137. Antiplatelet α-Methylidene-γ-butyrolactones: Synthesis and Evaluation of Quinoline, Flavone, and Xanthone Derivatives

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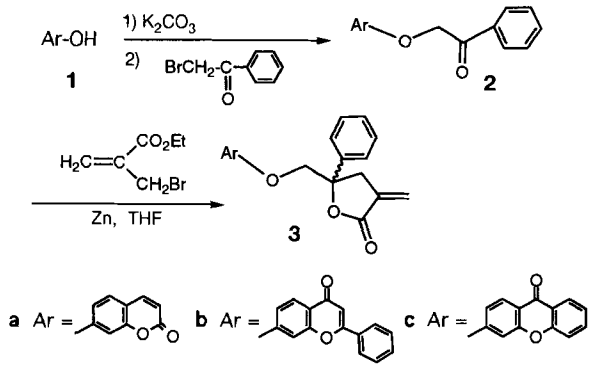
As a continuation of our previous studies on the synthesis and antiplatelet activity of coumarin derivatives of α-methylidene-γ-butyrolactones, certain quinoline, flavone, and xanthone derivatives were synthesized and evaluated for antiplatelet activity against thrombin (Thr)-, arachidonic acid (AA)-, collagen (Col)-, and platelet-activating factor (PAF)-induced aggregation in washed rabbit platelets. These compounds were synthesized from quinolin-8-ol, flavon-7-ol, and xanthon-3-ol, respectively, *via* alkylation and *Reformatsky*-type condensation (*Schemes 1–3*). By the comparison with coumarin α-methylidene-γ-butyrolactone **3a**, flavone and xanthone derivatives, **3b** and **3c**, respectively, are more selective in which only AA- and collagen-induced aggregation are strongly inhibited. Most of the quinoline derivatives (**9a–e**) exhibited broad-spectrum antiplatelet activities.

Introduction. – A number of natural products bearing an α-methylidene-γ-butyrolactone functionality exhibit wide-ranging biological activities which include antitumoral, bacteriocidal, fungicidal, and anthelminthic properties [1–5]. Recently, we have synthesized certain coumarins and naphthalenes containing α-methylidene-γ-butyrolactones as potential antiplatelet agents [6] [7]. Among them, 7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**3a**) and its 4-substituted counterpart have shown potent and broad-spectrum antiplatelet effects in which thrombin (Thr)-, arachidonic acid (AA)-, collagen (Col)-, and platelet-activating factor (PAF)-induced aggregation of rabbit platelets were inhibited. To determine the effect of structural modification with respect to the optimal antiplatelet activity, we have synthesized analogs of **3a** in which coumarin (= 2*H*-1-benzopyran-2-one) moiety was replaced by flavone (= 4*H*-1-benzopyran-4-one) and xanthone (= 9*H*-xanthen-9-one) to increase the lipophilic property of α-methylidene-γ-butyrolactones and thus increase their penetration into the target sites of platelets. The flavonoids are a ubiquitous family of phytochemicals that possess a wide variety of biological activities. A number of natural and synthetic xanthones were also found to exhibit antiplatelet activity [8–11]. On the other hand, the hydrophilic analogs of **3a** were synthesized in which coumarin was replaced by quinoline, a constituent of many therapeutical drugs such as antimalarial agents. Their antiplatelet structure-activity relationships are also discussed.

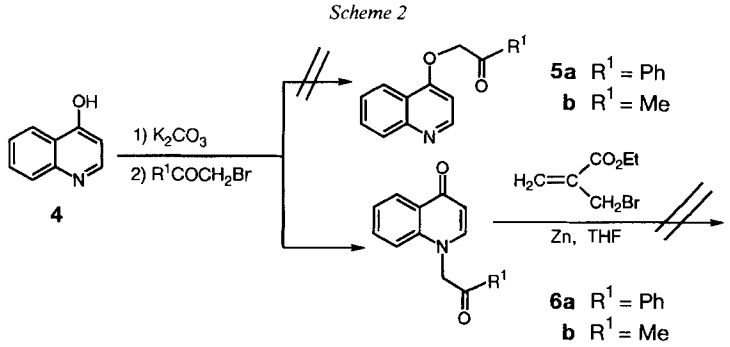
Results and Discussion. – The preparation of aryl-α-methylidene-γ-butyrolactones **3a–c** is illustrated in *Scheme 1*. Alkylation of **1a–c** with 2-bromoacetophenone under basic conditions afforded 2-(aryloxy)acetophenones **2a–c** which were then reacted with ethyl 2-(bromomethyl)acrylate and Zn powder in dry THF (*Reformatsky*-type condensation) to give the target compounds **3a–c** in 47–75% overall yield.

Scheme 1



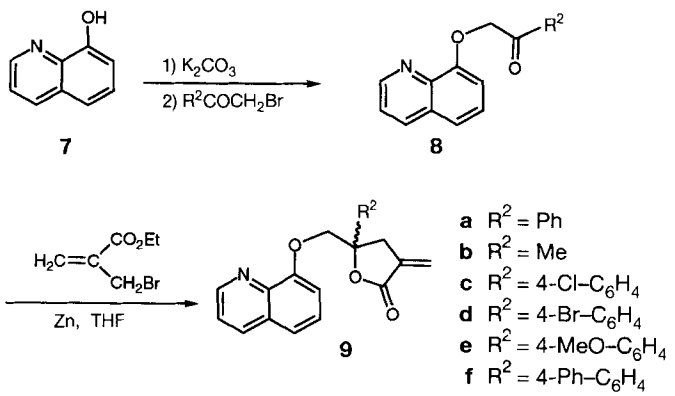
Since 4- and 8-substituted quinolines constitute many chemotherapeutical drugs such as antimalarial agents, chloroquine and primaquine, respectively, both quinolin-4-ol (**4**) and quinolin-8-ol (**7**) were chosen as starting materials. Compound **4** was treated with K_2CO_3 and 2-bromoacetophenone in dry DMF (*Scheme 2*). The product thus obtained was 1-(2-oxo-2-phenylethyl)quinolin-4-one (**6a**) but not 4-(2-oxo-2-phenylethoxy)-quinoline (**5a**) based on the ^1H,^{13}C heteronuclear-correlation (HETCOR) NMR experiments. The singlet C(1′)H_2 protons (δ at 6.06 ppm) were clearly coupled to C-atoms with resonances of 140.69 (^3J), 145.24 (^3J), and 193.37 (^2J) corresponding to C(8a), C(2), and C(2′), respectively. Besides aromatic protons resonated at 7.34–8.25 ppm, there are two *doublet* peaks (J = 7.6 Hz) appeared at 6.15 and 7.95 ppm. The downfield peak (δ 7.95) in coupling with C(8a) (140.69, ^3J), C(2) (145.24, ^1J), and C(4) (176.62, ^3J) was assigned to H–C(2) and the upfield peak (δ 6.15) assigned to H–C(3). The *N*- but not *O*-alkylation was also observed when the alkylating agent was bromoacetone, and 1-(2-oxopropyl)quinolin-4-one (**6b**) was obtained. Attempts to achieve the *Reformatsky*-type

Scheme 2



condensation of **6** under different reaction conditions were not successful. However, treatment of **7** with K_2CO_3 and 2-bromoacetophenone in dry THF afforded 8-(2-oxo-2-phenylethoxy)quinoline (**8a**), an O-alkylated product (*Scheme 3*). The structure of **8a** was determined through the $^1H,^{13}C$ heteronuclear-correlation NMR experiments in which the *singlet* C(1′)H_2 protons (δ at 5.65 ppm) were clearly coupled to C-atoms with resonances of 153.82 (^3J) and 194.43 (^2J) corresponding to C(8) and C(2′), respectively. *Reformatsky*-type condensation of **8a** gave the desired 8-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinoline (**9a**) in 75% yield. Accordingly, compounds **9b–f** were prepared from **7** *via O*-alkylation and *Reformatsky*-type condensation in good overall yield.

Scheme 3



The antiplatelet activities of 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 test compounds was 100 μg/ml, and the results are shown in *Table 1*. Compound **3a** inhibited the platelet aggregation caused by four inducers, while its flavone and xanthone analogs, **3b** and **3c**, respectively, inhibited AA- and Col-induced platelet aggregation completely, and those by thrombin and PAF partially. The compound **9a** and its 2-Me counterpart **9b** exhibited potent and broad-spectrum antiplatelet effects in which Thr-, AA-, Col-, and PAF-induced platelet aggregation were inhibited. Significant antiplatelet activities were also observed when the 2-Ph group of **9a** was replaced by a 4-Cl-, 4-Br-, or 4-MeO-substituted phenyl group (see **9c–e**). However, a 4-Ph-substituted phenyl substituent (**9f**) decreased antiplatelet spectrum in which only AA- and Col-induced aggregation were inhibited. The inhibitory concentrations for 50% aggregation (IC_{50}) induced by AA and PAF are given in *Table 2*. The coumarin derivative **3a** showed the most significant antiplatelet effects on AA- and PAF-induced platelet aggregation, while its flavone and xanthone counterparts, **3b** and **3c**, respectively, were more selective. The quinoline derivative **9a** possessing a 2-Ph substituent was more active than its 2-Me counterpart **9b**. The poor inhibitory potency of **9f** against PAF-induced platelet aggregation implies that a bulky substituent at aromatic benzene reduced its antiplatelet potency. In contrary, **9a** and **9c** are two of the best.

Table 1. *Effect of α-Methylidene-γ-butyrolactones on the Platelet Aggregation Induced by Thrombin (Thr), Arachidonic Acid (AA), Collagen (Col), and Platelet-Activating Factor (PAF) in Washed Rabbit Platelets*[a])

	Aggregation [%]			
	Thr (0.1 U/ml)	AA (100 μM)	Col (10 μg/ml)	PAF (2nM)
Control	92.8 ± 1.5	87.2 ± 1.0	88.8 ± 1.5	90.3 ± 1.6
3a	0[b])[c])	0	0	0
3b	65.6 ± 9.3[d])	0	0	36.8 ± 4.2[c])
3c	81.7 ± 3.7[d])	0	0	70.3 ± 4.1[c])
9a	0	0	0	0
9b	17.4 ± 7.9[c])	0	0	0
9c	0	0	0	0
9d	0	0	0	0
9e	0	0	0	0
9f	70.5 ± 4.1[c])	0	0	78.0 ± 1.6[c])
Aspirin	91.9 ± 1.4	0	85.4 ± 3.9	90.5 ± 1.2

[a]) Platelets were preincubated with DMSO (0.5%, control), aspirin (10 μg/ml), or α-methylidene-γ-butyrolactones (100 μg/ml) 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 $p < 0.01$.

Table 2. IC_{50} *Values* (μM) *of α-Methylidene-γ-butyrolactones on the Platelet Aggregation Induced by AA and PAF*

	AA	PAF
3a	3.7	16.4
3b	6.1	> 200
3c	18.5	> 200
9a	14.2	33.6
9b	88.9	177.9
9c	17.3	33.9
9d	19.1	60.0
9e	41.9	128.3
9f	25.4	> 200

As a result of these studies, compound **3a** was found to possess broad and potent *in vitro* antiplatelet activity. Its lipophilic flavone and xanthone analogs, **3b** and **3c**, respectively, were less active in potency but were more selective. The hydrophilic quinoline analogs **9a–f** were also less active than **3a** in the inhibitory potency against platelet aggregation induced by Thr, AA, Col, and PAF.

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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.: *YANACO* micromelting-point apparatus; uncorrrected. UV Spectra (λ_{max}(log ε) in nm): *Beckman* UV-VIS spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Varian-Gemini-200* spectrometer, chemical shifts 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 theoretical values.

*7-[2-Oxo-2-phenylethoxy]-2-phenyl-4*H*-1-benzopyran-4-one* (**2b**). *Flavon-7-ol* (**1b**) (1.19 g, 5 mmol), K_2CO_3 (0.69 g, 5 mmol), and dry DMF (40 ml) were stirred at r.t. for 30 min. To this soln. was added 2-bromoacetophenone (1.00 g, 5 mmol) in dry DMF (10 ml) in one portion. The resulting mixture was continued to stir at r.t. for 12 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/Et_2O 1:10: **2b** (0.99 g, 73%). Pale-yellow needle crystals. M.p. 174–175°. ^{1}H-NMR ($CDCl_3$): 5.45 (*s*, 2 H–C(1′)); 6.75 (*s*, H–C(3)); 6.98–8.17 (*m*, 13 arom. H). ^{13}C-NMR ($CDCl_3$): 70.77 (C(1′)); 101.78, 109.59, 114.48, 118.56, 126.21, 127.40, 128.12, 128.47, 128.68, 129.03, 131.47, 134.19, 134.27, 157.77, 162.47, 163.18 (arom. C); 177.71 (C(4)); 193.12 (C(2′)). Anal. calc. for $C_{23}H_{16}O_4$: C 77.51, H 4.53; found: C 77.15, H 4.57.

*3-(2-Oxo-2-phenylethoxy)-9*H*-xanthen-9-one* (**2c**). Prepared by the same procedure as described for **2b**: 97% yield. M.p. 174–175°. ^{1}H-NMR ($CDCl_3$): 5.43 (*s*, 2 H–C(1′)); 6.87–8.33 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 70.74 (C(1′)); 101.51, 113.31, 116.52, 117.72, 121.94, 123.96, 126.68, 128.11, 128.61, 129.04, 134.22, 134.26, 134.42, 156.21, 157.84, 163.32 (arom. C); 176.21 (C(9)); 193.10 (C(2′)). Anal. calc. for $C_{21}H_{14}\cdot 0.2\ H_2O$: C 75.52, H 4.35; found: C 75.78, H 4.31.

*2-Phenyl-7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-4*H*-1-benzopyran-4-one* (**3b**). To a soln. of **2b** (1.07 g, 3 mmol) in dry THF (60 ml) were added activated Zn powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and ethyl 2-(bromomethyl)acrylate (0.78 g, 4 mmol). The mixture was refluxed under N_2 atmosphere for 6 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl soln. (300 ml) and extracted with CH_2Cl_2 (3 × 60 ml). The CH_2Cl_2 extracts were combined and washed with H_2O, dried (Na_2SO_4), and then evaporated to give a brown solid which was purified by column chromatography on silica gel using CH_2Cl_2 to afford a residual solid which was crystallized from CH_2Cl_2/Et_2O 1:10: **3b** (0.82 g, 64%). M.p. 190–191°. UV: 250 (4.25), 305 (4.34; 0.1N HCl/MeOH); 251 (4.23), 305 (4.33) (MeOH); 305 (4.35; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 3.26 (*dt*, *J* = 17.0, 2.9, 1 H–C(3′)); 3.69 (*dt*, *J* = 17.0, 2.5, 1 H–C(3′)); 4.27 (*AB* type, CH_2O); 5.73 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.34 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.75 (*s*, H–C(3)); 6.91–8.14 (*m*, 13 arom. H). ^{13}C-NMR ($CDCl_3$): 37.33 (C(3′)); 74.56 (CH_2O); 83.78 (C(2′)); 101.63, 107.57, 114.36, 118.53, 122.03, 125.08, 126.16, 127.36, 128.78, 128.93, 129.02, 131.51, 131.72, 134.58, 139.91, 157.71, 162.37, 163.15 (arom. C); 169.05 (C(5′)); 177.68 (C(4)). Anal. calc. for $C_{27}H_{20}O_5$: C 76.40, H 4.75; found: C 76.13, H 4.80.

*3-[(2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-9*H*-xanthen-9-one* (**3c**). Prepared by the same procedure as described for **3b**: 77% yield. M.p. 160–161°. UV: 235 (sh, 4.62), 265 (4.05), 298 (4.19; 0.1N HCl/MeOH); 235 (sh, 4.64), 266 (4.08), 297 (4.22; MeOH); 265 (4.27), 298 (4.25; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 3.25 (*dt*, *J* = 16.9, 2.9, 1 H–C(3′)); 3.68 (*dt*, *J* = 16.9, 2.5, 1 H–C(3′)); 4.26 (*AB* type, CH_2O); 5.72 (*t*, *J* = 2.6, 1 H, CH_2=C(4′)); 6.33 (*t*, *J* = 2.9, 1 H, CH_2=C(4′)); 6.82–8.33 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 37.35 (C(3′)); 74.47 (CH_2O); 83.79 (C(2′)); 101.34, 113.20, 116.47, 117.72, 121.91, 122.02, 124.00, 125.08, 126.67, 128.54, 128.77, 128.93, 134.44, 134.59, 139.92, 156.18, 157.79, 163.25 (arom. C); 169.06 (C(5′)); 176.19 (C(9)). Anal. calc. for $C_{25}H_{18}O_5$: C 75.37, H 4.55; found: C 75.30, H 4.60.

1-(2-Oxo-2-phenylethyl)quinolin-4-one (**6a**). Quinolin-4-ol (1.45 g, 10 mmol), K_2CO_3 (1.37 g, 10 mmol), and dry DMF (50 ml) were stirred at r.t. for 30 min. To this soln. was added 2-bromoacetophenone (1.99 g, 10 mmol) in dry DMF (10 ml) 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/Et_2O 1:10: **6a** (2.21 g, 84%). M.p. 219–220°. ^{1}H-NMR (DMSO): 6.06 (*s*, 2 H–C(1′)); 6.15 (*d*, *J* = 7.6, H–C(3)); 7.95 (*d*, *J* = 7.6, H–C(2)); 7.34–8.25 (*m*, 9 arom. H). ^{13}C-NMR (DMSO): 57.94 (C(1′)); 109.08 (C(3)); 116.72, 123.22, 125.58, 126.43, 128.22, 128.95, 131.96, 134.22, 134.28 (arom. C); 140.69 (C(8a)); 145.24 (C(2)); 176.62 (C(4)); 193.37 (C(2′)). Anal. calc. for $C_{17}H_{13}NO_2$: C 77.55, H 4.98, N 5.32; found: C 77.55, H 5.03, N 5.35.

1-(2-Oxopropyl)quinolin-4-one (**6b**). From bromoacetone as described for **6a**: 75% yield. M.p. 161–162°. ^{1}H-NMR (DMSO): 2.29 (*s*, Me); 5.32 (*s*, 2 H–C(1′)); 6.10 (*d*, *J* = 7.6, H–C(3)); 7.81 (*d*, *J* = 7.6, H–C(2)); 7.33–8.21 (*m*, 4 arom. H). ^{13}C-NMR (DMSO): 27.02 (C(3′)); 60.46 (C(1′)); 108.91 (C(3)); 116.69, 123.26, 125.55, 126.32, 131.94 (arom. C); 140.48 (C(8a)); 144.98 (C(2)); 176.55 (C(4)); 202.36 (C(2′)). Anal. calc. for $C_{12}H_{11}NO_2$: C 71.62, H 5.51, N 6.96; found: C 71.47, H 5.57, N 7.03.

8-(2-Oxo-2-phenylethoxy)quinoline (**8a**). *Quinolin-8-ol* (**7**; 0.73 g, 5 mmol), K_2CO_3 (0.69 g, 5 mmol), and dry DMF (40 ml) were stirred at r.t. for 30 min. To this soln. was added 2-bromoacetophenone (1.0 g, 5 mmol) in dry DMF (10 ml) 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/Et_2O (1:10): **8a** (0.91 g, 69%). Pale-yellow needle crystals. M.p. 124–125°. ^{1}H-NMR ($CDCl_3$): 5.65 (*s*, 2 H–C(1′)); 6.95–8.97 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 71.85 (C(1′)); 110.09, 120.81, 121.72, 126.41, 128.17, 128.84, 129.60, 133.88, 134.53, 135.93, 140.24, 149.41 (arom. C); 153.82 (C(8)); 194.43 (C(2′)). Anal. calc. for $C_{17}H_{13}NO_2$: C 77.55, H 4.98, N 5.32; found: C 77.59, H 4.97, N 5.37.

8-(2-Oxopropoxy)quinoline (**8b**). From bromoacetone as described for **8a**: 67% yield. M.p. 58–59°. ^{1}H-NMR ($CDCl_3$): 2.32 (*s*, Me); 4.88 (*s*, 2 H–C(1′)); 6.88–8.97 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 26.46 (C(3′)); 74.13 (C(1′)); 109.51, 121.03, 121.90, 126.46, 129.69, 136.02, 140.12, 149.53 (arom. C); 153.69 (C(8)); 206.21 (C(2′)). Anal. calc. for $C_{12}H_{11}NO_2$ 2 H_2O: C 60.75, H 6.37, N 5.90; found: C 60.80, H 6.33, N 5.90.

8-[2-(4-Chlorophenyl)-2-oxoethoxy]quinoline (**8c**). From 2-bromo-4′-chloroacetophenone as described for **8a**: 76% yield. M.p. 111–112°. ^{1}H-NMR ($CDCl_3$): 5.56 (*s*, 2 H–C(1′)); 6.96–8.96 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 72.23 (C(1′)); 110.30, 121.05, 121.77, 126.40, 129.14, 129.64, 129.83, 132.88, 135.95, 140.26, 140.35, 149.47, 153.71 (arom. C); 193.96 (C(2′)). Anal. calc. for $C_{17}H_{12}ClNO_2$: C 68.58, H 4.06, N 4.70; found: C 68.54, H 4.08, N 4.77.

8-[2-(4-Bromophenyl)-2-oxoethoxy]quinoline (**8d**). From 2-bromo-4′-bromoacetophenone as described for **8a**: 75% yield. M.p. 109–110°. ^{1}H-NMR ($CDCl_3$): 5.55 (*s*, 2 H–C(1′)); 6.96–8.96 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 72.20 (C(1′)); 110.30, 121.06, 121.77, 126.39, 129.13, 129.64, 129.89, 132.13, 133.26, 135.95, 140.23, 149.46, 153.68 (arom. C); 194.18 (C(2′)). Anal. calc. for $C_{17}H_{12}BrNO_2$ 0.5 H_2O: C 58.14, H 3.73, N 3.99; found: C 57.89, H 3.81, N 4.03.

8-[2-(4-Methoxyphenyl)-2-oxoethoxy]quinoline (**8e**). From 2-bromo-4′-methoxyacetophenone as described for **8a**: 89% yield. M.p. 121–122°. ^{1}H-NMR ($CDCl_3$): 3.86 (*s*, MeO); 5.56 (*s*, 2 H–C(1′)); 6.92–8.97 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 55.43 (Me); 71.86 (C(1′)); 109.99, 113.94, 120.60, 121.61, 126.39, 127.60, 129.53, 130.60, 135.81, 140.25, 149.33, 153.92, 164.00 (arom. C); 193.11 (C(2′)). Anal. calc. for $C_{18}H_{15}NO_3$: C 73.70, H 5.16, N 4.78; found: C 73.67, H 5.17, N 4.81.

8-[2-Oxo-2-(4-phenylphenyl)ethoxy]quinoline (**8f**). From 2-bromo-4′-phenylacetophenone as described for **8a**: 73% yield. M.p. 135–136°. ^{1}H-NMR ($CDCl_3$): 5.66 (*s*, 2 H–C(1′)); 6.99–8.98 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 72.07 (C(1′)); 110.16, 120.80, 121.68, 126.40, 127.24, 127.40, 128.34, 128.84, 128.94, 129.61, 133.22, 135.87, 139.67, 140.29, 146.50, 149.40, 153.88 (arom. C); 194.21 (C(2′)). Anal. calc. for $C_{23}H_{17}NO_2$: C 81.39, H 5.05, N 4.13; found: C 81.15, H 5.11, N 4.13.

8-[(2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinoline (**9a**). To a soln. of **8a** (0.79 g, 3 mmol) in dry THF (60 ml) were added activated Zn powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and ethyl 2-(bromomethyl)acrylate (0.78 g, 4 mmol). The mixture was refluxed under N_2 atmosphere for 6 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl soln. (300 ml), neutralized with 1.0N $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 60 ml). The CH_2Cl_2 extracts were combined and washed with H_2O, dried (Na_2SO_4), and then evaporated to give a residual solid which was crystallized from a mixed solvent of CH_2Cl_2/Et_2O 1:10: **9a** (0.75 g, 75%). M.p. 101–102°. UV: 250 (4.69; 0.1N HCl/MeOH); 237 (4.62; MeOH); 237 (4.67; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 3.25 (*dt*, *J* = 16.8, 2.8, 1 H–C(3′)); 4.09 (*dt*, *J* = 16.9, 2.6, 1 H–C(3′)); 4.54 (*AB* type, CH_2O); 5.68 (*t*, *J* = 2.6, 1 H, CH_2=C(4′)); 6.25 (*t*, *J* = 2.9, 1 H, CH_2=C(4′)); 7.16–8.90 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 37.31 (C(3′)); 76.68 (CH_2O); 85.08 (C(2′)); 113.49, 121.45, 121.64, 121.88, 125.20, 126.55, 128.30, 128.64, 129.62, 134.89, 135.82, 140.70, 141.06, 149.31, 154.73 (arom. C); 169.48 (C(5′)). Anal. calc. for $C_{21}H_{17}NO_3$: C 76.11, H 5.17, N 4.23; found: C 76.10, H 5.19, N 4.27.

The same procedure was used to convert each of the compounds **8b–g** to **9b–g**, respectively. Compounds **9b** was obtained as a residual oil which was purified by column chromatography on silica gel using CH_2Cl_2.

8-[(2,3,4,5-Tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]quinoline (**9b**). Yield: 82%. UV: 250 (4.69; 0.1N HCl/MeOH); 237 (4.60; MeOH); 238 (4.64; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 1.64 (*s*, Me); 2.84 (*dt*, *J* = 17.2, 2.8, 1 H–C(3′)); 3.48 (*dt*, *J* = 17.2, 2.6, 1 H–C(3′)); 4.29 (*AB* type, CH_2O); 5.66 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.26 (*t*, *J* = 2.9, 1 H, CH_2=C(4′)); 7.13–8.91 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 24.33 (Me); 36.81 (C(3′)); 74.86 (CH_2O); 82.18 (C(2′)); 112.11, 121.28, 121.53, 122.36, 126.56, 129.62, 135.31, 135.89, 140.77, 149.36, 154.62 (arom. C); 169.69 (C(5′)). Anal. calc. for $C_{16}H_{15}NO_3 \cdot 0.125$ H_2O: C 70.77, H 5.66, N 5.16; found: C 70.80, H 5.75, N 5.08.

8-{[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}quinoline (**9c**). Yield: 63%. M.p. 107–108°. UV: 249 (4.75; 0.1N HCl/MeOH); 236 (4.69; MeOH); 238 (4.28; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 3.20 (*dt*, *J* = 16.9, 2.6, 1 H–C(3′)); 4.06 (*dt*, *J* = 16.9, 2.6, 1 H–C(3′)); 4.42 (*AB* type, CH_2O); 5.70 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.28 (*t*, *J* = 2.9, 1 H, CH_2=C(4′)); 7.13–8.91 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 37.43 (C(3′)); 76.39 (CH_2O); 84.46 (C(2′)); 113.40, 121.56, 121.80, 122.47, 126.56, 126.81, 128.82, 129.66, 134.35, 134.45, 135.89, 139.30, 141.02, 149.40, 154.57 (arom. C); 169.24 (C(5′)). Anal. calc. for $C_{21}H_{16}ClNO_3$: C 68.95, H 4.41, N 3.83; found: C 68.91, H 4.44, N 3.87.

8-{[2-(4-Bromophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}quinoline (**9d**). Yield: 58%. M.p. 123–124°. UV: 250 (4.68; 0.1N HCl/MeOH); 236 (4.66; MeOH); 238 (4.55; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 3.20 (*dt*, *J* = 17.0, 2.8, 1 H–C(3′)); 4.06 (*dt*, *J* = 17.0, 2.5, 1 H–C(3′)); 4.49 (*AB* type, CH_2O); 5.70 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.28 (*t*, *J* = 2.9, 1 H, CH_2=C(4′)); 7.13–8.91 (*m*, 10 arom. H). ^{13}C-NMR

($CDCl_3$): 37.36 (C(3')); 76.26 (CH_2O); 84.44 (C(2')); 113.37, 121.53, 121.78, 122.48, 126.53, 127.09, 129.63, 131.75, 134.37, 135.86, 139.81, 140.98, 149.37, 154.53 (arom. C); 169.19 (C(5')). Anal. calc. for $C_{21}H_{16}BrNO_3$: C 61.48, H 3.93, N 3.41; found: C 61.32, H 3.96, N 3.43.

8-{[2,3,4,5-Tetrahydro-2-(4-methoxyphenyl)-4-methylidene-5-oxofuran-2-yl]methoxy}quinoline (**9e**). Yield: 56%. M.p. 125–126°. UV: 250 (4.29; 0.1N HCl/MeOH); 236 (4.37; MeOH); 238 (4.18; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 3.22 (*dt*, *J* = 16.9, 2.8, 1 H–C(3')); 3.81 (*s*, MeO); 4.05 (*dt*, *J* = 16.8, 2.6, 1 H–C(3')); 4.50 (*AB* type, CH_2O); 5.67 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.24 (*t*, *J* = 2.8, 1 H, CH_2=C(4')); 6.90–8.90 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 37.34 (C(3')); 55.33 (MeO); 76.67 (CH_2O); 85.02 (C(2')); 113.35, 114.01, 121.48, 121.59, 121.89, 126.58, 129.64, 132.73, 135.06, 135.84, 141.08, 149.35, 154.77, 159.52 (arom. C); 169.60 (C(5')). Anal. calc. for $C_{22}H_{19}NO_4$: C 73.11, H 5.30, N 3.88; found: C 73.08, H 5.34, N 3.92.

8-{[2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-(4-phenylphenyl)furan-2-yl]methoxy}quinoline (**9f**). Yield: 65%. M.p. 154–155°. UV: 251 (4.88; 0.1N HCl/MeOH); 238 (4.86; MeOH); 240 (4.71; 0.1N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$): 3.29 (*dt*, *J* = 16.9, 2.8, 1 H–C(3')); 4.11 (*dt*, *J* = 16.9, 2.6, 1 H–C(3')); 4.57 (*AB* type, CH_2O); 5.70 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.28 (*t*, *J* = 2.8, 1 H, CH_2=C(4')); 7.19–8.92 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 37.35 (C(3')); 76.57 (CH_2O); 85.02 (C(2')); 113.43, 121.49, 121.66, 122.09, 125.73, 126.57, 127.08, 127.35, 127.57, 128.82, 129.63, 134.82, 135.85, 139.63, 140.29, 141.05, 141.27, 149.35, 154.71 (arom. C); 169.50 (C(5')). Anal. calc. for $C_{27}H_{21}NO_3$: C 79.59, H 5.20, N 3.44; found: C 79.53, H 5.25, N 3.50.

Pharmacological 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 in [12]. 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* [13] 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.

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