve.

imidazole and carboxylate pharmacophores could be maintained by replacing the benzyl group with between four and six methylene groups. As shown in Tables I and II, the hexanoic acid derivatives **9** and **10** were more active than the analogues derived from pentanoic (**7** and **8**) or heptanoic acid (**11** and **12**) both in vitro and in vivo. Consequently, in this series of compounds the pharmacophore separation appears to be optimal for compounds incorporating five methylene groups in the acid side chain. In an attempt to increase potency by conformational restriction, olefinic linkages were incorporated into the hexanoate side chain. Compound **19**, incorporating the *cis*-alkenoic side chain of $TxA_2$ at the expense of an ether linkage, showed no change in activity over its saturated ether analogue **10** in vitro, although in vivo it was significantly less active. The *trans*-2(*E*)-hexenoate derivatives **16** and **17** showed a 15-fold drop in potency compared to their saturated analogues **9** and **10**; an unexpected finding considering the trans-$\alpha,\beta$-unsaturated geometry of OKY 0046 (**2**).

Despite being twice as active as the prototype $TxA_2$ synthase inhibitor dazoxiben (**4**)[13] in vitro, **9** was only of comparable activity in vivo (Table II). We thought that this was probably due to metabolic deactivation through $\beta$-oxidation of the alkanoic acid moiety, although glucuronidation of the acid or poor absorption could not be completely discounted. In prostaglandins the incorporation of either a 3-heteroatom, double bonds, or methyl groups at the 2- or 3-position have all been used to slow

(13) For a detailed discussion of the pharmacology of dazoxiben, consult: *Br. J. Pharmacol.* **1983**, *15* (Suppl. 1), 7–140S.

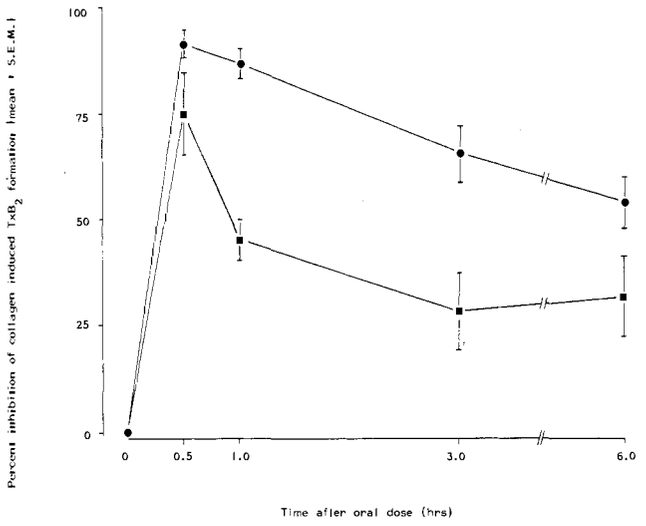



**Figure 1.** Effect of **13** (●) and dazoxiben (■) on collagen-induced $TxB_2$ formation in stirred guinea pig citrated whole blood ex vivo: oral duration of action (both compounds at 30 mg/kg; $n$ = 4–9 animals per treatment group).

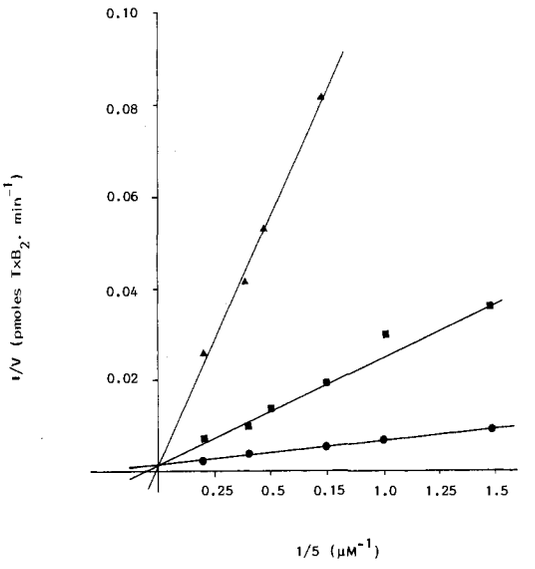



**Figure 2.** Lineweaver–Burk plot of the inhibition of thromboxane synthase activity by compound **13**. Inhibitor (**13**) concentrations: 0 (●), 0.1 (■), and 1.0 μM (▲). Computer analysis of data typified by that shown above indicated that a competitive effect of **13** against the enzyme is significantly more likely than noncompetitive or uncompetitive inhibition in each of four experiments ($p < 0.01$).

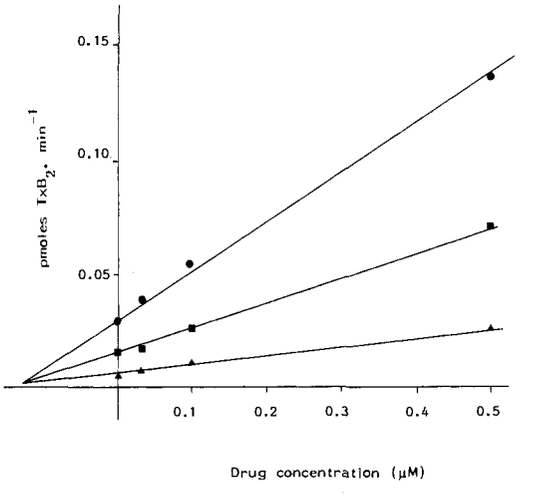



**Figure 3.** Dixon plot of the inhibition of thromboxane synthase activity by compound **13**. Substrate ($PGH_2$) concentrations: 2.5 (●), 5.0 (■), and 15.0 μM (▲). Computer analysis of Dixon plots typified by that above gave a mean $K_i$ for **13** of $(9.6 \pm 2.3) \times 10^{-8}$ M ($n$ = 4).

β-oxidation.[14-16] Metabolism via acid conjugation is also slowed by steric hindrance. Consequently, incorporation of a geminal dimethyl group α to the carboxylic acid in **9** could inhibit both of these potential metabolic pathways. Adopting this strategy resulted in compound **13**, which had an $IC_{50}$ value of $(0.117 \pm 0.019) \times 10^{-6}$ M ($n$ = 21) in human platelet-rich plasma (Table I). Furthermore, in vivo **13** had an oral $ED_{50}$ of 3.4 mg/kg in the guinea pig (Table II) and a duration of action (>50% inhibition) in the same species following an $ED_{90}$ dose (30 mg/kg) of longer than 6 h (Figure 1). In contrast dazoxiben (also 30 mg/kg) after an initial effect of 75% inhibition at 0.5 h exhibited only moderate activity (less than 50% inhibition) at the 1-, 3-, and 6-h time points.

A kinetic analysis of the inhibition of human platelet microsomal $TxA_2$ synthase by **13** was undertaken. Linear regression analysis and comparison of likelihood ratios by $\chi^2$ test for the Lineweaver–Burk data plot (Figure 2) demonstrated that the compound is a competitive inhibitor of $TxA_2$ synthase (good data fit; $p < 0.01$). From the Dixon plot (Figure 3), a mean value of $(9.6 \pm 2.3) \times 10^{-8}$ M ($n$ = 4) was estimated for the equilibrium dissociation constant ($K_i$) of the enzyme–inhibitor complex. These results suggest that **13** affects $TxA_2$ synthase activity by interacting directly at the $PGH_2$ binding site within the heme active center of the enzyme, presumably in a similar manner to that postulated for other $TxA_2$ synthase inhibitors.[3,17]

In order to establish that compound **13** was a selective inhibitor of $TxA_2$ synthase and had no significant effect on the release of arachidonic acid from membrane phospholipid, or its subsequent conversion to $PGH_2$, $PGE_2$ production in collagen-stimulated human platelet-rich plasma was examined as previously described.[8] Compound **13** demonstrated the characteristic profile of a selective $TxA_2$ synthase inhibitor, in that it caused a dose-related (0.01–1.0 μM) potentiation of $PGE_2$ formation (16-fold at 1.0 μM), presumably by an increase in the availability of the $PGH_2$ precursor. In addition, in order to ascertain whether this increased pool of $PGH_2$ was available for synthesis of the vasodilator and antiaggregatory agent prostacyclin ($PGI_2$) the effect of **13** on leukocyte-derived $PGI_2$ (determined by radioimmunoassay of 6-keto$PGF_{1\alpha}$ immunological equivalents) in human citrated whole blood was examined. Whereas basal levels were near the limit of detection of the assay, within 1 min of the addition of collagen, 6-keto$PGF_{1\alpha}$ levels rose markedly (Figure 4), indicating that $PGI_2$ synthase was not significantly inhibited at concentrations of **13** necessary to completely inhibit $TxA_2$ formation, and that the increased pool of $PGH_2$ in the platelets was available to other cells for $PGI_2$ production. These findings are consistent with those reported for dazoxiben,[13,18] which also enhances $PGI_2$ levels

(14) Bundy, G.; Lincoln, F.; Nelson, N.; Pike, J.; Schneider, W. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 76.
(15) Skotnicki, J. S.; Schaub, R. E.; Bernady, K. F.; Siuta, G. J.; Poletto, J. F.; Weiss, M. J. *J. Med. Chem.* **1977**, *20*, 1551.
(16) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.
(17) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. *J. Med. Chem.* **1985**, *28*, 287.
(18) Defryn, G.; Deckmyn, H.; Vermylen, J. *Thromb. Res.* **1982**, *26*, 389.

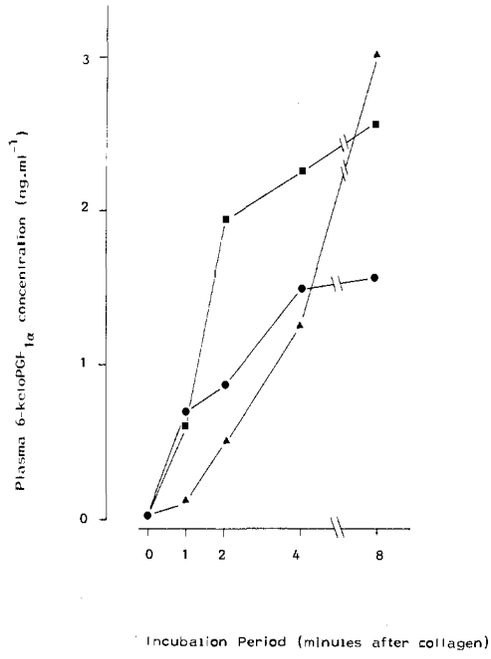



**Figure 4.** Effect of **13** at 0.3 (●), 1.0 (■), and 10.0 μM (▲) on 6-ketoPGF$_{1\alpha}$ levels (immunological equivalents) in collagen (3 μg/mL) stimulatd citrated human whole blood in vitro. Results are the mean of two experiments, each carried out with duplicate determinations for all treatments.

at the same time as reducing $TxA_2$ when whole blood is exposed to a thrombogenic stimuli such as collagen.

In practice, it is generally preferable to replace racemic drugs with their more potent and/or safer enantiomer.[19] Apart from the advantageous increase in inhibitory activity, differences are also often observed between enantiomers in vivo in terms of peak plasma concentrations achieved, elimination half-lives, and various other pharmacokinetic parameters.[20,21] Consequently we synthesized and evaluated the *R* and *S* enantiomers of **13**. As shown in Table I the *S* enantiomer **13b** was 10-fold more active than the corresponding *R* isomer **13a**, having an $IC_{50}$ value of (0.036 ± 0.010) × $10^{-6}$ M vs. human platelet $TxB_2$ generation. This difference in activity was also reflected in the ex vivo guinea pig model in which **13b** displayed an $ED_{50}$ of 1.4 mg/kg compared to a value of 12.0 mg/kg for **13a** in the guinea pig.

In conclusion, we have shown that the racemic compound **13** and in particular the *S* enantiomer **13a** are potent and selective inhibitors of platetlet $TxA_2$ synthase with good oral activity and duration of action. Furthermore, we have demonstrated that the inhibition of $TxA_2$ synthase by **13** in human whole blood increases the availability of $PGH_2$ as a substrate for $PGI_2$ production in other cells.

## Experimental Section

Melting points (uncorrected) were determined on a Reichart Thermovar melting point apparatus. Proton NMR spectra were run at ambient temperature on a Bruker WM-250 spectrometer at 250 MHz, with $Me_4Si$ as an internal standard. IR spectra were run on a Perkin-Elmer 197 spectrometer. Elemental analyses were performed by C.H.N. Analysis Ltd., Leicester, England, and the results are within ±0.40% of the theoretical values.

**(*S*)-2,2-Dimethyl-4-[[(4-methoxyphenyl)methoxy]methyl]-1,3-dioxolane (22a).** A solution of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol (26.65 g, 0.20 mol) in dry THF (30 mL) was added to a stirred slurry of KO-*t*-Bu (24.6 g, 0.22 mol) in dry THF (50 mL) at 0 °C. The mixture was stirred for 0.5 h and then treated with 4-methoxybenzyl chloride (34.4 g, 0.22 mol). The mixture was stirred for 15 h and the solvent was evaporated to give a residue, which was treated with water (80 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried ($Na_2SO_4$) and the solvent was evaporated off the give **22a** (43 g, 85%) as a yellow oil, which was used without further purification; NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.40 (s, 3 H), 3.37–4.37 (m, 5 H), 3.77 (s, 3 H), 4.47 (s, 2 H), 6.83 and 7.23 (AB q, 4 H).

**(*R*)-3-[(4-Methoxyphenyl)methoxy]-1,2-propanediol (23a).** A solution of **22a** (43 g, 0.17 mol) in MeOH (60 mL) was treated with HCl (45 mL of 1.0 M) and stirred for 0.7 h. The solvent was evaporated and the residue was treated with water (200 mL) and extracted with EtOAc (3 × 150 mL). The combined extracts were dried ($Na_2SO_4$), and the solvent was evaporated to give the crude product which was purified by column chromatography (silica gel, 2% MeOH in $CHCl_3$) to give **23a** (32 g, 87%) as an oil; NMR ($CDCl_3$) δ 3.27–4.03 (m, 7 H), 3.73 (s, 3 H), 4.42 (s, 2 H), 6.83 and 7.23 (AB q, 4 H).

**(*R*)-α-[[(4-Methoxyphenyl)methoxy]methyl]-1*H*-imidazole-1-ethanol (5a).** A solution of **23a** (26.5 g, 0.125 mol) in dry pyridine (150 mL) was treated with triisopropylbenzenesulfonyl chloride (38 g, 0.125 mol) and stirred for 36 h. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 10% EtOAc in toluene) to give **(*S*)-3-[(4-methoxyphenyl)methoxy]-1,3-propanediol 1-(2,4,6-triisopropylbenzene sulfonate)** (24a) as a colorless oil (47.5 g, 80%), which was dissolved in dry $CH_3CN$, treated with imidazole (60 g, 0.882 mol), and heated under reflux for 18 h. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ (200 mL), washed with water (3 × 250 mL), and dried ($Na_2SO_4$). The solvent was evaporated off and the crude product was purified by column chromatography (silica gel, 2% MeOH in $CHCl_3$) and recrystallized from toluene to give the *R* isomer **5a** (10 g, 26%) as colorless needles; mp 72–74 °C; $[\alpha]^{20}_D$ −22.91° (*c* 6.330 g $dL^{-1}$, MeOH). Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

**(*S*)-α-[[(4-Methoxyphenyl)methoxy]methyl]-1*H*-imidazole-1-ethanol (23b)**, prepared from (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol by the above procedure, was obtained as colorless needles; mp 72–73 °C; $[\alpha]^{20}_D$ −22.22° (*c* 2.210 g $dL^{-1}$; MeOH). Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

**Ethyl 2,2-Dimethyl-6-bromohexanoate.** A solution of *n*-BuLi (63 mL of 1.6 M, 0.10 mol) in hexane was added dropwise to a solution of diisopropylamine (10.1 g, 0.10 mol) in anhydrous THF (100 mL) at −50 °C. The mixture was stirred for 0.5 h and then cooled to −70 °C. A solution of ethyl isobutyrate (12.2 g, 0.105 mol) in THF (20 mL) was then added and the resulting mixture was stirred at −70 °C for 1 h. 1,4-Dibromobutane (30.4 g, 0.14 mol) was then added, followed by HMPA (30 g). The mixture was maintained at −70 °C for 0.5 h, then warmed to room temperature over 1 h, and evaporated to dryness under reduced pressure. The residue was treated with saturated aqueous $NH_4Cl$ (500 mL) and extracted with EtOAc (2 × 150 mL). The combined extracts were washed with water (100 mL), HCl (2 × 100 mL of 1 M), and saturated aqueous $NaHCO_3$ (100 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was distilled to give the title compound as a pale yellow oil (bp 73 °C (0.06 mmHg)); NMR ($CDCl_3$) δ 1.20 (s, 6 H), 1.28 (t, 3 H), 1.35–1.62 (m, 4 H), 1.78–2.00 (quintet, 2 H), 3.42 (t, 2 H), 4.15 (q, 2 H).

**Method A. 2,2-Dimethyl-6-[2-(1*H*-imidazol-1-yl)-1-[[(4-methoxyphenyl)methoxy]methyl]ethoxy]hexanoic Acid (13).** A stirred suspension of powdered KOH (10 g, 0.18 mol) in dry DMSO (20 mL) was treated with **5**[8] (10.0 g, 0.038 mol) and stirred for 0.5 h. The mixture was then treated with ethyl 2,2-dimethyl-6-bromohexanoate (10.0 g, 0.040 mol) and stirred for 12 h. Water (200 mL) was added and the resulting solution was washed with EtOAc (5 × 100 mL), acidified to pH 6 (HCl), and extracted with EtOAc (3 × 150 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated to give a crude product which was purified by column chromatography (silica gel, 10% EtOH in EtOAc) and recrystallized from EtOAc–$Et_2O$

(19) Simonyi, M. *Med. Res. Rev.* **1984**, *4*, 359.
(20) Trager, W. F.; Testa, B. In *Drug Metabolism and Disposition: Considerations in Clinical Pharmacology*; Wilkinson, G. R., Rawlins, D. M., Eds.; M.T.P.: Lancaster, England, 1985; Chapter 3.
(21) Drayer, D. E. *Clin. Pharmacol. Ther.* **1986**, *40*, 125.

to give **13** (4.8 g, 31%) as a colorless crystalline solid; mp 69–70 °C; NMR ($CDCl_3$) δ 1.19 (s, 6 H), 1.15–1.60 (m, 6 H), 3.15–3.37 (m, 2 H), 3.37–3.65 (m, 3 H), 3.82 (s, 3 H), 4.12 (ABM oct, 2 H), 4.44 (s, 2 H), 6.90 (s, 1 H), 6.91 and 7.25 (AB q, 4 H), 7.04 (s, 1 H), 7.65 (s, 1 H), 9.20 (br s, 1 H). Anal. ($C_{22}H_{32}N_2O_5$) C, H, N.

This method was used for the preparation of the *R* isomer **13a**, ($[\alpha]^{20}_D$ −38.1° (*c* 2.00 g $dL^{-1}$, EtOH)) and the *S* isomer **13b** ($[\alpha]^{20}_D$ +38.7° (*c* 2.00 g $dL^{-1}$, EtOH)) and for compounds **7**, **9**, **11**, and **15** with use of the appropriate ω-bromoalkanoic acid ethyl esters.

**Method B. 1-(1*H*-Imidazol-1-yl)-3-[(4-methoxyphenyl)-methoxy]-2-propanone.** A solution of dry DMSO (18.8 g, 0.24 mol) in $CH_2Cl_2$ (50 mL) was added dropwise over 10 min to a stirred solution of oxalyl chloride (14.5 g, 0.11 mol) in $CH_2Cl_2$ (200 mL) at −60 °C. The resulting solution was stirred for 2 min and then treated with a solution of **5** (24.2 g, 0.092 mol) in $CH_2Cl_2$ (50 mL) and stirred for an additional 15 min. $Et_3N$ (50 g, 0.5 mol) was added and the resulting solution was allowed to equilibrate to room temperature, stirred for 10 min, diluted with $CH_2Cl_2$ (500 mL), washed with water (3 × 250 mL) and aqueous saturated $NH_4Cl$ (2 × 500 mL), and dried ($Na_2SO_4$). The solvent was evaporated to give the title compound (22 g, 92%) as an orange oil, which was used directly without further purification; NMR ($CDCl_3$) δ 3.80 (s, $CH_3$), 4.09 (s, $CH_2$), 4.51 (s, 2 H), 4.92 (s, 2 H), 6.75 (s, 1 H), 6.93 and 7.29 (AB q, 4 H), 7.08 (s, 1 H), 7.38 (s, 1 H).

**Methyl 4-(1*H*-Imidazol-1-yl)-3-[[(4-methoxyphenyl)-methoxy]methyl]-2-butenoate (6).** A mixture of the 2-propanone (8.80 g, 0.0338 mol) and [(carbomethoxy)-methylene]triphenylphosphorane (16.7, 0.050 mol) in dry THF (100 mL) was stirred at 18 °C for 72 h. The solvent was evaporated and the residue was treated with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with saturated aqueous $NH_4Cl$ (2 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography (silica gel, gradient 10–80% EtOAc in hexane) to give **6** (5.7 g, 53%) as a pale yellow oil; NMR ($CDCl_3$) δ 3.67 (s, 3 H), 3.82 (s, 3 H), 4.46 (s, 2 H), 4.63 (d, 2 H), 4.78 (d, 2 H), 5.42 (t, 1 H), 6.85 (s, 1 H), 6.90 and 7.26 (AB q, 4 H), 7.09 (s, 1 H), 7.44 (s, 1 H). Anal. ($C_{17}H_{20}N_2O_4$) C, H, N.

**Ethyl 9-(1*H*-Imidazol-1-yl)-8-[[(4-methoxyphenyl)methoxy]methyl]-5(*Z*)-nonenoate (19).** A stirred solution of **6** (6.86 g, 0.0217 mol) in dry THF (50 mL) was treated with $LiAlH_4$ (2.40 g, 0.063 mol) and stirred for 12 h. The solution was washed with saturated aqueous $NH_4Cl$ (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated off to give the crude alcohol (5.6 g; >90% pure by NMR) as an oil. Swern oxidation of the crude alcohol (method B) gave the corresponding aldehyde (5.0 g, 90%), which was used directly without further purification; NMR ($CDCl_3$) δ 2.30–2.70 (m, 3 H), 3.29 (ABM oct, 2 H), 3.82 (s, 3 H), 3.96–4.12 (m, 2 H), 4.40 (s, 2 H), 6.90 (s, 1 H), 6.91 and 7.25 (AB q, 4 H), 7.06 (s, 1 H), 7.41 (s, 1 H), 9.73 (s, 1 H); IR (neat) 1720 $cm^{-1}$ (C=O).

A suspension of (4-carboxybutyl)triphenylphosphonium bromide (13.2 g, 0.030 mol) in dry THF (50 mL) was treated with KO-*t*-Bu (6.72 g, 0.060 mol) at 0 °C under an $N_2$ atmosphere and stirred for 30 min. A solution of the crude aldehyde (5.00 g, 0.0174 mol) in dry THF (60 mL) was then added and the mixture was stirred for 16 h at room temperature. The solvent was evaporated and the residue was treated with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were extracted with NaOH (3 × 100 mL of 1.0 M). The aqueous solution was adjusted to pH 6.5 with HCl (4.0 M) and extracted with EtOAc (3 × 100 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated to give the crude product which was purified by column chromatography (silica gel, $CHCl_3$) to give the acid **18** (4.1 g, 51% overall) as a hygroscopic oil; NMR ($CDCl_3$) δ 1.60–1.80 (m, 2 H), 1.92–2.14 (m, 5 H), 2.24–2.40 (m, 2 H), 3.15–3.31 (m, 2 H), 3.81 (s, 3 H), 3.89–4.08 (m, 2 H), 4.38 (s, 2 H), 5.28–5.56 (d of m, 2 H, *J* = 12 Hz), 6.84 (s, 1 H), 6.89 and 7.24 (AB q, 4 H), 7.05 (s, 1 H), 7.61 (s, 1 H), 9.32 (br s, 1 H); no satisfactory elemental analysis could be obtained for this compound, which was further characterized by esterification (method C below) to give **19** as a pale yellow oil; NMR ($CDCl_3$) δ 1.26 (t, 3 H), 1.68 (h, 2 H), 1.92–2.16 (m, 5 H), 2.29 (t, 2 H), 3.25 (d, 2 H), 3.82 (s, 3 H), 3.98 (ABM oct, 2 H), 4.12 (q, 2 H), 4.39 (s, 2 H), 5.28–5.53 (m, 2 H), 6.84 (s, 1 H), 6.90 and 7.25 (AB q, 4 H), 7.04 (s, 1 H), 7.40 (s, 1 H). Anal. ($C_{23}H_{32}N_2O_4$) C, H, N.

**Ethyl 2,2-Dimethyl-6-[2-(1*H*-imidazol-1-yl)-1-[[(4-methoxyphenyl)methoxy]methyl]ethoxy]hexanoate (14).** A suspension of NaH (0.91 g of an 80% dispersion in oil, 0.030 mol) in dry DMF (50 mL) was treated with **5** and stirred at room temperature for 1 h. The resulting mixture was treated dropwise with ethyl 2,2-dimethyl-6-bromohexanoate (9.03 g, 0.036 mol) and stirred for a further 12 h. The solvent was evaporated and the residue was quenched with saturated aqueous $NH_4Cl$ (100 mL) and extracted with EtOAc (2 × 100 mL). The combined extracts were dried ($Na_2SO_4$), and the solvent was evaporated to give a crude product which was purified by column chromatography (silica gel, $CHCl_3$) to give **14** (1.70 g, 14%) as a colorless oil; NMR ($CDCl_3$) δ 1.14 (s, 6 H), 1.23 (t, 3 H), 1.37–1.55 (m, 6 H), 3.20–3.35 (m, 2 H), 3.40–3.65 (m, 3 H), 3.81 (s, 3 H), 4.08 (ABM oct, 2 H), 4.10 (AB q, 2 H), 4.45 (s, 2 H), 6.91 and 7.25 (AB q, 4 H), 6.92 (s, 1 H), 7.02 (s, 1 H), 7.46 (s, 1 H). Anal. ($C_{24}H_{36}N_2O_5$) C, H, N.

**9-(1*H*-Imidazol-1-yl)-8-[[(4-methoxyphenyl)methoxy]-methyl]nonanoic Acid (20).** A solution of **18** (1.17 g, 0.00316 mol) in EtOH (100 mL) was hydrogenated at atmospheric pressure over 10% Pd/C (0.10 g). The calculated amount of $H_2$ was taken up in 2 h. The catalyst was removed by filtration and the solvent was evaporated to give the crude product which was purified by column chromatography (silica gel, gradient 5–10% EtOH in $CHCl_3$) and recrystallized from $CH_2Cl_2$–$Et_2O$ to give **20** (1.00 g, 85%) as a colorless crystalline solid; mp 79–80 °C; NMR ($CDCl_3$) δ 1.22–1.42 (m, 8 H), 1.54–1.71 (m, 2 H), 1.88–2.01 (m, 1 H), 2.33 (t, 2 H), 3.24 (ABM oct, 2 H), 3.81 (s, 3 H), 3.98 (ABM oct, 2 H), 4.40 (AB q, 2 H), 6.82 (s, 1 H), 6.89 and 7.25 (AB q, 4 H), 7.06 (s, 1 H), 7.52 (br s, 1 H), 7.61 (s, 1 H). Anal. ($C_{21}H_{30}N_2O_4$) C, H, N.

**Method C. Ethyl 6-[2-(1*H*-Imidazol-1-yl)-1-[[(4-methoxyphenyl)methoxy]methyl]ethoxy]hexanoate (10).** A stirred solution of **9** (10 g, 0.026 mol) and triethylamine (3.0 g, 0.030 mol) in dry $CH_2Cl_2$ (100 mL) at −50 °C was treated dropwise with ethyl chloroformate (3.2 g, 0.029 mol). The solution was allowed to warm up to 0 °C over 0.5 h, cooled back to −50 °C, and treated with EtOH (6 mL, 0.1 mol). The solution was allowed to warm up and then stirred for 15 h at 18 °C. The resulting mixture was shaken with saturated aqueous $Na_2CO_3$ (500 mL) and the organic layer was separated. The solution was dried ($Na_2SO_4$) and the solvent was evaporated to give the crude product which was purified by column chromatography (silica gel, 5% EtOH in $CHCl_3$) to give **10** as a pale yellow oil; bp 240 °C (0.05 mmHg); NMR ($CDCl_3$) δ 1.20–1.35 (m, 2 H), 1.26 (t, 3 H), 1.44–1.68 (m, 4 H), 2.27 (t, 2 H), 3.22–3.36 (m, 2 H), 3.52–3.64 (m, 1 H), 3.81 (s, 3 H), 4.05 (ABM oct, 2 H), 4.12 (AB q, 2 H), 4.45 (s, 2 H), 6.90 and 7.28 (AB q, 4 H), 6.91 (s, 1 H), 7.02 (s, 1 H), 7.46 (s, 1 H). Anal. ($C_{22}H_{32}N_2O_5$) C, H, N.

This method was used for the preparation of compounds **8**, **12**, **19**, and **21**.

**4-[2-(1*H*-Imidazol-1-yl)-1-[[(4-methoxyphenyl)methoxy]-methyl]ethoxy]butanal.** A stirred suspension of NaH (1.50 g of a 60% dispersion in oil, 0.0375 mol) in dry DMSO (30 mL) was heated at 70 °C for 1 h. The resulting solution was cooled to 18 °C, treated with a solution of **5** (6.0 g, 0.0229 mol) in DMSO (25 mL), stirred for 5 min, and then treated with a solution of 2-(3-iodopropyl)-1,3-dioxolane[12] (8.30 g, 0.0343 mol) in DMSO (10 mL). The reaction mixture was stirred for 16 h, poured into water (250 mL), and extracted with $CH_2Cl_2$ (3 × 150 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated to give the crude product which was purified by column chromatography (silica gel, 2% EtOH in $CHCl_3$) to give the acetal as a pale yellow oil, which was treated with $H_2SO_4$ (25 mL of 0.5 M) and stirred under an $N_2$ atmosphere for 25 min. The solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated to give the title compound (3.1 g, 32%), which was used directly; NMR ($CDCl_3$) δ 1.82 (h, 2 H), 2.43 (d of t, 2 H), 3.27–3.36 (m, 2 H), 3.40–3.66 (m, 3 H), 3.82 (s, 3 H), 4.05 (ABM oct, 2 H), 4.45 (s, 2 H), 6.91 and 7.28 (AB q, 4 H), 6.90 (s, 1 H), 7.03 (s, 1 H), 7.47 (s, 1 H), 9.70 (s, 1 H).

**Ethyl 6-[2-(1*H*-Imidazol-1-yl)-1-[[(4-methoxyphenyl)-methoxy]methyl]ethoxy]-2(*E*)-hexenoate (17).** A mixture of the 4-butanal (3.20 g, 0.0096 mol) and [(carboethoxy)-

methylene]triphenylphosphorane (5.0 g, 0.0144 mol) in benzene (100 mL) was stirred for 1 h. The solution was extracted with HCl (4 × 100 mL of 1.0 M), and the combined extracts were basified with $NaHCO_3$ and extracted with EtOAc (3 × 150 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated to give the crude product which was purified by column chromatography (silica gel, 2% EtOH in $CHCl_3$) to give **17** (1.51 g, 39%) as a yellow oil; NMR ($CDCl_3$) δ 1.29 (t, 3 H), 1.64 (h, 2 H), 2.16 (q, 2 H), 3.24–3.36 (m, 2 H), 3.42–3.64 (m, 3 H), 3.80 (s, 3 H), 4.06 (ABM oct, 2 H), 4.18 (AB q, 2 H), 4.46 (s, 2 H), 5.78 (d, 1 H, $J$ = 15.8 Hz), 6.84–6.96 (m, 2 H), 6.89 and 7.25 (AB q, 4 H), 7.02 (s, 1 H), 7.46 (s, 1 H). Anal. ($C_{22}H_{30}N_2O_5$) C, H, N.

**6-[2-(1*H*-Imidazol-1-yl)-1-[[(4-methoxyphenyl)methoxy]methyl]ethoxy]-2(*E*)-hexenoic Acid (16).** A mixture of **17** (0.60 g) in ethanolic KOH (30 mL of 10%) was stirred at 40 °C for 1 h. The solvent was evaporated and the residue was dissolved in NaOH (100 mL of 2 M). The solution was washed with EtOAc (2 × 20 mL), acidified to pH 6.0 with HCl (1 M), and extracted with EtOAc (3 × 50 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated to give the crude product which was purified by column chromatography (silica gel, 5% EtOH in $CHCl_3$) to give **16** (0.32 g, 57%) as a hygroscopic oil; NMR ($CDCl_3$) δ 1.64 (h, 2 H), 2.15 (q, 2 H), 3.21–3.35 (m, 2 H), 3.45–3.62 (m, 3 H), 3.81 (s, 3 H), 4.07 (ABM oct, 2 H), 4.45 (s, 2 H), 5.81 (d, 1 H, $J$ = 15.6 Hz), 6.84–6.96 (m, 2 H), 6.90 and 7.25 (AB q, 2 H), 7.07 (s, 1 H), 7.70 (s, 1 H), 8.74 (br s, 1 H). Anal. ($C_{20}H_{26}N_2O_5 \cdot 0.5H_2O$) C, H, N.

**Pharmacological Evaluation. In Vitro Assay of Human Platelet Thromboxane Synthase.** The methodology used for the determination of activity against human whole platelet and human platelet microsomal thromboxane synthase have been described previously.[8]

**Ex Vivo Evaluation of Compounds vs. Collagen-Induced Whole Blood Thromboxane $B_2$ Formation.** Conscious guinea pigs (Dunkin–Hartley males, 300–350 g) were fasted overnight prior to being dosed orally by gavage with drug or vehicle alone (a formulation of 50% polyethylene glycol 400 and 50% v/v (carboxymethyl)cellulose). Oral dose volumes were always 0.1 mL/100 g body weight. Animals were anesthetized with pentabarbitone sodium (60 mg/kg) given intraperioneally 10 min before the bleed time. Animals were dosed and bled at 0.5-, 1.0-, 3.0-, and 6.0-h time points, with an interval of 1.0 h being used for basic screening, and groups of at least four animals per drug and time treatment. At the bleed time the intraperitoneal cavity was opened and 4.5 mL of blood was drawn into a syringe containing 3% trisodium citrate (0.5 mL) from the abdominal aorta via a 21/23 gauge butterfly needle. The blood was gently mixed with the citrate in the syringe, and aliquots (0.5 mL) were removed into micro-Eppendorf tubes and stirred at 1000 rpm and equilibrated at 37 °C for 2 min prior to the addition of collagen (10 μg $mL^{-1}$) or buffer as control. The incubation was continued for 5 min, at which time formation of $TxB_2$ reaches a plateau, and terminated by addition of indomethacin (1 μL of 10 μg $mL^{-1}$ in DMSO) and chilling on ice. Plasma samples were obtained by centrifugation (10000$g$ for min) and kept at −30 °C until RIA for $TxB_2$ as previously described.[8]

The raw results obtained in the RIA from a 0.1-mL sample of 1:20 diluted plasma were corrected to pg $mL^{-1}$ in original plasma sample (×200). The RIA values were then normalized for initial platelet count within the blood sample to $5.0 \times 10^8$ $mL^{-1}$ (range of platelet count in citrated guinea pig whole blood is variable between the limits $2.0 \times 10^8$ and $7.0 \times 10^8$ $mL^{-1}$). The test and control results were then compared, and inhibition (percent) calculated in the normay way. Statistical analysis was by the Student's $t$ test.

**In Vitro Assay of 6-KetoPGF$_{1\alpha}$ in Collagen-Stimulated Human Whole Blood.** Formation of prostacyclin in whole blood was estimated by using the method reported by Defreyn, Deckmyn, and Vermylen.[17] Citrated human whole blood was obtained as described for PRP studies. Aliquots of blood (1.0 mL) were preincubated for 2 min at 37 °C and stirred (1000 rpm) in an aggregometer cuvette. Vehicle or drug was added (1-μL volume) and sequential samples (50 μL) removed over a 5-min time period before addition of collagen (3 μg $mL^{-1}$). Further samples were removed 1, 2, 4, and 8 min after the addition of collagen. Plasma was obtained from each sample by rapid centrifugation (1 min at 10000$g$), left at room temperature for 1 h to facilitate breakdown of $PGI_2$, and then deep frozen until subsequent estimation of 6-ketoPGF$_{1\alpha}$ immunological equivalents by radioimmunoassay.

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# Antipsychotic Activity of Substituted γ-Carbolines

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Several novel substituted γ-carbolines were synthesized and examined in a series of in vitro and in vivo pharmacological tests to determine potential antipsychotic activity. Most compounds were orally active in blocking the conditioned avoidance response (CAR) in rats but did not antagonize apomorphine-induced stereotyped behavior. Compound **17** (Wy-47,384), a γ-carboline with a 3-(3-pyridinyl)propyl side chain, was selected for development as an atypical antipsychotic agent because of its potent and selective profile in preclinical psychopharmacological tests. It blocked CAR in rats with an $AB_{50}$ of 14 mg/kg po, showed weak affinity for the $D_2$ receptor site ($K_i$ = 104 nM), and showed differential potency in antagonizing apomorphine-induced stereotyped behavior ($ED_{50}$ = 11 mg/kg ip) and climbing behavior ($ED_{50}$ = 4 mg/kg ip). Such activities are suggestive of antipsychotic efficacy combined with a low potential for extrapyramidal side effect (EPS) liability.

We recently reported the discovery of potential antipsychotic activity in a series of substituted β-carbolines (**1**) that may have a low potential for extrapyramidal side effect (EPS) liability.[1] One of these, Wy-46,320,

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