α-Methylidene-γ-butyrolactones: Synthesis and Evaluation of Quinolin-2(1*H*)-one Derivatives

by **Tai-Chi Wang**, **Yeh-Long Chen**, and **Cherng-Chyi Tzeng***

School of Chemistry, Kaohsiung Medical College, Kaohsiung 807, Taiwan, Republic of China

and **Shorong-Shii Liou** and **Weng-Feng Tzeng**

Tajen Junior College of Pharmacy, Pingtung, Taiwan, Republic of China

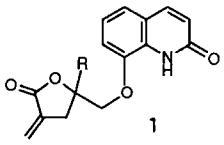
and **Ya-Ling Chang** and **Che-Ming Teng**

Pharmacological Institute, College of Medicine, National Taiwan University, Taipei 100, Taiwan, Republic of China

As a continuation of our previous studies on the synthesis and antiplatelet activity of quinolin-2(1*H*)-ones with an α-methylidene-γ-butyrolactone substituted at O(8), the O(6)- and N(1)-substituted isomers were synthesized and evaluated for antiplatelet activity against thrombin (Thr)-, arachidonic acid (AA)-, collagen (Col)-, and platelet-activating-factor (PAF)-induced aggregation in washed rabbit platelets. These compounds were synthesized from 6-hydroxyquinolin-2(1*H*)-one *via* alkylation and *Reformatsky*-type condensation (*Schemes 1* and *2*). All of them were found to inhibit the platelet aggregation perfectly which was induced by AA and Col. 6-Substituted isomers **5b–g** exhibited very strong inhibitory activities against AA- and PAF-induced aggregation and are approximately ten times more potent than their 8-substituted counterparts. However, the 1-substituted (**11a** and **11b**) and the 1,6-disubstituted (**6**) counterparts were relatively inactive. Their effects on the Ca^{2+}-dependent vasoconstriction induced by high K^+, and the phasic and tonic vasoconstrictions induced by norepinephrine (NE) in rat aorta were also evaluated. Except **5g**, all of them were found to have significant inhibitory activity on the NE-induced phasic and tonic vasoconstrictions. Compounds **6** and **11b** also exhibited strong inhibitory activity on high-K^+ medium, Ca^{2+}-induced vasoconstriction.

Introduction. – Cardiovascular diseases, especially various forms of thrombosis, such as coronary, embolic, venous, and traumatic thrombosis, account for a large number of deaths per year. Since the initiation of thrombus formation is dependent on platelet aggregation, the inhibitors of platelet aggregation could be prototypes for more effective drugs against thrombosis that leads to heart attacks and strokes. Therefore, we decided to search for novel compounds possessing more potent inhibiting activity on platelet aggregation. A number of α-methylidene-γ-butyrolactone-bearing heterocycles were synthesized and evaluated for antiplatelet and vasorelaxing activities [1–6]. One of our recent reports described the preparation and evaluation of certain 8-[(2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1*H*)-ones (**1**) [4]. However, according to *Nishi et al.*, the positional isomers display quite different biological effects. For example, the 6-substituted isomer exhibited the highest antiplatelet potency, while the 7- and 8-substituted isomers were much less active when the side chain was maintained as $OCH_2CH_2CH_2COOEt$ in the 1,2,3,4-tetrahydroquinolin-2(1*H*)-one series [7]. To study the positional isomers of α-methylidene-γ-butyrolactone-bearing quinolin-2(1*H*)-

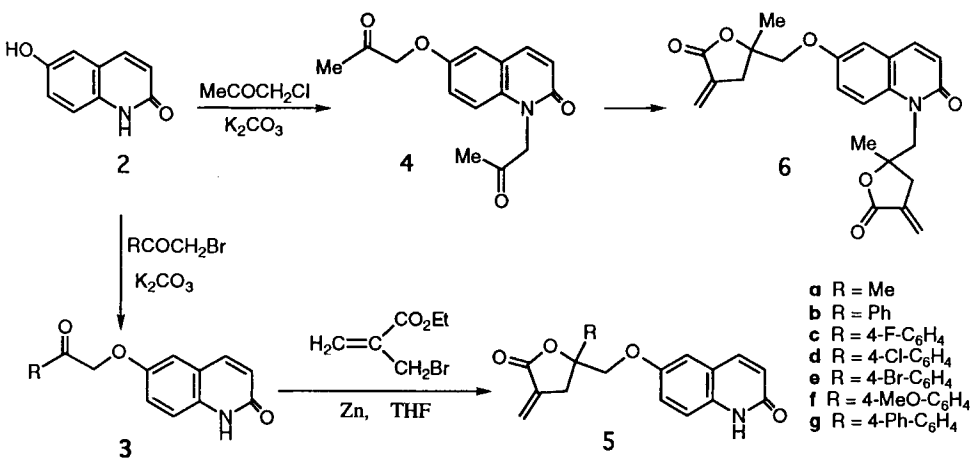
ones with respect to the optimal cardiovascular activity, the 6- and 1-substituted isomers of **1** have been synthesized and evaluated.



1

Results and Discussion. – The preparation of 6-[(2-substituted 2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1*H*)-ones (**5a**–**g**) is illustrated in *Scheme 1*. 6-Hydroxyquinolin-2(1*H*)-one (**2**), prepared either from 6-hydroxyquinoline or from 4-methoxyaniline [8][9], was treated with with 2-bromoacetophenone or its 4-substituted derivative to give 6-(2-aryl-2-oxoethoxy)quinolin-2(1*H*)-ones (**3b**–**g**). The possibility of *N*(1)- or *O*(2)-alkylation was excluded based on the long-range ^{1}H, ^{13}C-HETCOR spectral evidences of the product (*e.g.*, **3b**) in which CH_2 protons (5.61 ppm) were coupled to C-atoms with resonances of 194.44 (^2J), 152.76 (^3J), and 70.53 (^1J) ppm corresponding to C(2′), C(6), and C(1′), respectively. However, when the alkylation of **2** was carried out under the same conditions with chloroacetone and K_2CO_3 as described for the preparation of **3b**, the ^{1}H-NMR spectrum of the sole product showed two *singlets* at 4.87 and 5.20 ppm, corresponding to O(6)–CH_2 and N(1)–CH_2 protons, respectively, indicated that both *O*- and *N*-alkylation occurred leading to the formation of 6-(2-oxopropoxy)-1-(2-oxopropyl)quinolin-2(1*H*)-one (**4**). The downfield (5.20 ppm) *singlet* was assigned to N(1)–CH_2 according to the long-range ^{1}H, ^{13}C-HETCOR spectra in which it was coupled to C-atoms with resonances of 202.32 (^2J), 160.54 (^3J), 134.04 (^3J), and 51.53 (^1J) ppm corresponding to C(2′), C(2), C(8a), and C(1′), respectively. *Reformatsky*-type condensation of **3b**–**g** and **4** gave **5b**–**g** and **6**, respectively.

Scheme 1

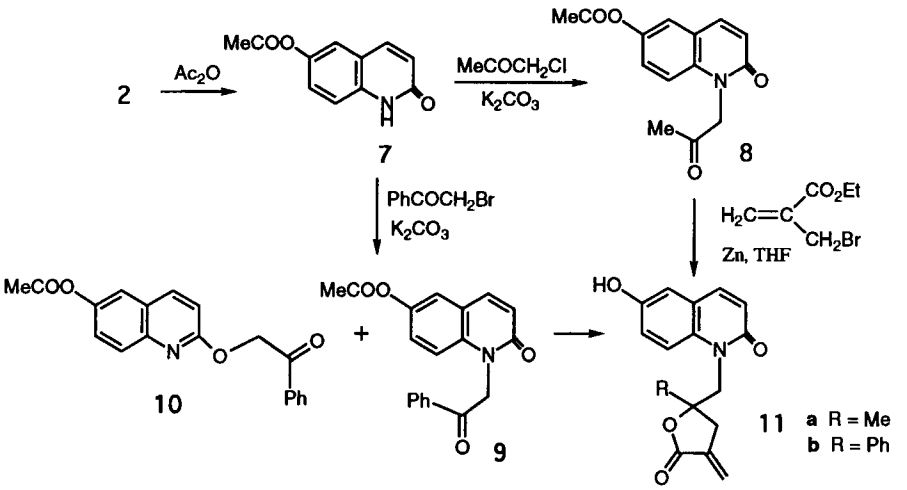


2 4 6

3 5

To prepare the isomeric 1-[(2-substituted 2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)methyl]-6-hydroxyquinolin-2(1*H*)-ones **11a–b** for the comparison of antiplatelet potency, 6-hydroxyquinolin-2(1*H*)-one (**2**) was treated with Ac_2O to give 6-acetoxyquinolin-2(1*H*)-one (**7**; *Scheme 2*). Compound **7** can also be obtained from 6-hydroxyquinoline *via* *N*-oxidation followed by acetylation [9]. Alkylation of **7** with chloroacetone afforded 6-acetoxy-1-(2-oxopropyl)quinolin-2(1*H*)-one (**8**) in 73% yield. Since alkylation of the isomeric 8-acetoxyquinolin-2(1*H*)-one occurred at O(2) rather than at N(1) [5], the structure of **8** was unambiguously assigned by the long-range $^1H,^{13}C$-HETCOR spectra in which the CH_2 *singlet* (5.10 ppm) was coupled to the C-atoms with resonances at 202.11 (^2J), 161.57 (^3J), 137.06 (^3J), and 52.17 (^1J) ppm corresponding to C(2'), C(2), C(8a), and C(1'), respectively. However, when **7** was alkylated with 2-bromoacetophenone, in addition to 6-acetoxy-1-(2-oxo-2-phenylethyl)quinolin-2(1*H*)-one (**9**), which was obtained as the major and expected product, a minor product was also isolated. The long-range $^1H,^{13}C$-HETCOR spectra of this minor product showed coupling of its CH_2 protons (5.75 ppm) with the C-atoms of resonances at 194.36 (^2J), 160.72 (^3J), and 67.57 (^1J) ppm corresponding to C(2'), C(2), and C(1'), respectively, suggesting that the minor product was 6-acetoxy-2-(2-oxo-2-phenylethoxy)quinoline (**10**). To establish the structure, its X-ray crystallographic analysis was carried out. A view of a single molecule of **10** is given in the *Figure*, indicating that the alkylation occurred at O(2). *Reformatsky*-type condensation of **8** and **9** gave **11a** and **11b**, respectively.

Scheme 2



The antiplatelet activities of quinolin-2(1*H*)-one-containing α-methylidene-γ-butyrolactones were evaluated in washed rabbit platelets. Platelet aggregation was induced by thrombin (Thr, 0.1 U/ml), arachidonic acid (AA, 100 μM), collagen (Col, 10 μg/ml), and platelet-activating factor (PAF, 2 nM). The final concentration of compounds was 100 μg/ml, and the results were shown in *Table 1*. All of them were found to inhibit the platelet aggregation perfectly which was induced by AA and Col. For compounds **5b–f**,

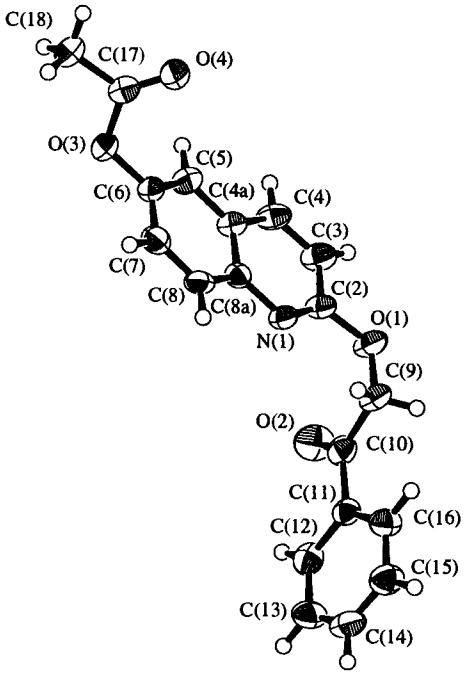


Fig. *X-Ray crystallographic structure of* **10**

a complete inhibition against all the four inducers were obtained. However, the 1,6-disubstituted derivative **6** and 1-substituted isomer **11a** became less active against Thr- and PAF-induced aggregation. The inhibitory concentrations for 50% aggregation

Table 1. *Effect of Quinolin-2(1*H*)-ones on the Platelet Aggregation* [%] *Induced by Thrombin (Thr), Arachidonic acid (AA), Collagen (Col), and Platelet-Activating Factor (PAF) in Washed Rabbit Platelets*[a])

Compounds	Inducer			
	Thr (0.1 U/ml)	AA (100 μM)	Col (10 μg/ml)	PAF (2 nM)
Control	91.7 ± 1.0	86.4 ± 1.0	89.2 ± 1.4	88.2 ± 0.8
5b	0[b])[c])	0	0	0
5c	0	0	0	0
5d	0	0	0	0
5e	0	0	0	0
5f	0	0	0	0
5g	38.7 ± 7.1[c])	0	0	0
6	77.8 ± 0.9[c])	0	0	45.3 ± 5.4[c])
11a	86.5 ± 1.1[d])	0	0	72.0 ± 3.1[c])
11b	10.3 ± 3.4[c])	0	0	0
Aspirin	91.9 ± 1.4	0	85.4 ± 3.9	90.5 ± 1.2

[a]) Platelets were preincubated with quinolin-2(1*H*)-ones (100 μg/ml), aspirin (50 μg/ml), or DMSO (0.5%, control) at 37° for 3 min, and the inducer was then added. Percentages of aggregation are presented as means ± standard errors of the mean ($n = 3-7$). [b]) Complete inhibition in all experiments. [c]) Significantly different from control value at $p < 0.001$. [d]) Significantly different from control value at $p < 0.01$.

(IC_{50}) induced by AA and PAF are given in *Table 2*. Compounds **5b–g** exhibited very strong inhibitory activities against AA- and PAF-induced aggregation and is approximately ten times more potent than their 8-substituted counterparts [4]. However, the 1-substituted (**11a** and **11b**) and the 1,6-disubstituted (**6**) counterparts were relatively inactive.

Table 2. IC_{50} *Values* [μM] *of Quinolin-2(1H)-ones on the Platelet Aggregation Induced by AA and PAF*

	AA	PAF
5b	0.9	8.5
5c	0.9	6.5
5d	0.6	6.8
5e	0.6	9.3
5f	2.1	7.7
5g	7.4	19.0
6	139	>150
11a	104	>150
11b	38.3	86.1
Aspirin	118	>150

The effects of quinolin-2(1*H*)-ones on the Ca^{2+}-dependent vasoconstriction induced by high K^+, and the phasic and tonic vasoconstrictions induced by norepinephrine (NE) in rat aorta are given in *Table 3*. Except **5g**, all of them were found to have significant inhibitory activity on the NE-induced phasic and tonic vasoconstrictions. Compounds **6** and **11b** were also found to exhibit strong inhibitory activity on high-K^+ medium, Ca^{2+}-induced vasoconstriction.

Table 3. *Effects of Quinolin-2(1H)-ones on High K^+- and Ca^{2+}-Induced, and Norepinephrine-Induced Vasoconstriction of Rat Thoracic Aorta*[a])

Agonist	K^+ (80 mM) + Ca^{2+} (1.9 mM)	NE (3 μM), phasic	NE (3 μM), tonic
Control	100 ± 5.2	100 ± 5.0	100 ± 2.8
5b	22.3 ± 4.4	8.7 ± 2.1	13.1 ± 0.1
5c	32.9 ± 6.8	0	11.5 ± 1.5
5d	68.7 ± 2.9	5.2 ± 3.7	8.4 ± 2.1
5e	75.3 ± 9.1	4.1 ± 2.9	5.9 ± 0.1
5f	39.8 ± 1.9	21.7 ± 1.2	36.1 ± 5.1
5g	98.7 ± 2.8	81.8 ± 3.4	103.9 ± 7.3
6	9.7 ± 0.8	0	2.8 ± 2.0
11a	21.9 ± 2.6	3.4 ± 2.4	8.5 ± 1.8
11b	5.4 ± 0.5	0	3.7 ± 0.9
Nifedipine	0	98.7 ± 0.7	96.5 ± 2.1
Prazosin	100 ± 2.0	0	0

[a]) Rat aorta were preincubated with quinolin-2(1*H*)-ones (100 μg/ml), DMSO (0.5%, control), nifedipine (1 μg/ml), or prazosin (1 μg/ml) at 37° for 15 min; then high K^+ (80 mM) and Ca^{2+} (1.9 mM), or norepinephrine (NE, 3 μM) was added. Percentages of the control vasoconstriction were calculated and presented as means ± standard erros of the mean (n = 3).

Experimental Part

General. TLC: precoated (0.2 mm) silica gel *60 F-254* plates from *EM Laboratories, Inc.*; detection by UV light (254 nm). M.p.: *Electrothermal IA 9000* micromelting-point apparatus; uncorrected. UV Spectra (λ_{max}(log ε) in nm): *Beckman* UV-VIS spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Varian-Gemini-200* spectrometer, δ in ppm with Me_4Si as an internal standard. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer and results were within ± 0.4% of calculated values.

6-(2-Oxo-2-phenylethoxy)quinolin-2(1H)-one (**3b**). *6-Hydroxyquinolin-2(1H)-one* (**2**) (1.61 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol), and dry DMF (50 ml) were stirred at r.t. for 30 min. To this soln., 2-bromoacetophenone (1.99 g, 10 mmol) in dry DMF (10 ml) was added in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 ml). The pale-yellow solid thus obtained was collected and crystallized from CH_2Cl_2: **3b** (2.15 g, 77%). M.p. 189–190°. ^{1}H-NMR (DMSO): 5.61 (*s*, 2 H–C(1')); 6.49 (*d*, *J* = 10.0, H–C(3)); 7.81 (*d*, *J* = 10.0, H–C(4)); 7.26–8.06 (*m*, 8 arom. H); 11.66 (br. *s*, NH). ^{13}C-NMR (DMSO): 70.53 (C(1')); 110.57; 116.29; 119.56; 119.80; 122.36; 127.84; 128.81; 133.56; 133.76; 134.40; 139.68; 152.76 (C(6)); 161.50 (C(2)); 194.44 (C(2')). Anal. calc. for $C_{17}H_{13}NO_3$: C 73.11, H 4.69, N 5.02; found: C 73.12, H 4.62, N 5.04.

6-[2-(4-Fluorophenyl)-2-oxoethoxy]quinolin-2(1H)-one (**3c**). From 2-bromo-4'-fluoroacetophenone as described for **3b**: 72% yield. M.p. 212–213°. ^{1}H-NMR (DMSO): 5.59 (*s*, 2 H–C(1')); 6.49 (*d*, *J* = 9.6, H–C(3)); 7.80 (*d*, *J* = 9.6, H–C(4)); 7.25–8.16 (*m*, 7 arom. H); 11.66 (br. *s*, NH). ^{13}C-NMR (DMSO): 70.45 (C(1')); 110.56; 115.67; 116.10; 116.29; 119.54; 119.78; 122.38; 130.83; 131.02; 131.13; 131.19; 133.58; 139.66; 152.71 (C(6)); 161.49 (C(2)); 162.79; 167.81; 193.12 (C(2')). Anal. calc. for $C_{17}H_{12}FNO_3$: C 68.68, H 4.07, N 4.71; found: C 68.33, H 4.15, N 4.65.

6-[2-(4-Chlorophenyl)-2-oxoethoxy]quinolin-2(1H)-one (**3d**). From 2-bromo-4'-chloroacetophenone as described for **3b**: 74% yield. M.p. 202–203°. ^{1}H-NMR (DMSO): 5.59 (*s*, 2 H–C(1')); 6.49 (*d*, *J* = 9.5, H–C(3)); 7.80 (*d*, *J* = 9.5, H–C(4)); 7.25–8.08 (*m*, 7 arom. H); 11.66 (br. *s*, NH). ^{13}C-NMR (DMSO): 70.52 (C(1')); 110.57; 116.29; 119.53; 119.77; 122.39; 128.92; 129.80; 133.06; 133.58; 138.64; 139.65; 152.67 ((6)); 161.48 (C(2)); 193.58 (C(2')). Anal. calc. for $C_{17}H_{12}ClNO_3$: C 65.08, H 3.86, N 4.46; found: C 64.90, H 3.88, N 4.46.

6-[2-(4-Bromophenyl)-2-oxoethoxy]quinolin-2(1H)-one (**3e**). From 2-bromo-4'-bromoacetophenone as described for **3b**: 70% yield. M.p. 189–190°. ^{1}H-NMR (DMSO): 5.57 (*s*, 2 H–C(1')); 6.48 (*d*, *J* = 9.5, H–C(3)); 7.80 (*d*, *J* = 9.5, H–C(4)); 7.24–7.98 (*m*, 7 arom. H); 11.65 (br. *s*, NH). ^{13}C-NMR (DMSO): 70.53 (C(1')); 110.63; 116.31; 119.55; 119.76; 122.36; 127.82; 129.87; 131.86; 133.40; 133.60; 139.64; 152.67 (C(6)); 161.50 (C(2)); 193.82 (C(2')). Anal. calc. for $C_{17}H_{12}BrNO_3$ 1.0 H_2O: C 54.28, H 3.75, N 3.72; found: C 54.27, H 3.75, N 3.80.

6-[2-(4-Methoxyphenyl)-2-oxoethoxy]quinolin-2(1H)-one (**3f**). From 2-bromo-4'-methoxyacetophenone as described for **3b**: 85% yield. M.p. 199–200°. ^{1}H-NMR (DMSO): 3.87 (*s*, MeO); 5.53 (*s*, 2 H–C(1')); 6.48 (*d*, *J* = 9.6, H–C(3)); 7.80 (*d*, *J* = 9.6, H–C(4)); 7.08–8.04 (*m*, 7 arom. H); 11.65 (br. *s*, NH). ^{13}C-NMR (DMSO): 55.61 (MeO); 70.25 (C(1')); 110.52; 114.03; 116.26; 119.53; 119.79; 122.35; 127.30; 130.20; 133.52; 139.67; 152.83 (C(6)); 161.48 (C(2)); 163.55; 192.74 (C(2')). Anal. calc. for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53; found: C 69.51, H 4.94, N 4.44.

6-[2-(1,1'-Biphenyl-4-yl)-2-oxoethoxy]quinolin-2(1H)-one (**3g**). From 2-bromo-4'-phenylacetophenone as described for **3b**: 85% yield. M.p. 192–193°. ^{1}H-NMR (DMSO): 5.64 (*s*, 2 H–C(1')); 6.49 (*d*, *J* = 9.5, H–C(3)); 7.82 (*d*, *J* = 9.5, H–C(4)); 7.27–8.15 (*m*, 12 arom. H); 11.67 (br. *s*, NH). ^{13}C-NMR (DMSO): 70.55 (C(1')); 110.56; 116.31; 119.57; 119.82; 122.37; 126.98; 127.03; 128.50; 128.60; 129.11; 133.18; 133.56; 138.81; 139.69; 145.12; 152.77 (C(6)); 161.51 (C(2)); 193.99 (C(2')). Anal. calc. for $C_{23}H_{17}NO_3 \cdot 0.75\ H_2O$: C 74.88, H 5.05, N 3.80; found: C 74.88, H 5.15, N 3.84.

6-(2-Oxopropoxy)-1-(2-oxopropyl)quinolin-2(1H)-one (**4**). *6-Hydroxyquinolin-2(1H)-one* (**2**; 1.61 g, 10 mmol), K_2CO_3 (2.76 g, 20 mmol), and dry DMF (50 ml) were stirred at r.t. for 30 min. To this soln., chloroacetone (1.84 g, 20 mmol) in dry DMF (10 ml) was added in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 ml). The white solid thus obtained was collected and crystallized from CH_2Cl_2: **4** (2.27 g, 83%). White crystals. M.p. 138–139°. ^{1}H-NMR (DMSO): 2.18, 2.29 (*s*, Me); 4.87 (*s*, CH_2O); 5.20 (*s*, CH_2N); 6.63 (*d*, *J* = 9.5, H–C(3)); 7.14–7.29 (*m*, 3 arom. H); 7.87 (*d*, *J* = 9.5, H–C(4)). ^{13}C-NMR (DMSO): 26.23, 27.33 (Me); 51.53 (CH_2N); 72.45 (CH_2O); 111.66; 116.01; 119.28; 120.68; 121.22; 134.04; 139.37; 152.62 (C(6)); 160.54 (C(2)); 202.32 (C=O); 203.95 (C=O). Anal. calc. for $C_{15}H_{15}NO_4$: C 65.92, H 5.53, N 5.13; found: C 65.96, H 5.51, N 5.20.

6-[(2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinolin-2(1H)-one (**5b**). To a soln. of **3b** (0.84 g, 3 mmol) in dry THF (60 ml), activated Zn powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and

ethyl 2-(bromomethyl)acrylate (0.78 g, 4 mmol) were added. The mixture was refluxed under N_2 for 6 h (TLC monitoring). After cooling, it was poured into ice-cold 5% HCl soln. (300 ml) and extracted with CH_2Cl_2 (3 × 75 ml). The CH_2Cl_2 extracts were combined and washed with H_2O, dried (Na_2SO_4), and evaporated to give a residual solid which was crystallized from CH_2Cl_2/Et_2O 1:10: **5b** (0.91 g, 87%). White crystals. M.p. 99–100°. UV (0.1N HCl/MeOH): 230 (sh, 4.58), 343 (3.77). UV (MeOH): 231 (4.70), 346 (3.79). UV (0.1N NaOH/MeOH): 231 (sh, 4.77), 350 (3.78). ^{1}H-NMR (DMSO): 3.23 (*dt*, *J* = 17.4, 2.8, 1 H–C(3′)); 3.65 (*dt*, *J* = 17.4, 2.6, 1 H–C(3′)); 4.26, 4.37 (*AB*, *J* = 10.6, CH_2O); 5.80 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.13 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.49 (*d*, *J* = 9.6, H–C(3)); 7.06–7.56 (*m*, 8 arom. H); 7.69 (*d*, *J* = 9.6, H–C(4)); 11.67 (br. *s*, NH). ^{13}C-NMR (DMSO): 37.10 (C(3′)); 73.84 (CH_2O); 84.32 (C(2′)); 110.84; 116.34; 119.62; 119.70; 121.49; 122.45; 125.14; 128.25; 128.62; 133.71; 135.08; 139.67; 140.52; 152.73 (C(6)); 161.54 (C(2)); 168.96 (C(5′)). Anal. calc. for $C_{21}H_{17}NO_4$: C 72.61, H 4.93, N 4.03; found: C 72.38, H 5.00, N 4.07.

The same procedure was applied to convert **3c–g** to **5c–g**, respectively.

*6-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**5c**). Yield: 90%. M.p. 204–205°. UV (0.1N HCl/MeOH): 231 (sh, 4.57), 344 (3.77). UV (MeOH): 231 (4.71), 347 (3.81). UV (0.1N NaOH/MeOH): 231 (sh, 4.76), 350 (3.78). ^{1}H-NMR (DMSO): 3.17 (*dt*, *J* = 17.4, 2.8, 1 H–C(3′)); 3.63 (*dt*, *J* = 17.3, 2.5, 1 H–C(3′)); 4.25, 4.37 (*AB*, *J* = 10.6, CH_2O); 5.81 (*t*, *J* = 2.2, 1 H, CH_2=C(4′)); 6.13 (*t*, *J* = 2.6, 1 H, CH_2=C(4′)); 6.49 (*d*, *J* = 9.5, H–C(3)); 7.05–7.62 (*m*, 7 arom. H); 7.80 (*d*, *J* = 9.5, H–C(4)); 11.67 (br. *s*, NH). ^{13}C-NMR (DMSO): 37.10 (C(3′)); 73.75 (CH_2O); 83.99 (C(2′)); 110.85; 115.20; 115.63; 116.34; 119.60; 119.66; 121.61; 122.45; 127.41; 127.58; 133.72; 134.96; 136.67; 136.73; 139.65; 152.68 (C(6)); 159.43; 161.53 (C(2)); 164.29; 168.84 (C(5′)). Anal. calc. for $C_{21}H_{16}FNO_4$: C 69.03, H 4.41, N 3.83; found: C 68.94, H 4.45, N 3.98.

*6-{[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**5d**). Yield: 85%. M.p. 199–200°. UV (0.1N HCl/MeOH): 227 (sh, 4.54), 345 (3.69). UV (MeOH): 231 (4.68), 347 (3.76). UV (0.1N NaOH/MeOH): 230 (sh, 4.72), 349 (3.75). ^{1}H-NMR (DMSO): 3.16 (*dt*, *J* = 17.2, 2.8, 1 H–C(3′)); 3.62 (*dt*, *J* = 17.2, 2.4, 1 H–C(3′)); 4.27, 4.37 (*AB*, *J* = 10.4, CH_2O); 5.81 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.14 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.49 (*d*, *J* = 9.6, H–C(3)); 7.07–7.57 (*m*, 7 arom. H); 7.80 (*d*, *J* = 9.6, H–C(4)); 11.67 (br. *s*, NH). ^{13}C-NMR (DMSO): 37.02 (C(3′)); 73.60 (CH_2O); 83.92 (C(2′)); 110.86; 116.33; 119.59; 119.65; 121.76; 122.46; 127.20; 128.57; 132.98; 133.73; 134.77; 139.47; 139.63; 152.66 (C(6)); 161.52 (C(2)); 168.78 (C(5′)). Anal. calc. for $C_{21}H_{16}ClNO_4$: C 66.06, H 4.22, N 3.67; found: C 65.94, H 4.34, N 3.70.

*6-{[2-(4-Bromophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**5e**). Yield: 90%. M.p. 199–200°. UV (0.1N HCl/MeOH): 230 (sh, 4.72), 343 (3.81). UV (MeOH): 229 (4.79), 347 (3.82). UV (0.1N NaOH/MeOH): 227 (sh, 4.98), 349 (3.84). ^{1}H-NMR (DMSO): 3.15 (*dt*, *J* = 17.6, 2.8, 1 H–C(3′)); 3.60 (*dt*, *J* = 17.6, 2.4, 1 H–C(3′)); 4.26, 4.35 (*AB*, *J* = 10.8, CH_2O); 5.80 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.12 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.48 (*d*, *J* = 9.6, H–C(3)); 7.06–7.67 (*m*, 7 arom. H); 7.78 (*d*, *J* = 10.0, H–C(4)); 11.64 (br. *s*, NH). ^{13}C-NMR (DMSO): 36.96 (C(3′)); 73.56 (CH_2O); 83.93 (C(2′)); 110.90; 116.32; 119.57; 119.62; 121.53; 121.75; 122.43; 127.48; 131.46; 133.72; 134.70; 139.60; 139.88; 152.66 (C(6)); 161.49 (C(2)); 168.74 (C(5′)). Anal. calc. for $C_{21}H_{16}BrNO_4$: C 59.17, H 3.78, N 3.29; found: C 58.88, H 3.85, N 3.35.

*6-{[2,3,4,5-Tetrahydro-2-(4-methoxyphenyl)-4-methylidene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**5f**). Yield: 80%. M.p. 192–193°. UV (0.1N HCl/MeOH): 230 (sh, 4.59), 347 (3.68). UV (MeOH): 231 (4.63), 347 (3.67). UV (0.1N NaOH/MeOH): 230 (sh, 4.69), 349 (3.68). ^{1}H-NMR (DMSO): 3.16 (*dt*, *J* = 17.4, 2.6, 1 H–C(3′)); 3.60 (*dt*, *J* = 17.4, 2.4, 1 H–C(3′)); 3.78 (*s*, MeO); 4.18, 4.32 (*AB*, *J* = 10.4, CH_2O); 5.79 (*t*, *J* = 2.6, 1 H, CH_2=C(4′)); 6.12 (*t*, *J* = 2.6, 1 H, CH_2=C(4′)); 6.49 (*d*, *J* = 9.6, H–C(3)); 6.99–7.48 (*m*, 7 arom. H); 7.80 (*d*, *J* = 9.6, H–C(4)); 11.66 (br. *s*, NH). ^{13}C-NMR (DMSO): 37.02 (C(3′)); 55.21 (MeO); 73.85 (CH_2O); 84.22 (C(2′)); 110.83; 113.95; 116.35; 119.63; 119.70; 121.36; 122.43; 126.56; 132.33; 133.70; 135.30; 139.68; 152.76 (C(6)); 159.12; 161.54 (C(2)); 169.02 (C(5′)). Anal. calc. for $C_{22}H_{19}NO_5$: C 70.02, H 5.07, N 3.71; found: C 69.70, H 5.15, N 3.77.

*6-{[2-(1,1′-Biphenyl-4-yl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**5g**). Yield: 76%. M.p. 198–199°. UV (0.1N HCl/MeOH): 231 (sh, 4.77), 250 (4.74), 344 (3.88). UV (MeOH): 232 (4.79), 346 (3.83). UV (0.1N NaOH/MeOH): 232 (sh, 4.82), 348 (3.89). ^{1}H-NMR (DMSO): 3.22 (*dt*, *J* = 17.4, 2.5, 1 H–C(3′)); 3.67 (*dt*, *J* = 17.3, 2.4, 1 H–C(3′)); 4.31, 4.42 (*AB*, *J* = 10.5, CH_2O); 5.82 (*t*, *J* = 2.5, 1 H, CH_2=C(4)); 6.15 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.49 (*d*, *J* = 9.5, H–C(3)); 7.08–7.77 (*m*, 12 arom. H); 7.68 (*d*, *J* = 9.6, H–C(4)); 11.67 (br. *s*, NH). ^{13}C-NMR (DMSO): 37.05 (C(3′)); 73.73 (CH_2O); 84.26 (C(2′)); 110.85; 116.34; 119.61; 119.69; 121.59; 122.44; 125.79; 126.73; 126.90; 127.68; 128.98; 133.70; 135.03; 139.46; 139.59; 139.66; 140.11; 152.73 (C(6)); 161.53 (C(2)); 168.95 (C(5′)). Anal. calc. for $C_{27}H_{21}NO_4$: C 76.58, H 5.00, N 3.31; found: C 76.40, H 5.09, N 3.36.

6-[(2,3,4,5-Tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-1-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methyl]quinolin-2(1H)-one (**6**). To a soln. of **4** (0.82 g, 3 mmol) in dry THF (60 ml), activated Zn powder (0.51 g, 7.8 mmol), hydroquinone (8 mg), and ethyl 2-(bromomethyl)acrylate (1.56 g, 7.8 mmol) were added. The mixture was treated and then worked up as described for **5b** to afford **6** (0.87 g, 71%). White crystals. M.p. 148–149°. UV (0.1N HCl/MeOH): 232 (sh, 4.80), 350 (3.84). UV (MeOH): 231 (4.85), 350 (3.87). UV (0.1N NaOH/MeOH): 230 (sh, 4.86), 350 (3.88). ^{1}H-NMR (DMSO): 1.44, 1.49 (2*s*, 2 Me); 2.71–3.35 (*m*, 4 H–C(3')); 4.12 (*s*, CH_2N); 4.51, 4.70 (*AB*, J = 15.0, CH_2O); 5.55–6.10 (*m*, 4 H, 2 CH_2=C(4')); 6.61 (*d*, J = 9.5, H–C(3)); 7.13–7.67 (*m*, 3 arom. H); 7.84 (*d*, J = 9.5, H–C(4)). ^{13}C-NMR (DMSO): 23.38, 25.13 (Me); 35.92, 37.20 (C(3')); 48.16 (CH_2N); 73.02 (CH_2O); 81.76, 84.22 (C(2')); 111.50; 111.59; 117.73; 118.77; 120.70; 121.07; 121.26; 134.38; 135.48; 136.00; 139.64; 152.94 (C(6)); 161.67 (C(2)); 168.46, 169.23 (C(5')). Anal. calc. for $C_{23}H_{23}NO_6$: C 67.47, H 5.66, N 3.42; found: C 67.40, H 5.72, N 3.56.

6-Acetoxyquinolin-2(1H)-one (**7**). A mixture of **2** (1.61 g, 10 mmol), Ac_2O (10 ml), and pyridine (10 ml) was stirred at r.t. for 2 h (TLC monitoring) and then poured into ice-water (100 ml). The white solid thus obtained was collected and crystallized from CH_2Cl_2: **7** (1.77 g, 87%). M.p. 221–222°. ^{1}H-NMR (DMSO): 229 (*s*, Me); 6.55 (*d*, J = 9.6, H–C(3)); 7.26–7.47 (*m*, 3 arom. H); 7.90 (*d*, J = 9.6, H–C(4)); 11.85 (br. *s*, NH). ^{13}C-NMR (DMSO): 20.79 (Me); 116.09; 119.40; 119.93; 122.72; 124.66; 136.67; 139.66; 144.67; 161.80 (C(2)); 169.50 (COMe). Anal. calc. for $C_{11}H_9NO_3$: C 65.02, H 4.46, N 6.89; found: C 65.00, H 4.48, N 6.98.

6-Acetoxy-1-(2-oxopropyl)quinolin-2(1H)-one (**8**). Compound **7** (2.03 g, 10 mmol), K_2CO_3 (2.38 g, 10 mmol), and dry DMF (50 ml) were stirred at r.t. for 30 min. To this soln., chloroacetone (0.92 g, 10 mmol) in dry DMF (10 ml) was added in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 ml). The white solid thus obtained was collected and crystallized from CH_2Cl_2/Et_2O 1:10: **8** (1.89 g, 73%). White crystals. M.p. 120–121°. ^{1}H-NMR ($CDCl_3$): 2.25, 2.33 (*s*, Me); 5.10 (*s*, CH_2N); 6.76 (*d*, J = 9.6, H–C(3)); 6.98–7.35 (*m*, 3 arom. H); 7.68 (*d*, J = 9.6, H–C(4)). ^{13}C-NMR ($CDCl_3$): 20.98, 27.09 (Me); 52.17 (CH_2N); 114.73; 121.01; 121.15; 122.10; 124.52; 137.06 (C(8a)); 139.24; 145.46 (C(6)); 161.57 (C(2)); 169.33 (COO); 202.11 (C(2')). Anal. calc. for $C_{14}H_{13}NO_4$: C 64.86, H 5.05, N 5.40; found: C 64.84, H 5.09, N 5.50.

6-Acetoxy-1-(2-oxo-2-phenylethyl)quinolin-2(1H)-one (**9**) *and 6-Acetoxy-2-(2-oxo-2-phenylethoxy)quinoline* (**10**). Compound **7** (0.81 g, 4 mmol), K_2CO_3 (0.55 g, 4 mmol), and dry DMF (50 ml) were stirred at r.t. for 30 min. To this soln. 2-bromoacetophenone (0.80 g, 4 mmol) in dry DMF (10 ml) was added in one portion. The resulting mixture was stirred at r.t. for 24 h. (TLC monitoring) and then poured into ice-water (100 ml). The brown solid thus obtained was purified by column chromatography (silica gel; hexane/AcOEt 1:1) and crystallization from hexane/CH_2Cl_2 10:1: **9** (0.50 g, 39%) and **10** (0.20 g, 16%).

Data for **9**: M.p. 152–153°. ^{1}H-NMR ($CDCl_3$): 2.31 (*s*, Me); 5.79 (*s*, 2 H–C(1')); 6.78 (*d*, J = 9.5, H–C(3)); 6.95–8.11 (*m*, 8 arom. H); 7.70 (*d*, J = 8.8, H–C(4)). ^{13}C-NMR ($CDCl_3$): 21.02 (Me); 48.88 (C(1')); 115.08; 120.90; 121.23; 122.12; 124.34; 128.13; 128.94; 134.08; 134.71; 137.35; 139.19; 145.30 (C(6)); 161.85 (C(2)); 169.41 (O–C=O); 192.17 (C(2')). Anal. calc. for $C_{19}H_{15}NO_4$: C 71.02, H 4.71, N 4.36; found: C 71.01, H 4.69, N 4.40.

Data for **10**: M.p. 131–132°. ^{1}H-NMR ($CDCl_3$): 2.33 (*s*, Me); 5.75 (*s*, 2 H–C(1')); 7.12 (*d*, J = 8.8, H–C(3)); 7.27–8.07 (*m*, 8 arom. H); 7.69 (*d*, J = 8.8, H–C(4)). ^{13}C-NMR ($CDCl_3$): 21.15 (Me); 67.57 (C(1')); 113.46; 118.43; 124.28; 125.49; 127.94; 128.55; 128.79; 133.56; 135.04; 138.87; 143.98; 146.87 (C(6)); 160.72 (C(2)); 169.60 (O–C=O); 194.36 (C(2')). Anal. calc. for $C_{19}H_{15}NO_4$: C 71.02, H 4.71, N 4.36; found: C 70.80, H 4.70, N 4.54.

6-Hydroxy-1-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methyl]quinolin-2(1H)-one (**11a**). From **8** as described for **5b**: 73% yield. White crystals. M.p. 208–209°. UV (0.1N HCl/MeOH): 228 (sh, 4.86), 275 (4.01), 355 (3.84). UV (MeOH): 227 (sh, 4.86), 275 (4.04), 356 (3.83). UV (0.1N NaOH/MeOH): 241 (4.85), 383 (3.96). ^{1}H-NMR (DMSO): 1.44 (*s*, Me); 2.76 (*dt*, J = 17.4, 2.6, 1 H–C(3')); 3.20 (*dt*, J = 17.2, 2.5, 1 H–C(3')); 4.47, 4.67 (*AB*, J = 15.0, CH_2N); 5.55 (*t*, J = 2.4, 1 H, CH_2=C(4')); 5.79 (*t*, J = 2.7, 1 H, CH_2=C(4')); 6.55 (*d*, J = 9.4, H–C(3)); 6.98–7.56 (*m*, 3 arom. H); 7.79 (*d*, J = 9.5, H–C(4)); 9.55 (*s*, OH). ^{13}C-NMR (DMSO): 25.18 (Me); 37.20 (C(3')); 48.16 (CH_2N); 84.24 (C(2')); 112.35; 117.49; 119.15; 120.67; 120.84; 121.29; 132.95; 135.52; 139.65; 152.17 (C(6)); 161.60 (C(2)); 168.50 (C(5')). Anal. calc. for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91; found: C 66.98, H 5.31, N 4.95.

6-Hydroxy-1-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methyl]quinolin-2(1H)-one (**11b**). From **9** as described for **5b**: 72% yield. White crystals. M.p. 212–213°. UV (0.1N HCl/MeOH): 234 (sh, 4.48), 276 (3.83), 357 (3.65). UV (MeOH): 234 (sh, 4.51), 276 (3.86), 357 (3.64). UV (0.1N NaOH/MeOH): 249 (4.57), 382 (3.77). ^{1}H-NMR (DMSO): 3.11 (*dt*, J = 17.1, 2.8, 1 H–C(3')); 3.65 (*dt*, J = 17.1, 2.4, 1 H–C(3')); 4.48, 4.99 (*AB*, J = 14.0, CH_2N); 5.51 (*t*, J = 2.4, 1 H, CH_2=C(4')); 5.72 (*t*, J = 2.6, 1 H, CH_2=C(4')); 6.55 (*d*, J = 9.4,

H–C(3)); 6.97–7.57 (*m*, 8 arom. H); 7.79 (*d*, J = 9.5, H–C(4)); 9.56 (*s*, OH). ^{13}C-NMR (DMSO): 37.97 (C(3')); 49.66 (CH_2N); 86.56 (C(2')); 112.44; 117.24; 119.27; 120.73; 120.91; 121.29; 124.94; 128.24; 128.69; 132.74; 134.29; 139.87; 141.74; 152.19 (C(6)); 161.82 (C(2)); 168.04 (C(5')). Anal. calc. for $C_{21}H_{17}NO_4$: C 72.61, H 4.93, N 4.03; found: C 72.69, H 4.91, N 4.08.

X-Ray Structure Determination of **10**[1]): Crystallographic data $C_{19}H_{15}NO_4$, M = 321.33, monoclinic, space group P_1 (# 2), a = 9.398(1) Å, b = 11.892(2) Å, c = 7.303(2) Å, α = 93.65(2)°, β = 101.27(2)°, γ = 97.59(1)°, V = 790.1(3) Å^3, Z = 2, D_{calc} = 1.351 g/cm^3. Crystal dimensions 0.30 × 0.34 × 0.40 mm. F_{000} = 336.00, μ(MoK_α) = 0.95 cm^{-1}. Radiation: MoK_α (λ = 0.7169 Å), ω-2θ scanning technique. The crystal structure was solved by direct methods (SIR92). Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, N, O; fixed H contributions) converged at R = 0.053 (R_w = 0.041) for 2988 reflections.

Pharmacological Evaluation: Aortic Vasoconstriction. Wistar rats of either sex weighing 250 to 300 g were killed by a blow to the head. The thoracic aorta was isolated, and excess fat and connective tissue were removed. Vessels were cut into rings of *ca.* 5 mm in length and mounted in an organ bath containing 5 ml of *Krebs* soln. of the following composition (mM): NaCl, 94.7; KCl, 4.7; $CaCl_2$, 1.9; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; and glucose 11.7 at pH 7.4, The bath soln. was maintained at 37° and bubbled with a 95% O_2 and 5% CO_2 mixture. Two stainless steel hooks were inserted into the aortic lumen; one was fixed while the other was connected to a transducer. Aorta were equilibrated in the medium for 90 min with three changes of *Krebs* soln. and maintained under an optimal tension of 1 g before specific experimental protocols were initiated; contractions were recorded isometrically *via* a force displacement transducer connected to a *Gould* polygraph (model *2400*). The final concentration of DMSO was fixed at 0.5%.

Antiplatelet Evaluation. Reagents: Collagen (type I, bovine *Achilles* tendon) obtained from *Sigma Chem. Co.* was homogenized in 25 mM AcOH and stored (1 mg/ml) at −70°. Platelet-activating factor (PAF) was purchased from *Calbiochem-Behring Co.* and dissolved in $CHCl_3$. Arachidonic acid (AA), EDTA, and bovine serum albumin were purchased from *Sigma Chem. Co.*

Platelet Aggregation. Blood was collected from the rabbit marginal ear vein, anticoagulated with EDTA (6 mM), and centrifuged for 10 min at 90 × *g* and r.t. Platelet suspension was prepared from this EDTA-anticoagulated platelet-rich plasma according to the washing procedures described previously [10]. Platelet numbers were counted with a *Coulter* counter (model *ZM*) and adjusted to 4.5 × 10^8 platelets/ml. The platelet pellets were finally suspended in *Tyrode*'s soln. of the following composition (mM): NaCl, 136.8; KCl, 2.8; $NaHCO_3$, 11.9; $MgCl_2$, 2.1; NaH_2PO_4,0.33; $CaCl_2$, 1.0; and glucose, 11.2, containing bovine serum albumin (0.35%). The platelet suspension was stirred at 1200 rpm and the aggregation was measured at 37° by the turbidimetric method as described by *O'Brien* [11] using a *Chrono-Log Lumi-aggregometer*. To eliminate the effect of the solvent on the aggregation, the final concentration of DMSO was fixed at 0.5%. Percentage of aggregation was calculated using the absorbance of platelet suspension as 0% aggregation and the absorbance of *Tyrode*'s soln. as 100% aggregation. The inhibitory concentration for 50% aggregation (IC_{50}) was calculated from computerization of *CA-Cricket Graph III* for five or six dose-effect levels.

We thank the *National Science Council* of the Republic of China for financial support, and Dr. *Michael Y. Chiang* and Miss *I-Ting Chen* of the Department of Chemistry, National Sun Yat-sen University, for carrying out the X-ray crystallographic analysis.

REFERENCES

[1] Y. L. Chen, T. C. Wang, K. H. Lee, Y. L. Chang, C. M. Teng, C. C. Tzeng, *Helv. Chim. Acta* **1996**, *79*, 651.
[2] Y. L. Chen, T. C. Wang, S. C. Liang, C. M. Teng, C. C. Tzeng, *Chem. Pharm. Bull.* **1996**, *44*, 1591.
[3] T. C. Wang, Y. L. Chen, S. S. Liou, Y. L. Chang, C. M. Teng, C. C. Tzeng, *Helv. Chim. Acta* **1996**, *79*, 1620.
[4] C. C. Tzeng, T. C. Wang, Y. L. Chen, C. J. Wang, Y. L. Chang, C. M. Teng, *Helv. Chim. Acta* **1997**, *80*, 1161.
[5] S. S. Liou, Y. L. Zhao, Y. L. Chang, C. M. Teng, C. C. Tzeng, *Chem. Pharm. Bull.* **1997**, *45*, 1777.
[6] C. C. Tzeng, Y. L. Zhao, Y. L. Chen, S. S. Liou, T. C. Wang, Y. L. Chang, C. M. Teng, *Helv. Chim. Acta* **1997**, *80*, 2337.

[1]) Crystallographic data for this structure have been deposited with the *Cambridge Crystallographic Data Centre*. Copies of the data can be obtained, free of charge, on application to the *CCDC*, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: + 44-(0)1228-336033 or e-mail: deposit(*a*) ccd.cam.ac.uk).

[7] T. Nishi, K. Yamamoto, T. Shimizu, T. Kanbe, Y. Kimura, K. Nakagawa, *Chem. Pharm. Bull.* **1983**, *31*, 798.
[8] T. C. Wang, Y. L. Chen, K. H. Lee, C. C. Tzeng, *Tetrahedron Lett.* **1996**, 6369.
[9] T. C. Wang, Y. L. Chen, K. H. Lee, C. C. Tzeng, *Synthesis* **1997**, 87.
[10] C. M. Teng, F. N. Ko, *Thromb. Haemost.* **1988**, *59*, 304.
[11] J. R. O'Brien, *J. Clin. Pathol.* **1962**, *15*, 452.

Received March 2, 1998