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Thromboxane A_2 Synthetase Inhibitors. I. Syntheses and Activities of Various *N*-Heteroaromatic Derivatives

MUNEFUMI KANAO,* YOSHIFUMI WATANABE, YOUICHI KIMURA, HIDEYUKI KANNO, HIDEO KUBO, and SHIN-ICHIRO ASHIDA

Daiichi Seiyaku Co., Ltd., Research Institute, 13 Kita-kasai 1–16, Edogawa-ku, Tokyo 134, Japan

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Basic *N*-heteroaromatic derivatives (1,2,4-triazole, thiazole and pyrimidine derivatives) having a 2-[4-(carboxy)phenoxy]ethyl moiety or a 4-[2-(carboxy)vinyl]benzyl moiety were prepared, and evaluated for ability to inhibit thromboxane A_2 (TXA_2) synthesis. Among the compounds prepared in this study, the 5-substituted thiazole derivatives **14d**, **27** and **28** were more potent inhibitors of TXA_2 production than the corresponding imidazole derivatives, and the 1-substituted 1*H*-1,2,4-triazole derivatives **14a** and **15a** were almost as potent as the corresponding imidazole derivatives.

Keywords——thiazole; 1*H*-1,2,4-triazole; pyrimidine; imidazole; thromboxane A_2; TXA_2 synthetase inhibitor

Thromboxane A_2 (TXA_2) is a kind of prostaglandin endoperoxide metabolite, and possesses potent vascular constricting and platelet aggregating activities. Prostacyclin (PGI_2) is another such compound, and has potent vasodilating and platelet antiaggregating activities. TXA_2 and PGI_2 are produced from prostaglandin G_2 (PGG_2) and/or prostaglandin H_2 (PGH_2) by TXA_2 synthetase and PGI_2 synthetase, respectively. It was postulated that, under normal conditions, there is a balance between the biological effects of TXA_2 and PGI_2, but an increased plasma TXA_2 level has been observed among patients with ischemic heart diseases.[1] Reduction of TXA_2 level or increase of PGI_2 level may be one approach to the treatment of these diseases. Thus, many selective TXA_2 synthetase inhibitors without inhibitory effects on PGI_2 synthetase and cyclooxygenase have been synthesized,[2-7] and several of these compounds have been subjected to clinical trials for a variety of diseases such as ischemic heart disease, thromboembolic disorders and cerebral circulatory disorders. Most of the compounds possessing a potent selective inhibitory effect on TXA_2 synthesis are 1-substituted imidazole, 3-substituted pyridine and imidazo[1,5-*a*]pyridine derivatives. Several investigators[2-7] reported that introduction of a carboxyl moiety at the terminal of the side chain on the imidazole or pyridine ring increased the inhibitory activity, and the optimum distance between the carboxyl group and the heterocycle was between 8.5 and 10 Å.[2] This distance appears to correspond to that between the carboxyl group and the endoperoxide moiety of PGG_2 or PGH_2. Thus, it has been assumed that compounds having a weakly basic *N*-heteroaromatic ring at one end of the molecule and a carboxyl group at the other possess a potent activity, and the most suitable distance between the two is about 9 Å.

On the basis of these hypotheses, some series of compounds having a weakly basic *N*-heterocyclic ring were synthesized and tested for TXA_2 synthetase inhibitory activity. This paper deals with the syntheses and activities of a series of 1-substituted 1*H*-1,2,4-triazole, 4-substituted 4*H*-1,2,4-triazole, 5-substituted pyrimidine and 5-substituted thiazole derivatives.

Chemistry

The compounds prepared in this paper are shown in Table I, and the synthetic pathways employed are outlined in Charts 1, 2 and 3.

Preparation of 1-substituted 1*H*-1,2,4-triazoles was carried out by alkylation of 1*H*-1,2,4-triazole with the halide (**1**, X=I) to give a 1-substituted derivative (**2a**) as a main product.

Synthesis of a 4-substituted analog (**2b**) was carried out by another route from ethyl 4-(2-aminoethoxy)benzoate (**3**)[8] *via* the thiosemicarbazide (**4**), because only a small amount of **2b** was formed by the alkylation described above. Compound **4**, prepared from **3**, was treated with formic acid, and then heated in ethanol in the presence of pyridine to give **5**. Treatment of **5** with hydrogen peroxide in acetic acid gave the desired **2b**.

A pyrimidine derivative (**2c**) was prepared from **1** (X=Br). Condensation of compound

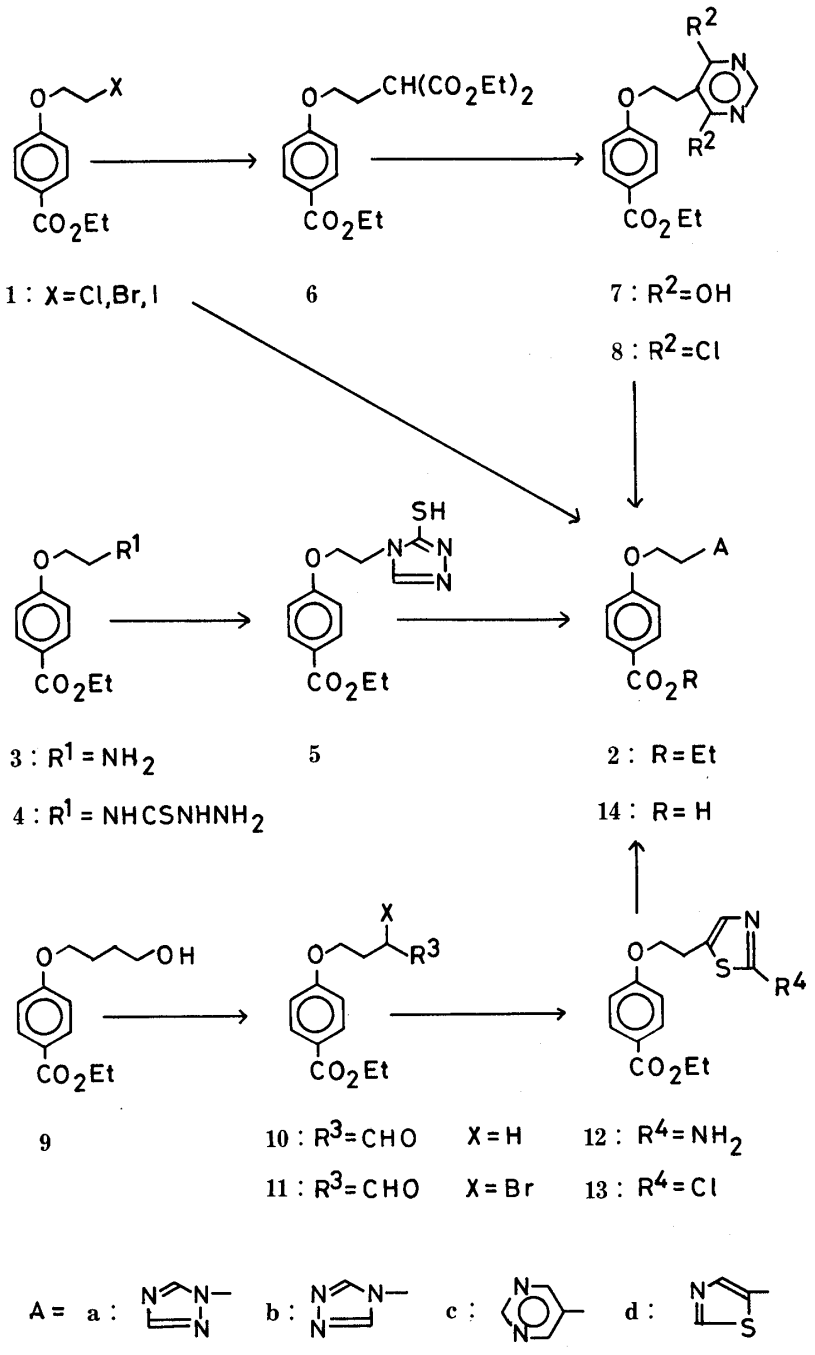


Chart 1

6, prepared from **1** (X=Br), with formamidine acetate in a solution of sodium ethoxide in ethanol gave a 5-substituted-4,6-dihydroxypyrimidine (**7**). Chlorination of **7**, followed by hydrogenation gave a 5-substituted pyrimidine derivative (**2c**).

A thiazole derivative substituted with a 2-[4-(carboethoxy)phenoxy]ethyl moiety at the 5 position on the thiazole ring was prepared from ethyl 4-(4-hydroxybutoxy)benzoate (**9**). Oxidation of **9** with pyridinium chlorochromate (PCC), followed by bromination, and treatment with thiourea afforded a 2-aminothiazole derivative (**12**). Sandmeyer reaction of **12**

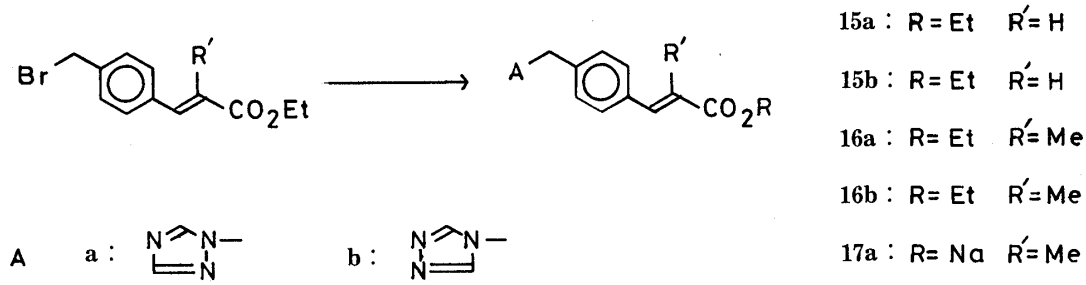


Chart 2

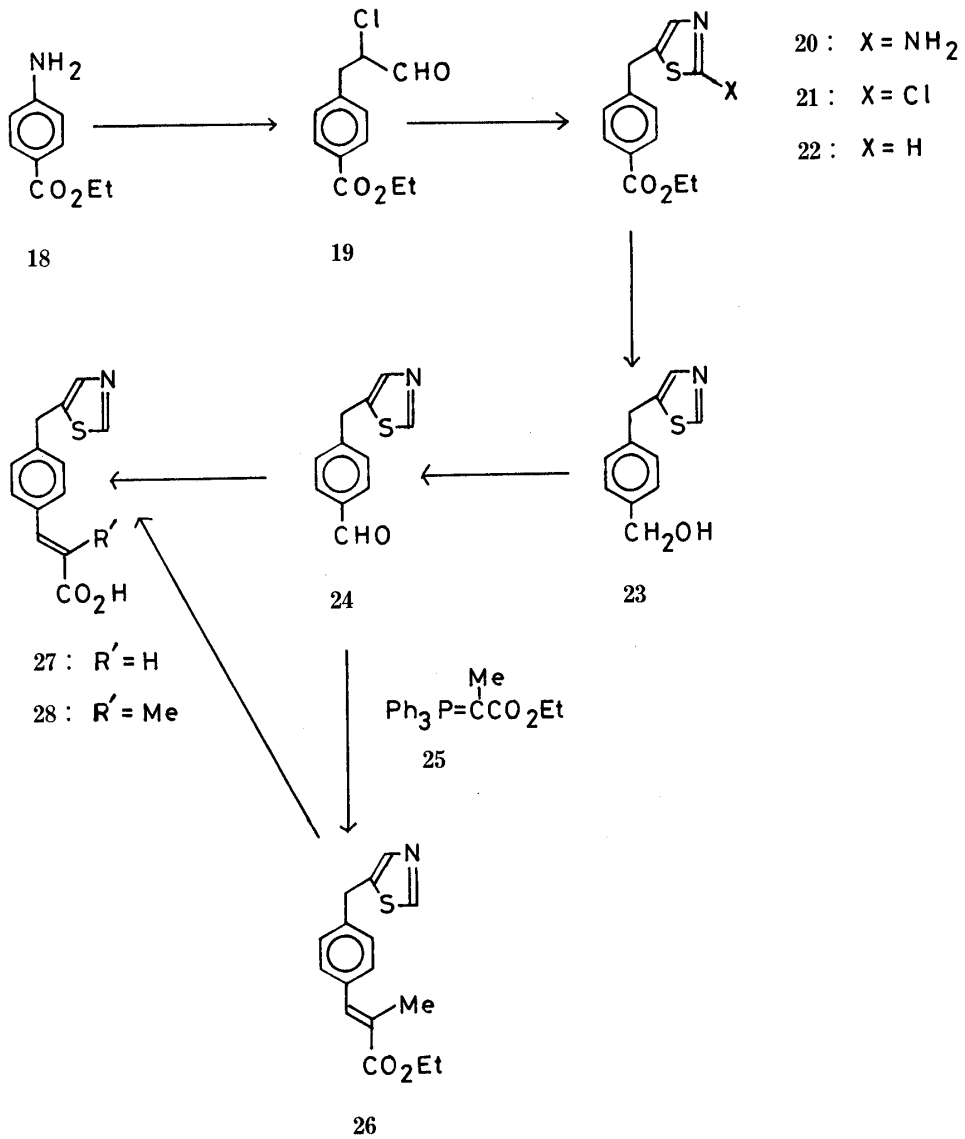


Chart 3

gave the crude chloride **13**, which was reduced with zinc powder in acetic acid to give the desired thiazole compound (**2d**).

The esters (**2a**—**d**) were hydrolyzed in aqueous sodium hydroxide solution to give the corresponding carboxylic acids (**14a**—**d**).

Alkylation of 1*H*-1,2,4-triazole with ethyl 3-[4-(bromomethyl)phenyl]-2-propenoate gave **15a** as a main product. However, alkylation with ethyl 3-[4-(bromomethyl)phenyl]-2-methyl-2-propenoate afforded a mixture of the 1-substituted isomer (**16a**) and 4-substituted isomer (**16b**). Compound **16a** was transformed to **17a** by hydrolysis.

Reaction of the chloroaldehyde derivative (**19**), prepared from **18** by a method similar to that described by Dombrovskii *et al.*,[9] with thiourea gave the 5-substituted-2-aminothiazole (**20**). Compound **20** was treated with cupric chloride and tertiary butyl nitrite to give the 2-chlorothiazole **21**, which was reduced by a similar method to that described for the preparation of **2d** to give **22**. Reduction of **22** with lithium aluminum hydride, followed by oxidation with *N*,*N*-dicyclohexylcarbodiimide in dimethylsulfoxide afforded 4-(5-thiazolylmethyl)benzaldehyde (**24**). Wittig reaction of **24** with **25**, followed by hydrolysis gave **28**. The cinnamic acid derivative (**27**) was prepared by condensation of **24** with malonic acid.

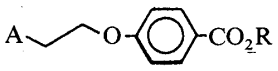
Biological Activities

The activities of the compounds were expressed as the IC_{50} values for the inhibition of TXA_2 synthesis in rat platelet-rich plasma (PRP). Usually the potency of a TXA_2 synthetase inhibitory compound is indicated as its inhibitory activity against the TXA_2 synthesis reaction mediated by a partially purified enzyme fraction such as platelet microsomes.[2-7] However, we think that the value of the inhibitory activity obtained from a less purified assay system using PRP may be more practical than that obtained from the more purified enzyme assay system, because the former reflects not only the inhibitory activity against the enzyme itself but also the ability of the compound to permeate through the plasma membrane of platelets and the effects of its interaction with proteins, lipids and many other substances in blood plasma and the cytoplasm of platelets.

Table I shows the *in vitro* inhibitory activities of the compounds obtained here on TXA_2 production in rat PRP. 1-Substituted-1*H*-1,2,4-triazole derivatives (**14a**, **15a**, **17a**) exhibited potent inhibitory activities against TXA_2 synthesis, and were as potent as the corresponding imidazole derivatives (Dazoxiben and OKY-046). On the other hand, introduction of a 4*H*-1,2,4-triazol-4-yl or 5-pyrimidinyl moiety diminished the activity (compare **14b** and **14c** with Dazoxiben). Replacement of the imidazole ring by a thiazole ring increased the activities (compare **14d** and **27** with Dazoxiben and OKY-046, respectively).

In some kinds of cells, tissues and organs, some selective TXA_2 synthetase inhibitors have been found to increase the production of particular prostaglandins (PGs) such as PGE_2, $PGF_{2\alpha}$, PGD_2 and PGI_2 along with the inhibition of TXA_2 production.[10] On the other hand, cyclooxygenase inhibitors inhibit the production of not only TXA_2, but also PGs synthesized through the reaction catalyzed by fatty acid cyclooxygenase. The suppression of the production of certain PGs, especially PGI_2 and PGD_2 is undesirable for the treatment of ischemic heart disease, because the former has a potent vasodilating activity and both have potent antiaggregative activities against platelets.[6,10] In rat platelets the selective inhibition of TXA_2 synthetase results in a marked increase in PGE_2 production and in a much smaller increase in other PGs such as $PGF_{2\alpha}$, PGD_2 and PGI_2. Therefore in the assay system using rat PRP, the selectivity of the inhibitory activity of a compound to TXA_2 synthetase as against cyclooxygenase can be estimated by measuring the increase in PGE_2 production along with the inhibition of TXA_2 production. In this paper, the selectivities of the tested compounds are indicated as the "conversion ratio (PGE_2/TXA_2)," obtained by dividing the individual amounts of the increase in PGE_2 production by those of the decrease in TXA_2 production at

TABLE I. Preparation of *N*-Heteroaromatic Derivatives and Inhibitory Activities of TXA_2 Production



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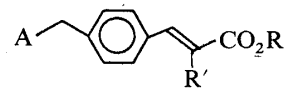
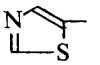
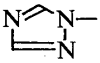
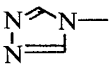
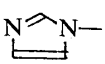
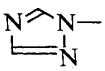
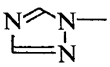
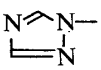
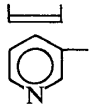


II

No.	Structure	A	R	R′	Yield (%)	mp (°C)	Formula Calcd (Found) C	H	N	Inhibition of TXA_2 production *in vitro* (rat PRP) IC_{50} (μM)	Converting ratio
2a	I		Et	—	55	118—131[a]	$C_{13}H_{15}N_3O_3 \cdot HCl$ 52.44 (52.14)	5.42 (5.18)	14.11 (14.03)	22	0.53
2b	I		Et	—	75	125—127[b]	$C_{13}H_{15}N_3O_3$ 59.76 (59.59)	5.79 (5.83)	16.08 (16.03)	1300	—
2c	I		Et	—	51	93—95[b]	$C_{15}H_{16}N_2O_3$ 66.16 (16.32)	5.92 (5.98)	10.29 (10.03)	>50	—
2d	I		Et	—	57	116—126[a]	$C_{14}H_{15}NO_3S \cdot HCl$ 53.59 (53.19)	5.14 (5.14)	4.46 (4.38)	39	—
14a	I		Na	—	39	>280[a]	$C_{11}H_{10}N_3NaO_3$ 51.77 (51.74)	3.95 (3.97)	16.47 (16.37)	11	0.43
14b	I		Na	—	56	>280[a]	$C_{11}H_{10}N_3NaO_3$ 51.77 (51.47)	3.95 (3.91)	16.47 (16.33)	>1000	—
14c	I		Na	—	76	>280[a]	$C_{13}H_{11}N_2NaO_3$ 58.65 (58.71)	4.16 (4.22)	10.52 (10.59)	65	0.61
14d	I		Na	—	92	>280[a]	$C_{12}H_{10}NNaO_3S$ 53.13 (53.41)	3.72 (3.80)	5.16 (5.01)	3.8	0.84
Dazoxiben[d]	I		H	—						11	0.62
15a	II		Et	H	48	139—145[a]	$C_{14}H_{15}N_3O_2 \cdot HCl$ 57.24 (57.50)	5.49 (5.28)	14.31 (11.49)	6.6	0.53
16a	II		Et	Me	54	135—147[a]	$C_{15}H_{17}N_3O_2 \cdot HCl$ 58.54 (58.69)	5.89 (5.91)	13.65 (13.81)	16	1.04
16b	II		Et	Me	10	182—195[a]	$C_{15}H_{17}N_3O_2 \cdot HCl$ 58.54 (58.48)	5.89 (5.96)	13.65 (13.95)	200	—
17a	II		Na	Me	82	>280[a]	$C_{13}H_{12}N_3NaO_2$ 58.87 (59.02)	4.56 (4.60)	15.84 (15.56)	5.8	0.36
27	II		H	H	54	183—185[c]	$C_{13}H_{11}NO_2S$ 63.65 (63.61)	4.52 (4.47)	5.71 (5.76)	1.5	0.68
28	II		H	Me	48	182—184[c]	$C_{14}H_{13}NO_2S$ 64.84 (64.81)	5.05 (5.21)	5.40 (5.31)	0.22	1.22
OKY-046[d]	II		H	H						4.5	0.54
OKY-1581[d]	II		Na	Me						0.15	0.60

a) Recrystallized from EtOH–ether. *b*) Recrystallized from EtOAc–petr. ether. *c*) Recrystallized from 50% EtOH. *d*) These compounds were prepared in our institute for experimental use. See references 2 and 3.

the concentrations of the tested compounds that gave about 90% inhibition of TXA_2 production in rat PRP stimulated by arachidonic acid. Theoretically the ratios will be high (about 0.5 to above 1.0) for highly selective TXA_2 synthetase inhibitors but low (near to 0) for the less selective ones or cyclooxygenase inhibitors.

Dazoxiben and OKY-046 (both are imidazole derivatives), which were reported[2] to be highly selective TXA_2 synthetase inhibitors, showed conversion ratios of 0.62 and 0.54, respectively, in our experiment.

The conversion ratios of thiazole derivatives (**14d**, **27**, **28**) were 0.84, 0.68 and 1.22, respectively, being higher than those for the corresponding imidazole derivatives. However, those for triazole derivatives (**14a** and **17a**) were 0.43 and 0.36, respectively, being lower than those for Dazoxiben and OKY-046.

From these results, it can be assumed that the inhibitory activities of the thiazole derivatives against the TXA_2 production in PRP are due to the selective inhibition of TXA_2 synthetase.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were taken on a Hitachi 285 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with Hitachi R40 and JEOL JNM-FX90Q spectrometers (Me_4Si as an internal standard). For column chromatography, silica gel (Merck, Kieselgel 60, 0.05—0.2 mm) was used.

1-[2-[4-(Ethoxycarbonyl)phenoxy]ethyl]-1*H*-1,2,4-triazole Hydrochloride (2a)——A mixture of ethyl 4-(2-iodoethoxy)benzoate (**1**, X=I)[11] (2.24 g, 7.0 mmol), 1*H*-1,2,4-triazole (0.49 g, 7.0 mmol) and NaOEt (0.5 g, 7.4 mmol) in EtOH (40 ml) was refluxed for 5 h, and concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated *in vacuo*. The residue was purified by silica gel (30 g) chromatography using $CHCl_3$–MeOH (98 : 2) as an eluent to give the free base of **2a** (1.01 g, 55%) as colorless needles; mp 92—93 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t), 4.24—4.74 (6H, m), 6.87 (2H, d, J=9 Hz), 7.89 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.91; H, 5.91; N, 16.01.

The free base of **2a** obtained above was treated with 23% HCl–EtOH solution to give **2a** as a colorless powder.

4-[2-[4-(Ethoxycarbonyl)phenoxy]ethyl]thiosemicarbazide (4)——A mixture of CS_2 (2.92 g, 38.3 mmol) and $CHCl_3$ (4 ml) was added dropwise to a suspension of ethyl 4-(2-aminoethoxy)benzoate (**3**)[8] (9.42 g, 38.3 mmol) and Et_3N (7.76 g, 76.7 mmol) in $CHCl_3$ 70 ml at −13——15 °C, and the whole was stirred at 10 °C for 10 min. After addition of a solution of ethyl chloroformate (4.1 g, 38.3 mmol) in $CHCl_3$ (7 ml), stirring was continued at room temperature for 0.5 h. After addition of ice-cold water, the organic layer was separated, washed with water, dried, and concentrated *in vacuo* to give a pale yellow oil. A solution of this oil in EtOH (100 ml) was added to a solution of hydrazine hydrate (1.93 g, 38.3 mmol) in water (2 ml), and the mixture was stirred at 5 °C for 0.5 h. The precipitate was collected by filtration, and washed with a small volume of EtOH to give **4** (5.77 g, 53%) as a colorless powder; mp 125—128 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 3.80 (2H, br), 4.0—4.5 (6H, m), 6.93 (2H, d, J=9 Hz), 7.4—8.2 (2H, m), 7.98 (2H, d, J=9 Hz).

4-[2-[4-(Ethoxycarbonyl)phenoxy]ethyl]-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (5)——A mixture of **4** (1.0 g, 3.5 mmol) and 80% HCOOH (3 ml) was heated at 60—70 °C for 25 min to give a solid, which was heated under reflux in pyridine (380 mg) and EtOH (20 ml) for 19 h. The mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The extract was washed, dried, and concentrated *in vacuo* to give **5** (460 mg, 98%) as a colorless powder; mp 149—151 °C (EtOAc–petr. ether). ^{1}H-NMR (DMSO-d_6) δ: 1.30 (3H, t, J=9 Hz), 4.27 (2H, q, J=7 Hz), 4.39 (2H, s), 7.05 (2H, d, J=9 Hz), 7.88 (2H, d, J=9 Hz), 8.47 (1H, s), 13.4—14.0 (1H, br).

Ethyl 4-[2-(4*H*-1,2,4-Triazol-4-yl)ethoxy]benzoate (2b)——H_2O_2 (35%, 0.25 ml) was added dropwise to a suspension of **5** (182 mg, 0.62 mmol) in AcOH (3 ml). The mixture was refluxed for 1 h, and concentrated *in vacuo*. The extract was washed with water, dried, and concentrated *in vacuo* to dryness to give **2b** (122 mg, 75%) as colorless prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 4.22—4.56 (6H, m), 6.88 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz), 8.32 (2H, s).

Diethyl 2-[2-[4-(Ethoxycarbonyl)phenoxy]ethyl]malonate (6)——Diethyl malonate (6.41 g, 40 mmol) was added dropwise to a solution of Na (920 mg, 40 mmol) in EtOH (80 ml). The mixture was stirred at room temperature for 0.5 h, the bromide (**1**, X=Br) (10.9 g, 40 mmol) was added, and the whole was refluxed for 4 h. The mixture was concentrated *in vacuo*, and the residue was extracted with benzene. The extract was washed, dried, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography to give **6** as an oil (8.85 g, 63%). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz), 3.42 (2H, t, J=7 Hz), 4.30 (2H, t, J=7 Hz), 4.33 (2H, q, J=7 Hz), 6.91 (2H, d, J=9 Hz), 7.98 (2H, t, J=7 Hz).

5-[2-[4-(Ethoxycarbonyl)phenoxy]ethyl]pyrimidine-4,6-dione (7)——Compound **6** (16.5 g, 4.7 mmol) was added

to a cold solution of formamidine acetate (4.87 g, 4.7 mmol) in NaOEt solution [prepared from Na (3.23 g) and EtOH (70 ml)], and the mixture was stirred at room temperature for 24 h. After cooling, the mixture was neutralized with concentrated HCl. The precipitate was collected by filtration, and washed with EtOH to give a colorless powder (7.46 g, 52%); mp 261—267 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.30 (3H, t, J=6 Hz), 2.77 (2H, t, J=6 Hz), 4.10 (2H, t, J=6 Hz), 7.03 (2H, d, J=9 Hz), 7.88 (2H, d, J=9 Hz), 7.96 (1H, s).

This compound was used for the next reaction without further purification.

4,6-Dichloro-5-[2-[4-(ethoxycarbonyl)phenoxy]ethyl]pyrimidine (8)——A mixture of **7** (3.04 g, 10 mmol) and $POCl_3$ (3 ml) was refluxed for 1 h and concentrated *in vacuo*. The residue was poured into ice-water. The mixture was neutralized with Na_2CO_3, and extracted with $CHCl_3$. The extract was washed, dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using $CHCl_3$ as an eluent to give colorless needles (2.5 g, 73%); mp 99—102 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=6 Hz), 3.36 (2H, t, J=6 Hz), 4.33 (2H, t, J=6 Hz), 4.37 (2H, q, J=6 Hz), 7.91 (2H, d, J=9 Hz), 7.99 (2H, d, J=9 Hz), 8.68 (1H, s).

This compound was used for the next reaction without further purification.

5-[2-[4-(Ethoxycarbonyl)phenoxy]ethyl]pyrimidine (2c)——A suspension of **8** (0.44 g, 1.3 mmol) and MgO (0.12 g) in 33% aqueous EtOH (12 ml) was treated with H_2 in the presence of 10% Pd–carbon (0.22 g). After absorption of the theoretical amount of H_2, the catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography to give colorless needles (0.18 g, 51%). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=6 Hz), 3.08 (2H, d, J=6 Hz), 4.23 (2H, t, J=9 Hz), 4.32 (2H, q, J=6 Hz), 6.86 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz), 8.72 (2H, s), 9.13 (1H, s).

Ethyl 4-(3-Formylpropoxy)benzoate (10)——A solution of ethyl 4-(3-hydroxybutoxy)benzoate (**9**)[12] (26.5 g, 0.11 mol) in CH_2Cl_2 (22 ml) was added to a suspension of PCC (35.6 g, 0.17 mol) in CH_2Cl_2 (220 ml). After being stirred at room temperature for 1.5 h, the mixture was treated with ether (220 ml). The ether layer was washed with water, dried, and concentrated *in vacuo* to give a colorless oil (21.5 g, 82%). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=6 Hz), 1.98—2.27 (2H, m), 2.66 (2H, t, J=6 Hz), 4.04 (2H, t, J=6 Hz), 4.33 (2H, q, J=6 Hz), 6.87 (2H, d, J=9 Hz), 7.96 (2H, d, J=9 Hz), 9.82 (1H, s).

This oil was used for the next step without further purification.

Ethyl 4-[2-(2-Aminothiazol-5-yl)ethoxy]benzoate Hydrochloride (12)——Br_2 (1 ml) was added dropwise to dioxane (3 ml), and the mixture was stirred for 10 min, and diluted with CH_2Cl_2 (10 ml). The solution was added dropwise to an ice-cooled solution of **10** (4.72 g, 20 mmol) in CH_2Cl_2 (10 ml) over 3 h under N_2 atmosphere. The mixture was stirred for 0.5 h, then a solution of Na_2CO_3 (1.5 g) in water (6 ml) was added. After being stirred for 1 h, the reaction mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated *in vacuo* to give the crude **11** as an oil. The crude **11** was stirred in a solution of thiourea (1.47 g, 19 mmol) in EtOH (40 ml) for 13 h, and then refluxed for 24 h. The mixture was neutralized with 2 N NaOH, and concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed, dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give colorless prisms of the free base of **12**; mp 171—177 °C (EtOH–ether). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7 Hz), 3.10 (2H, t, J=6 Hz), 4.14 (2H, t, J=6 Hz), 4.33 (2H, q, J=7 Hz), 5.20 (2H, br), 6.83 (1H, s), 6.88 (2H, d, J=9 Hz), 7.97 (2H, d, J=9 Hz).

The free base obtained above was treated with HCl–EtOH solution by the usual method to give **12** (2.67 g, 31%) as colorless prisms; mp 174—182 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O_3S \cdot HCl$: C, 51.14; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 50.76; H, 5.03; N, 8.52; Cl, 10.87.

Ethyl 4-[2-(5-Thiazolyl)ethoxy]benzoate Hydrochloride (2d)——A solution of $NaNO_2$ (1.52 g, 0.22 mol) in H_2O (3 ml) was added dropwise to a mixture of the free base of **12** (5.84 g, 0.02 mol) in H_3PO_4 (70 ml) and concentrated HNO_3 (35 ml) under −5 °C. After being stirred at −5 °C for 1 h, the mixture was added to an ice-cooled solution of CuCl (15.9 g, 0.16 mol) in concentrated HCl (20 ml), and the whole was stirred at the same temperature for 3 h, neutralized with Na_2CO_3, and extracted with $CHCl_3$. The extract was washed, dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the crude **13** as an oil. Zn (2.17 g) was added to a solution of the crude **13** in HOAc (40 ml), and the mixture was refluxed for 2 h. The insoluble material was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, and the solution was washed with water, dried, and concentrated *in vacuo*. The residue was treated with HCl–EtOH solution to give **2d** (3.03 g, 48%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 3.39 (3H, t, J=6 Hz), 4.28 (2H, q, J=7 Hz), 4.31 (2H, t, J=6 Hz), 7.08 (2H, d, J=9 Hz), 7.92 (2H, d, J=9 Hz), 8.03 (1H, s), 9.40 (1H, s).

Sodium 4-[2-(1*H*-1,2,4-Triazol-1-yl)ethoxy]benzoate (14a)——A mixture of **2a** (0.77 g, 2.95 mmol) and NaOH (10 ml) was stirred at room temperature for 8 h, and then concentrated *in vacuo*. The residue was dissolved in water (15 ml), and the pH was ajusted to 6 with 1 N HCl. The precipitate was collected by filltration to give the free acid (312 mg) of **14a** as colorless needles; mp 198—200 °C. A suspension of this material in water was treated with 5% NaOH (1.1 ml), and concentrated to dryness *in vacuo* to give **14a** (0.92 g, 39%) as colorless needles. IR (KBr) cm^{-1}: 3425, 1600, 1545, 1395.

Compounds **14b—d** were prepared from **2b—d**, respectively, in a fashion analogous to that used for **14a**. The results are shown in Table I.

Ethyl (*E*)-2-Methyl-3-[4-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-2-propenoate Hydrochloride (16a)——A solution

of 1*H*-1,2,4-triazole (0.68 g, 9.8 mmol) in NaOEt solution [prepared from Na (0.33 g, 10 mmol) and EtOH (20 ml)] was stirred at room temperature. Ethyl (*E*)-2-methyl-3-[4-(bromomethyl)phenyl]-2-propenoate[2] (2.77 g, 9.8 mmol) was added, and after being refluxed for 14 h, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in benzene. This solution was washed, dried, and concentrated *in vacuo*. The residual oil was chromatographed on silica gel (20 g).

The oily material obtained from the first elution with $CHCl_3$ was treated with HCl–EtOH solution to give **16a** (1.62 g, 48%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, t, J=7 Hz), 2.03 (3H, s), 4.18 (2H, q, J=7 Hz), 5.48 (2H, s), 7.25—7.55 (4H, m), 7.54 (1H, s), 8.23 (1H, s), 9.04 (1H, s).

Further elution with $CHCl_3$–MeOH (98:2) gave the free base of **16b**, which was treated with HCl–EtOH solution to give **16b** (0.31 g, 10%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, t, J=7 Hz), 2.04 (3H, s), 4.18 (2H, q, J=7 Hz), 5.53 (2H, s), 7.48 (4H, s), 7.56 (1H, s), 9.59 (1H, s).

Compound **15a** was prepared in the same manner as described above for **16a**.

Sodium (*E*)-3-[4-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-2-methyl-2-propenoate (**17a**) was synthesized from **16a** in the same manner as described above for **14a**.

17a: Yield 82%, colorless powder; mp >280 °C.

2-Chloro-3-[4-(ethoxycarbonyl)phenyl]propionaldehyde (19)——A solution of Na_2NO_2 (6.0 g, 87 mmol) in water (27 ml) was added dropwise to a solution of **18** (11.9 g, 72 mmol) in 20% HCl (36 ml) at −5—0 °C. After being stirred at 0 °C for 20 min, the mixture was neutralized with $NaHCO_3$, and added to a cooled mixture of acrolein (11.7 ml, 224 mmol), $CuCl_2$ (4.49 g, 33.4 mmol) and CaO (1.8 g, 32.1 mmol) in acetone (90 ml). The whole was stirred at 5 °C for 1.7 h, and the acetone was evaporated off. The insoluble materials were filtered off, and the filtrate was extracted with benzene. The extract was washed with water, dried, and concentrated *in vacuo* to give an oil (15.1 g, 87.1%). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 3.18 (1H, dd, J=8, 14 Hz), 3.45 (1H, dd, J=5, 14 Hz), 4.25—4.50 (1H, m), 4.37 (2H, q, J=7 Hz), 7.31 (2H, d, J=8 Hz), 8.01 (2H, d, J=8 Hz), 9.55 (1H, d, J=2 Hz).

Ethyl 4-(2-aminothiazol-5-ylmethyl)benzoate (**20**) was synthesized from **19** in the same manner as described above for **12**. Yield, quantitative, colorless prisms; mp 108—110 °C (benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz), 4.01 (2H, s), 4.36 (2H, q, J=7 Hz), 4.50—5.00 (2H, br), 6.81 (1H, s), 7.28 (2H, d, J=8 Hz), 7.90 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.52; H, 5.41; N, 10.07.

Ethyl 4-(2-Chlorothiazol-5-ylmethyl)benzoate (21)——A solution of **20** (18.8 g) in MeCN (80 ml) was added dropwise to a mixture of $CuCl_2$ (11.6 g, 86.1 mmol) and *tert*-butyl nitrite (10.35 g, 101 mmol) in MeCN (200 ml) at 55—65 °C. The mixture was stirred for 20 min, 15% HCl (150 ml) was added under ice-cooling, and the mixture was extracted with $CHCl_3$. The extract was washed, dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **21** (12.1 g, 68.5%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 4.13 (2H, s), 4.37 (2H, q, J=7 Hz), 7.31 (2H, d, J=8 Hz), 8.01 (2H, d, J=8 Hz).

Compound **22** was obtained in the same manner as described above for **2d**. Yield 81.8%, a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz), 4.23 (2H, s), 4.37 (2H, q, J=7 Hz), 7.28 (2H, d, J=8 Hz), 7.65 (1H, s), 8.00 (2H, d, J=8 Hz), 8.69 (1H, s).

5-[4-(Hydroxymethyl)benzyl]thiazole (23)——A solution of **22** (8.49 g, 34.3 mmol) in tetrahydrofuran (THF) (60 ml) was added to a suspension of $LiAlH_4$ (1.3 g, 34.3 mmol) in THF (30 ml). The mixture was stirred at room temperature for 5 h, then water (2 ml), 15% NaOH (2 ml) and water (6 ml) were added successively. The insoluble material was filtered off, and the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed, dried, and concentrated *in vacuo* to give **23** as an oil (6.3 g, 89.4%). ^{1}H-NMR ($CDCl_3$) δ: 3.25—3.75 (1H, br), 4.15 (2H, s), 4.64 (2H, s), 7.17 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz), 7.58 (1H, s), 8.60 (1H, s).

The crude **23** obtained above was used for the next reaction without further purification.

4-(Thiazol-5-ylmethyl)benzaldehyde (**24**) was prepared from **23** in a fashion analogous to that used for **10**.

Ethyl (*E*)-2-Methyl-3-[4-(thiazol-5-ylmethyl)phenyl]-2-propenoate (26)——A mixture of **24** (1.0 g, 5.0 mmol) and **25**[13] (1.51 g, 2.78 mmol) in CH_2Cl_2 (25 ml) was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **26** as a pale yellow oil (0.79 g, 66%). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7 Hz), 2.11 (3H, d, J=1.3 Hz), 4.20 (2H, s), 4.27 (2H, q, J=7 Hz), 7.22 (2H, d, J=8 Hz), 7.37 (2H, d, J=8 Hz), 7.67 (2H, s), 8.68 (1H, s).

3-[4-(Thiazol-5-ylmethyl)phenyl]-2-propenoic Acid (27)——A mixture of **24** (0.2 g, 1.0 mmol) and malonic acid (0.104 g, 1.0 mmol) in pyridine (0.3 ml) was heated at 100 °C for 4 h. After cooling of the mixture, dilute NH_4OH was added, and insoluble material was filtered off. The filtrate was made weakly acidic with concentrated HCl. The precipitate was filtered, washed with water, and recrystallized from 50% EtOH to give **27** (0.13 g, 53.9%) as a colorless powder. ^{1}H-NMR ($CDCl_3$) δ: 4.21 (2H, s), 6.43 (1H, d, J=16 Hz), 7.25 (2H, d, J=8 Hz), 7.52 (2H, d, J=8 Hz), 7.67 (1H, s), 7.76 (1H, d, J=16 Hz), 8.72 (1H, s).

2-Methyl-3-[4-(thiazol-5-ylmethyl)phenyl]-2-propenoic acid (**28**) was prepared from **26** in the same manner as described for **14a**. Yield: 47.7%; colorless powder. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, d, J=1.3 Hz), 4.21 (2H, s), 7.26 (2H, d, J=8 Hz), 7.41 (2H, d, J=8 Hz), 7.69 (1H, s), 7.79 (1H, s), 8.73 (1H, s).

Biological Assays for Inhibition of TXA_2 Synthesis——(a) *In Vitro* Assay of the Inhibition of TXA_2 Production in PRP: Citrated PRP (4×10^7 platelets) from rats was preincubated with the test compound for 1 min at room

temperature with gentle shaking, and then sodium arachidonate (final concentration was 0.5 mM) was added to initiate the reaction. The reaction mixture (total volume 0.1 ml) was incubated for 5 min at room temperature with vigorous shaking and indomethacin (final concentration 0.1 mM) was added to stop the reaction. Then the mixture was centrifuged at $1000 \times g$ for 5 min and the supernatant was subjected to the measurement of TXB_2 (the stable breakdown product of TXA_2) and PGE_2 by the radioimmunoassay method.

(b) Calculation of the Conversion Ratio (PGE_2/TXA_2): The conversion ratio (PGE_2/TXA_2) was used to estimate the selectivity of the inhibition of TXA_2 synthetase. The conversion ratio was calculated at a concentration of the tested compound that gave about 90% inhibition of the TXB_2 production in (a) according to the following equation.

the conversion ratio (PGE_2/TXA_2)
=(the amount of the increase in PGE_2 production compared to the control)/
(the amount of the decrease in TXB_2 production compared to the control)

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