Studies on Anti-platelet Agents. IV.[1] A Series of 2-Substituted 4,5-Bis(4-methoxyphenyl)pyrimidines as Novel Anti-platelet Agents

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The syntheses and structure–activity relationships of a series of 2-substituted 4,5-bis(4-methoxyphenyl)pyrimidines, designed on the basis of structural analyses of several cyclooxygenase (CO) inhibitors, and their derivatives as anti-platelet agents based on CO inhibition are described. Among them, 4,5-bis(4-methoxyphenyl)-2-morpholinopyrimidine (8) and 4,5-bis(4-methoxyphenyl)-2-(3,5-dimethylmorpholin-4-yl)pyrimidine (9) showed potent inhibitory activity on malondialdehyde, formed by the CO-catalyzed oxygenation of arachidonic acid (A.A.) in prostanoids, production *in vitro* (73.4% inhibition at 10^{-8} M and $IC_{50} = 1.4 \times 10^{-8}$ M, respectively). Certain compounds were also examined in *ex vivo* studies. Of these compounds, 4,5-bis(4-methoxyphenyl)-2-(1-methyl-1,2,3,6-tetrahydropyrid-4-yl)pyrimidine (11a) exhibited potent and long-lasting anti-platelet activity *ex vivo*, that is, 11a showed 97% inhibition of platelet aggregation induced by A.A. even 24 h after oral administration of 3.2 mg/kg in guinea pigs, and 60—70% inhibition at 6 h after lower doses (1.0 mg/kg). The *ex vivo* activity of 11a is more than three times that of aspirin (aspirin showed 81% inhibitory activity on platelet aggregation induced by A. A. at 6 h after oral administration at 10 mg/kg in this study). Compound 11a also showed vasodilatory activity ($ED_{50} = 5.3 \times 10^{-6}$ M, while aspirin has no vasodilatory activity at 6.0×10^{-4} M).

Keywords platelet aggregation; inhibitor; vasodilatory activity; cyclooxygenase inhibition; aspirin; 2-substituted 4,5-bis(4-methoxyphenyl)pyrimidine

Medical research has significantly advanced clinical treatment of thromboembolic diseases. Such diseases, however, still remain the leading cause of human morbidity and mortality.[2] Many compounds regulating specific mediators involved in platelet aggregation have been synthesized and tested in clinical trials. Among them, aspirin has shown its effectiveness in clinical trials,[3] and is the most widely used thromboembolic drug. The use of aspirin, however, is restricted by the aspirin dilemma,[4] that is, aspirin often induces stomach ulcers since it inhibits not only the synthesis of prostaglandin H_2 (PGH_2) and thromboxane A_2 (TXA_2) in platelets but also that of PGI_2 in endothelial cells. Development of a novel aspirin-like anti-platelet drug, based on cyclooxygenase (CO) inhibition and being free from side effects, is a major goal of thromboembolic research.

We have recently reported 4,5-bis(4-methoxyphenyl)-2-[(4-methylpiperadin-1-yl)carbonyl]thiazole (FR122047,[1] Fig. 1), as a potent anti-platelet agent based on CO inhibition with vasodilatory activity. Structural analyses of FR122047 and several CO inhibitors[1,5–7] indicated that both the bis(4-methoxyphenyl) moiety is essential for potent CO inhibition and a hetero-cyclic ring including a nitrogen atom between substituents and the 4-methoxyphenyl moiety are suitable for the A moiety of compound **1** (Fig. 1). Pyrimidine rings have not been tried yet, though compounds with some hetero rings, such as thiazole, imidazole, and triazine rings, are already known. On the basis of this information, we synthesized a series of 2-substituted 4,5-bis(4-methoxyphenyl)pyrimidines as novel anti-platelet agents, and conducted *in vitro* and *ex vivo* assays. We consider that the vasodilatory activity of FR122047 is beneficial since thrombus reduces blood flow at the lesion site, and therefore the vasodilatory activity of several compounds was examined, in addition to the anti-platelet assay.

We describe here the syntheses and structure–activity relationships of 2-substituted 4,5-bis(4-methoxyphenyl)-pyrimidines and derivatives, together with their pharmacological effects on platelet aggregation *in vitro* and *ex vivo*, and vasodilatory activity *in vitro*.

Chemistry

Reaction of deoxyanisoin (**2**) with *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine in tetrahydrofuran (THF) at 50—60 °C gave 3-dimethylamino-1,2-bis(4-methoxyphenyl)-2-propen-1-one (**3** Chart 1), as a mixture of *E* and *Z* isomers. Condensation of **3** with several amidine derivatives in the presence of sodium methoxide provided 2-substituted 4,5-bis(4-methoxyphenyl)pyrimidines (**4**—**9**).

Addition of several amines to cyano moiety of **6** in refluxing ethanol (EtOH) gave 2-guanidino-4,5-bis(4-methoxyphenyl)pyrimidine derivatives (**10a**—**l**).

Reaction of 4,5-bis(4-methoxyphenyl)-2-(4-pyridyl)pyrimidine (**7**) with several alkyl halides and subsequent reduction with sodium borohydride provided 2-(1-alkyl-1,2,3,6-tetrahydropyrid-4-yl)-4,5-bis(4-methoxyphenyl)-pyrimidines (**11a**—**g**) as shown in Chart 2. Reduction of **11a** and **11d** with ammonium formate in the presence of 10% Pd on carbon at 100—110 °C afforded 4,5-bis(4-methoxyphenyl)-2-(1-methylpiperidin-4-yl)pyrimidine (**12a**) and the 2-[1-(3′-fluorobenzyl)piperidin-4-yl] derivative (**12b**), respectively.

Reaction of 4-pyridinecarbothioamide (**13**) with hydrazine hydrate in EtOH and subsequent condensation with 1,2-bis(4-methoxyphenyl)-1,2-ethanedione (**15**) gave 5,6-bis(4-methoxyphenyl)-3-(4-pyridyl)-1,2,4-triazine (**16**). Conversion from triazine to pyridine with bicyclo[2.2.1]-hepta-2,5-diene in refluxing xylene was reported by Elix *et al.*[9] We have applied this reaction to convert **16** into 2,3-bis(4-methoxyphenyl)-6-(4-pyridyl)pyridine (**17**, Chart 3). Alkylation of **16** and **17** with 4′-fluorobenzyl chloride

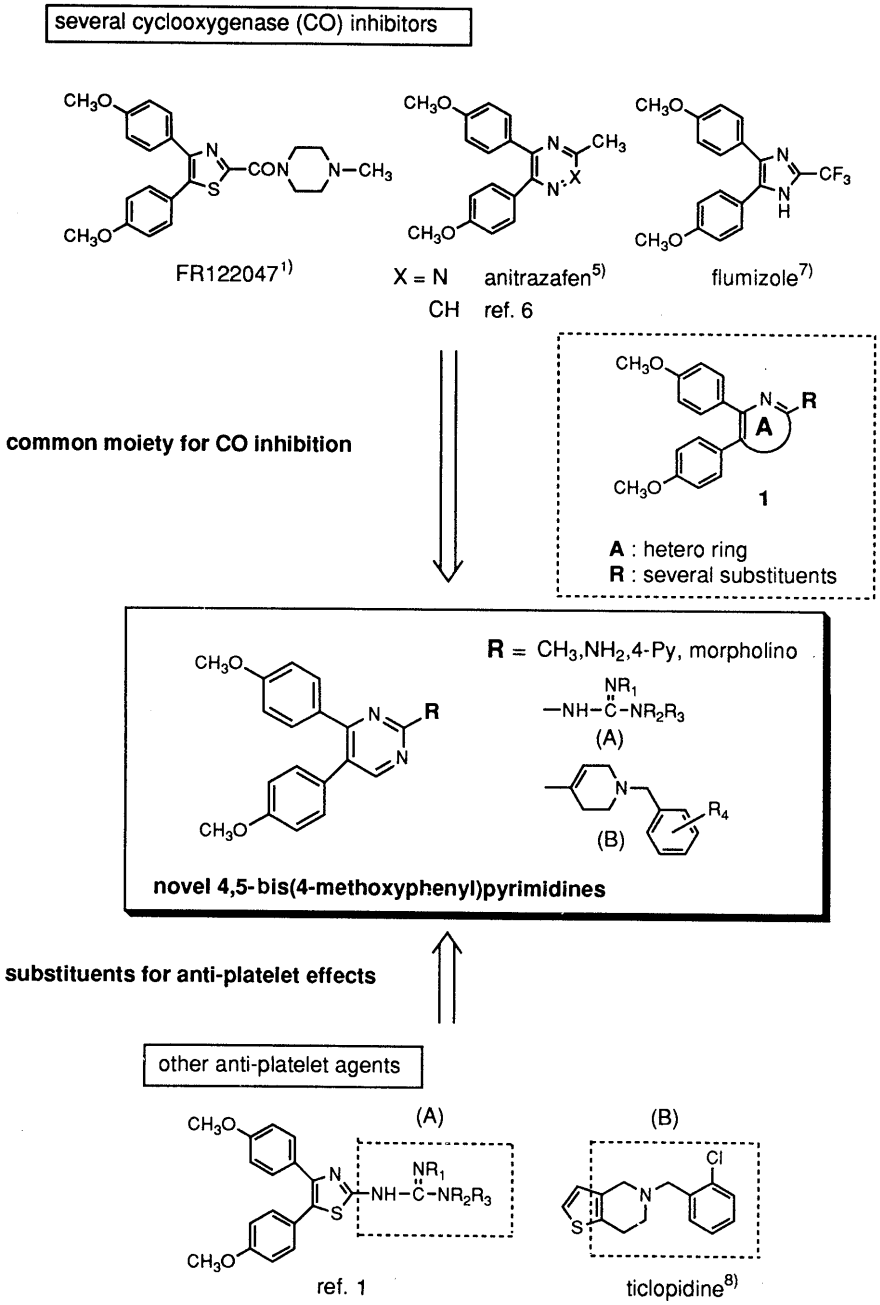


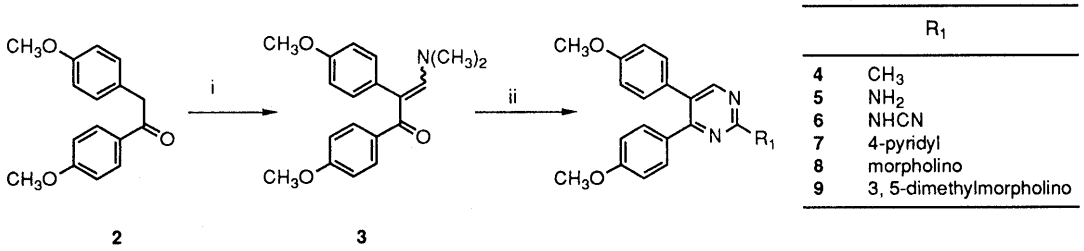
Fig. 1. Evolution of Novel 4,5-Bis(4-methoxyphenyl)pyrimidines as Antiplatelet Agents

and subsequent reduction with sodium borohydride afforded 1-[(4′-fluorobenzyl)-1,2,3,6-tetrahydropyrid-4-yl] derivatives (**18** and **19**).

Biological Results and Discussion

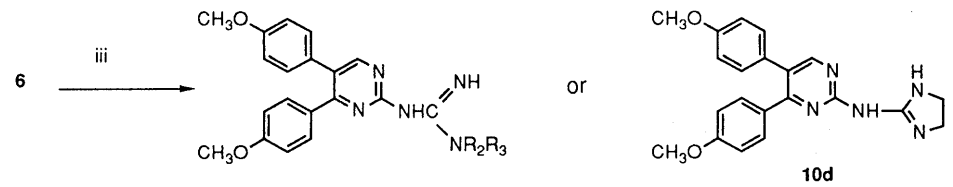
Inhibitory activities on malondialdehyde (MDA) synthesis was measured to evaluate the CO inhibition of the compounds prepared in this study. MDA is formed from the CO-catalyzed oxygenation of arachidonic acid (A.A.) during the synthesis of prostanoids, so that inhibitory activity on MDA synthesis is considered to be consistent with CO-inhibitory activity. Vasodilatory activity of several derivatives was also tested since we consider that such activity may be beneficial in the treatment of thrombotic disease [aspirin has no vasodilatory activity ($ED_{50} > 6.0 \times 10^{-4}$ M) as shown in Table I].

We first tested compound **4**, which has a methyl group at the 2-position of the pyrimidine ring, since a methyl group is present in other CO inhibitors such as antitrazafen (Fig. 1). Compound **4** showed moderate activity on MDA synthesis (43.9% inhibition at 10^{-7} M) with vasodilatory activity ($ED_{50} = 3.2 \times 10^{-5}$ M). In order to increase the MDA activity while retaining the vasodilatory activity, several modifications of the methyl group were carried out, as shown in Table I. Replacement of the methyl group with a morpholino group (**8**) or a 3,5-dimethylmorpholino group (**9**) resulted in potent anti-MDA activity (73.4% inhibition at 10^{-8} M and $IC_{50} = 1.4 \times 10^{-8}$ M, respectively) while replacement with amine (**5**) and 4-pyridine (**7**) resulted in weak anti-MDA activities ($IC_{50} > 10^{-7}$ M). Interestingly, addition of methyl



	R_1
4	CH_3
5	NH_2
6	NHCN
7	4-pyridyl
8	morpholino
9	3, 5-dimethylmorpholino

2 **3**

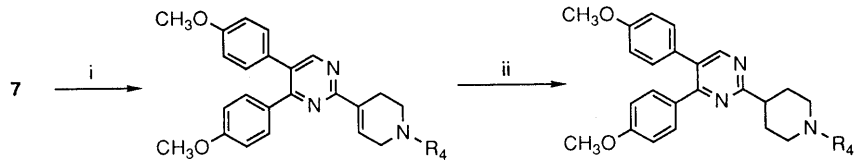


10d

	NR_2R_3
10a	$N(CH_3)_2$
10b	$NHCH(CH_3)_2$
10c	NH–benzyl
10e	NH–cyclohexyl
10f	morpholino
10g	piperidino
10h	–N N–CH_3
10i	–N –benzyl
10j	–N N–benzyl
10k	–NH– N–benzyl
10l	–N N–phenyl(o-MeO)

reagents: (i) $(CH_3)_2NCH(OCH_3)_2$/THF, 50—60 °C, 4 h; (ii) R_1–C(=NH)NH_2 and CH_3ONa/EtOH, reflux, 1.5 h; (iii) HNR_2R_3 ($H_2NCH_2CH_2NH_2$ for **10d**)/EtOH, reflux, 8 h

Chart 1



	R_4
11a	CH_3
11b	CH_2CH_3
11c	benzyl
11d	-(3'-F-benzyl)
11e	-(4'-F-benzyl)
11f	-(2'-F-benzyl)
11g	CH_2CH_2-C_6H_5

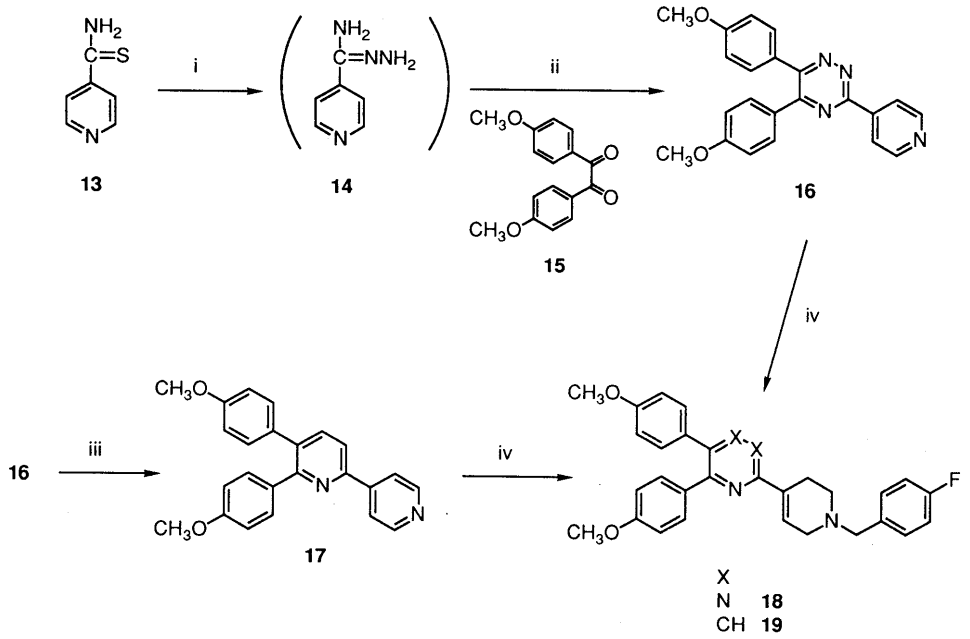
	R_4
12a	CH_3
12b	-(3'-F-benzyl)

reagents: (i) a) R_4–X (X=Cl, Br, I)/$CHCl_3$–MeOH, r.t., 3 d, b) $NaBH_4$/MeOH–H_2O, r.t., 0.5 h; (ii) $HCOONH_4$ and 10% Pd–C/AcOH, 100—110 °C, 2.5 h

Chart 2

groups to the morpholine ring of **8** (**9**) conferred enhanced vasodilatory activity ($ED_{50}=7.6\times10^{-6}$ M) compared to **8** ($ED_{50}>10^{-4}$ M), which was 4.2 times as potent as the parent compound **4**.

Next, several 2-guanidino derivatives (**10a**—**l**) were evaluated, since we have observed previously that 4,5-bis(4-methoxyphenyl)-2-(substituted guanidino)thiazoles showed both anti-platelet and vasodilatory activities (Fig. 1).[4] Of these compounds, the piperidino amidine derivative (**10g**) exhibited the most potent vasodilatory activity ($ED_{50}=4.6\times10^{-6}$ M) in this study. However, all these derivatives showed only weak anti-MDA activity



reagents: (i) $NH_2NH_2 \cdot H_2O$/EtOH, 0°C, 1 h; (ii) **15** with a small amount of HCl/EtOH, reflux, overnight; (iii) bicyclo[2.2.1]hepta-2,5-diene/xylene, reflux, overnight; (iv) a) 4-fluorobenzyl chloride/$CHCl_3$–MeOH, r.t., 3 d, b) $NaBH_4$/MeOH–H_2O, 0°C, 0.5 h

Chart 3

TABLE I. Yields, Analytical Data, and Pharmacological Data of Compounds

	Yields[a] (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	MDA Inhibition[b,c] *in vitro* IC_{50} (M)	Vasodilatory[c] rat aorta, *in vitro* ED_{50} (M)
4	31.0	92—94	$C_{23}H_{19}N_3O_2$	74.49	5.92	9.15	74.81	5.92	8.96	$>10^{-7}$ (43.9%)	3.2×10^{-5}
5	55.9	198—200	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67	70.28	5.57	13.59	$>10^{-7}$ (−5.0%)	—
7	20.3	175—177	$C_{23}H_{19}N_3O_2$	74.78	5.18	11.38	74.88	5.16	11.77	$>10^{-7}$ (20.4%)	—
8	12.5	147—150	$C_{22}H_{23}N_3O_3$	70.01	6.14	11.13	70.25	6.26	11.25	$<10^{-8}$ (73.4%)	$>10^{-4}$ (49.0%)
9	62.0	138—140	$C_{24}H_{27}N_3O_3$	71.09	6.71	10.36	70.82	6.69	10.30	1.4×10^{-8}	7.6×10^{-6}
10a	33.7	238—239	$C_{21}H_{23}N_5O_2$	60.94	5.84	16.92	60.90	5.64	16.78	$>10^{-6}$ (24.0%)	1.1×10^{-5}
10b	15.4	167—169	$C_{23}H_{25}N_5O_2 \cdot H_2O$	64.53	6.65	17.10	64.26	6.52	16.93	$>10^{-6}$ (2.0%)	—
10c	59.1	204—206	$C_{26}H_{25}N_5O_2 \cdot 1/4H_2O$	70.32	5.79	15.77	70.60	5.43	15.68	$>10^{-6}$ (5.0%)	—
10d	30.0	190—192	$C_{21}H_{21}N_5O_2$	67.18	5.64	18.65	67.56	5.80	18.71	$>10^{-6}$ (25.0%)	—
10e	50.0	203—205	$C_{25}H_{29}N_5O_2 \cdot H_2O$	66.80	6.95	15.58	66.99	6.64	15.54	$>10^{-6}$ (−6.0%)	—
10f	57.1	175—178	$C_{23}H_{25}N_5O_3$	65.85	6.01	16.70	65.60	6.07	16.67	$>10^{-7}$ (7.0%)	—
10g	52.0	185—187	$C_{24}H_{27}N_5O_2$	69.04	6.52	16.78	68.76	6.50	16.64	$>10^{-7}$ (4.2%)	4.6×10^{-6}
10h	53.8	137—140	$C_{24}H_{28}N_6O_2$	66.64	6.53	19.43	66.23	6.80	19.10	$>10^{-7}$ (−1.0%)	—
10i	34.0	129—136	$C_{31}H_{33}N_5O_2$	73.35	6.55	13.80	73.25	6.69	13.41	$>10^{-7}$ (−5.5%)	—
10j	88.5	175—177	$C_{30}H_{32}N_6O_2$	70.84	6.34	16.53	70.51	6.36	16.19	$>10^{-7}$ (1.9%)	—
10k	50.7	157—159	$C_{31}H_{34}N_6O_2 \cdot H_2O$	68.86	6.71	15.54	69.19	6.41	15.30	$>10^{-7}$ (−0.5%)	—
10l	48.7	199—200	$C_{30}H_{32}N_6O_3$	68.68	6.15	16.02	68.45	6.23	15.79	$>10^{-7}$ (−5.4%)	—
11a	45.3	131—133	$C_{24}H_{25}N_3O_2 \cdot 1/2H_2O$	72.70	6.63	10.60	72.53	6.41	10.54	$>10^{-7}$ (39.3%)	5.3×10^{-6}
11b	53.0	183—186	$C_{25}H_{27}N_3O_2 \cdot 2HCl \cdot H_2O$	60.98	6.35	8.53	60.89	6.49	8.47	$>10^{-7}$ (20.8%)	5.4×10^{-6}
11c	17.7	128—130	$C_{30}H_{29}N_3O_2$	77.72	6.31	9.07	77.67	6.40	8.91	$>10^{-7}$ (−26.9%)	—
11d	39.5	130—132	$C_{30}H_{28}FN_3O_2$	74.82	5.86	8.73	75.21	6.01	8.87	$>10^{-7}$ (46.2%)	$>3.2\times10^{-5}$ (31%)
11e	33.0	118—120	$C_{31}H_{29}FN_3O_2$	74.82	5.86	8.73	74.81	5.93	8.64	$>10^{-7}$ (19.4%)	—
11f	44.0	96—99	$C_{30}H_{28}FN_3O_2$	74.82	5.86	8.73	74.54	6.01	8.45	$>10^{-7}$ (26.2%)	—
11g	9.2	135—136	$C_{31}H_{31}N_3O_2$	77.96	6.54	8.80	77.66	6.46	8.78	$>10^{-7}$ (−2.9%)	—
12a	14.3	227—230	$C_{24}H_{27}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$	61.15	6.41	8.91	60.94	6.40	9.15	$>10^{-7}$ (17.9%)	1.0×10^{-5}
12b	53.0	209—211	$C_{30}H_{30}FN_3O \cdot 2HCl \cdot 2H_2O$	62.50	6.29	7.29	62.17	6.28	7.22	$>10^{-7}$ (20.8%)	5.4×10^{-6}
18	31.2	137—138	$C_{29}H_{27}FN_4O_2$	72.18	5.64	11.61	72.41	5.68	11.72	$>10^{-7}$ (7.3%)	—
19	25.8	115—117	$C_{31}H_{29}FN_2O_2$	77.48	6.08	5.83	77.87	6.08	5.75	$>10^{-6}$ (42.2%)	—
Aspirin										1.6×10^{-5}	$>6.0\times10^{-4}$
Ticlopidine										—	2.7×10^{-5}

a) Yields from the corresponding precursors. *b*) MDA production induced by A.A. MDA is formed during the CO catalyzed oxygenation of A.A. in the synthesis of prostanoids, so that inhibition of MDA synthesis is considered to be consistent with CO-inhibitory activity. *c*) The evaluation methods are described in the Experimental section. When the IC_{50} or ED_{50} values could not be defined even at the maximum concentration employed, the activity percentage values are shown in parentheses. —, not tested.

(Table I).

Next, 1-alkylpiperidin-4-yl derivatives (**11a—g**, **12a—b**, and **18**, **19**) were evaluated (Table I). The 1-alkylpiperidin-4-yl derivatives were designed from ticlopidine[8] which is a widely used anti-platelet drug and has vasodilatory activity as well (Table I); that is, the 1-alkylpiperidin-4-yl moiety corresponded to the (B) moiety of ticlopidine (Fig. 1). The 1-methyl (**11a**) and 1-ethyl-1,2,3,6-tetrahydropyridyl derivatives (**11b**) showed potent vasodilatory activities ($ED_{50} = 5.3 \times 10^{-6}$ and 5.4×10^{-6} M, respectively) while all these derivatives showed weak CO inhibition *in vitro* ($IC_{50} > 10^{-7}$ or 10^{-6} M). The vasodilatory activities of **11a** and **11b** were about five times more potent than that of ticlopidine (Table I). Conversion of the pyrimidine ring of **11e** to triazine (**18**) and pyridine (**19**), which are known in the A moiety of other CO inhibitors (Fig. 1),[5,6] was also carried out. These compounds showed weak anti-MDA activities (Table I).

Finally, we carried out *ex vivo* studies on certain compounds, and these results are shown in Table II. Compound **8**, the most potent MDA-production inhibitor in this study, exhibited potent and long-lasting *ex vivo* activity, that is, **8** completely inhibited platelet aggregation even at 6 h after administration of 3.2 mg/kg. It was much more potent than aspirin, which showed 81% and 5% inhibitory activity on platelet aggregation induced by A.A. and collagen, respectively, at 6 h after oral administration (10 mg/kg) in our study. Compound **8**, however, was excluded from additional studies since it showed only weak vasodilatory activity (49% effect at 10^{-4} M). Compound **10a**, a representive guanidino derivative, was tested *ex vivo*. It showed weak *ex vivo* potency (28% inhibition after 1 h at 3.2 mg/kg), probably because of the weak anti-MDA production activity. The activity of **10a** is about half that of aspirin. Surprisingly, compound **11a**, one of the 1-alkylpiperidin-4-yl derivatives, completely prevented platelet aggregation induced by A.A. and collagen even 6 h after oral administration of 3.2 mg/kg in guinea pigs, and still showed 97% inhibition of platelet aggregation induced by A.A. after 24 h, even though it did not show potent anti-MDA production activity *in vitro* (39.3% inhibition at 10^{-7} M). Moreover **11a** showed 60—70% inhibition after 6 h at lower doses (1.0 mg/kg). The reason for the difference in potency of **11a** between *ex vivo* and *in vitro* is not known.

Further pharmacological studies on **11a** *e.g.*, to evaluate ulcerogenicity, are being carried out to help select useful compounds for clinical trials.

TABLE II. *Ex Vivo* Activities of Novel Pyrimidine Derivatives in Guinea Pigs[a]

	Dose[b] (mg/kg)	A.A.			Collagen		
		1 h	6 h	24 h	1 h	6 h	24 h
8	3.2	—	100	—	—	100	—
10a	3.2	28	—	—	5	—	—
11a	1.0	81	69	—	70	60	—
	3.2	100	100	97	99	83	8
Aspirin	1.0	21	—	—	4	—	—
	3.2	64	—	—	9	—	—
	10.0	81	81	64	24	5	6
	32.0	100	100	100	68	66	1

a) The evaluation methods are described in the experimental section. *b*) Inhibitory activities on guinea pig platelet aggregation induced by A.A. and collagen were measured 1, 6, or/and 24 h after oral administration of each compound. —, not tested.

Conclusion

In order to obtain novel aspirin-like anti-platelet agents, we have synthesized a series of 2-substituted 4,5-bis(4-methoxyphenyl)pyrimidines. Among them, 4,5-bis(4-methoxyphenyl)-2-morpholinopyrimidine (**8**) and 4,5-bis-(4-methoxyphenyl)-2-(3,5-dimethylmorpholin-4-yl)pyrimidine (**9**) showed potent inhibitory activity on MDA production *in vitro* (73.4% inhibition at 10^{-8} M and $IC_{50} = 1.4 \times 10^{-8}$ M, respectively).

We also carried out *ex vivo* studies on certain compounds, such as **8**, 2-(3,3-dimethylguanidino)-4,5-bis(4-methoxyphenyl)pyrimidine (**10a**), and 4,5-bis(4-methoxyphenyl)-2-(1-methyl-1,2,3,6-tetrahydropyrid-4-yl)pyrimidine (**11a**). Among them, compounds **8** and **11a** exhibited potent and long-lasting anti-platelet activity *ex vivo*, that is, **8** and **11a** completely prevented platelet aggregation induced by A.A. and collagen even 6 h after oral administration of 3.2 mg/kg in guinea pigs. Moreover **11a** showed 97% inhibition of platelet aggregation induced by A.A. even after 24 h, and 60—70% inhibition after 6 h at lower doses (1.0 mg/kg). These results indicated that the *ex vivo* activity of **8** and **11a** is more than three times that of aspirin (aspirin showed 81% and 5% inhibitory activity on platelet aggregation induced by A.A. and collagen, respectively, at 6 h after oral administration (10 mg/kg) in this study).

We have also carried out a vasodilation assay besides anti-platelet assays on several compounds. Compound **11a** showed vasodilatory activity ($ED_{50} = 5.3 \times 10^{-6}$ M) while aspirin and **8** did not. We consider that the vasodilatory activity of **11a** may be beneficial in the treatment of thrombotic disease.

Experimental

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. For normal chromatography, Merck Silica gel type 60 (size 70—230 mesh) was 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, Finigann MAT TSQ70 mass spectrometer), and 200 MHz proton nuclear magnetic resonance (^{1}H-NMR, Brucker AC200P) spectra. The chemical shift values are reported in ppm on the δ scale from the internal standard, tetramethylsilane. All compounds evaluated in bio-assays were analyzed for C, H. N and the results were within 0.4% of the calculated theoretical values. 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.

3-Dimethylamino-1,2-bis(4-methoxyphenyl)-2-propen-1-one (3) A mixture of deoxyanisoin (2.60 g, 10 mmol), and *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine (3.60 g, 30 mmol) in THF (6 ml) was stirred at 50—60 °C for 4 h. Then diisopropyl ether (IPE, 50 ml) was added, and the resulting precipitate was collected by filtration. The precipitate was washed with IPE, and dried to give crude **3** (2.50 g, 80.4%), mp 116—118 °C, which was used in the following reaction without purification. IR (Nujol): 1660, 1620, 1600, 1580, 1550, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.75 (6H, s, 2 × NCH_3), 3.81 (6H, s, 2 × OCH_3), 6.75—7.70 (9H, m).

4,5-Bis(4-methoxyphenyl)-2-methylpyrimidine (4) A mixture of **3**

(2.11 g, 6.8 mmol), acetamidine hydrochloride (1.30 g, 20 mmol), and sodium methoxide (28% methanol (MeOH) solution, 4.8 ml, 25 mmol) in EtOH (20 ml) was stirred under reflux for 1.5 h. After removal of the solvent, the mixture was poured onto a mixture of water and ethyl acetate (AcOEt). The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified by silica gel column chromatography [IPE–AcOEt (7:3)], and recrystallization from IPE to give **4** (0.95 g, 31.0%), mp 92—94 °C. IR (Nujol): 1600, 1575, 1560, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.69 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.83 (2H, d, J=9 Hz), 6.92 (2H, d, J=9 Hz), 7.15 (2H, d, J=9 Hz), 7.35 (2H, d, J=9 Hz), 8.66 (1H, s, pyrimidine ring). MS m/z: 305 (M^+-1).

Compounds **5**—**9** were prepared similarly. For syntheses of **5**—**9**, guanidine hydrochloride, *N*-cyanoguanidine, 4-amidinopyridine,[10] 4-amidinomorpholine,[11] and 4-amidino-3,5-dimethylmorpholine[12] were used in place of acetoamidine hydrochloride, respectively. The analytical data are shown in Table I.

2-(3,3-Dimethylguanidino)-4,5-bis(4-methoxyphenyl)pyrimidine (10a) A mixture of **6** (0.67 g, 2 mmol) and dimethylamine hydrochloride (0.40 g, 5 mmol) in EtOH (20 ml) was stirred under reflux for 8 h. After removal of the solvent, the resulting residue was dissolved in water and AcOEt. The mixture was adjusted to pH 1 with 10% HCl, and the water layer was separated and neutralized with a 20% aqueous solution of potassium carbonate. After extraction with AcOEt, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The resulting oil was dissolved in AcOEt, and then an excess of EtOH solution of hydrogen chloride was added. The resulting precipitate was recrystallized from EtOH and diethyl ether (Et_2O) to give **10a** hydrochloride (0.28 g, 33.7%), mp 238—239 °C. IR (Nujol): 1640, 1605, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.20 (6H, s, NCH_3), 3.78 (6H, s, OCH_3), 6.88 (2H, d, J=9 Hz), 6.95 (2H, d, J=9 Hz), 7.18 (2H, d, J=9 Hz), 7.39 (2H, d, J=9 Hz), 8.62 (1H, s), 9.22 (1H, br s), 10.68 (1H, br s). MS m/z: 337 (M^+).

Other 2-guanidinopyrimidine derivatives (**10b—l**) were obtained similarly. Their analytical data are shown in Table I.

4,5-Bis(4-methoxyphenyl)-2-(1-methyl-1,2,3,6-tetrahydropyrid-4-yl)-pyrimidine (11a) A mixture of **7** (3.70 g, 10 mmol) and methyl iodide (4.00 ml, 12.4 mmol) in a mixture of chloroform ($CHCl_3$, 27 ml) and MeOH (3 ml) was stirred at room temperature for 3 d. After removal of the solvent, the resulting residue was suspended in MeOH (50 ml) and water (10 ml), and then $NaBH_4$ (0.76 g, 20 mmol) was added in portions with ice cooling. The reaction mixture was stirred at room temperature for 30 min. The resulting precipitate was collected by filtration, and washed with water. The precipitate was recrystallized from EtOH and water to give **11a** (1.73 g, 45.3%), mp 131—133 °C. IR (Nujol): 1605, 1580, 1560, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.4—2.8 (4H, m), 3.0—3.2 (2H, m), 3.20 (6H, s, NCH_3), 3.76 (3H, s), 3.78 (3H, s), 6.83 (2H, d, J=9 Hz), 6.89 (2H, d, J=9 Hz), 7.1—7.3 (1H, m, C=CH), 7.13 (2H, d, J=9 Hz), 7.37 (2H, d, J=9 Hz), 8.58 (1H, s).

Compounds **11b—g** and **18**, **19** were prepared similarly. Ethyl bromide (for **11b**), benzyl iodide (for **11c**), 3′-*F*-benzyl chloride (for **11d**), 4′-*F*-benzyl chloride (for **11e**, **18**, and **19**), 2′-*F*-benzyl chloride (for **11f**), and 2-phenyl-1-iodoethane (for **11g**) were used in place of methyl iodide. Their analytical data are shown in Table I.

4,5-Bis(4-methoxyphenyl)-2-(1-methylpiperidin-4-yl)pyrimidine (12a) A mixture of **11a** (2.10 g, 5.4 mmol), 10% Pd–C (0.6 g), and ammonium formate (1.71 g, 27 mmol) in acetic acid (AcOH, 40 ml) was stirred at 100—110 °C for 2.5 h. After removal of the solvent, the resulting residue was dissolved with water and AcOEt, and then was adjusted to pH 8 with 20% aqueous potassium carbonate. The separated organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified by silica gel column chromatography [$CHCl_3$–MeOH (19:1)]. The appropriate fractions were combined and evaporated. The resulting oil was dissolved with AcOEt, and then an excess of EtOH solution of hydrogen chloride was added. The resulting precipitate was recrystallized from EtOH and Et_2O to give **12a** hydrochloride (0.34 g, 14.3%), mp 227—230 °C. IR (Nujol): 2380 (br), 1590, 1510, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.0—3.6 (13H, m), 3.77 (6H, s), 6.90 (2H, d, J=9 Hz), 6.96 (2H, d, J=9 Hz), 7.21 (2H, d, J=9 Hz), 7.42 (2H, d, J=9 Hz), 8.72 (1H, s).

Compound **12b** was prepared similarly. The analytical data are shown in Table I.

5,6-Bis(4-methoxyphenyl)-3-(4-pyridyl)-1,2,4-triazine (16) Hydrazine hydrate (0.87 ml, 17.4 mmol) was added to a solution of 4-pyridinecarbothioamide (**13**, 2.00 g, 14.5 mmol) in EtOH at −25 °C. The reaction mixture was stirred at 0 °C for 1 h. 1,2-Bis(4-methoxyphenyl)-1,2-ethanedione (**15**, 3.91 g, 14.5 mmol) and a few drops of 6 N EtOH solution of hydrogen chloride were added thereto, and the mixture was refluxed with stirring overnight. After removal of the solvent, the resulting residue was dissolved in a mixture of $CHCl_3$ and saturated aqueous solution of $NaHCO_3$. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, then dried over $MgSO_4$, and evaporated. The resulting residue was purified by silica gel column chromatography [$CHCl_3$] to give **16** (3.31 g, 61.8%), mp 158—159 °C. Compound **16** was immediately used in the next reaction without further purification. IR (Nujol): 1600, 1575, 1510, 1480 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.81 (3H, s), 3.82 (3H, s), 7.00 (2H, d, J=9 Hz), 7.04 (2H, d, J=9 Hz), 7.56 (2H, d, J=9 Hz), 7.67 (2H, d, J=9 Hz), 8.41 (2H, d, J=5 Hz), 8.86 (2H, d, J=5 Hz).

2,3-Bis(4-methoxyphenyl)-6-(4-pyridyl)pyridine (17) A mixture of **16** (0.50 g, 1.35 mmol), bicyclo[2.2.1]hepta-2,5-diene (1.30 ml, 11.9 mmol) and xylene (20 ml) was refluxed under nitrogen overnight. The resulting precipitate was washed with IPE to give **17** (0.47 g, 94.5%), mp 175—178 °C. Compound **17** was immediately used in the next reaction without further purification. IR (Nujol): 1605, 1580, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.77 (6H, s), 6.8—7.0 (4H, m), 7.19 (2H, d, J=8 Hz), 7.37 (2H, d, J=8 Hz), 7.93 (1H, m), 8.1—8.3 (3H, m), 8.7—8.8 (2H, m). MS m/z: 368 (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[13] 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.*[14] A 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 A.A.; 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 the 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 30 mM). After the tonus reached a plateau, drug solution (dissolved in DMSO) was added cumulatively and, finally, 10^{-4} M papaverine was added to obtain maximum relaxation. Activities of test compounds were expressed as ED_{50} values, *i.e.*, 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. A.A. was used at 50 μM in guinea-pigs. The percent inhibition was calculated from the total aggregation.

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