Antiplatelet Agents Based on Cyclooxygenase Inhibition without Ulcerogenesis. Evaluation and Synthesis of 4,5-Bis(4-methoxyphenyl)-2-substituted-thiazoles

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The syntheses, biological evaluations, and structure–activity relationships of a series of 4,5-bis-(4-methoxyphenyl)-2-substituted-thiazoles as potent antiplatelet agents with vasodilatory activity are described. 2-Guanidino-4,5-bis(4-methoxyphenyl)thiazole (**3**), designed from two parent compounds (itazigrel and timegadine), showed inhibitory activity of malondialdehyde (MDA, IC_{50} = 31 μM) production which is formed from the cyclooxygenase (CO)-catalyzed oxygenation of arachidonic acid in the synthesis of prostanoids in platelets, with vasodilatory activity (ED_{50} = 2.0 μM). Further structure–activity relationship studies on **3** culminated in the preparation of 4,5-bis(4-methoxyphenyl)-2-[(1-methylpiperazin-4-yl)carbonyl]thiazole (**10a**, FR122047) which exhibited potent inhibitory activity on MDA synthesis in vitro (IC_{50} = 0.088 μM) and platelet aggregation in guinea pigs ex vivo (100% inhibition even 6 h after 1.0 mg/kg administration) with vasodilatory activity in vitro (ED_{50} = 6.2 μM). Moreover, **10a** demonstrated no ulcerogenesis effect in rats even at 100 mg/kg dosage (safety margin in rats is more than 70 while that of aspirin is only 1.2) in spite of its potent CO inhibition (IC_{50} = 0.43 μM[14]), while the use of aspirin, a CO inhibitor and the most popular thromboembolic drug, is restricted by the side effect.[8] Pharmacokinetic studies on **10a** have revealed that **10a** is detectable in platelet-rich plasma but not in platelet-poor plasma 1 day after oral administration, which indicates that **10a** tends to be localized in platelets. This property could be responsible for its low toxicity and reduction of side effects in clinical studies.

Introduction

Medicinal research has significantly advanced clinical treatment of thromboembolic diseases. Nevertheless, such diseases still remain the leading cause of human morbidity and mortality.[1] Many compounds based on specific mediators such as thromboxane A_2 (TXA_2),[2] prostacyclin,[3] phosphodiesterase (PDE),[4] and thrombin,[5] have been synthesized and tested in clinical trials to verify their effectiveness in the treatment of thromboembolic diseases.

The most popular thromboembolic drug, aspirin, which inhibits cyclooxygenase irreversibly,[6] has shown its effectiveness in clinical trials.[7] Aspirin, however, prevents not only the synthesis of TXA_2 in platelets but also that of prostaglandin I_2 in vascular endothelial cells. As a result, it induces stomach ulcers ("aspirin dilemma"),[8] restricting its clinical use. Development of a new aspirin-like compound, based on cyclooxygenase inhibition and free from the side effects, is a major goal of thromboembolic research. To accomplish this purpose, some compounds which inhibit cyclooxygenase reversibly, such as itazigrel,[9] KBT-3022,[10] and E-5510[11] have been synthesized and clinically tested (other activities of these compounds have been also reported. For example, phospholipase C and/or A_2 are inhibited by E-5510[11]).

We have reported[12] a new type of antiplatelet agent, 5-alkyl-2-(substituted aryl)-4-pyridylimidazoles, which exhibited potent antiplatelet activity with vasodilation activity without the gastric side effect. We think that vasodilatory activity could be beneficial in treatment of thromboembolic diseases and are continuing our studies aimed at the development of potent aspirin-like antiplatelet agents with vasodilatory activities without gastrointestinal side effect.

Structural analyses of itazigrel, E-5510, and KBT-3022 have shown that the bis(4-methoxyphenyl) moiety is essential for potent cyclooxygenase inhibition (Figure 1). We have also observed that a guanidino derivative, timegadine,[13] shows antiplatelet and vasodilatory properties (Table 1). On the basis of this information, we synthesized a fused compound, 2-guanidino-4,5-bis(4-methoxyphenyl)thiazole (**3**, Figure 1). Compound **3**, our lead compound in this study, showed the desired properties: inhibitory activity of MDA production (IC_{50} = 31 μM) and vasodilatory activity (ED_{50} = 2.0 μM).

We describe here the syntheses and structure–activity relationships of 4,5-bis(4-methoxyphenyl)-2-substituted-thiazoles and their pharmacological effects on platelet aggregation and vasodilation. Further pharmacological results of the most potent derivative, 4,5-bis(4-methoxyphenyl)-2-[(1-methylpiperazin-4-yl)carbonyl]thiazole (**10a**, FR122047[14]), are also described.

Chemistry

4,5-Bis(4-methoxyphenyl)-2-(substituted guanidino)-thiazoles (**3**, **7a–i**) were prepared as shown in Scheme 1. Conversion of the hydroxy group of anisoin (**1**) into a chloro group by thionyl chloride gave 2-chloro-1,2-bis(4-methoxyphenyl)-1-ethanone (**2**). Condensation of **2** with guanidinothioamide or thiourea provided 2-guanidino- (**3**) or 2-amino-4,5-bis(4-methoxyphenyl)thiazole (**4**), respectively. The synthetic approach to N-substituted-guanidino derivatives (**7a–e,g–i**) was to convert **4** into 4,5-bis(4-methoxyphenyl)-2-thioureidothiazole (**5a**) via 2-(3-benzoylthioureido)-4,5-bis(4-methoxyphenyl)thiazole (**6**), followed by methylation of the thiourea moiety with methyl iodide and subsequently substitution of the methylthio group with corresponding amines. Condensation of **4** with methyl isothiocyanate afforded 4,5-bis(4-methoxyphenyl)-3-(methylthioureido)thiazole (**5b**), which was converted into *N,N'*-dimethylguanidino derivative (**7f**).

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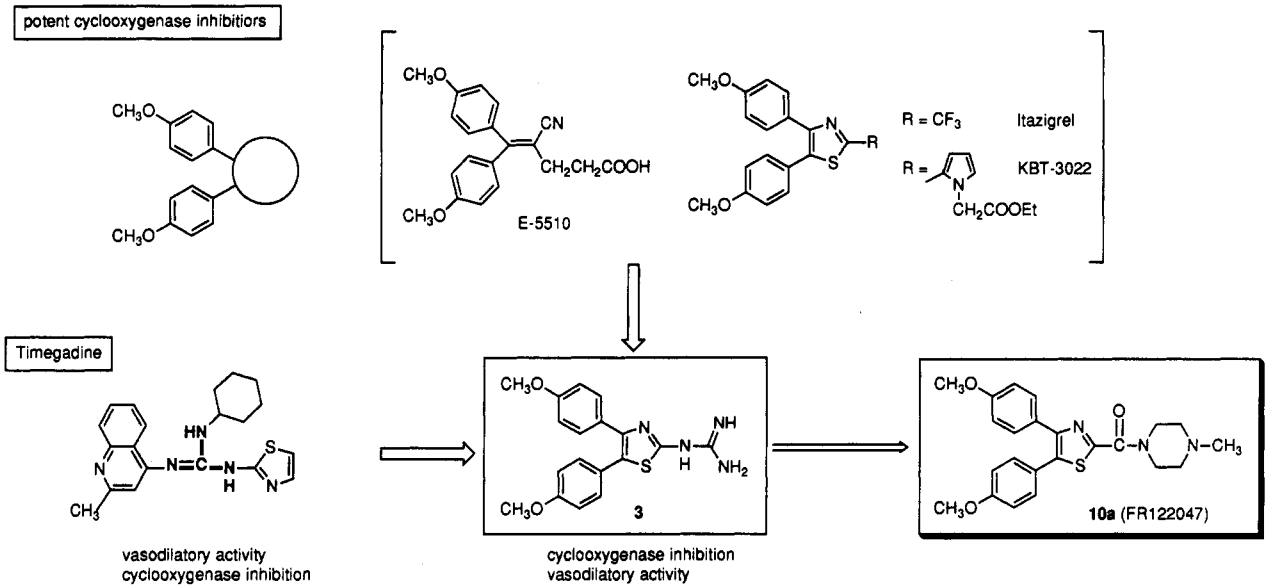
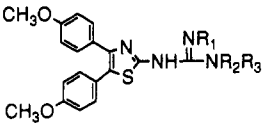


Figure 1. Design of **3** from two kind of parent compounds and evolution of 4,5-bis(4-methoxyphenyl)-2-[(4-methylpiperazin-1-yl)-carbonyl]thiazole (**10a**, FR122047).

Table 1. Product Characterization and in Vitro Activity: 4,5-Bis(4-methoxyphenyl)-2-(substituted guanidino)thiazole Derivatives



compd	R_1	R_2	R_3	yield, %	mp, °C	formula	anal.[a]	antiplatelet[b] MDA[c] IC_{50}, μM	vasodilation[b] rat aorta, in vitro ED_{50}, μM
3	H	H	H	46.2	167–8	$C_{18}H_{18}N_4O_2S$	C, H, N	31	2.0
7a	H	H	CH_3	58.1	155–6	$C_{19}H_{20}N_4O_2S$	C, H, N	0.062	1.2
7b	H	H	Et	59.4	183–5	$C_{20}H_{22}N_4O_2S$	C, H, N	>0.1	NT[d]
7c	H	H	*i*-Pr	84.5	195–7	$C_{21}H_{24}N_4O_2S{\cdot}CH_3SO_3H$	C, H, N	>0.1	9.1
7d	H	CH_3	CH_3	30.3	233–5	$C_{20}H_{22}N_4O_2S{\cdot}HCl$	C, H, N	0.037	4.8
7e	H	H	c-hex	74.5	162–4	$C_{24}H_{28}N_4O_2S$	C, H, N	>1.0	>100
7f	CH_3	H	CH_3	32.1	231–3	$C_{18}H_{18}N_4O_2S{\cdot}CH_3SO_3H$	C, H, N	0.97	2.4
7g	H	*N*-Me-piperidine		21.9	161–2	$C_{23}H_{27}N_5O_2S$	C, H, N	>1.0	21
7h	H	morpholine		50.9	172–3	$C_{22}H_{24}N_4O_3S$	C, H, N	<1.0[e]	66
7i	H	imidazoline		44.9	211–4	$C_{20}H_{20}N_4O_2S$	C, H, N	>0.1	NT
aspirin								16	>600
itazigrel								0.0056	>300
timegadine								0.031	2.5

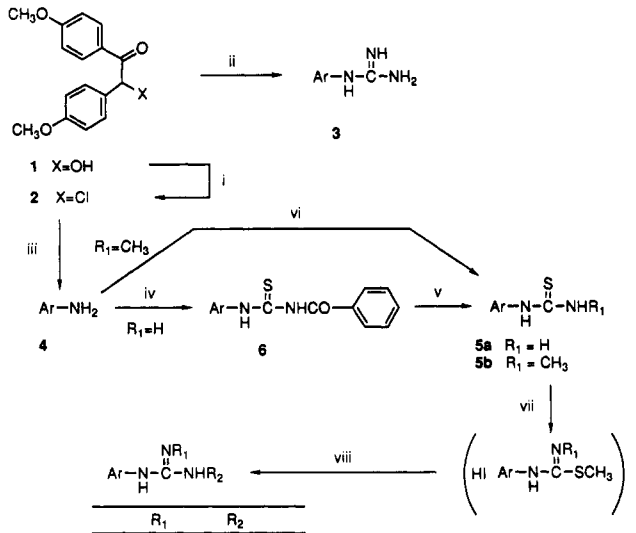
[a] Analytical results were within ±0.4% of the theoretical value. [b] The evaluation methods are described in Experimental Section. [c] MDA: inhibitory activity of malondialdehyde production induced by AA. [d] NT: not tested. [e] Inhibitory activity of **7h** on the MDA production at 1 μM was 79.9%.

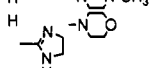
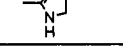
The synthesis of 2-((substituted amino)methyl)thiazoles (**8a–j**) is shown in Scheme 2. Condensation of **2** with ((dimethylamino)methyl)thioamide or ((acetylamino)-methyl)thioamide provided 4,5-bis(4-methoxyphenyl)-2-((dimethylamino)methyl)thiazole (**8a**) or 2-((acetylamino)-methyl)-4,5-bis(4-methoxyphenyl)thiazole (**8b**), respectively. Hydrolysis of **8b** with 35% HCl provided 2-(aminomethyl)thiazole (**8c**). Condensations of **8c** with acyl chlorides, carboxylic acids, or isocyanates gave 2-((acylamino)methyl)- (**8d–h**) and 2-ureidothiazoles (**8i–j**), respectively.

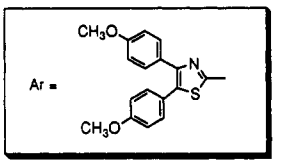
2-(Substituted amido)thiazoles (**10a–m**) were synthesized as shown in Scheme 3. Condensation of (ethoxycarbonyl)thiourea with **2** provided 2-(ethoxycarbonyl)-4,5-bis(4-methoxyphenyl)thiazole (**9**), an oily compound, which was used for the next reactions without purification. Aminolysis of **9** with various amines gave 2-(substituted amido)thiazoles (**10a–l**). Reaction of **10g** with isopropyl isocyanate afforded 2-[4-((isopropylamino)carbonyl)piperazin-1-yl]thiazole (**10m**).

Reduction of the ester **9** with $LiAlH_4$ and subsequent oxidation with activated MnO_2 gave 2-formyl-4,5-bis(4-methoxyphenyl)thiazole (**11**) (Scheme 4). The Knoevenagel condensation of **11** with ethyl cyanoacetate afforded ethyl 2-cyano-3-[4,5-bis(4-methoxyphenyl)thiazolyl]propenoate (**12**). The Knoevenagel condensation of **11** with ethyl acetoacetate and subsequent condensation with ethyl 3-aminocrotonate provided 2-(1,4-dihydro-3,5-bis(ethoxycarbonyl)-2,6-dimethylpyrid-4-yl)-4,5-bis(4-methoxyphenyl)thiazole (**13**). The Wittig reaction of **11** with ethyl (triphenylphosphoranylidene)acetate gave ethyl 3-[4,5-bis(4-methoxyphenyl)thiazolyl]-(*E*)-propenoate (**14**). The configuration of the ethenyl moiety was determined by coupling constants from ^{1}H-NMR analysis. Hydrolysis of **14** gave 3-[4,5-bis(4-methoxyphenyl)thiazol-2-yl]-(*E*)-propenoic acid (**15**), which was coupled with *N*-methylpiperazine to yield 3-[4,5-bis(4-methoxyphenyl)thiazol-2-yl]propenoyl-*N*-methylpiperazine (**16**). Catalytic hydrogenation of **15** over 10% Pd–C at atmospheric pressure afforded 3-[4,5-bis(4-methoxyphenyl)thiazol-2-yl]pro-

Scheme 1[a]

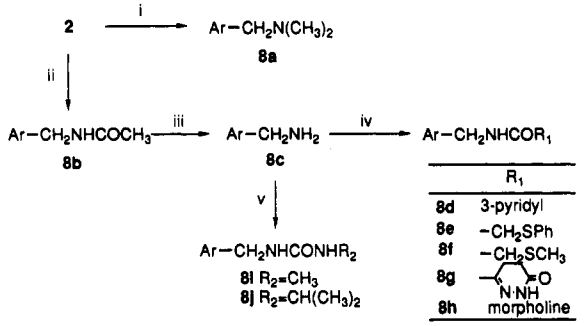


	R_1	R_2
7a	H	$NHCH_3$
7b	H	$NHCH_2CH_3$
7c	H	$NHCH(CH_3)_2$
7d	H	$N(CH_3)_2$
7e	H	NHC_6H_{11}
7f	CH_3	$NHCH_3$
7g	H	
7h	H	
7i	H	



[a] Reagents: (i) $SOCl_2$, rt, 1 h; (ii) $H_2NC(=S)NHC(=NH)NH_2$/EtOH, reflux, 2 h; (iii) $H_2NC(=S)NH_2/CH_3CN$, reflux, 3 h; (iv) PhCONCS, 0 °C, 1 h; (v) NaOH/MeOH, 60 °C, 2 h; (vi) CH_3NCS/DMF, 90 °C, 4 h; (vii) CH_3I/MeOH, $CHCl_3$, reflux, 1 h; (viii) R_2NH_2/EtOH, reflux.

Scheme 2[a,b]



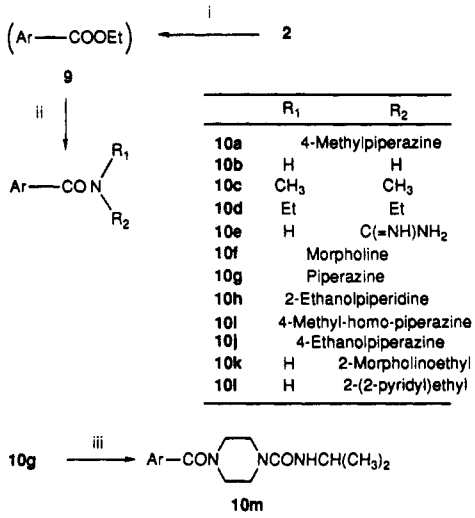
	R_1
8d	3-pyridyl
8e	$-CH_2SPh$
8f	$-CH_2SCH_3$
8g	
8h	morpholine

[a] Reagents: (i) $H_2NC(=S)CH_2N(CH_3)_2$/EtOH, reflux, 3 h; (ii) $H_2NC(=S)CH_2NHCOCH_3$ in EtOH, reflux, 1 h; (iii) 35% HCl, rt, 0.5 h; (iv) (a) R_1COOH, EDC/DMF, rt, 3 h (for 8e–g), (b) R_1COCl, NEt_3/CH_2Cl_2, reflux, 1 h (for 8d and 8h); (v) R_2NCO/THF, MeOH, rt, 1.5 h.[b] Ar = 4,5-bis(4-methoxyphenyl)thiazol-2-yl.

panoic acid (17). Reaction of 14 with *N*-methylpiperazine provided ethyl 3-[4,5-bis(4-methoxyphenyl)thiazol-2-yl]-3-(4-methylpiperazin-1-yl)propionate (18).

The synthesis of other derivatives (19–22) is shown in Scheme 5. 2,3,4,5-Tetrahydro-6-thiocarbamoyl-3-pyridazinone was condensed with 2 to give 4,5-bis(4-methoxyphenyl)-2-(2,3,4,5-tetrahydro-3-oxopyridazin-6-yl)thiazole (19). Reaction of 4-thiocarbamoylpyridine with 2 afforded 2-(4-pyridyl)thiazole (20). N-Methylation of 20 by methyl iodide and subsequent reduction with $NaBH_4$ provided 4,5-bis(4-methoxyphenyl)-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)thiazole (21). Reaction of 2-chloro-4,5-bis(4-methoxyphenyl)thiazole with *N*-methylpiperazine afforded the 2-(4-methylpiperazin-1-yl)thiazole derivative (22).

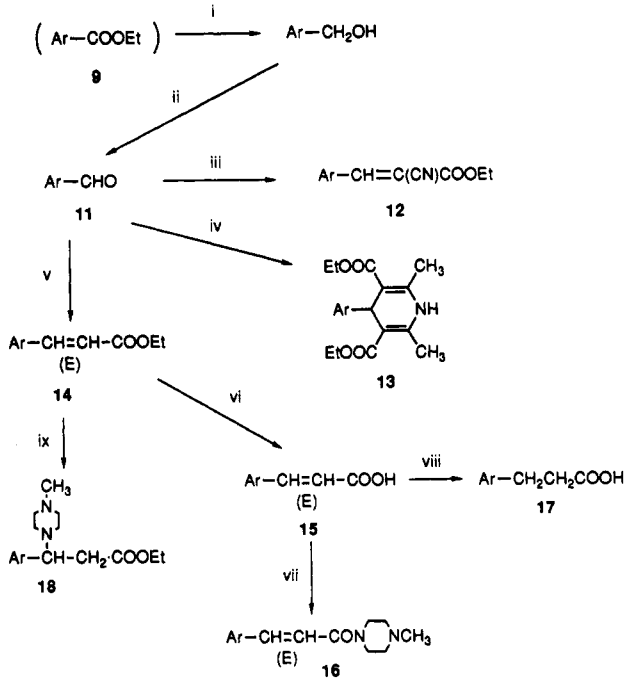
Scheme 3[a,b]



	R_1	R_2
10a	4-Methylpiperazine	
10b	H	H
10c	CH_3	CH_3
10d	Et	Et
10e	H	$C(=NH)NH_2$
10f	Morpholine	
10g	Piperazine	
10h	2-Ethanolpiperidine	
10i	4-Methyl-homo-piperazine	
10j	4-Ethanolpiperazine	
10k	H	2-Morpholinoethyl
10l	H	2-(2-pyridyl)ethyl

[a] Reagents: (i) $EtOCOCSNH_2$/EtOH, reflux, 4 h; (ii) aminolysis by HNR_1R_2; (iii) *i*-C_3H_7-NCO/THF, MeOH, rt, 2 h.[b] Ar = 4,5-bis(4-methoxyphenyl)thiazol-2-yl.

Scheme 4[a,b]

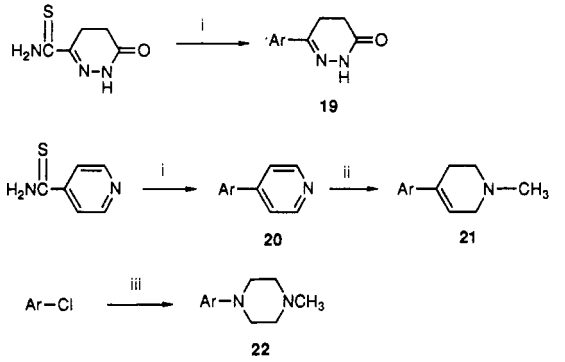


[a] Reagents: (i) $LiAlH_4$/THF, 0 °C, 30 min; (ii) MnO_2/AcOEt, rt, 5.5 h; (iii) $NCCH_2COOEt$, AcOH, $AcONH_4/C_6H_6$, reflux, 7.5 h; (iv) (a) CH_3COCH_2COOEt, AcOH, morpholine/C_6H_6, reflux, (b) H_2N-$(H_3C)CCHCOOEt$/EtOH, reflux, overnight; (v) $(C_6H_5)_3P{=}CHCOOEt$/CH_2Cl_2, reflux, 4 h; (vi) 0.1 N NaOH, reflux, overnight; (vii) Me-piperazine, EDC, NEt_3/DMF, rt, 5 h; (viii) $H_2/Pd(OH)_2$, rt, 1 atm, 4 h; (ix) Me-piperazine, 80–90 °C, 6 h.[b] Ar = 4,5-bis(4-methoxyphenyl)thiazol-2-yl.

Biological Results and Discussion

Inhibitory activities on malondialdehyde (MDA) synthesis and KCl-induced contraction were measured to evaluate the cyclooxygenase (CO) inhibition and vasodilation activity of the novel thiazoles in this study. MDA is formed from the CO-catalyzed oxygenation of arachidonic acid (AA) in the synthesis of prostanoids so that inhibitory activity on MDA synthesis is considered to be consistent with CO inhibition activity. The reason for evaluation of vasodilation activity in this study is that we consider that it may be beneficial in the treatment of

Scheme 5[a,b]



[a] Reagents: (i) **2**/EtOH, reflux, 2 h; (ii) (a) CH_3I, rt, 10 h, (b) $NaBH_4$/MeOH, rt, 1 h; (iii) *N*-methylpiperazine, 80–90 °C, 6 h.[b] Ar = 4,5-bis(4-methoxyphenyl)thiazol-2-yl.

thrombotic disease. Inhibitors active in both tests, at or below 0.1 μM on the MDA and 10 μM on the vasodilation assay, were tested for their ex vivo abilities to prevent platelet aggregation induced by AA or collagen 1 or 6 h after oral administration (3.2 and/or 1.0 mg/kg) in guinea pigs.

2-(Substituted guanidino)-4,5-bis(4-methoxyphenyl)thiazoles. Aspirin and itazigrel, CO inhibitors, showed inhibition of MDA synthesis but no effect in the vasodilation assay (Table 1). Timegadine, one of our reference compounds, showed inhibition of MDA production (IC_{50} = 0.031 μM) and vasodilation activities (ED_{50} = 2.5 μM). Ex vivo potency of timegadine, however, is much less than that of itazigrel (Table 5).

Fusion of these two kinds of compounds (Figure 1) has been attempted to obtain a potent platelet aggregation inhibition based on CO inhibition with vasodilatory activity and provided 2-guanidino-4,5-bis(4-methoxyphenyl)thiazole (**3**). Compound **3** showed inhibitory activity of MDA synthesis (IC_{50} = 31 μM) with vasodilatory activity (ED_{50} = 2.0 μM) as expected. The vasodilatory activity of **3** was equipotent to that of timegadine, but the MDA-inhibitory activity was much weaker than that of itazigrel (IC_{50} = 0.0056 μM). Our initial efforts focused on increasing the potency of MDA-inhibition activity while retaining the vasodilation activity.

Modification of guanidino moiety of **3** (**7a–i**) was carried out (Table 1). Introduction of a methyl group onto the guanidino moiety provided **7a** (IC_{50} = 0.062 μM) and **7d** (IC_{50} = 0.037 μM) with an increase of the MDA-inhibition activity of 500 and 1000 times, respectively, compared with **3**. Compounds **7a** and **7d** also showed comparable vasodilatory activity to **3**. The *N,N'*-dimethylated guanidine (**7f**) was less potent than the singly methylated derivative (**7a**). Substitution with morpholine (**7h**) showed potent inhibition of MDA synthesis (79.9% inhibition at 1.0 μM) with weak vasodilation activity (ED_{50} = 66 μM).

Compounds **7a** and **7d** were subsequent evaluated ex vivo (Table 5) since they were active in the two tests. Compound **7a** inhibited platelet aggregation induced by AA 1 h after oral administration of 1.0 mg/kg. Compound **7a**, however, did not completely prevent collagen-induced aggregation at the same dose while itazigrel did. Compound **7d** was slightly more potent than **7a**. These studies showed that the novel thiazoles were much stronger than aspirin and timegadine in an ex vivo study, which indicated that these thiazoles were suitable as lead compounds for further study. Our next efforts focused on increasing ex vivo potency while retaining vasodilatory activity since their ex vivo activities were much less potent than that of itazigrel. In order to accomplish this purpose, various 4,5-bis(4-methoxyphenyl)-2-substituted-thiazoles were synthesized and tested.

2-((Substituted amino)methyl)thiazoles. 2-((Substituted amino)methyl)-4,5-bis(4-methoxyphenyl)thiazoles (**8a–j**) were synthesized and tested, and their results are shown in Table 2.

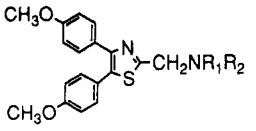
2-(Aminomethyl)-4,5-bis(4-methoxyphenyl)thiazole (**8c**) showed vasodilation activity (ED_{50} = 7.7 μM) with little inhibition of MDA synthesis (IC_{50} > 0.1 μM). Dimethylation of the amino moiety (**8a**) increased the inhibitory activity on MDA synthesis (IC_{50} = 0.096 μM) while retaining vasodilatory activity (ED_{50} = 8.4 μM). Since acetylation of **8c** produced potent MDA synthesis inhibition (IC_{50} = 0.015 μM) while retaining vasodilatory activity (ED_{50} = 8.1 μM), several (substituted amino)-methyl derivatives (**8d–j**) were tested. 2,3,4,5-Tetrahydro-3-pyridazinone ring (**8g**), the nucleus of potent phosphodiesterase inhibitors,[15] was introduced onto the amino group in an attempt to increase vasodilution activity. Compound **8g**, however, showed only similar vasodilation activity (ED_{50} = 7.3 μM) to that of **8c**. Substitution of the 2,3,4,5-tetrahydro-3-pyridazinone ring with 3-pyridyl (**8d**), phenyl thioether (**8e**), and methyl thioether (**8f**) also exhibited potent anti-MDA synthesis activity while retaining vasodilation activity. 4,5-Bis(4-methoxyphenyl)-2-((substituted ureido)methyl)thiazoles (**8h–j**) were also synthesized and tested. Among them, *N*-(isopropylureido) derivative (**8j**) showed potent activities in both assays (MDA, IC_{50} = 0.022 μM; vasodilation, ED_{50} = 5.7 μM).

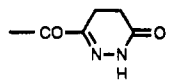
Active compounds from the above aminomethyl derivatives, **8a–b,d–g,j**, were then assessed in an ex vivo study alongside itazigrel (Table 5). Among them, **8g** and **8j** exhibited potent ex vivo activity, that is, complete inhibition of platelet aggregation for 6 h at a low dose (1.0 mg/kg). These ex vivo potencies are much higher than that of the guanidino derivatives and equal to that of itazigrel. Further pharmacological studies on these compounds are now underway.

2-(Substituted amido)thiazoles. 2-(Substituted amido)thiazoles (**10a–m**, Table 3) and derivatives (**13**, **21–22**, Table 4) were also synthesized and evaluated.

N,N-Dialkylamido derivatives (**10c**, **10d**) showed potent inhibition of MDA synthesis (IC_{50} < 0.1 μM and IC_{50} < 0.01 μM, respectively) while that of the unsubstituted amido derivative (**10b**) was very weak (IC_{50} > 1 μM). Compound **10d**, however, was precluded from further studies due to its weak vasodilatory activity (ED_{50} = 14 μM). Since compounds with a basic functional group tend to show vasodilation activity,[12] introduction of a basic group onto the amido moiety (**10a**, FR122047) was carried out. Compound **10a** exhibited potent MDA-synthesis inhibition (IC_{50} = 0.088 μM) with vasodilation activity (ED_{50} = 6.2 μM); therefore, derivatives of **10a** (**10f–m**, **13**, **21–22**) were prepared. Replacement of the *N*-methylpiperazine of **10a** by morpholine (**10f**) gave much stronger inhibitory activity of MDA synthesis (IC_{50} < 0.01 μM) while diminishing the vasodilation effect (ED_{50} > 100 μM). (2-Hydroxyethyl)piperidine derivative (**10h**) showed inhibitory activity of MDA synthesis (IC_{50} = 0.045 μM) with vasodilation activity (ED_{50} = 6.8 μM) while other modifications of the *N*-methylpiperazine moiety (**10g,i–k**) resulted in decreasing anti-MDA production activity.

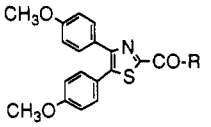
Table 2. Product Characterization and in Vitro Activity: 4,5-Bis(4-methoxyphenyl)-2-((substituted aminomethyl)thiazole Derivatives



compd	R_1	R_2	yield, %	mp, °C	formula	anal.[a]	antiplatelet[b] MDA[c] IC_{50}, μM	vasodilation[b] rat aorta, in vitro ED_{50}, μM
8a	CH_3	CH_3	12.3	204–6	$C_{20}H_{22}N_2O_2S$·HCl	C, H, N	0.096	8.4
8b	$COCH_3$	H	33.2	138–41	$C_{20}H_{20}N_2O_3S$	C, H, N	0.015	8.1
8c	H	H	86.3	146–8	$C_{18}H_{18}N_2O_2S$·HCl	C, H, N, S	>0.1	7.7
8d	CO-3-C_5H_4N	H	49.7	135–44	$C_{24}H_{21}N_4O_2S$·HCl	C, H, N	0.025	8.2
8e	$COCH_2S$-C_6H_5	H	56.6	132–3	$C_{26}H_{24}N_2O_3S_2$	C, H, N, S	<0.1[d]	4.2
8f	$COCH_2SCH_3$	H	28.1	74–5	$C_{21}H_{22}N_2O_3S$	C, H, N, S	<0.1[d]	6.0
8g		H	40.1	174–5	$C_{23}H_{22}N_4O_4S$	C, H, N	0.055	7.3
8h	CO-morpholino	H	82.4	111–6	$C_{23}H_{25}N_3O_4S$·H_2O	C, H, N, S	0.66	12
8i	$CONHCH_3$	H	84.1	115–8	$C_{20}H_{21}N_3O_3S$	C, H, N, S	0.022	15
8j	CONH-*i*-C_3H_7	H	91.6	146–9	$C_{22}H_{25}N_3O_3S$	C, H, N, S	0.042	5.7

[a–c] See Table 1. [d] Inhibitory activities of **8e** and **8f** on the MDA production at 0.1 μM were 73.6 and 73.3%, respectively.

Table 3. Product Characterization and in Vitro Activity: 4,5-Bis(4-methoxyphenyl)-2-(substituted amido)thiazole Derivatives



compd	R	yield, %	mp, °C	formula	anal.[a]	antiplatelet[b] MDA[c] IC_{50}, μM	vasodilation[b] rat aorta, in vitro ED_{50}, μM
10a (FR122047)	4-CH_3-piperazine	46.5	254–6	$C_{23}H_{25}N_3O_3S$·HCl	C, H, N	0.088	6.2
10b	NH_2	28.9	syrup	$C_{18}H_{16}N_2O_3S$	C, H, N	>1	NT[d]
10c	$N(CH_3)_2$	24.1	syrup	$C_{20}H_{20}N_2O_3S$	C, H, N[e]	<0.1[f]	3.0
10d	NEt_2	8.3	syrup	$C_{22}H_{24}N_2O_3S$	C, H, N	<0.01[f]	14
10e	$NHC(NH)NH_2$	56.0	253–5	$C_{19}H_{18}N_4O_3S$	C, H, N	>0.1	>100
10f	morpholine	25.2	118–22	$C_{22}H_{22}N_2O_4S$	C, H, N	<0.01[f]	>100
10g	piperidine	22.6	109–14	$C_{22}H_{23}N_3O_3S$·HCl·H_2O	C, H, N	>1	11
10h	2-ethanolpiperidine	42.1	syrup	$C_{25}H_{28}N_2O_4S$	C, H, N	0.045	6.8
10i	4-CH_3-homopiperazine	74.0	106–16	$C_{24}H_{27}N_3O_3S$·HCl·$2H_2O$	C, H, N	>0.1	4.3
10j	4-(2-hydroxyethyl)piperazine	20.6	198–201	$C_{24}H_{27}N_3O_4S$·HCl·$^1/_5H_2O$	C, H, N	>1	9.5
10k	$NHCH_2CH_2$-morpholine	58.1	249–51	$C_{24}H_{27}N_3O_4S$·HCl·$^1/_2H_2O$	C, H, N	>1	8.7
10l	$NHCH_2CH_2$-3-pyridyl	29.1	125–7	$C_{25}H_{23}N_3O_3S$	C< H, N	<0.1[f]	20
10m	-piperazino-CONH-*i*-Pr	65.0	157–9	$C_{26}H_{30}N_4O_4S$·$^1/_5H_2O$	C, H, N	>1	15

[a–d] See Table 1. [e] C: calcd, 65.20; found, 65.76. [f] Inhibitory activities of **10c**, **10d**, **10f**, and **10l** on the MDA production at 0.1 μM (for **10c**, **10l**) or 0.01 μM (for **10d**, **10f**) were 51.4, 65.0, 74.8, and 56.6%, respectively.

Deletion of the carbonyl moiety of **10a** (**22**) and its derivative (**21**) resulted in similar potencies in the MDA and vasodilation assays, compared to those of **10a**. Introduction of a 1,4-dihydropyridine ring, the nucleus of the Ca^{2+} antagonists,[16] to the 2-position of the thiazole ring in an attempt to increase vasodilatory activity provided **13** with disappointing poor vasodilation activity (ED_{50} > 3.2 μM).

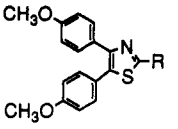
The active amido derivatives in the both tests (**10a,c,h**, **21**, **22**) were subjected to ex vivo evaluation (Table 5) to assess their in vivo potency. Compound **10h** inhibited platelet aggregation, even 6 h after oral administration of 3.2 mg/kg. Compound **10h**, however, was excluded from additional studies due to its physical form (oil). Compound **10a** demonstrated potent ex vivo potency, that is, **10a** completely prevented the platelet aggregation induced by AA and showed 83.1% (79% for itazigrel) inhibition induced by collagen after 6 h at 1.0 mg/kg. These results exhibited that **10a** has potent and long-lasting antiplatelet activity that is much more potent than that of aspirin and timegadine and a little more potent than that of itazigrel. Other amido derivatives (**10c**, **21–22**) were less potent than **10a** in ex vivo studies. Therefore, **10a** was subjected to further pharmacological tests as shown below.

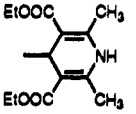
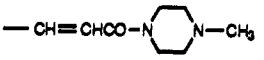
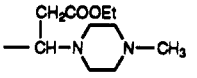
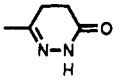
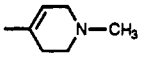
Other 4,5-Bis(4-methoxyphenyl)thiazoles. Some compounds with a carboxylic acid or ester at the 2-position of the thiazole ring (**12**, **14**, **15**, **17**, and **18**) were synthesized to compare with the above nonacidic compounds since CO inhibitors are often classified into acidic compounds, for example, aspirin, indomethacin, E-5510, and KBT-3022. The results are shown in Table 4. The acidic compounds showed potent MDA-production inhibition and little vasodilation activity. Consequently, these compounds were excluded from our further studies.

Pharmacokinetic Studies on 10a (FR122047). Because **10a** showed potent and long-lasting antiplatelet activity as shown above, pharmacokinetic studies were carried out in guinea pigs to determine the reason for its long duration of activity.

Interestingly, **10a** remains in PRP for more than 48 h, but it is almost undetectable after 6 h and completely undetectable after 24 and 48 h in PPP as shown in Figure 2. The ex vivo activity of **10a** correlated with the concentration in PRP but not that in PPP. These results

Table 4. Product Characterization and in Vitro Activity: 4,5-Bis(4-methoxyphenyl)-2-substituted-thiazole Derivatives



compd	R	yield, %	mp, °C	formula	anal.[a]	antiplatelet[b] MDA[c] IC_{50}, μM	vasodilation[b] rat aorta, in vitro ED_{50}, μM
12	CH=C(CN)COOEt	35.4	138–40	$C_{23}H_{20}N_2O_6S$	C, H, N	<0.01[e]	>100
13		10.2	177–8	$C_{30}H_{32}N_2O_6S$	C, H, N	<0.1[e]	>32
14	CH=CHCOOEt	70.6	94–5	$C_{22}H_{21}NO_4S$	C, H, N	0.020	>100
15	CH=CHCOOH	34.6	170–81	$C_{20}H_{17}NO_4S$	C, H, N	>0.1	55
16		27.1	83–93	$C_{25}H_{27}N_3O_3S·6H_2O$	C, H, N	>1	20
17	CH_2CH_2COOH	31.6	218–25	$C_{20}H_{25}NO_4S$	C, H, N	<0.1[e]	>100
18		34.3	157–61	$C_{27}H_{33}N_3O_5S·HCl$	C, H, N	>1	2.6
19		34.1	242–7	$C_{21}H_{19}N_4O_3S$	C, H, N	>1	NT[d]
21		8.6	131–2	$C_{23}H_{24}N_2O_2S$	C, H, N	<0.01[e]	5.9
22	4-CH_3-piperazine	50.2	135–6	$C_{22}H_{25}N_3O_2S$	C, H, N	0.039	5.2

[a–d] See Table 1. [e] Inhibitory activities of **12**, **13**, **17**, and **21** on the MDA production at 0.1 μM (for **13**, **17**) or 0.01 μM (for **12**, **21**) were 66.2, 64.7, 72.1, and 64.7%, respectively.

Table 5. Inhibitory Effects of Selected Compounds 1 and/or 6 h after Oral Administration on Platelet Aggregation Induced by Arachidonic Acid (AA) and Collagen in Guinea Pigs ex Vivo[a]

	AA, dose, mg/kg				collagen dose, mg/kg			
	3.2		1.0		3.2		1.0	
	1 h	6 h	1 h	6 h	1 h	6 h	1 h	6 h
aspirin	64	–[b]	–	–	9	–	–	–
itazigrel	–	–	100	100	–	–	100	79
timegadine	–	–	–	–	52.4	–	14.5	–
7a	100	–	100	–	76.2	–	9	–
7d	100	100	48.5	–	100	98	33.1	–
8a	100	0	–	–	100	0	–	–
8b	–	–	–	60.9	–	–	–	26.6
8d	–	40.3	–	–	–	37.4	–	–
8e	–	–	–	16.5	–	–	–	–2.6
8f	–	–	–	–3.9	–	–	–	–13.3
8g	–	100	–	100	–	94.1	–	84.3
8j	–	100	–	100	–	100	–	100
10a	–	100	–	100	–	100	–	83.1
10c	–	89	–	–	–	4.1	–	–
10h	–	100	–	–	–	100	–	–
21	–	100	–	–	–	69.3	–	–
22	–	–	–	60.9	–	–	–	65.4

[a] The evaluation methods are described in the Experimental Section. [b] –: not tested.

indicated that **10a** is localized in platelets after oral administration, inhibiting platelet aggregation. We believe that the reason for the localization is that **10a** is easily metabolized[17] and excreted after oral administration except that which binds to CO in platelets with a low K_{off} value.

As we mentioned in the introduction section, the use of aspirin, the most widely-used antiplatelet drug, for treatment of thromboembolic disease is limited by its ulcerogenic properties. Development of a CO inhibitor without the ulcerogenesis is a major goal in thromboembolic

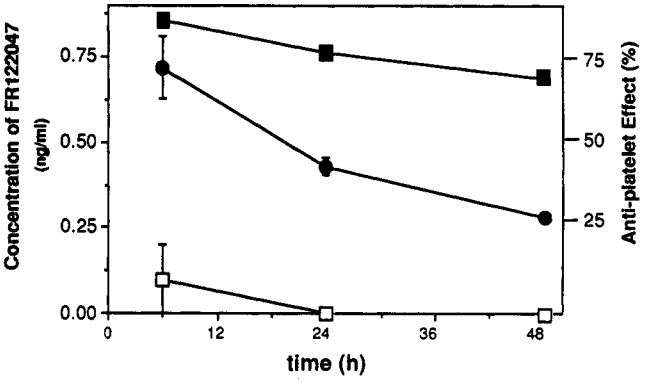


Figure 2. The time dependence of the concentration of FR122047 (● in PRP, □ in PPP) and antiplatelet effect (■) induced by collagen after oral administration (1 mg/kg) in guinea pigs. Each concentration value is the mean ± SE for three animals. Antiplatelet value is the mean for three animals.

research. We evaluated ulcerogenic activity of **10a** in rats (Table 6) according to our two presumptions: (1) compounds with a basic function like **10a** are less likely to cause gastric damage because they exist predominantly in an ionized, lipid-insoluble form, at the low pH levels characteristic of the stomach and (2) **10a** is localized in platelets after oral administration as shown above so that inhibition of PGI_2 synthesis in vascular endothelial cells is short-lived compared with that in platelets, that is, **10a** may be free from the "aspirin dilemma".[18] As expected, **10a** demonstrated no ulcerogenic activity even at 100 mg/kg, which is 70 times higher than the effective dose (ED_{50} = 1.4 mg/kg in rats), while aspirin damaged the stomachs at its effective doses (the safety margin of aspirin in rats is only 1.2). Itazigrel showed a little ulceration in a dose-dependent manner (32 and 100 mg/kg, Table 6).

Table 6. Induction of Acute Stomach Lesion and Inhibition of Collagen-Induced Platelet Aggregation in Rats by **10a**, Itazigrel, and Aspirin

compd	dose, mg/kg	ulcer index[a]	no. of rats with ulceration	ex vivo[b] ED_{50}, mg/kg
10a	100	0.0 ± 0.0	0/5	1.4
aspirin	10	0.6 ± 0.6	1/5	
	32	2.0 ± 0.8	3/5	8.4
	100	2.2 ± 0.6	4/5	
	320	3.8 ± 0.2	5/5	
itazigrel	32	0.4[c]	1/5	
	100	1.4	2/5	

[a] Values are means ± SE for five animals. [b] ED_{50} values for collagen-induced platelet aggregation in rat. [c] Values are means for three animals.

Conclusion

2-Guanidino-4,5-bis(4-methoxyphenyl)thiazole (**3**), our lead compound in this study, was designed from two parent compounds (itazigrel and timegadine) to aim at development of compounds which show potent antiplatelet activity based on CO inhibition in vivo with vasodilatory activity. Structure–activity relationship studies on **3** culminated in the synthesis of 4,5-bis(4-methoxyphenyl)-2-[(1-methylpiperazin-4-yl)carbonyl]thiazole (**10a**, FR122047). Compound **10** demonstrated potent inhibitory activity on MDA synthesis (IC_{50} = 0.088 μM) with vasodilatory activity (ED_{50} = 6.2 μM) in in vitro studies. Compound **10a** completely inhibited platelet aggregation induced by AA or collagen 6 h after oral administration of 1.0 mg/kg in guinea pigs ex vivo. Moreover, **10a** has no ulcerogenesis in rats even at 100 mg/kg dose in spite of its potent cyclooxygenase inhibition (IC_{50} = 0.43 μM[14]), while the use of aspirin, the most widely-used antiplatelet drug, is limited by its ulcerogenesis (the safety margin of aspirin is only 1.2 while that of **10a** is more than 70). Pharmacokinetic studies revealed that **10a** is detectable in PRP after 48 h but not in PPP after 6 h, which indicates that **10a** is localized in platelets. We think that the reason for the lack of the ulcerogesis are that (1) compounds with a basic function like **10a** exist predominantly in an ionized, lipid-insoluble form, at the low pH levels characteristic of the stomach, and (2) **10a** is localized in platelets after oral administration as shown above so that inhibition of PGI_2 synthesis in vascular endothelial cells is short-lived compared with that in platelets.[18] We also believe that the localization in platelets after oral administration could help prevent side effects and reduce its toxicity in clinical studies of **10a**. Preclinical studies on **10a** are now underway to evaluate the effectiveness of its potent antiplatelet and vasodilatory activities.

Experimental Section

Melting point determinations were performed in a capillary melting point apparatus (Thomas-Hoover). All melting points are uncorrected. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254 plate and Merck aluminum oxide 60 F-254 (type E). For normal chromatography, Merck silica gel type 60 (size 70–230 mesh) and Wako activated alumina (size 300 mesh) were used. All evaporations were performed with a rotary evaporator under water aspirator. The structures of all compounds were confirmed by their infrared (IR, Hitachi 260-10), mass (MASS, Finiganat TSQ70 and an Hitachi M-80 mass spectrometer), and 60-, 90-, and 200-MHz proton nuclear magnetic resonance (^{1}H-NMR, JEOL PMX-60SI, Varian EM-390, and Brucker AC200P) spectra. The chemical shift values are reported in parts per million on the δ scale from internal standard tetramethylsilane. No attempt was made to maximize the yields. All in vitro values are means for three experiments. Ex vivo values are means for five animals.

2-Chloro-1,2-bis(4-methoxyphenyl)-1-ethanone (2). A mixture of anisoin (**1**, 27.2 g, 10 mmol) and $SOCl_2$ (15.5 g, 13 mmol) in CH_2Cl_2 was stirred at room temperature for 1 h. After evaporation, the resulting precipitate was recrystallized from diethyl ether (Et_2O)–isopropyl ether (IPE) to give **2** (16.4 g, 55.6%): mp 80–4 °C; IR (Nujol) 1665, 1600, 1560, 1500 cm^{-1}; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 3.90 (s, 6 H), 7.18 (d, 4 H, J = 8 Hz), 7.92 (d, 4 H, J = 8 Hz); mass spectrum m/e 290 (M^+).

2-Guanidino-4,5-bis(4-methoxyphenyl)thiazole (3). A mixture of **2** (8.00 g, 27.5 mmol) and 2-guanidinothioamide (4.88 g, 41.3 mmol) in ethanol (EtOH, 160 mL) was stirred and refluxed for 2 h. After cooling, the resulting precipitate was removed through filtration. The filtrate was evaporated, and then the resulting residue was purified by chromatography over Al_2O_3 [chloroform ($CHCl_3$)–methanol (MeOH) as eluent] and subsequently recrystallized from EtOH to give **3** (4.50 g, 46.2%): mp 167–168 °C; IR (Nujol) 3450, 3370, 3300, 3200, 1625, 1610, 1580, 1540, 1510, 1490 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 3.75 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.88 (d, 2H, J = 8.8 Hz), 6.94 (d, 2 H, J = 8.8 Hz), 7.12 (d, 2 H, J = 8.8 Hz), 7.28 (d, 2 H, J = 8.8 Hz).

Compound **9** was obtained in a similar manner to **3**. Compound **9** was used for the subsequent reactions without purification, and the yield of this condensation was assumed to be 100% for the next reaction.

2-Amino-4,5-bis(4-methoxyphenyl)thiazole Hydrochloride (4·HCl). A mixture of **2** (10.00 g, 34.4 mmol), thiourea (7.11 g, 55.1 mmol), and a small amount of NaI in acetonitrile (CH_3CN, 100 mL) was stirred and refluxed for 3 h. After cooling, the resulting precipitate was collected by filtration. The precipitate was washed with CH_3CN and subsequently recrystallized from CH_3CN–EtOH–Et_2O to give **4**·HCl (10.00 g, 93.1%): mp 174–5 °C; IR (Nujol) 3250, 3150, 1625, 1600, 1560, 1500 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 3.68 (s, 6 H), 6.7–7.4 (m, 8 H); mass spectrum, m/e 312 (M^+, free).

2-(3-Benzoylthioureido)-4,5-bis(4-methoxyphenyl)thiazole (6). A mixture of NH_4SCN (12.2 g, 171 mmol) and benzoyl chloride (24.0 g, 171 mmol) in acetone (300 mL) was stirred and refluxed for 5 min. To a suspension of NaH (4.58 g, 114 mmol) in dimethylformamide (DMF, 60 mL) and toluene (60 mL) was added a suspension of **3** (35.7 g, 114 mmol) in DMF (60 mL) and toluene (60 mL) dropwise over 30 min at 0 °C and then was stirred at the same temperature for 30 min. To this reaction mixture was added the above mixture, including benzoyl isocyanate, at 0–5 °C. The whole mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The reaction mixture was poured into a mixture of water and ice and was extracted with a mixture of ethyl acetate (AcOEt) and tetrahydrofuran (THF). The organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation, the resulting precipitate was recrystallized from AcOEt to give **6** (41.86 g, 77.1%): mp 184–5 °C; IR (Nujol) 3220, 1660, 1605 cm^{-1}; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 3.75 (s, 3 H), 3.80 (s, 3 H), 6.8–8.2 (m, 13 H), 11.97 (s, 1 H); mass spectrum, m/e 475 (M^+).

4,5-Bis(methoxyphenyl)-2-thioureidothiazole (5a). To a suspension of **6** (20.90 g, 43.9 mmol) in MeOH (110 mL) and water (2.2 mL) was added a mixture of NaOH (1.76 g, 43.9 mmol) in MeOH (20 mL) dropwise over 10 min at 55–60 °C. The reaction mixture was stirred at the same temperature for 2 h. After the mixture was concentrated to ca. 20 mL, 400 mL of water was added to the resulting mixture. The resulting precipitate was collected by filtration and washed with water to afford **5a** (16.4 g, 100%): mp 229–231 °C; IR (Nujol) 1600, 1560, 1510, 1500 cm^{-1}; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 3.69 (s, 3 H), 3.73 (s, 3 H), 6.7–7.5 (m, 8 H), 11.70 (br s, 1 H); mass spectrum, m/e 371 (M^+).

4,5-Bis(4-methoxyphenyl)-2-(3-methylguanidino)thiazole (7a). A mixture of **5a** (10.5 g, 28.3 mmol) and MeI (17.6 mL, 283 mmol) in MeOH (140 mL) and $CHCl_3$ (140 mL) was stirred and refluxed for 1 h. After evaporation, the resulting residue was dissolved with EtOH (70 mL). The solution was transferred into a sealed tube, and then methylamine hydrochloride (9.54 g, 141 mmol) and triethylamine (19.7 mL, 141 mmol) were added. After the tube was sealed, the mixture was heated at 100 °C for 12 h. After removal of solvents, the resulting residue was dissolved

with water and AcOEt. The organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation, the resulting residue was purified by chromatography over silica gel ($CHCl_3$–AcOEt as eluent) and subsequently recrystallized from EtOH to give **7a** (6.06 g, 58.1%): mp 155–6 °C; IR (Nujol) 3400, 1660, 1610, 1590, 1505 cm^{-1}; ^1H-NMR (60 MHz, DMSO-d_6) δ 2.72 and 2.77 (both s, 3 H, $NHCH_3$), 3.73 (s, 6 H), 6.7–7.6 (m, 11 H); mass spectrum, *m/e* 368 (M^+).

Compounds **7b–e,g–i** were prepared in a similar manner to **7a**. Ethylamine hydrochloride (for **7b**, 59.4% yield), isopropylamine (for **7c**, 84.5% yield), dimethylamine hydrochloride (for **7d**, 30.3% yield), cyclohexylamine (for **7e**, 74.5% yield), *N*-methylpiperazine (for **7g**, 32.1% yield), morpholine (for **7h**, 50.9% yield), and 1,2-diaminoethane (for **7i**, 44.9% yield) were used in place of methylamine hydrochloride.

4,5-Bis(4-methoxyphenyl)-2-(3-methylthioureido)thiazole (5b). Compound **4** (1.00 g, 3.20 mmol) was added to a mixture of NaH (0.08 g, 3.20 mmol) in DMF (5 mL) dropwise over 15 min at room temperature. After the reaction mixture was stirred at room temperature for 20 min, CH_3NCS (2.19 mL, 32.0 mmol) was added. The whole mixture was stirred at room temperature for 30 min and then stirred at 80–90 °C for 5 h. After cooling, the mixture was poured into water (100 mL). The resulting precipitate was collected by filtration and washed with IPE to afford **5b** (0.81 g, 65.7%): mp 201–2 °C; IR (Nujol) 3380, 3170, 1610, 1590, 1570, 1510 cm^{-1}; ^1H-NMR (60 MHz, DMSO-d_6) δ 3.20 (s, 3 H), 4.00 (s, 6 H), 6.9–7.7 (m, 8 H); mass spectrum, *m/e* 385 (M^+).

4,5-Bis(4-methoxyphenyl)-2-(*N,N*-dimethylguanidino)thiazole (7f). Compound **5b** (0.75 g, 1.95 mmol) and methylamine hydrochloride (0.66 g, 9.73 mmol), reacted as described for **7a**, yielded 32.1% (0.30 g) of **7f**: mp 231–3 °C; IR (Nujol) 3150, 1680, 1630, 1610, 1540, 1510, 1490 cm^{-1}; ^1H-NMR (60 MHz, DMSO-d_6) δ 2.82 (s, 3 H, NCH_2), 2.90 (s, 3 H, NCH_3), 3.69 (s, 6 H, 2 × OCH_3), 6.7–7.4 (m, 8 H), 8.7 (br s, 3 H); mass spectrum, *m/e* 382 (M^+).

4,5-Bis(methoxyphenyl)-2-((dimethylamino)methyl)thiazole (8a). A mixture of **2** (2.00 g, 6.88 mmol) and ((dimethylamino)methyl)thioformamide (1.22 g, 10.3 mmol) in EtOH (20 mL) was stirred and refluxed for 3.5 h. After cooling, the mixture was poured into a mixture of saturated $NaHCO_3$ solution and AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over $MgSO_4$. After evaporation, the resulting residue was purified by chromatography over Al_2O_3 (benzene and AcOEt as eluent). The fractions containing the desired compound were combined and concentrated to one-tenth volume, and HCl/EtOH was added to the solution. The resulting precipitate was washed with Et_2O to give **8a**·HCl (0.30 g, 12.3%): mp 204–6 °C; IR (Nujol) 2560, 2530, 2470, 1610, 1510 cm^{-1}; ^1H-NMR (60 MHz, D_2O) δ 3.30 (s, 6 H, 2 × NH_3), 3.85 (s, 6 H), 4.91 (s, 2 H, CH_2), 6.7–7.8 (m, 8 H); mass spectrum, *m/e* 354 (M^+).

Compound **8b** (33.2% yield) was prepared in a manner similar to **8a**.

2-(Aminomethyl)-4,5-bis(4-methoxyphenyl)thiazole (8c). A mixture of **8b** (6.43 g, 17.5 mmol) in 35% HCl (35 mL) was stirred at room temperature for 30 min and then stirred and refluxed for 30 min. After cooling, the reaction mixture was poured into water. The resulting precipitate was collected by filtration and washed with water to afford **8c**·HCl (5.48 g, 86.3%): mp 146–8 °C; IR (Nujol) 3350, 1600, 1540, 1505 cm^{-1}; ^1H-NMR (90 MHz, DMSO-d_6) δ 3.69 (s, 3 H), 3.73 (s, 3 H), 4.38 (s, 2 H), 6.7–7.5 (m, 8 H), 8.85 (br s, 3 H); mass spectrum, *m/e* 326 (M^+).

4,5-Bis(4-methoxyphenyl)-2-((nicotinylamino)methyl)thiazole (8d). A mixture of **8b** (1.00 g, 2.71 mmol) and 35% HCl (7 mL) was stirred and refluxed for 3 h. After cooling, the reaction mixture was poured into a mixture of water and AcOEt. After the aqueous layer was alkalized with saturated K_2CO_3 solution, the separated organic layer was washed with water and brine and dried over $MgSO_4$. The organic layer was evaporated. The resulting syrup (compound **8c**) was dissolved in dichloromethane (CH_2Cl_2, 10 mL), and triethylamine (0.33 mL, 3.25 mmol) was added. To the reaction mixture was added dropwise over 10 min at room temperature a suspension of nicotinyl chloride hydrochloride (0.58 g, 3.25 mmol) in CH_2Cl_2, and then the mixture was refluxed for 1.5 h. After cooling, the reaction mixture was poured into water. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over $MgSO_4$. After evaporation, to the resulting residue was added HCl/EtOH with water cooling. The resulting precipitate was recrystallized from CH_2Cl_2–Et_2O to give **8d** (0.63 g, 49.7%): mp 135–44 °C; IR (Nujol) 3400, 3200, 1680, 1610, 1520 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 3.75 (s, 3 H), 3.77 (s, 3 H), 4.83 (d, 2 H, J = 5.6 Hz, CH_2), 6.88 (d, 2 H, J = 8.5 Hz), 6.94 (d, 2 H, J = 8.5 Hz), 7.12 (d, 2 H, J = 8.5 Hz), 7.30 (d, 2H, J = 8.5 Hz), 8.15 (dd, 1 H, J = 8.1, 5.6 Hz), 9.0–9.2 (m, 2 H), 10.42 (t, 1 H, J = 5.6 Hz); mass spectrum, *m/e* 431 (M^+).

4,5-Bis(4-methoxyphenyl)-2-[[*N*-(2-phenylthioacetyl)amino]methyl]thiazole (8e). A suspension of **8c**·HCl (4.00 g, 11.0 mmol) in CH_2Cl_2 and water was neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the resulting residue was dissolved in DMF (60 mL). To the mixture were added 2-(phenylthio)acetic acid (1.85 g, 11.0 mmol) and 1-ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride (EDC·HCl, 2.34 g, 11.0 mmol), and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and then extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, 1 N HCl, water, and brine and dried over $MgSO_4$. After evaporation, the resulting residue was recrystallized from AcOEt–Et_2O to give **8e** (2.77 g, 56.6%): mp 132–3 °C; IR (Nujol) 3320, 1660, 1610, 1550, 1520 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 3.7–3.8 (m, 8 H, 2 × OCH_2 and CH_2S), 4.56 (d, 2 H, J = 6.0 Hz, CH_2NH), 6.8–7.0 (m, 4 H), 7.3–7.4 (m, 4 H), 9.05 (t, 1 H, J = 6.0 Hz, NHCO); mass spectrum, *m/e* 476 (M^+).

Compounds **8f,g** (28.1 and 40.1% yield, respectively) were prepared in a manner similar to **8e**.

4,5-Bis(4-methoxyphenyl)-2-((3-methylureido)methyl)thiazole (8i). A suspension of **8c**·HCl (1.00 g, 2.76 mmol) in CH_2Cl_2 and water was neutralized with saturated $NaHCO_3$ solution, and the separated organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the resulting mixture was dissolved in THF (20 mL) and MeOH (7 mL). To the mixture was added CH_3NCO (0.23 mL, 3.86 mmol), and the mixture was stirred for 4.5 h. After evaporation, the resulting precipitate was recrystallized from a mixture of THF, MeOH, and AcOEt to give **8i** (0.89 g, 84.1%): mp 115–8 °C; IR (Nujol) 3300, 1620, 1600, 1500 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 2.60 (s, 3 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 4.48 (s, 2 H), 6.86 (d, 2 H, J = 8.8 Hz), 6.93 (d, 2 H, J = 8.8 Hz), 7.23 (d, 2 H, J = 8.8 Hz), 7.36 (d, 2 H, J = 8.8 Hz); mass spectrum, *m/e* 383 (M^+).

Compound **8j** (91.6% yield) was obtained in a manner similar to that of **8i**.

4,5-Bis(4-methoxyphenyl)-2-(((morpholinocarbonyl)amino)methyl)thiazole (8h). A suspension of **8c**·HCl (1.00 g, 2.76 mmol) in CH_2Cl_2 and water was neutralized with saturated $NaHCO_3$ solution, and the separated organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the resulting residue was dissolved in THF (20 mL), and pyridine (0.50 mL, 6.18 mmol) was added. A solution of morpholinocarbonyl chloride (0.7 mL, 6.00 mmol) in THF (10 mL) was added to the reaction mixture at room temperature, and the resultant mixture was stirred overnight. The reaction mixture was poured into water and then extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over $MgSO_4$. After evaporation, the resulting residue was purified by chromatography over silica gel (acetone–$CHCl_3$ as eluent) to give **8e** (1.00 g, 82.4%): mp 111–6 °C; IR (Nujol) 3300, 1630, 1600, 1540, 1515 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 3.33 (s, 8 H, morpholino), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.50 (d, 2 H, J = 6.0 Hz), 6.86 (d, 2 H, J = 8.8 Hz), 6.95 (d, 2 H, J = 8.8 Hz), 7.23 (d, 2 H, J = 8.8 Hz), 7.36 (d, 2 H, J = 8.8 Hz), 7.54 (t, 1 H, J = 6.0 Hz); mass spectrum, *m/e* 439 (M^+).

4,5-Bis(4-methoxyphenyl)-2-[(4-methylpiperazin-1-yl)carbonyl]thiazole (10a). A mixture of **9** (1.00 g, 2.71 mmol) and *N*-methylpiperazine (1.80 mL, 16.2 mmol) was stirred at 80–90 °C for 14 h. After cooling, the mixture was poured into a mixture of water and AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The resulting residue was dissolved in EtOH and Et_2O, and then HCl/

EtOH was added to give white precipitate. The precipitate was washed with Et_2O and dried to afford **10a** (0.58 g, 46.5%): mp 254–6 °C; IR (Nujol) 3400, 2430, 1625, 1610, 1560, 1535, 1510 cm^{-1}; ^1H-NMR (60 MHz, DMSO-d_6) δ 2.75 (s, 3 H, NCH_3), 3.0–3.6 (m, 8 H, piperidino), 3.72 (s, 3 H), 3.83 (s, 3 H), 6.89 (d, 2 H, J = 9 Hz), 6.92 (d, 2 H, J = 9 Hz), 7.28 (d, 2 H, J = 9 Hz), 7.36 (d, 2 H, J = 9 Hz); mass spectrum, m/e 423 (M^+).

Ammonia bubbling to a solution of **9** in MeOH afforded **10b** (28.9% yield) in a similar manner to **10a**.

The aminolysis for preparation of **10c–d** (24.1 and 8.3% yields, respectively) was carried out in a sealed tube in a similar manner to **10a**.

Compounds **10f–l** (25.2, 22.6, 42.1, 74.0, 20.6, 58.1, and 29.1% yields, respectively) were obtained in a similar manner to **10a**.

2-(Guanidinocarbonyl)-4,5-bis(4-methoxyphenyl)thiazole (10e). Guanidine hydrochloride (1.42 g, 14.9 mmol) was added to a mixture of 28% sodium methoxide (2.61 mL, 13.5 mmol) in MeOH (5 mL) at room temperature, and the mixture was stirred at the same temperature for 15 min. After removal of the resulting precipitate, the filtrate was added dropwise to a mixture of **9** in MeOH (10 mL) at room temperature and was stirred at room temperature for 2 h. The resulting precipitate was collected by filtration and was recrystallized from EtOH and Et_2O to give **10e** (0.58 g, 56.0%): mp 253–5 °C; IR (Nujol) 3420, 3180, 1660, 1630, 1610, 1530 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 3.76 (s, 3 H), 3.78 (s, 3 H), 6.90 (d, 2 H, J = 9.0 Hz), 6.95 (d, 2 H, J = 9.0 Hz), 7.28 (d, 2 H, J = 9.0 Hz), 7.38 (d, 2 H, J = 9.0 Hz); mass spectrum, m/e 382 (M^+).

4,5-Bis(4-methoxyphenyl)-2-[4-((isopropylamino)carbonyl)piperazin-1-yl]thiazole (10m). A mixture of **10g** (1.00 g, 2.25 mmol) in CH_2Cl_2 and water was neutralized with saturated $NaHCO_3$ solution, and the organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The resulting residue was dissolved with THF (20 mL) and MeOH (7 mL), and isopropyl isocyanate (0.32 mL, 3.15 mmol) was added. The mixture was stirred at room temperature for 2 h. After removal of the solvents, the resulting precipitate was recrystallized from IPE and EtOH to give **10m** (0.72 g, 65.0%): mp 157–9 °C; IR (Nujol) 3260, 1610, 1530, 1510 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 1.07 (d, 6 H, J = 6.6 Hz, CH_3), 3.4–4.4 (m, 9 H, piperidino and CH), 3.76 (s, 3 H), 3.79 (s, 3 H), 6.28 (d, 1 H, J = 7.4 Hz, NHCH), 6.92 (d, 2 H, J = 8.6 Hz), 6.97 (d, 2 H, J = 8.6 Hz), 7.32 (d, 2 H, J = 8.6 Hz), 7.39 (d, 2 H, J = 8.6 Hz); mass spectrum, m/e 494 (M^+).

2-Formyl-4,5-bis(4-methoxyphenyl)thiazole (11). A mixture of **9** (19.66 g, 53.2 mmol) and THF (25 mL) was added to a suspension of $LiAlH_4$ (2.22 g, 58.5 mmol) in THF (20 mL) at 0 °C and was stirred at room temperature for 30 min. After quenching and removal of the resulting precipitates, the filtrate was evaporated. The resulting residue was purified by chromatography over silica gel (AcOEt and benzene as eluent) to give 2-(hydroxymethyl)-4,5-bis(4-methoxyphenyl)thiazole (5.22 g, 30.0%), a oily compound: IR (Nujol) 3200, 1600, 1570, 1500 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 3.74 (s, 3 H), 3.78 (s, 3 H), 4.75 (d, 2 H, J = 5.8 Hz, CH_2), 6.10 (d, 1 H, J = 5.8 Hz, OH), 6.82 (d, 2 H, J = 8.8 Hz), 6.92 (d, 2 H, J = 8.8 Hz), 7.23 (d, 2 H, J = 8.8 Hz), 7.38 (d, 2 H, J = 8.8 Hz); mass spectrum, m/e 327 (M^+). A mixture of the above alcohol (5.04 g, 15.4 mmol) and activated MnO_2 (25.2 g, 5 w/w) in AcOEt (250 mL) was stirred at room temperature for 5.5 h. After removal of the insoluble material, the filtrate was evaporated. The resulting precipitate was recrystallized from AcOEt and n-hexane to give **11** (4.10 g, 81.9%): mp 82–5 °C; IR (Nujol) 1690, 1605, 1515 cm^{-1}; ^1H-NMR (60 MHz, $CDCl_3$) δ 3.84 (s, 6 H), 6.8–6.9 (m, 4 H), 7.33 (d, 2 H, J = 9 Hz), 7.45 (d, 2 H, J = 9 Hz), 9.28 (s, 1 H, CHO); mass spectrum, m/e 325 (M^+).

Ethyl 3-[4,5-Bis(4-methoxyphenyl)thiazol-2-yl]-2-cyanopropenate (12). A mixture of **11** (0.70 g, 2.15 mmol), ethyl cyanoacetate (0.23 mL, 2.15 mmol), ammonium acetate (0.03 g, 0.4 mmol), and AcOH (0.10 mL, 1.7 mmol) in benzene (20 mL) was stirred and refluxed for 7.5 h while the resulting water was removed using a Dean–Stark apparatus. After cooling, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified by chromatography over silica gel (benzene–AcOEt as eluent) to afford **12** (0.32 g, 35.4%): mp 138–40 °C; IR (Nujol) 2200, 1720, 1590, 1505 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 1.33 (t, 3 H, J = 7.1 Hz, Et), 3.77 (s, 3 H), 3.81 (s, 3 H), 4.34 (q, 2 H, J = 7.1 Hz, Et), 6.93 (d, 2 H, J = 8.8 Hz), 7.01 (d, 2 H, J = 8.8 Hz), 7.36 (d, 2 H, J = 8.8 Hz), 7.46 (d, 2 H, J = 8.8 Hz), 8.45 (s, 1 H, CH); mass spectrum, m/e 418 (M^+ – 2).

3,5-Bis(ethoxycarbonyl)-4-[4,5-bis(4-methoxyphenyl)thiazol-yl]-2,6-dimethyl-1,4-dihydropyridine (13). A mixture of **11** (0.992 g, 30.5 mmol), ethyl acetoacetate (0.43 mL, 3.36 mmol), morpholine (0.027 mL, 0.31 mmol), and AcOH (0.017 mL, 0.31 mmol) in benzene (10 mL) was stirred and refluxed for 30 min. After cooling, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The resulting residue was dissolved with EtOH (10 mL) and ethyl 3-aminocrotonate (0.42 mL, 3.36 mmol), and the mixture was stirred and refluxed overnight. The mixture was evaporated, and to the resulting residue were added water and AcOEt. The separated organic layer was washed with 1 N HCl, water, and brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified over Al_2O_3 (benzene–AcOEt as eluent) to give **13** (0.17 g, 10.2%): mp 177–8 °C; IR (Nujol) 1690, 1675, 1610, 1500 cm^{-1}; ^1H-NMR (90 MHz, DMSO-d_6) δ 1.27 (t, 6 H, J = 7 Hz, Et), 2.33 (s, 3 H, CH_3), 3.75 (s, 3 H), 3.78 (s, 3 H), 4.15 (q, 2 H, J = 7 Hz, Et), 5.36 (s, 1 H, CH), 6.81 (d, 2 H, J = 9 Hz), 6.87 (d, 2 H, J = 9 Hz), 7.18 (d, 2 H, J = 9 Hz), 7.28 (d, 2 H, J = 9 Hz), 9.05 (s, 1 H, NH); mass spectrum, m/e 547 (M^+ – 1).

Ethyl 3-[4,5-Bis(4-methoxyphenyl)thiazol-2-yl]-(*E*)-propeonate (14). A mixture of **11** (0.14 g, 0.43 mmol) and (carbethoxymethylene)triphenylphosphorane (0.18 g, 0.52 mmol) in CH_2Cl_2 (5 mL) was stirred and refluxed for 4 h. After evaporation, the resulting residue was purified over silica gel (CH_2Cl_2 as eluent) to give **14** (0.12 g, 70.6%): mp 94–5 °C; IR (Nujol) 1703, 1620, 1600, 1500 cm^{-1}; ^1H-NMR (90 MHz, DMSO-d_6) δ 1.31 (t, 3 H, J = 6 Hz), 3.78 (s, 3 H), 3.80 (s, 3 H), 4.22 (q, 2 H, J = 6 Hz), 6.70 (d, 1 H, J = 15 Hz, (*E*)-CH=CH), 6.82 (d, 2 H, J = 9 Hz), 6.85 (d, 2 H, J = 9 Hz), 7.26 (d, 2 H, J = 9 Hz), 7.38 (d, 2 H, J = 9 Hz), 7.68 (d, 1 H, J = 15 Hz, (*E*)-CH=CH); mass spectrum, m/e 395 (M^+).

3-[4,5-Bis(4-methoxyphenyl)thiazol-2-yl]-(*E*)-propeonic Acid (15). A mixture of **14** (0.50 g, 12.6 mmol) and 0.1 N NaOH (5 mL) in dioxane (5 mL) was stirred and refluxed overnight. The reaction mixture was acidified with 10% HCl and extracted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified over silica gel ($CHCl_3$–MeOH as eluent) to give **15** (0.16 g, 34.6%): mp 170–181 °C; IR (Nujol) 1660, 1620, 1600, 1560, 1500 cm^{-1}; ^1H-NMR (60 MHz, DMSO-d_6) δ 3.70 (s, 6 H), 6.65 (d, 1 H, J = 15 Hz), 6.80 (d, 2 H, J = 7 Hz), 6.85 (d, 2 H, J = 7 Hz), 7.15 (d, 2 H, J = 7 Hz), 7.30 (d, 2 H, J = 7 Hz), 7.51 (d, 1 H, J = 15 Hz); mass spectrum, m/e 367 (M^+).

4,5-Bis(4-methoxyphenyl)-2-[2-[(4-methylpiperazin-1-yl)carbonyl]ethenyl]thiazole (16). A mixture of **15** (0.42 g, 1.14 mmol), *N*-methylpiperazine (0.13 mL, 1.14 mmol), EDC·HCl (0.22 g, 1.14 mmol), and NEt_3 (0.16 mL, 1.14 mmol) in DMF (10 mL) was stirred at room temperature for 7 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified over silica gel ($CHCl_3$–MeOh as eluent). After concentration, HCl/EtOAc was added to give a white precipitate, which was washed with Et_2O to afford **16**·HCl (0.15 g, 27.1%): mp 83–93 °C; IR (Nujol) 1640, 1600, 1510 cm^{-1}; ^1H-NMR (200 MHz, DMSO-d_6) δ 2.76 (d, 3 H, J = 4.4 Hz), 3.4–3.8 (m, 2 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.2–4.8 (m, 6 H), 6.91 (d, 2 H, J = 8.9 Hz), 6.97 (d, 2 H, J = 8.9 Hz), 7.29 (d, 2 H, J = 8.9 Hz), 7.40 (d, 2 H, J = 8.9 Hz), 7.42 (d, 1 H, J = 15.2 Hz), 7.62 (d, 1 H, J = 15.2 Hz), 11.48 (br s, 1 H); mass spectrum, m/e 449 (M^+).

3-[4,5-Bis(4-methoxyphenyl)thiazol-2-yl]propionic Acid (17). Compound **15** (1.04 g, 2.83 mmol) was dissolved with $CHCl_3$ (10 mL) and MeOH (10 mL), and the reaction mixture was hydrogenated at room temperature and atmospheric pressure over 5% $Pd(OH)_2$–C (0.8 g) for 4 h. After filtration and evaporation of the filtrate, the resulting precipitate was recrystallized from EtOH and Et_2O to give **17** (0.35 g, 31.6%): mp 218–225 °C; IR (Nujol) 3300, 1600, 1560, 1505 cm^{-1}; ^1H-NMR (60

MHz, DMSO-d_6) δ 2.59 (br s, 2 H), 3.4 (br s, 2 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 6.6–7.4 (m, 8 H); mass spectrum, *m/e* 369 (M^+).

Ethyl 3-[4,5-Bis(4-methoxyphenyl)thiazol-2-yl]-3-(4-methylpiperazin-1-yl)propionate (18). Compound 14 (0.50 g, 1.26 mmol) and *N*-methylpiperazine (5 mL), condensed as described for **10a**, yielded 34.3% of **18**·HCl: mp 157–61 °C; IR (Nujol) 2350, 1735, 1605, 1510 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 1.16 (t, 3 H, *J* = 7 Hz, Et), 2.81 (br s, 3 H, NCH_3), 2.5–3.8 (m, 10 H, morpholino and CH_2), 3.75 (s, 3 H), 3.78 (s, 3 H), 4.11 (q, 2 H, *J* = 7 Hz, Et), 4.73 (m, 1 H, thiazole-CH), 6.87 (d, 2 H, *J* = 9 Hz), 6.96 (d, 2 H, *J* = 9 Hz), 7.26 (d, 2 H, *J* = 9 Hz), 7.38 (d, 2 H, *J* = 9 Hz), 11.01 (br s, 1 H, NH^+); mass spectrum, *m/e* 495 (M^+ of free).

2-(4,5-Dihydro-3-oxopyridazin-6-yl)-4,5-bis(4-methoxyphenyl)thiazole (19). Compound **2** (1.24 g, 4.27 mmol) and 4,5-dihydro-6-thiocarbamoyl-3-pyridazinone (0.61 g, 3.88 mmol), condensed as described for **10a**, yielded 34.1% of **19**: mp 242–7 °C; IR (Nujol) 3200, 3100, 1680, 1610, 1580, 1520 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 2.51 (t, 2 H, *J* = 8.4 Hz, oxopyridazino), 3.27 (t, 2 H, *J* = 8.4 Hz, oxopyridazino), 3.76 (s, 3 H), 3.78 (s, 3 H), 6.90 (d, 2 H, *J* = 8.8 Hz), 6.97 (d, 2 H, *J* = 8.8 Hz), 7.29 (d, 2 H, *J* = 8.8 Hz), 7.39 (d, 2 H, *J* = 8.8 Hz), 11.17 (s, 1H); mass spectrum, *m/e* 393 (M^+).

4,5-Bis(4-methoxyphenyl)-2-(1-methyl-1,2,5,6-tetrahydropyridin-4-yl)thiazole (21). **2** (3.00 g, 10.3 mmol) and 4-thiocarbamoylpyridine (1.57 g, 11.3 mmol), condensed as described for **10a**, yielded 50.6% of 4,5-bis(4-methoxyphenyl)-2-(4-pyridyl)-thiazole (**20**): mp 113–7 °C; IR (Nujol) 3225, 1670, 1600, 1505 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 3.77 (s, 3 H), 3.80 (s, 3 H), 6.83 (d, 2 H, *J* = 8.9 Hz), 6.95 (d, 2 H, *J* = 8.9 Hz), 7.35 (d, 2 H, *J* = 8.9 Hz), 7.43 (d, 2 H, *J* = 8.9 Hz), 8.6–8.8 (m, 4 H, 4-pyridyl); mass spectrum, *m/e* 374 (M^+). A mixture of the above thiazole (1.78 g, 4.75 mmol), methyl iodide (2.96 mL, 47.5 mmol), MeOH (8 mL), and $CHCl_3$ (20 mL) was stirred at room temperature for 10.5 h. After evaporation, the resulting precipitate was removed by filtration and washed with $CHCl_3$. To a solution of the combined filtrate were added dropwise MeOH (20 mL) and subsequently $NaBH_4$ (0.54 g, 14.3 mmol) at room temperature, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified over silica gel ($CHCl_3$–MeOh as eluent) to give **21** (0.16 g, 8.6%): mp 131–2 °C; IR (Nujol) 1603, 1505, 1485 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 2.31–3.4 (m, 6 H, $CH_2CH_2NCH_2$), 2.60 (br s, 3 H, NCH_3), 3.67 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 6.55 (m, 1 H, =CH), 6.83 (d, 2 H, *J* = 8 Hz), 6.91 (d, 2 H, *J* = 8 Hz), 7.22 (d, 2 H, *J* = 8 Hz), 7.35 (d, 2 H, *J* = 8 Hz); mass spectrum, *m/e* 392 (M^+).

4,5-Bis(4-methoxyphenyl)-2-(4-methylpiperazin-1-yl)thiazole (22). 2-Chloro-4,5-bis(4-methoxyphenyl)thiazole (0.50 g, 1.51 mmol) and *N*-methylpiperazine (1.67 mL, 15.1 mmol), condensed as described for **10a**, yielded 50.2% of **22**: mp 135–6 °C; IR (Nujol) 1605, 1570, 1505 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 2.23 (s, 3 H, NCH_3), 2.4–2.6 (br s, 4 H, 2 × CH_2), 3.3–3.5 (br s, 4 H, CH_2NCH_2), 3.73 (s, 3 H), 3.75 (s, 3 H), 6.82 (d, 2 H, *J* = 8.8 Hz), 6.89 (d, 2 H, *J* = 8.8 Hz), 7.16 (d, 2 H, *J* = 8.8 Hz), 7.34 (d, 2 H, *J* = 8.8 Hz); mass spectrum, *m/e* 395 (M^+).

Pharmacological Tests. Blood from male Hartley guinea pigs was collected into plastic tubes containing 3.8% sodium citrate (1/10 volume of blood), and blood from male Sprague–Dawley rats was collected into tubes containing 2.2% sodium citrate. Platelet-rich plasma (PRP) was obtained by centrifugation of blood at 120*g* for 10 min, and platelet-poor plasma (PPP) was obtained by centrifugation of the remaining blood at 1500*g* for 15 min. Platelet aggregation was studied by the turbidimetric method of Born and Cross[19] with an NKK HEMATRACER 1.

MDA Formation. PRP from rabbits was centrifuged at 150*g* for 15 min. The pellets were suspended in 0.002% saponin–1% ammonium oxalate solution (Technicon). After further centrifugation of the tubes for 10 min, the platelets were resuspended in phosphate-buffered saline (PBS, pH = 7.4) at a concentration of 10^9 platelets/mL. MDA was measured by the modified method of Placer et al.[20] Platelet suspension (0.9 mL) was preincubated with 0.1 mL of a solution of drug for 5 min at 37 °C, and the reaction was started by the addition of 20 μL of 2.5 mM AA; the incubation lasted 3 min. The reaction was terminated by addition of 1 mL of thiobarbituric acid reagent, followed by boiling for 10 min. After centrifugation of the test tubes at 1500*g* for 10 min, the absorption of supernatant solution was measured at 532 nm.

Vasodilatory Activity. Helical strips of rat thoracic aorta were suspended in an organ bath containing Tyrode solution gassed with 95% O_2–5% CO_2 at 37 °C under 0.5 g load. Contraction was induced by addition of KCl solution (final concentration was 30 mM). After the tonus reached a plateau, drug solution (dissolved in DMSO) was added cumulatively and, finally, 10^{-4} M of papaverine was added to obtain maximum relaxation. Activities of the test compound were expressed as ED_{50} values, *i.e.*, the dose required to relax the isolated rat aorta by 50%.

Ex Vivo Studies on Platelet Aggregation. Male Hartley guinea pigs weighing 200–300 g were used after a 24-h fast, and male Sprague–Dawley rats weighing about 200 g were used after an overnight fast. Blood was obtained from the abdominal aorta under ether anesthesia at scheduled times after oral administration of drugs. The final concentration of collagen was 0.5 μg/mL for guinea pigs and 2.0 μg/mL for rats. AA was used at 50 μM in guinea pigs. The percent inhibition was calculated from the total aggregation.

Gastroulcerogenic Activity. Male Sprague–Dawley rats were used after a 24-h fast. Drugs were orally administered to groups of five rats 5 h before autopsy. The stomachs were macroscopically inspected and scored as follows: 0, no evidence of gastric lesions; 1, spotty submucosal hemorrhage; 2, some areas of submucosal hemorrhage or appearance of erosion; 3, widespread adherence of blood and large areas of submucosal hemorrhage or one to four small ulcers; 4, more than four small ulcers or one large ulcer (diameter: >3 mm); 5, numerous large ulcers.

Measurement of FR122047 Concentration in Plasma. PRP and PPP were obtained from guinea pigs after oral drug administration as above described. To 0.1 mL of PRP or PPP was added 0.1 mL of 50% EtOH, 1 mL of pH = 8 buffer solution (Merck), and 4 mL of AcOEt. The mixture was shaken for 10 min and centrifuged at 2500 rpm for 10 min. The organic phase was dried with nitrogen gas and dissolved in 2.3 mM Na_2PO_4, 1.2 mM KH_2PO_4, and 50% CH_3CN. Twenty-five microliters of the resulting solution was injected automatically into a HPLC (pump, Waters 6000A; detector, JASCO 821-FD; injector, Waters 710B) with a 15-cm stainless steel column (3.9-mm internal diameter) packed μBONDASPHERE 5μCN100A. The flow rate was 1 mL/min.

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Supplementary Material Available: Table listing IR, mass, and ^{1}H-NMR data of compounds **3**, **7a–i**, **8a–j**, **10a–m**, **12–19**, and **21–22** (4 pages). Ordering information is given on any current masthead page.

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