Studies on Antiatherosclerotic Agents.[1] Synthesis and Inhibitory Activities on Platelet Aggregation of 4-Aryl Derivatives of 7-Ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone

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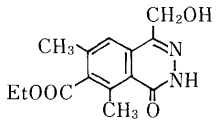
Received February 21, 1991

4-Aryl derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone and related derivatives were newly synthesized in order to test for their inhibitory activities on platelet aggregation. 4-(2-Anisyl) compound and the corresponding 1-chloro derivative demonstrated significant activity.

Keywords synthesis; arylcadmium reagent; coupling reaction; 4-(2-anisyl)-7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone; inhibitory effect; platelet aggregation

In the course of studies on the search for antiatherosclerotic agents, we have found that 7-ethoxycarbonyl-6,8-dimethyl-4-hydroxymethyl-1(2*H*)-phthalazinone[1b] (I) showed potent inhibitory activity on platelet aggregation and cyclic-adenosine monophosphate (AMP) phosphodiesterase. In subsequent studies, compound I was examined for its bioavailability in animals as a potential agent. The examination revealed rapid metabolism of the 4-hydroxymethyl group to the 4-carboxylic acid, which was devoid of the biological activity. It was considered difficult to maintain the activity as an effective plasma level in animals due to low solubility of compound I in water and lipid. Compound I was therefore modified[1a,d,2] in part or the 4-hydroxymethyl group was replaced with other alkyl moieties[1a,b] to improve bioavailability without loss of the activity. Some of the other compounds exhibited fairly potent inhibitory activity on platelet aggregation, however they did not show good balance as a potential agent.

According to the literature, the phthalazines with substituents on their α (1 and/or 4) position such as azelastine[3] with a benzyl, carbazeran[4] with a cyclic amino, and MY-5445[5] with a phenyl, and also aromatic amino moieties have been reported to possess anti-allergic, phosphodiesterase inhibitory, and anti-platelet aggregatory effects, respectively. Considering the structure–activity requirements of the phthalazines, the activities might be primarily attributable to the ring system, but the substituents are also considered to have a role in providing adequate bioavailability.



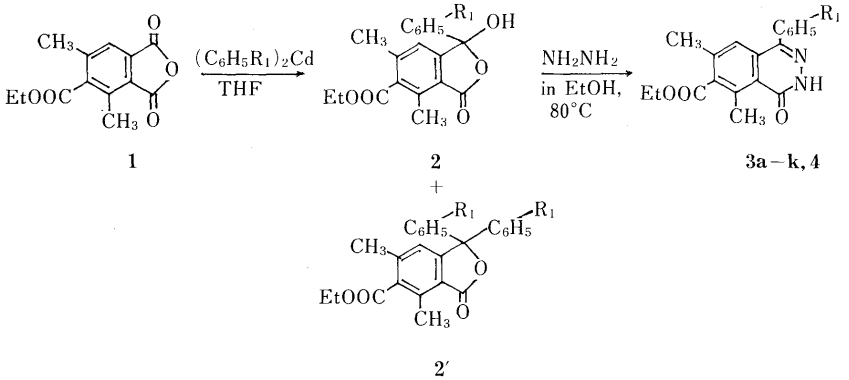
I

Fig. 1

Based on the structure–activity requirements of the phthalazines, compound I was subjected to construction of an aryl moiety in place of the 4-hydroxymethyl group, and a series of derivatives was synthesized.

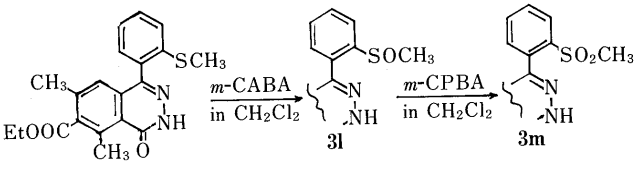
This paper deals with the synthesis and inhibitory activities on platelet aggregation of 4-aryl derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone and the related α substituted phthalazines.

Chemistry The synthesis of 4-aryl compounds (**3a—k**) and the analogous 4-(2-thienyl) compound (**4**) were attainable as outlined in Chart 1 by the reactions of 4-ethoxycarbonyl-3,5-dimethylphthalic anhydride (**1**)[1b] with the corresponding arylcadmium reagents to afford the aroyl benzoic acid intermediates (**2**), which, in turn, were condensed by treatment with hydrazine hydrate in ethanol (EtOH). Since the reactions were accompanied by an amount of 1,1-diarylphthalides (**2′**), which arose from subsidiary reaction between the initially formed intermediate **2** and cadmium reagents, column chromatographical purification of the compounds was necessary, and the yields were rather low: 23—60%. Compounds **3k**, **3i**, and **3e** were further modified as shown in Chart 2; oxidation of 4-(2-thioanisyl) compound **3k** using an equimolar amount of *m*-chloroperbenzoic acid (*m*-CPBA) afforded 4-(2-methylsulfinylphenyl) derivative (**3l**) in 75% yield,

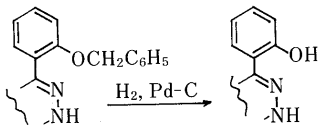


	R_1	yield (%)
3a	H	37
3b	*o*-Me	60
3c	*m*-Me	25
3d	*p*-Me	23
3e	*o*-OMe	51
3f	*p*-OMe	38
3g	*o*-Cl	43
3h	*p*-Cl	38
3i	*o*-OCH_2Ph	24
3j	*p*-OCH_2Ph	32
3k	*o*-SMe	36
4	$C_6H_5R_1$ = 	49

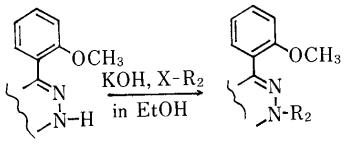
Chart 1



3k 3l 3m

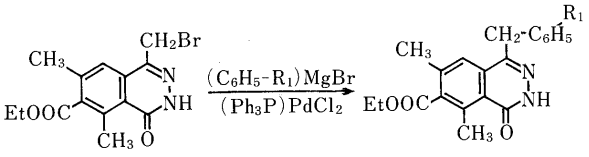


3i 3n



3e 3o, p

	R_2	yield (%)
3o	Me	62
3p	$(CH_2)_2N(Me)_2$	40



5 6a, b

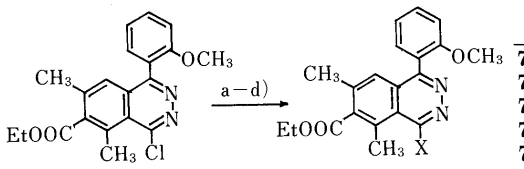
	R_1	yield (%)
6a	H	72
6b	o-OMe	58

Chart 2

while the treatment of an excess *m*-CPBA gave 4-(2-methylsulfonylphenyl) derivative (**3m**) in good yield. Catalytic debenzylation of **3i** over palladium on carbon (Pd–C) under atmospheric pressure led smoothly to the corresponding 4-(2-hydroxyphenyl) derivative (**3n**). Meanwhile, compound **3e** was reacted with methyl iodide and dimethylaminoethyl chloride in 5% potassium hydroxide (KOH) in EtOH, and the N^2-alkylated derivatives (**3o, p**) were obtained in 62 and 40% yields, respectively.

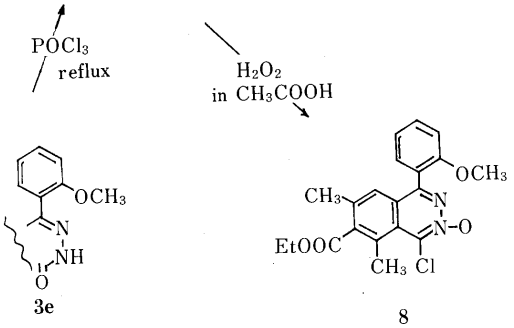
Additionally, the other 4-benzyl analogues (**6a, b**) were prepared by coupling reactions of a related 4-bromomethyl compound (**5**)[1b] with aryl magnesium reagents catalyzed by bis(triphenylphosphine)palladium(II) chloride in the described manner.[6,7]

Conversion of the phthalazinone to phthalazine was readily accomplished by heating **3e** with $POCl_3$ for half an hour to afford an α chlorinated derivative (**7a**) in 80% yield. The resulting compound **7a** was transformed into the requisite α substituted phthalazines by the following procedures (a—d): (a) The chlorine atom of **7a** was substituted with methoxy and ethylthio moieties by the conventional synthetic procedure[8] to afford **7b** and **7c**, respectively. (b) Several amino derivatives (**7d—j**) were derivatized from **7a** by treatment of the corresponding amines without solvents, with moderate yields. Since dimethylamino and *o*-chloroanilino derivatives (**7d, h**) were obtained as an oil, they led to oxalate and HCl salt, respectively. (c) Dechlorination of **7a** by hydrogen in the presence of Pd–C afforded a naked phthalazine (**7k**). The compound was converted into HCl salt with high solubility in water. (d) Phenylacetylenic moiety was also introduced

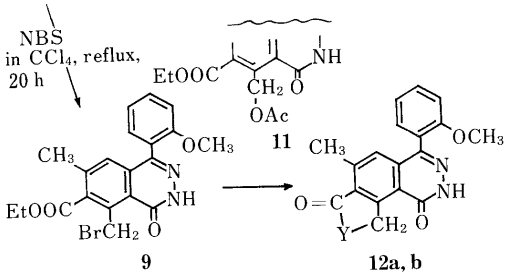


7a 7b—m

	method	agent	temp. (°C)	time (h)	X	yield (%)
7b	a	NaOEt	60	0.5	OEt	68
7c	a	NaSEt	80	0.5	SEt	63
7d	b	40%-dimethylamine	r.t.	12	$N(Me)_2 \cdot C_2O_4H_2$	76
7e	b	piperidine	80	3	N⟨⟩	58
7f	b	*N*-benzylpiperazine	100	2	N⟨⟩NCH2Ph	63
7g	b	*m*-chloroaniline	80	3	NHC_6H_4 (*m*-Cl)	65
7h	b	*o*-chloroaniline	80	3	NHC_6H_4 (*o*-Cl)·HCl	71
7i	b	*p*-methoxybenzylamine	80	3	$NHCH_2C_6H_4$ (*p*-OMe)	77
7j	b	benzylamine	90	2	$NHCH_2Ph$	81
7k	c	H_2, Pd-C	r.t.	8	H·HCl	44
7l	d	PhC≡CH, $(Ph_3P)PdCl_2$	90	4	C≡CPh	51
7m	d	H_2, Pd-C	r.t.	6	CH_2CH_2Ph	88



3e 8



11 9 12a, b

	Y	yield (%)
12a	O	82
12b	NH	84

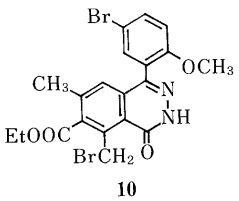


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Chart 3

to afford **7l** by the manner described[9] using phenylacetylene with a catalyst of palladium complex. This **7l** was then reduced in hydrogen over Pd–C, affording an α phenethyl derivative (**7m**) in good yield.

Since compound **7a** was considerably susceptible to hydrolysis to regenerate **3e** under conditions of even a weak hydrolytic medium, such as hot EtOH–water, it was possible that if **7a** were N^2-oxidized, it would not undergo hydrolytic change to generate **3e**. Compound **7a** was then subjected to *N*-oxidation reaction by means of hydrogen peroxide in glacial acetic acid; fortunately, an oxygen atom was directed to the N^2 position near the chlorine atom of **7a**, despite there being a result obtained[10] that an oxygen atom was introduced to the N^3 position, when *N*-oxidation reaction was carried out on related 1-chloro-4-methylphthalazine under a similar reaction condition. Location of the oxygen atom introduced was confirmed by the fact that compound **8** remained intact with prolonged heating in 5% KOH–EtOH. Presumably, an electronic repulsion of the 4-(2-anisyl) moiety near the N^3 atom resulted in a settlement of the oxygen atom on the N^2 position in the *N*-oxidation reaction.

When **3e** was reacted with *N*-bromosuccinimide in CCl_4, the 8-methyl hydrogen of **3e** was selectively brominated to give **9** with a minor quantity of dibrominated compound (**10**). The structure of **9** was determined by comparison of proton nuclear magnetic resonance (^{1}H-NMR) spectra of **3e** and **9**. 6-Methyl protons of **3e** appeared at 2.32 ppm, while the 8-methyl protons at 2.94 ppm. The latter signals demonstrated a lower value under influence of both carbonyls on adjacent sides of the 8-methyl protons. On the other hand, methyl signals of **9** exhibited at 2.37 ppm. The value approximates the 2.32 ppm observed in 6-methyl protons of **3e**. Compound **10** was consistent with an analysis[11] of spectra taken by high frequency ^{1}H-NMR spectroscopy. Checking on the signals appearing at 6.93 ppm in a doublet pattern with a coupling constant of 8.8 Hz suggests the existence of a methoxy group as well as a proton at the *ortho* position; the signals thus correspond to H_3 of the 4-(2-anisyl) moiety. Signals appearing at 7.61 ppm in a doublet-doublet with 8.8 and 2.5 Hz correspond to H_4 of the moiety due to a downfield shift by bromine effect with couplings between the *ortho* H_3 and the *meta* H_6. The 6-proton designated at 7.43 ppm was in a doublet pattern with 2.5 Hz.

Finally, compound **9** was converted to an acetoxy derivative (**11**) by reaction with acetic acid which, in turn, was reacted with 5% KOH in EtOH to provide the lactone derivative (**12a**). When **9** was reacted with ammonia in EtOH, the lactam derivative (**12b**) was obtained in good yield.

Results and Discussion

Compounds listed in Tables I and II were tested for their inhibitory activities on platelet aggregation induced by both arachidonic acid (AA, 100 μM) and adenosine diphosphate (ADP, 30 μM). The optical density method of Born[12] was used to assess the ability of test compounds. The inhibitory activities were expressed by the term IC_{50} as the concentration that inhibited the induced aggregation by 50%. The data obtained at several concentrations were presented as means of three runs.

Table I. Biological Activities of Compounds

Compd.	Inhibition of AA and ADP-induced platelet aggregation (IC_{50}, μM)	
	AA (100 μM)	ADP (30 μM)
3a	3—7	100
3b	20	100
3c	100	100
3d	50—70	100
3e	1—3	100
3f	50—70	100
3g	5—10	100
3h	30—50	100
3i	100	100
3j	100	100
3k	20	60
3l	50—70	100
3m	50—70	100
3n	20	100
3o	5—7	60
3p	100	60
4	30—50	100
6a	100	40
6b	70	40

Table II. Biological Activities of Compounds

Compd.	Inhibition of AA and ADP-induced platelet aggregation (IC_{50}, μM)	
	AA (100 μM)	ADP (30 μM)
7a	1—2	100
7b	50—100	60
7c	100	100
7d	30—50	60
7e	50—70	100
7f	70	100
7g	100	100
7h	100	100
7i	70	100
7j	70	60
7k	3—7	60
7l	100	100
7m	100	100
8	20—50	100
12a	100	100
12b	100	100

In a preliminary test, the reference phthalazinone I marked the IC_{50} 1—5 μM on AA, and 10—20 μM on ADP, respectively.

As can be seen, the results showed no effective compounds marked on ADP, except 4-benzyl compounds **6a**, **b** which exhibited activity to some extent. On the contrary, some compounds demonstrated considerable inhibitory activity on AA when compared to the referenced phthalazinone I. Among them, the 4-phenyl **3a**, *o*-anisyl **3e**, *o*-chlorophenyl **3g**, N^2-methylated *o*-anisyl compounds **3o** in Table I, an α chloro **7a** and its dechlorinated compound **7k** in Table II showed fairly potent activity, and *o*-anisyl and its α chlorinated compounds **3e**, **7a** demonstrated particularly significant activities. The potencies of the activities on AA of both compounds were comparable to the referenced phthalazinone I.

From the results of this test, the structure–activity relation of **3e** and **7a**, together with the tested compounds may be explained as follows.

TABLE III. Data for Compounds **3a**—**p**, **4**, and **6a**, **b**

Compd.	mp (°C) (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	UV (EtOH, nm)	^{1}H-NMR ($CDCl_3$, J=Hz)
3a	207—209 (EtOH)	$C_{19}H_{18}N_2O_3$	70.79 (70.72	5.63 5.65	8.69 8.72)	277, 293, 322	1.43 (3H, t, 7), 2.38 (3H, s), 2.96 (3H, s), 4.48 (2H, q, 7), 7.36 (1H, s), 7.51 (5H, s), 10.37 (1H, s)
3b	223—224 (EtOH)	$C_{20}H_{20}N_2O_3$	71.41 (71.31	5.99 6.00	8.33 8.46)	219, 298, 311, 324	1.42 (3H, t, 7), 2.14 (3H, s), 2.31 (3H, s), 2.95 (3H, s), 4.42 (2H, q, 7), 6.93 (1H, s), 7.34 (4H, s), 10.79 (1H, s)
3c	175—176 (EtOH)	$C_{20}H_{20}N_2O_3$	71.41 (71.41	5.99 6.04	8.33 8.38)	215, 225, 300, 312, 325	1.42 (3H, t, 7), 2.37 (3H, s), 2.45 (3H, s), 2.95 (3H, s), 4.46 (2H, q, 7), 7.34 (5H, s), 10.44 (1H, s)
3d	205—207 (EtOH)	$C_{20}H_{20}N_2O_3$	71.41 (71.37	5.99 6.05	8.33 8.40)	227, 301, 311, 325	1.42 (3H, t, 7), 2.36 (3H, s), 2.46 (3H, s), 2.95 (3H, s), 4.48 (2H, q, 7), 7.37 (5H, s), 10.43 (1H, s)
3e	185—187 (EtOAc–ether)	$C_{20}H_{20}N_2O_4$	68.17 (68.20	5.72 5.68	7.95 7.89)	217, 282, 295, 310, 321	1.41 (3H, t, 7), 2.32 (3H, s), 2.94 (3H, s), 3.72 (3H, s), 4.45 (2H, q, 7), 6.96—7.50 (5H, m), 10.46 (1H, s)
3f	210—211 (MeOH)	$C_{20}H_{20}N_2O_4$	68.17 (68.15	5.72 5.75	7.95 8.00)	229, 262, 303, 310	1.42 (3H, t, 7), 2.37 (3H, s), 2.95 (3H, s), 3.89 (3H, s), 4.46 (2H, q, 7), 7.22 (4H, d, d, 9, 4), 7.38 (1H, s), 10.66 (1H, s)
3g	224—225 (EtOH)	$C_{19}H_{17}ClN_2O_3$	63.90 (63.85	4.96 5.03	7.84 7.90)	227, 260, 297, 310, 323	1.41 (3H, t, 7), 2.34 (3H, s), 2.95 (3H, s), 4.48 (2H, q, 7), 6.92 (1H, s), 7.45 (4H, m), 10.62 (1H, s)
3h	245—247 (MeOH)	$C_{19}H_{17}ClN_2O_3$	63.90 (63.86	4.96 4.99	7.84 7.88)	265, 296, 320	1.42 (3H, t, 7), 2.35 (3H, s), 2.95 (3H, s), 4.50 (2H, q, 7), 6.95 (1H, s), 7.43 (4H, d, d, 9, 4), 10.46 (1H, s)
3i	186—188 (EtOH)	$C_{26}H_{24}N_2O_4$	72.88 (72.85	5.65 5.70	6.54 6.60)	218, 282, 296, 320	1.42 (3H, t, 7), 2.31 (3H, s), 2.95 (3H, s), 4.48 (2H, q, 7), 5.05 (2H, s), 7.19 (10H, m), 10.54 (1H, s)
3j	245—247 (MeOH)	$C_{26}H_{24}N_2O_4$	72.88 (73.00	5.65 5.70	6.54 6.59)	209, 227, 303	1.42 (3H, t, 7), 2.38 (3H, s), 2.95 (3H, s), 4.48 (2H, q, 7), 5.16 (2H, s), 7.00—7.50 (10H, m), 10.19 (1H, s)
3k	182—184 (EtOAc–ether)	$C_{20}H_{20}N_2O_3S$	65.21 (65.19	5.47 5.51	7.61 7.64)	219, 296	1.41 (3H, t, 7), 2.32 (3H, s), 2.38 (3H, s), 2.95 (3H, s), 4.46 (2H, q, 7), 6.92 (1H, s), 7.42 (4H, m), 10.77 (1H, s)
3l	210—212 (MeOH–ether)	$C_{20}H_{20}N_2O_4S$	62.49 (62.65	5.24 5.30	7.29 7.30)	202, 221, 300	1.41 (3H, t, 7), 2.32 (3H, s), 2.79 (3H, s), 2.92 (3H, s), 4.48 (2H, q, 7), 7.03 (1H, s), 7.26—8.40 (4H, m), 11.01 (1H, s)
3m	252—254 (MeOH)	$C_{20}H_{20}N_2O_5S$	59.99 (59.92	5.04 5.08	7.00 7.05)	219, 297	1.40 (3H, t, 7), 2.30 (3H, s), 2.91 (3H, s), 3.19 (3H, s), 4.45 (2H, q, 7), 6.80 (1H, s), 7.27—8.36 (4H, m), 11.01 (1H, s).
3n[b]	222—223 (EtOAc)	$C_{19}H_{18}N_2O_4$	67.44 (67.54	5.36 5.32	8.28 8.30)	217, 236, 284, 295, 310, 321	1.41 (3H, t, 7), 2.32 (3H, s), 2.89 (3H, s), 4.41 (2H, q, 7), 6.90—7.50 (5H, m), 9.12 (1H, OH), 12.07 (1H, s)
3o	113—115 (Ether–*n*-hexane)	$C_{21}H_{22}N_2O_4$	68.83 (68.87	6.05 6.07	7.65 7.69)	219, 235, 283, 301, 312, 325	1.40 (3H, t, 7), 2.30 (3H, s), 2.93 (3H, s), 3.72 (3H, s), 3.83 (3H, s), 4.45 (2H, q, 7), 6.80—7.65 (5H, m)
3p	106—108 (Ether)	$C_{24}H_{29}N_3O_4$	68.06 (68.13	6.90 6.94	9.92 9.98)	219, 302	1.41 (3H, t, 7), 2.33 (9H, s), 2.79 (2H, m), 2.93 (3H, s), 3.73 (3H, s), 4.25 (2H, m), 4.47 (2H, q, 7), 6.92—7.55 (5H, m)
4	186—188 (EtOAc)	$C_{17}H_{16}N_2O_3S$	62.19 (62.16	4.91 4.89	8.53 8.60)	213, 231, 263, 312	1.43 (3H, t, 7), 2.43 (3H, s), 2.95 (3H, s), 4.49 (2H, q, 7), 7.32 (3H, m), 7.76 (1H, s), 10.85 (1H, s)
6a	140—141 (EtOAc)	$C_{20}H_{20}N_2O_3$	71.41 (71.37	5.99 6.13	8.33 8.23)	216, 260, 296, 309, 321	1.40 (3H, t, 7), 2.36 (3H, s), 2.89 (3H, s), 4.22 (2H, s), 4.42 (2H, q, 7), 7.26 (5H, s), 7.41 (1H, s), 10.35 (1H, s)
6b	166—168 (EtOAc–ether)	$C_{21}H_{22}N_2O_4$	68.83 (68.85	6.05 6.02	7.65 7.70)	217, 260, 282, 296, 311, 323	1.40 (3H, t, 7), 2.37 (3H, s), 2.89 (3H, s), 3.92 (3H, s), 4.20 (2H, s), 4.45 (2H, q, 7), 6.80—7.20 (4H, m), 7.54 (1H, s), 10.10 (1H, s)

a) Recrystallization solvent. *b*) NMR spectra were taken in $CDCl_3$+DMSO-d_6.

In comparing the 4-tolyl compounds **3b**, **c**, **d**, the activities decreased in *ortho*-, *para*-, and *meta*-order. This tendency was also observed in the anisyl **3e**, **f**, chlorophenyl **3g**, **h**, and benzyloxyphenyl **3i**, **j** compounds. With regard to the *ortho*-substituents on the 4-aryl moieties, the unsubstituted and methoxy moieties seemed to be effective. Replacing the methoxy oxygen with sulfur decreased the activity. The aryl moiety had to be connected directly to the phthalazinone for the activity in this test.

In the derivatives of **3e** in Table II, the potencies of the activities were generally decreased only when the α carbonyl moiety was substituted for the other moieties. However, it was clear that the chlorine moiety **7a** significantly enhanced the activity of **3e**. Meanwhile, hydrolytic change of the chlorine moiety from **7a** to **3e** was definitely observed in a diluted hydrolytic media. The N^2-oxide **8** gained considerable durability from the change, but the activity was greatly decreased. Compound **7a** thus appeared to act as a precursor for **3e**.

The modified compound **3e**, and both **12a** and **12b** lost their activity. It was found that the 7-ethyl ester might have a role[1b] in the platelet aggregation inhibitory activity.

As described, although compounds **3e**, **7a** did not show the activity on ADP, these compounds were selected as candidates for further pharmacological evaluations from this experiment. Concerning the solubility in lipid, both compounds increased their ability in organic solvents. The 4-(*o*-anisyl) moiety might provide an adequate bioavailability, and hopefully protect from the rapid metabolic degradation which was seen in the referenced phthalazinone I.

Experimental

All melting points were determined in a capillary tube and are uncorrected. Mass spectra (MS) were recorded by a Hitachi RMU-7L spectrometer, ultraviolet (UV) spectra with a Hitachi model 323 and U-3200 spectrometers, infrared (IR) spectra were determined with a Hitachi model 285 spectrometer, and ^{1}H-NMR spectra with a JEOL JUM-C-60 HL machine. ^{1}H-NMR spectra of compound **10** were taken by a JEOL JNM-FX 270 spectrometer. Merck Silica gel 60 was used for column chromatography.

TABLE IV. Data for Compounds **7a—m**, **8**, and **12a, b**

Compd.	mp (°C) (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$, J=Hz)
7a	125—126 (Ether)	$C_{20}H_{19}ClN_2O_3$	64.70 (64.81)	5.12 5.11	7.54 7.61)	1.43 (3H, t, 7), 2.38 (3H, s), 2.94 (3H, s), 3.69 (3H, s), 4.51 (2H, q, 7), 6.90—7.70 (4H, m), 7.10 (1H, s)
7b	113—115 (Ether)	$C_{22}H_{24}N_2O_4$	69.45 (69.41)	6.36 6.41	7.36 7.39)	1.42 (3H, t, 7), 1.54 (3H, t, 7), 2.36 (3H, s), 2.85 (3H, s), 3.69 (3H, s), 4.46 (2H, q, 7), 4.73 (2H, q, 7), 6.95—7.50 (5H, m)
7c	119—121 (Ether)	$C_{22}H_{24}N_2O_3S$	66.65 (66.62	6.10 6.13	7.07 7.12)	1.39 (3H, t, 7), 1.48 (3H, t, 7), 2.34 (3H, s), 2.69 (3H, s), 3.44 (2H, q, 7), 3.69 (3H, s), 4.41 (2H, q, 7), 6.92—7.65 (5H, m)
7d	170—172 (Acetone–ether)	$C_{24}H_{27}N_3O_7$	61.40 (61.31	5.80 5.90	8.95 9.05)	1.44 (3H, t, 7), 2.42 (3H, s), 2.80 (3H, s), 3.18 (6H, s), 3.75 (3H, s), 4.49 (2H, q, 7), 6.90—7.71 (5H, m), 13.32 (2H, s, $(COO\underline{H})_2$)
7e	140—142 (Ether)	$C_{25}H_{29}N_3O_3$	71.57 (71.47	6.97 7.01	10.02 10.13)	1.42 (3H, t, 7), 1.77 (6H, br), 2.35 (3H, s), 2.94 (3H, s), 3.03 (2H, br), 3.56 (2H, br), 3.69 (3H, s), 4.47 (2H, q, 7), 6.94—7.52 (5H, m)
7f	196—198 (MeOH)	$C_{31}H_{34}N_4O_3$	72.91 (72.87	6.71 6.73	10.97 11.04)	1.41 (3H, t, 7), 2.36 (3H, s), 2.92 (3H, s), 2.50—3.10 (4H, m), 3.51 (4H, br), 3.60 (2H, s), 3.69 (3H, s), 4.46 (2H, q, 7), 6.90—7.55 (10H, m)
7g	151—153 (Ether)	$C_{26}H_{24}ClN_3O_3$	67.60 (67.58	5.41 5.43	9.10 9.20)	1.41 (3H, t, 7), 2.29 (3H, s), 2.91 (3H, s), 3.73 (3H, s), 4.46 (2H, q, 7), 6.75—7.50 (9H, m), 8.88 (1H, s)
7h	117—120 (Ether)	$C_{26}H_{25}Cl_2N_3O_3$	52.20 (52.17	5.22 5.27	8.43 8.72)	1.43 (3H, t, 7), 2.46 (3H, s), 2.95 (3H, s), 3.76 (3H, s), 4.49 (2H, q, 7), 7.00—8.20 (9H, m)
7i	120—121 (Ether)	$C_{28}H_{29}N_3O_4$	71.32 (71.31	6.20 6.25	8.91 8.94)	1.39 (3H, t, 7), 2.32 (3H, s), 2.77 (3H, s), 3.69 (3H, s), 3.82 (3H, s), 4.41 (2H, q, 7), 4.12 (2H, d, 4), 5.38 (1H, br), 6.80—7.48 (8H, m)
7j	136—138 (Benzene–ether)	$C_{27}H_{27}N_3O_3$	73.45 (73.50	6.16 6.20	9.52 9.60)	1.39 (3H, t, 7), 2.33 (3H, s), 2.79 (3H, s), 3.69 (3H, s), 4.42 (2H, q, 7), 4.90 (2H, d, 5), 5.50 (1H, br), 7.00—7.65 (5H, m), 7.35 (5H, m)
7k	110—112 (Ether)	$C_{20}H_{20}N_2O_3$	71.41 (71.39	5.99 5.90	8.33 8.29)	1.44 (3H, t, 7), 2.42 (3H, s), 2.76 (3H, s), 3.69 (3H, s), 4.50 (2H, q, 7), 7.00—7.65 (5H, m), 9.72 (1H, s)
7l	185—187 (EtOAc–ether)	$C_{28}H_{24}N_2O_3$	77.04 (77.01	5.54 5.60	6.42 6.49)	1.43 (3H, t, 7), 2.40 (3H, s), 3.19 (3H, s), 3.69 (3H, s), 4.49 (2H, q, 7), 7.00—7.75 (10H, m)
7m	123—125 (EtOAc)	$C_{28}H_{28}N_2O_3$	76.34 (76.31	6.41 6.43	6.36 6.38)	1.43 (3H, t, 7), 2.38 (3H, s), 2.87 (3H, s), 3.45 (2H, m), 3.69 (3H, s), 3.78 (2H, m), 4.45 (2H, q, 7), 7.70—8.59 (10H, m)
8	217—219 (MeOH)	$C_{20}H_{19}ClN_2O_4$	62.03 (62.21	4.91 5.07	7.23 7.31)	1.41 (3H, t, 7), 2.34 (3H, s), 2.93 (3H, s), 3.71 (3H, s), 4.44 (2H, q, 7), 6.88—7.55 (5H, m)
12a[b]	300 (MeOH)	$C_{18}H_{14}N_2O_4$	67.07 (67.06	4.38 4.40	8.69 8.70)	2.70 (3H, s), 3.76 (3H, s), 5.79 (2H, s), 7.31 (5H, m), 13.08 (1H, s)
12b[b]	285—287 (MeOH)	$C_{18}H_{15}N_3O_3$	67.28 (67.28	4.71 4.73	13.08 13.13)	2.67 (3H, s), 3.71 (3H, s), 4.79 (2H, s), 7.28 (5H, m), 8.79 (1H, s), 12.86 (1H, s)

a) Recrystallization solvent. *b*) NMR spectra were taken in DMSO-d_6.

Preparation of 3a—k, and 4. 4-(2-Anisyl)-7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone (3e) To the Grignard reagent [prepared from *o*-bromoanisole (9.35 g, 0.05 mol), Mg turning (1.94 g, 0.08 mol)] in anhydrous ether (120 ml) was added portionwise anhydrous $CdCl_2$ (9.2 g, 0.05 mol). The mixture was stirred for 30 min at room temperature, then was added dropwise a solution of **1** (8.68 g, 0.035 mol) in tetrahydrofuran (THF) (50 ml). The mixture was heated to reflux for 1 h. The reaction mixture was decomposed by addition of 5% H_2SO_4. The organic layer (A) was extracted with 10% K_2CO_3. The alkaline extract was acidified with 1 N HCl, and it was re-extracted with EtOAc. Working-up afforded an oil, which was dissolved in EtOH (100 ml) and treated with hydrazine hydrate (4 ml). The new mixture was heated to 80 °C for 2 h. Evaporation of the solvent and purification of the residue by column chromatography with benzene–EtOAc (100:3) afforded 6.8 g (51%) of **3e**, melted at 185—187 °C (EtOAc–ether). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: 68.20; H, 5.68; N, 7.89. MS *m/z*: 352 (M^+), 323 (M^+-Et), 321 (M^+-OMe), 307 (M^+-OEt), 293. UV λ_{max}^{EtOH} nm: 217, 282, 295, 310, 321. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 2.32 (3H, s), 2.94 (3H, s), 3.72 (3H, s), 4.45 (2H, q, J=7 Hz), 6.96—7.50 (5H, m), 10.46 (1H, s).

The organic mother layer (A) was purified by column chromatography with benzene to afford 2.1 g (13.4%) of 1,1-(2-anisyl)-5-ethoxycarbonyl-4,6-dimethylphthalide, melted at 147—149 °C (MeOH). *Anal.* Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.59; H, 5.88. MS *m/z*: 446 (M^+), 401 (M^+-OEt), 387, 371. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.38 (3H, s), 2.68 (3H, s), 3.50 (6H, s), 4.42 (2H, q, J=7 Hz), 6.60—7.41 (9H, m).

7-Ethoxycarbonyl-6,8-dimethyl-4-(2-methylsulfinylphenyl)-1(2*H*)-phthalazinone (31) A mixture of **3k** (368 mg, 1 mmol) and *m*-CPBA (173 mg, 1 mmol) in CH_2Cl_2 (20 ml) was placed for 5 h with external water cooling. The mixture was washed with 10% K_2CO_3 and water. Evaporation of the solvent and recrystallization of the residue from MeOH–ether afforded 290 mg (75.5%) of **3k**, melted at 210—212 °C. *Anal.* Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.65; H, 5.30; N, 7.30. MS *m/z*: 384 (M^+), 369 (M^+-Me), 355 (M^+-Et), 339 (M^+-OEt). UV λ_{max}^{EtOH} nm: 202, 221, 300. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 2.32 (2H, s), 2.79 (3H, s), 2.92 (3H, s), 4.48 (2H, q, J=7 Hz), 7.03 (1H, s), 7.26—8.40 (4H, m), 11.01 (1H, s).

Compound **3m** was prepared from **3k** in a similar manner using 3 times the amount of *m*-CPBA in a molar ratio.

7-Ethoxycarbonyl-4-(2-hydroxyphenyl)-6,8-dimethyl-1(2*H*)-phthalazinone (3n) Compound **3i** (350 mg) in EtOH (50 ml) was shaken in H_2 in the presence of 5% Pd–C (20 mg) under atmospheric pressure for 2 h. The catalyst was filtered off and the filtrate was evaporated to afford 250 mg (90.5%) of **3n**. mp 222—223 °C (EtOAc). *Anal.* Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.54; H, 5.32; N, 8.30. MS *m/z*: 338 (M^+), 323, 309 (M^+-Et), 293 (M^+-OEt). UV λ_{max}^{EtOH} nm: 217, 236, 284, 295, 310, 321. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.41 (3H, t, J=7 Hz), 2.32 (3H, s), 2.89 (3H, s), 4.41 (2H, q, J=7 Hz), 6.90—7.50 (5H, m), 9.12 (1H, OH), 12.07 (1H, s).

Preparation of 3o, p. 4-(2-Anisyl)-7-ethoxycarbonyl-2-(2-dimethylamino)ethyl-6,8-dimethyl-1(2*H*)-phthalazinone (3p) A mixture of **3e** (250 mg, 0.7 mmol) and dimethylaminoethylchloride (100 mg, 0.9 mmol) in MeOH (10 ml) containing 5% NaOH (2 ml) was stirred at room temperature for 2 d. The mixture was concentrated and extracted with EtOAc. Purification by chromatography with chloroform–MeOH (50:1) afforded 120 mg (40%) of **3p**. mp 106—108 °C (ether). *Anal.* Calcd for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 68.13; H, 6.94; N, 9.90. UV λ_{max}^{EtOH} nm: 219, 302. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 2.33 (9H, s), 2.79 (2H, m), 2.93 (3H, s), 3.73 (3H, s), 4.25 (2H, m), 4.47 (2H, q, J=7 Hz), 6.92—7.55 (5H, m).

Preparation of 6a, b. 4-(2-Anisyl)methyl-7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone (6b) To the Grignard reagent [prepared from *o*-bromoanisole (9.35 g, 0.05 mol), Mg turning (1.94 g, 0.08 mol)] in an-

hydrous THF (120 ml) was added **5** (4.0 g, 0.01 mol), and then bis-(triphenylphosphine)palladium(II) chloride (50 mg, 0.07 mmol). The reaction mixture was stirred at room temperature for 20 h and was decomposed by addition of 5% H_2SO_4. The organic layer was separated and washed with water, then evaporated to afford crude oil. The oil was purified by column chromatography with benzene–EtOAc (10 : 1) to afford 2.5 g (58%) of **6b**, melted at 166—168 °C (EtOAc–ether). *Anal.* Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68.85; H, 6.02; N, 7.70. MS *m/z*: 366, 335, 321, 307. UV λ_{max}^{EtOH} nm: 217, 260, 282, 296, 311, 323. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.37 (3H, s), 2.89 (3H, s), 3.92 (3H, s), 4.20 (2H, s), 4.45 (2H, q, J=7 Hz), 6.80—7.20 (4H, m), 7.54 (1H, s), 10.10 (1H, s).

4-(2-Anisyl)-1-chloro-7-ethoxycarbonyl-6,8-dimethylphthalazine (7a) A mixture of **3e** (3.0 g, 0.08 mol) and $POCl_3$ (10 ml) was refluxed for 30 min. Excess $POCl_3$ was concentrated under reduced pressure. The mixture was poured into ice-water with vigorous stirring. The aqueous mixture was neutralized with 5% K_2CO_3, then extracted with chloroform. The extract was washed with water and evaporated to afford crude **7a**. Recrystallization from ether gave 2.7 g (85.7%) of pale yellow crystals. mp 125—126 °C (ether). *Anal.* Calcd for $C_{20}H_{19}ClN_2O_3$:C, 64.70; H, 5.12; N, 7.54. Found: C, 64.81; H, 5.11; N, 7.61. MS *m/z*: 370 (M^+), 341 (M^+-Et), 335 (M^+-Cl), 325 (M^+-OEt). UV ν_{max}^{EtOH} nm: 235, 280, 292, 320. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 2.38 (3H, s), 2.94 (3H, s), 3.69 (3H, s), 4.51 (2H, q, J=7 Hz), 6.90—7.70 (4H, m), 7,10 (1H, s).

Compounds **7b—j** were prepared from **7a** by the conventional synthetic procedure.[6]

1-(2-Anisyl)-6-ethoxycarbonyl-5,7-dimethylphthalazine (7k) A suspension of **7a** (500 mg, 1.3 mmol) in EtOH (30 ml) containing a few drops of concd. NH_4OH was shaken in H_2 over 5% Pd–C (70 mg) under atmospheric pressure. Completion of the reaction took about 8 h at room temperature. Purification by column chromatography with chloroform–MeOH (50 : 1) afforded 200 mg (44%) of **7k**. mp 110—112 °C (ether). *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.39; H, 5.90; N, 8.29. MS *m/z*: 336, 335, 319, 308, 307, 291. UV λ_{max}^{EtOH} nm: 232, 282. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 2.42 (3H, s), 2.76 (3H, s), 3.69 (3H, s), 4.50 (2H, q, J=7 Hz), 7.00—7.65 (5H, m), 9.72 (1H, s). Oxalate: mp 172—173 °C (acetone–ether), HCl salt: mp 206—207 °C (acetone).

4-(2-Anisyl)-1-chloro-7-ethoxycarbonyl-6,8-dimethylphthalazine N^2-Oxide (8) A mixture of **7a** (185 mg, 0.5 mmol) in acetic acid (5 ml) containing 30% H_2O_2 (0.5 ml) was heated at 80 °C for 2 h. The mixture was concentrated to a volume of 2 ml and was left at room temperature. Precipitated crystals were filtered. Recrystallization from acetone–ether afforded 105 mg (54.4%) of **8**. mp 218—219 °C. *Anal.* Calcd for $C_{20}H_{19}ClN_2O_4$: C, 62.03; H, 4.91; N, 7.23. Found: C, 62.21; H, 5.07; N, 7.31. MS *m/z*: 386 (M^+), 357 (M^+-Et), 341 (M^+-OEt), 200. UV λ_{max}^{EtOH} nm: 221, 260, 294, 310, 323. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 2.34 (3H, s), 2.93 (3H, s), 3.71 (3H, s), 4.44 (2H, q, J=7 Hz), 6.88—7.55 (5H, m).

Test on 8 for Hydrolytic Reaction A mixture of **8** (100 mg) in MeOH (10 ml) containing 5% NaOH (1 ml) was heated at reflux for 5 h. Working-up gave crystals melted at 217—219 °C. Spectral data of this compound were identical with those of **8** in all respects.

1-(2-Anisyl)-6-ethoxycarbonyl-5,7-dimethyl-4-(2-phenylethynyl)-phthalazine (71) A mixture of **7a** (370 mg, 1 mmol), phenylacetylene (150 mg, 1.5 mmol), bis(triphenylphosphine)palladium(II) chloride (16 mg, 0.02 mmol), CuI (8 mg), and triethylamine (3 ml) in benzene (10 ml) was heated at reflux for 4 h. The mixture was applied to column chromatography with benzene–EtOAc (10 : 1) to afford 223 mg (51%) of **71** melted at 185—187 °C (EtOAc–ether). *Anal.* Calcd for $C_{28}H_{24}N_2O_3$: C, 77.04; H, 5.54; N, 6.42. Found: C, 77.01; H, 5.60; N, 6.49. MS *m/z*: 436, 421, 407, 391. UV λ_{max}^{EtOH} nm: 242, 333. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 2.40 (3H, s), 3.19 (3H, s), 3.69 (3H, s), 4.49 (2H, q, J=7 Hz), 7.00—7.75 (10H, m).

Compound **7m** was obtained from **71** by hydrogenolysis in H_2 in the presence of 5% Pd–C.

4-(2-Anisyl)-8-bromomethyl-7-ethoxycarbonyl-6-methyl-1(2*H*)-phthalazinone (9) A suspension of **3e** (2.0 g, 5.6 mmol), *N*-bromosuccinimide (NBS) (1.2 g, 6.7 mmol), and benzoylperoxide (0.05 g) in CCl_4 (100 ml) was heated to reflux for 20 h. The reaction mixture was diluted with chloroform (20 ml) and filtered. The filtrate was washed with water and dried over anhyd. Na_2SO_4, then evaporated. The residue was purified by column chromatography with benzene–EtOAc (10 : 1). The later fractions afforded 900 mg (38%) of **9**, which did not melt at 280 °C (EtOAc). *Anal.* Calcd for $C_{20}H_{19}BrN_2O_4$: C, 55.68; H, 4.64; N, 6.49. Found: C, 55.65; H, 4.65; N, 6.56. MS *m/z*: 432 (M+2), 430 (M^+), 385 (M^+-OEt), 350 (M^+-HBr), 321 (M^+-Et, HBr). IR ν_{max}^{KBr} cm^{-1}: 3400, 1710, 1660, 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 2.37 (3H, s), 3.75 (3H, s), 4.60 (2H, q, J=7 Hz), 5.51 (2H, m), 7.28 (5H, m), 10.38 (1H, br). The early fractions afforded 8-bromomethyl-7-ethoxycarbonyl-6-methyl-4-(2-methoxy-5-bromophenyl)-1(2*H*)-phthalazinone (**10**) in 260 mg (9.2%) yield. mp 300 °C (acetone). *Anal.* Calcd for $C_{20}H_{18}Br_2N_2O_4$: C, 47.05; H, 3.72; N, 5.49. Found: C, 47.10; H, 3.75; N, 5.60. MS *m/z*: 512, 510, 508, 463. ^{1}H-NMR (270 MHz in $CDCl_3$) δ: 1.47 (3H, t, J=7.4 Hz), 2.38 (3H, s), 3.72 (3H, s), 4.54 (2H, q, J=7.4 Hz), 5.48 (2H, q, J=9.4 Hz), 6.93 (1H, d, J=8.8 Hz), 7.09 (1H, s), 7.43 (1H, d, J=2.5 Hz), 7.61 (1H, dd, J=8.8, 2.5 Hz), 10.23 (1H, s).

8-Acetoxymethyl-4-(2-anisyl)-7-ethoxycarbonyl-6-methyl-1(2*H*)-phthalazinone (11) A mixture of **9** (400 mg) in acetic acid (20 ml) containing triethylamine (2 ml) was heated at 100 °C for 30 min. The mixture was diluted with water and extracted with EtOAc. The extract was evaporated to afford a crude product. It was recrystallized from acetone. Yield: 200 mg (53%), mp 210—212 °C. *Anal.* Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38: H, 5.40; N, 6.83. Found. C, 64.41; H, 5.36; N, 6.91. MS *m/z*: 410 (M^+), 367 (M^+-Ac), 350 (M^+-OAc), 337 (M^+-CH_2OAc). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.07 (3H, s), 2.38 (3H, s), 3.73 (3H, s), 4.38 (2H, q, J=7 Hz), 5.97 (2H, s), 7.17 (5H, m), 10.53 (1H, br).

Preparation of 12a A mixture of **11** (200 mg) in EtOH (10 ml) containing 5% KOH (1 ml) was heated at 60 °C for 2 h. The solvent was removed and the residue was extracted with EtOAc. The extract was purified by column chromatography with chloroform–EtOAc (20 : 1) to afford 130 mg of **12a**, which did not melt at 290 °C. *Anal.* Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.06; H, 4.40; N, 8.70. MS *m/z*: 322, 294. IR ν_{max}^{KBr} cm^{-1}: 3300, 1730, 1670, 1600. ^{1}H-NMR (DMSO-d_6) δ: 2.70 (3H, s), 3.76 (3H, s), 5.79 (2H, s), 7.31 (5H, m), 13.08 (1H, s).

Preparation of 12b A mixture of **9** (200 mg) in ammonia saturated EtOH (10 ml) was heated at 60 °C for 2 h. The solvent was evaporated and the residue was purified by column chromatography with chloroform–EtOAc (5 : 1) to afford 105 mg of **12b**, which melted at 285—287 °C (MeOH). *Anal.* Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.2; H, 4.73; N, 13.13. MS *m/z*: 321, 250. IR ν_{max}^{KBr} cm^{-1}: 3400, 3300, 1690, 1660, 1590. ^{1}H-NMR (DMSO-d_6) δ: 2.67 (3H, s), 3.71 (3H, s), 4.79 (2H, s), 7.28 (5H, m), 8.79 (1H, s), 12.86 (1H, s).

Preparation of Rabbit Platelet-Rich Plasma (PRP) Blood was collected from a catheter inserted into the carotid artery of ethyl ether anesthesized rabbits. The blood was citrated with 3.8% aqueous sodium citrate solution (1 ml of citrate/9 ml of blood) and separated from the red blood cells by centrifugation for 15 min at 150 g at room temperature. The supernatant thus obtained was used as PRP.

Platelet Aggregation Test The optical density method of Born[12] was used to assess the ability of test compounds to inhibit platelet aggregation induced by ADP and AA. A silicone treated cuvette containing 0.435 ml of the PRP sample was placed in an aggregometer (Sienco, DP-247E) set at 37 °C and 1200 rpm, and a solution of the test compound in 2.5 μl of DMSO was added. After preincubation for 3 min, 20 μl of an aqueous solution of ADP (30 μM) or 10 μM of an aqueous solution of AA (100 μM) was added to induce platelet aggregation. Inhibition of platelet aggregation by a test compound was calculated by dividing the maximum deflection in the optical density curve by that observed with the control (2.5 μl of DMSO alone).

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