87. Synthesis and Evaluation of 2-{[(2-Oxo-1*H*-quinolin-8-yl)oxy]methyl}-Substituted α-Methylidene-γ-butyrolactones

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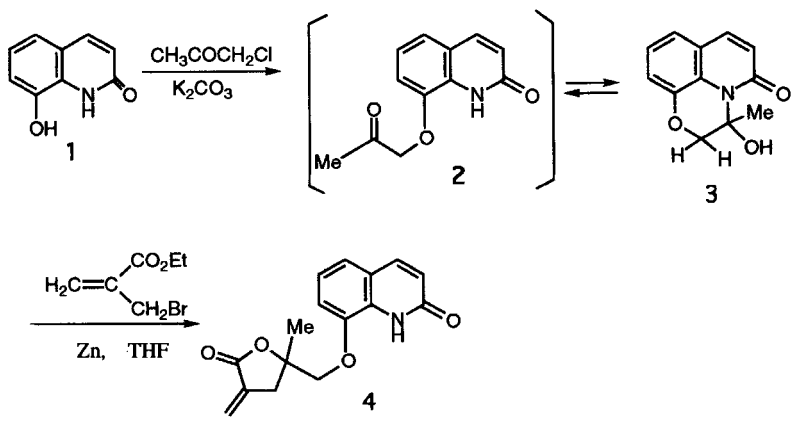
O-Alkylation of 8-hydroxy-1*H*-quinolin-2-one (**1**) afforded 8-(2-oxopropoxy)-1*H*-quinolin-2-one (**2**) which was immediately cyclized to form the tricyclic 2,3-dihydro-3-hydroxy-3-methyl-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-5-one (**3**). The *Reformatsky*-type condensation of **3** furnished antiplatelet 8-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-1*H*-quinolin-2-one (**4**). Its counterparts **7a–f**, Ph-substituted at C(2) of the furan ring, were obtained from **1** *via* alkylation and the *Reformatsky*-type condensation. Although compound **4** was less active against platelet aggregation than **7a–f**, it was the only compound which exhibited significant inhibitory activity on high-K^+ medium, Ca^{2+}-induced vasoconstriction and was more active than most of its Ph-substituted counterparts against norepinephrine-induced vasoconstrictions.

Introduction. – α-Methylidene-γ-butyrolactones constitute an important group of natural products which possess wide-ranging biological activities, including antitumor, bactericidal, fungicidal, antibiotic, and anthelminthic properties [1–3]. Because of their broad range of biological activities and their interesting structural features, α-methylidene-γ-butyrolactones present a challenge which is reflected in an increasing number of investigations and syntheses [4–10]. Recently, we have synthesized and evaluated the antiplatelet activities of certain coumarin α-methylidene-γ-butyrolactones [11] [12]. The present report describes the preparation of their bioisosteric isomers, [(2-oxo-1*H*-quinolin-8-yl)oxy]methyl derivatives of α-methylidene-γ-butyrolactones for the antiplatelet screening. Their vasorelaxing effects were also evaluated since certain antiplatelet agents have been found to be capable of inhibiting vasoconstrictions induced by norepinephrine [13–15]. The cardiovascular and neuroprotective activities of certain 1*H*-quinolin-2-ones substituted with various side chains have continuously been reported [16–20].

Results and Discussion. – The preparation of 8-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-1*H*-quinolin-2-one (**4**) is illustrated in *Scheme 1*. 8-Hydroxy-1*H*-quinolin-2-one (**1**) [21] [22] was chosen as the starting material. Although its alkylation usually gave the *O*-alkylation product [18], the results of treating **1**

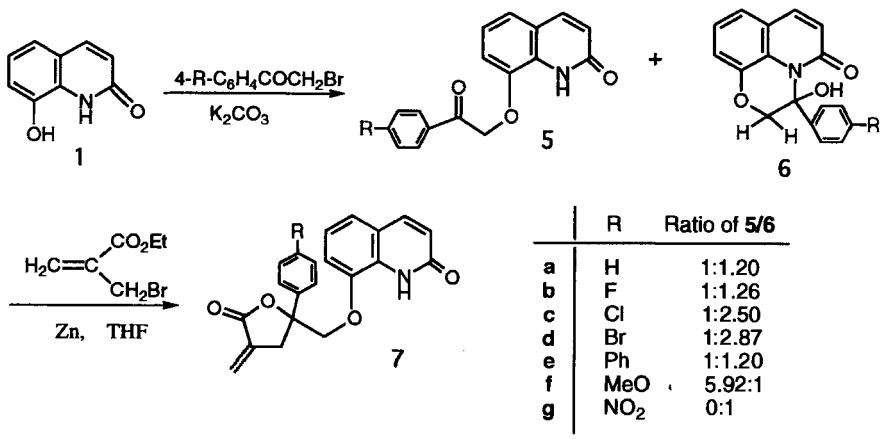
with K_2CO_3 and chloroacetone to afford the expected 8-(2-oxopropoxy)-1*H*-quinolin-2-one (**2**) were obscure. The ^{13}C-NMR of the sole product isolated in this reaction showed a quarternary C resonance at 84.48 ppm, and no peak was observed around 190 ppm, indicating the absence of the carbonyl C-atom. Cyclization must have occurred under alkylating conditions which led to the formation of the tricyclic 2,3-dihydro-3-hydroxy-3-methyl-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one (**3**) instead of the desired **2**. The structure of **3** was further supported by the ^{1}H-NMR spectrum in which the C(2)H_2 protons are magnetically nonequivalent, and two distinct *doublet* (J = 11.2 Hz) resonances at 4.05 and 4.25 ppm (*AB* type) were observed. Furthermore, the ^{1}H,^{13}C-HETCOR spectrum revealed the correlation of C(2)H_2 protons with C-atoms resonating at 72.07 (^1J), 84.48 (^2J), and 143.89 (^3J), corresponding to C(2), C(3), and C(11), respectively. The peak at 84.48 ppm was assigned to C(3) because of its correlation (^2J coupling) with Me protons at 1.89 ppm. Compounds **2** and **3** are interconvertable, because, when **3** was subjected to the *Reformatsky*-type condensation, **4** was obtained in 68% yield.

Scheme 1



To establish and to further confirm this cyclization pattern, **1** was reacted with 2-bromoacetophenone under the same reaction conditions (*Scheme 2*). A mixture of **5a** and **6a** was isolated in a 1:1.2 ratio based on the integration of CH_2O signals (**5a**: 5.74 (*s*); **6a**: 4.19 and 4.28 (*AB* type, J = 11.4)) in the ^{1}H-NMR spectra of the crude product. The steric effect of the Ph group is assumed to be responsible for the retardation of the cyclization. Certain 4′-substituted 2-bromoacetophenones were also subjected to the same reaction to study the influence of the inductive effect. The alkylated products were isolated, and the ratio **5b–g**/**6b–g** was determined by the integration of the CH_2O signals. The electron-donating substituents (Ph, MeO) on the Ph group retarded cyclization, while the electron-withdrawing substituents (Cl, Br, NO_2) favored the formation of **6**. Due to the strong electron-withdrawing capacity, the nitrophenyl substituent led to a complete cyclization in spite of its unfavorable steric factor. *Reformatsky*-type condensation of **5a–f** and **6a–f** afforded 8-[(2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)methoxy]-1*H*-quinolin-2-ones **7a–f**, respectively, in 46–62% yield, indicating that **5a–f** and their tricyclic counterparts **6a–f** are interconvertable.

Scheme 2



The antiplatelet activities of (oxoquinolinyloxy)methyl-α-methylidene-γ-butyrolactones **4** and **7a–f** 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 are shown in *Table 1*. All of them found to inhibit the platelet aggregation perfectly which was induced by AA and Col. Compounds **7b** and **7c** have also exhibited good inhibitory activity against the Thr- and PAF-induced aggregation. The inhibitory concentration for 50% aggregation (IC_{50}) induced by AA and PAF is expressed in *Table 2*. Compound **4**, with an aliphatic Me substituent at C(2) of

Table 1. *Effect of 1H-Quinolin-2-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
4	74.7 ± 1.4[b])	0[b])[c])	0	31.2 ± 11.1[b])
7a	70.9 ± 1.8[b])	0	0	27.8 ± 1.4[b])
7b	0	0	0	0
7c	0	0	0	0
7d	24.8 ± 13.2[b])	0	0	0
7e	76.7 ± 3.4[b])	0	0	66.8 ± 6.1[b])
7f	77.4 ± 0.6[b])	0	0	26.9 ± 12.5[b])
Aspirin	91.9 ± 1.4	0	85.4 ± 3.9	90.5 ± 1.2

[a]) Platelets were preincubated with 1*H*-quinolin-2-ones (100 μm/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]) Significantly different from control value at $p < 0.001$.

[c]) Complete inhibition in all experiments.

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

	AA	PAF
4	110	>200
7a	21.3	>200
7b	13.0	20.1
7c	9.49	20.6
7d	9.88	29.1
7e	28.7	>200
7f	21.8	>200

the lactone, was less active against AA-induced aggregation than its Ph–C(2) phenyl counterparts (**7a–f**). Compounds **7b–d**, which possess substituted benzene at C(2), were found to have broad antiplatelet activities in which both AA- and PAF-induced aggregations were inhibited. The lesser inhibitory potency of **7e** and **7f** implies that an electron-donating substituent at the aromatic benzene moiety reduced their antiplatelet activities.

The effects of 1*H*-quinolin-2-one derivatives on the Ca^{2+}-dependent constriction induced by high K^+, and the phasic and tonic constrictions induced by norepinephrine (NE) in rat aorta are given in *Table 3*. Compound **4**, with an aliphatic Me substituent at C(2) of the lactone, was the only compound which exhibited significant inhibitory activity on high-K^+ medium, Ca^{2+}-induced vasoconstriction, and was more active than most of its Ph–C(2) counterparts **7a–b** and **7d–f** against the NE-induced phasic and tonic constrictions. This finding is interesting, because Ph–C(2) lactones were found to be better antiplatelet agents than their respective Me–C(2) counterparts [11] [12].

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

Agonist	K (80 mM) + Ca (1.9 mM)	NE (3 μM)-phasic	NE (3 μM)-tonic
Control	100 ± 5.2	100 ± 5.0	100 ± 2.8
4	22.1 ± 2.7	40.6 ± 0.4	24.1 ± 3.7
7a	95.1 ± 0.1	92.7 ± 9.2	52.7 ± 6.9
7b	95.9 ± 2.9	77.1 ± 2.1	44.6 ± 4.8
7c	84.3 ± 4.0	23.7 ± 2.8	26.7 ± 2.1
7d	92.7 ± 1.6	58.3 ± 3.7	64.9 ± 0.9
7e	102.5 ± 1.8	101.2 ± 0.8	98.5 ± 3.3
7f	93.9 ± 0.9	44.0 ± 3.1	42.0 ± 0.9
Nifedipine	0	98.7 ± 0.7	96.5 ± 2.1
Prazosin	100 ± 2.0	0	0

[a]) Rat aorta were preincubated with 1*H*-quinolin-2-ones (100 μg/tnl), 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 constriction were calculated and presented as means ± standard errors 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.: *YANACO* 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, chemical

shifts δ in ppm with $SiMe_4$ as an internal standard. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer, and results were within $\pm 0.4\%$ of theoretical values.

2,3-Dihydro-3-hydroxy-3-methyl-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one (**3**). *8-Hydroxy-1H-quinolin-2-one* (**1**, 0,81 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 chloroacetone (0.46 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 white solid thus obtained was collected and crystallized from CH_2Cl_2/Et_2O 1:10 to afford **3** (0.91 g, 84%). M.p. 192–193°. ^{1}H-NMR ($CDCl_3$): 1.89 (*s*, Me); 4.05, 4.25 (*AB* type, $J = 11.2$, 2H–C(2)); 6.64 (*d*, $J = 9.5$, H–C(6)); 7.15–7.27 (*m*, 3 arom. H); 7.74 (*d*, $J = 9.5$, H–C(7)); 7.84 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 24.30(Me); 72.07(C(2)); 84.48(C(3)); 117.67, 121.35, 121.55, 122.62, 123.16, 125.51, 139.89, 143.89 (arom. C); 163.20(C(5)). Anal. calc. for $C_{12}H_{11}NO_3 \cdot 0.125\ H_2O$: C 65.67, H 5.05, N 6.38; found: C 65.63, H 5.12, N 6.41.

8-(2-Oxo-2-phenylethoxy)-1H-quinolin-2-one (**5a**) *and 2,3-Dihydro-3-hydroxy-3-phenyl-5H-pyrido-[1,2,3-de][1,4]benzoxazin-5-one* (**6a**). A mixture **5a**/**6a** 1:1.20 was obtained from 2-bromoacetophenone by the same procedure as for **3** in 95% yield. ^{1}H-NMR (DMSO): 5.74 (*s*, CH_2O) (**5a**); 4.19, 4.28 (*AB* type, $J = 11.4$, 2H–C(2)) (**6a**). ^{13}C-NMR (DMSO): 71.62(C(1')); 161.32(C(2)); 194.70(C(2')) (**5a**); 75.61(C(2)); 84.50(C(3)); 160.70(C(5)) (**6a**). Anal. calc. for $C_{17}H_{13}NO_3$: C 73.11, H 4.69, N 5.02; found: C 72.91, H 4.75, N 5.07.

8-[2-(4-Fluorophenyl)-2-oxoethoxy]-1H-quinolin-2-one (**5b**) *and 3-(4-Fluorophenyl)-2,3-dihydro-3-hydroxy-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one* (**6b**). A mixture **5b**/**6b** 1:1.26 was obtained from 2-bromo-4'-fluoroacetophenone by the same procedure as for **3** in 64% yield. ^{1}H-NMR (DMSO): 5.73 (*s*, CH_2O) (**5b**); 4.18, 4.26 (*AB* type, $J = 11.6$, 2H–C(2)) (**6b**). ^{13}C-NMR (DMSO): 71.52(C(1')); 161.30(C(2)); 193.34(C(2')) (**5b**); 73.55(C(2)); 83.99(C(3)); 160.48(C(5)) (**6b**). Anal. calc. for $C_{17}H_{12}FNO_3$: C 68.68, H 4.07, N 4.71; found C 68.37, H 4.10, N 4.67.

8-[2-(4-Chlorophenyl)-2-oxoethoxy]-1H-quinolin-2-one (**5c**) *and 3-(4-Chlorophenyl)-2,3-dihydro-3-hydroxy-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one* (**6c**). A mixture **5c**/**6c** 1:2.50 was obtained from 2-bromo-4'-chloroacetophenone by the same procedure as for **3** in 62% yield. ^{1}H-NMR (DMSO): 5.72 (*s*, CH_2O) (**5c**); 4.17, 4.24 (*AB* type, $J = 11.6$, 2H–C(2)) (**6c**). ^{13}C-NMR (DMSO): 71.57(C(1')); 161.31(C(2)); 193.81(C(2')) (**5c**); 73.51(C(2)); 83.72(C(3)); 160.22(C(5)) (**6c**). Anal. calc. for $C_{17}H_{12}ClNO_3$: C 65.08, H 3.86, N 4.46; found: C 64.83, H 3.87, N 4.49.

8-[2-(4-Bromophenyl)-2-oxoethoxy]-1H-quinolin-2-one (**5d**) *and 3-(4-Bromophenyl)-2,3-dihydro-3-hydroxy-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one* (**6d**). A mixture **5d**/**6d** 1:2.87 was obtained from 2-bromo-4'-bromoacetophenone by the same procedure as for **3** in 94% yield. ^{1}H-NMR (DMSO): 5.71 (*s*, CH_2O) (**5d**); 4.16, 4.23 (*AB* type, $J = 11.6$, 2H–C(2)) (**6d**). ^{13}C-NMR (DMSO): 71.57(C(1')); 161.32(C(2)); 194.05(C(2')) (**5d**); 73.49(C(2)); 83.76(C(3)); 160.19(C(5)) (**6d**). Anal. calc. for $C_{17}H_{12}BrNO_3$: C 57.00, H 3.38, N 3.91; found: C 56.64, H 3.34, N 4.01.

8-[2-Oxo-2-(4-phenylphenyl)ethoxy]-1H-quinolin-2-one (**5e**) *and 2,3-Dihydro-3-hydroxy-3-(4-phenylphenyl)-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one* (**6e**). A mixture **5e**/**6e** 1:1.20 was obtained from 2-bromo-4'-phenyl acetophenone by the same procedure as for **3** in 98% yield. ^{1}H-NMR ($CDCl_3$): 5.78 (*s*, CH_2O) (**5e**); 4.24, 4.32 (*AB* type, $J = 11.4$, 2H–C(2)) (**6e**). ^{13}C-NMR ($CDCl_3$): 71.62(C(1')); 161.33(C(2)); 194.33(C(2')) (**5e**); 73.56(C(2)); 84.35(C(3)); 160.67(C(5)) (**6e**). Anal. calc. for $C_{23}H_{17}NO_3$: C 77.73, H 4.82, N 3.94, found: C 77.65, H 4.90, N 4.00.

8-[2-(4-Methoxyphenyl)-2-oxoethoxy]-1H-quinolin-2-one (**5f**) *and 2,3-Dihydro-3-hydroxy-3-(4-methoxyphenyl)-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one* (**6f**). A mixture **5f**/**6f** 5.91:1 was obtained from 2-bromo-4'-methoxyacetophenone by the same procedure as for **3** in 87% yield. ^{1}H-NMR ($CDCl_3$): 3.88 (*s*, MeO); 5.40 (*s*, CH_2O) (**5f**); 3.76 (*s*, MeO); 4.31, 4.35 (*AB* type, $J = 10.8$, 2H–C(2)) (**6f**). ^{13}C-NMR ($CDCl_3$): 55.54(MeO); 71.56(C(1')); 164.31(C(2)); 191.83(C(2')) (**5f**); 55.21(MeO); 73.66(C(2)); 85.69(C(3)); 161.96(C(5)) (**6f**). Anal. calc. for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53; found: C 69.56, H 4.92, N 4.46.

2,3-Dihydro-3-hydroxy-3-(4-nitrophenyl)-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one (**6g**). Compound **6g** was obtained from 2-bromo-4'-nitroacetophenone by the same procedure as for **3** in 50% yield. M.p. 177–180°. ^{1}H-NMR ($CDCl_3$): 4.35, 4.38 (*AB* type, $J = 11.4$, 2H–C(2)); 6.67 (*d*, $J = 9.2$, H–C(6)); 7.20–8.21 (*m*, 7 arom. H); 7.88 (*d*, $J = 9.6$, H–C(7)); 7.83 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 73.16; 84.97; 118.20; 120.86; 122.17; 122.49; 123.72; 123.82; 126.45; 140.72; 143.80; 148.10; 148.47; 162.76. Anal. calc. for $C_{17}H_{12}N_2O_5$: C 62.97, H 3.73, N 8.64; found: C 62.75, H 3.75, N 8.53.

8-[(2,3,4,5-Tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-1H-quinolin-2-one (**4**). To a soln. of **3** (0.43 g, 2 mmol) in dry THF (60 ml) were added activated Zn powder (0.17 g, 2.6 mmol), hydroquinone (4 mg), and ethyl 2-(bromomethyl)acrylate (0.52 g, 2.6 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. (200 ml), and extracted with

CH_2Cl_2 (75 ml × 3). 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/acetone 20:1. The proper fractions were combined and evaporated to furnish a residual solid which was crystallized from CH_2Cl_2/Et_2O 1:5 to afford **4** (0.39 g, 68%). White crystals. M.p. 164–165°. UV (0.1N HCl/MeOH): 254 (sh, 4.21), 280(3.70), 334(3.35). UV (MeOH): 253 (sh, 4.20), 280(3.81), 334(3.44) UV (0.1N NaOH/MeOH): 250 (sh, 4.31), 335(3.59). ^{1}H-NMR ($CDCl_3$): 1.65 (*s*, Me–C(2′)); 2.88 (*dt*, *J* = 17.2, 3.0, 1H–C(3′)); 3.27 (*dt*, *J* = 17.2, 2.4, 1H–C(3′)); 4.08, 4.20 (*AB* type, *J* = 9.8, CH_2O); 5.78 (*t*, *J* = 2.4, 1H, CH_2=C(4′)); 6.39 (*t*, *J* = 2.8, 1H, CH_2=C(4′)); 6.64 (*d*, *J* = 9.6, H–C(3)); 6.95–7.28 (*m*, 3 arom. H); 7.71 (*d*, *J* = 9.6, H–C(4)); 9.29 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 24.06(Me); 37.07(C(3′)); 73.89(CH_2O); 81.22(C(2′)); 111.33; 120.30; 120.65; 122.13; 122.77; 128.55; 135.23; 140.34; 144.13(C(8)); 162.02(C(2)); 169.22(C(5′)). Anal. calc. for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91; found: C 67.22, H 5.31, N 4.90.

The same procedure was applied to convert each of the compounds **5a–f** and **6a–f** to **7a–f**, resp.

8-[(2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-1H-quinolin-2-one (**7a**). Yield: 47%. M.p. 210–211°. UV (0.1N HCl/MeOH): 253 (sh, 4.39), 281(3.86), 334(3.63). UV (MeOH): 253 (sh, 4.30), 281(3.89), 334(3.61). UV (0.1N NaOH/MeOH): 252 (sh, 4.39), 336(3.71). ^{1}H-NMR ($CDCl_3$): 3.30 (*dt*, *J* = 17.0, 3.0, 1H–C(3′)); 3.71 (*dt*, *J* = 16.8, 2.4, 1H–C(3′)); 4.25, 4.39 (*AB* type, *J* = 10.3, CH_2O); 5.88 (*t*, *J* = 2.8, 1H, CH_2=C(4′)); 6.48 (*t*, *J* = 3.0, 1H, CH_2=C(4′)); 6.64 (*d*, *J* = 9.6, 1H–C(3)); 6.89–7.55 (*m*, 8 arom. H); 7.69 (*d*, *J* = 9.6, H–C(4)); 8.81 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 37.68(C(3′)); 75.32 (CH_2O); 84.05(C(2′)); 111.47; 120.29; 120.76; 122.00; 122.74; 122.91; 125.00; 128.56; 128.88; 129.02; 134.79; 139.54; 140.18; 143.93(C(8)); 161.71(C(2)); 168.73(C(5′)). Anal. calc. for $C_{21}H_{17}NO_4$: C 72.61, H 4.93, N 4.03; found: C 72.33, H 4.92, N 4.10.

8-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-1H-quinolin-2-one (**7b**). Yield: 62%. M.p. 195–196°. UV (0.1N HCl/MeOH): 253 (sh, 4.05), 283(3.54), 334(3.38). UV (MeOH): 253 (sh, 3.95), 280(3.55), 334(3.31). UV (0.1N NaOH/MeOH): 252 (sh, 4.08), 337(3.50). ^{1}H-NMR ($CDCl_3$): 3.27 (*dt*, *J* = 16.8, 3.0, 1H–C(3′)); 3.73 (*dt*, *J* = 16.8, 2.2, 1H–C(3′)); 4.23, 4.36 (*AB* type, *J* = 10.2, CH_2O); 5.87 (*t*, *J* = 2.6, 1H, CH_2=C(4′)); 6.48 (*t*, *J* = 2.6, 1H, CH_2=C(4′)); 6.64 (*d*, *J* = 9.6, 1H–C(3)); 6.89–7.54 (*m*, 7 arom. H); 7.69 (*d*, *J* = 9.6, H–C(4)); 8.94 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 37.65(C(3′)); 75.19(CH_2O); 83.62(C(2′)); 111.53; 115.75; 116.19; 120.27; 120.82; 121.97; 122.82; 122.88; 126.86; 127.02; 128.52; 134.56; 135.38; 135.44; 140.16; 143.83; 160.26; 161.73; 165.21; 168.51. Anal. calc. for $C_{21}H_{16}FNO_4$: C 69.03, H 4.41, N 3.83; found: C 68.89, H 4.34, N 3.87.

8-{[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-1H-quinolin-2-one (**7c**). Yield: 54%. M.p. 199–200°. UV (0.1N HCl/MeOH): 253 (sh, 4.35), 280(3.86), 334(3.61). UV (MeOH): 252 (sh, 4.31), 280(3.92), 335(3.61). UV (0.1N NaOH/MeOH): 251 (sh, 4.39), 337(3.70). ^{1}H-NMR ($CDCl_3$): 3.25 (*dt*, *J* = 16.8, 3.0, 1H–C(3′)); 3.72 (*dt*, *J* = 16.8, 2.4, 1H–C(3′)); 4.23 4.36 (*AB* type, *J* = 10.3, CH_2O); 5.88 (*t*, *J* = 2.8, 1H, CH_2=C(4′)); 6.49 (*t*, *J* = 2.8, 1H, CH_2=C(4′)); 6.64 (*d*, *J* = 9.6, 1H–C(3)); 6.89–7.45 (*m*, 7 arom. H); 7.69 (*d*, *J* = 9.6, 1H–C(4)); 8.89 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 37.63(C(3′)); 75.11 (CH_2O); 83.61(C(2′)); 111.56; 120.36; 120.94; 122.05; 122.94; 123.12; 126.53; 128.58; 129.27; 134.44; 135.01; 138.12; 140.23; 143.86(C(8)); 161.07(C(2)); 168.48(C(5′)). Anal. calc. for $C_{21}H_{16}ClNO_4$: C 66.06, H 4.22, N 3.67; found: C 65.76, H 4.22, N 3.61.

8-{[2-(4-Bromophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-1H-quinolin-2-one (**7d**). Yield: 57%. M.p. 210–211°. UV (0.1N HCl/MeOH): 253 (sh, 4.29), 281(3.76), 334(3.52). UV (MeOH): 253 (sh, 4.21), 280(3.81), 334(3.54). UV (0.1N NaOH/MeOH): 252 (sh, 4.35), 336(3.63). ^{1}H-NMR ($CDCl_3$): 3.25 (*dt*, *J* = 17.0, 3.0, 1H–C(3′)); 3.72 (*dt*, *J* = 16.8, 2.4, 1H–C(3′)); 4.22, 4.36 (*AB* type, *J* = 10.2, CH_2O); 5.88 (*t*, *J* = 2.0, 1H, CH_2=C(4′)); 6.48 (*t*, *J* = 2.2, 1H, CH_2=C(4′)); 6.64 (*d*, *J* = 9.6, 1H–C(3)); 6.89–7.62 (*m*, 7 arom. H); 7.69 (*d*, *J* = 9.6, 1H–C(4)); 8.90 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 37.57(C(3′)); 75.03(CH_2O); 83.62(C(2′)); 111.56; 120.34; 120.94; 122.03; 122.92; 123.11; 126.80; 128.57; 132.21; 134.39; 138.65; 140.22; 143.84(C(8)); 161.77(C(2)); 168.45(C(5′)). Anal. calc. for. $C_{21}H_{16}BrNO_4$: C 59.17, H 3.78, N 3.29; found: C 58.85, H 3.76, N 3.22.

8-{[2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-(4-phenylphenyl)furan-2-yl]methoxy}-1H-quinolin-2-one (**7e**). Yield: 46%. M.p. 154–155°. UV (0.1N HCl/MeOH): 2.53 (sh, 4.51), 334 (3.42). UV (MeOH): 253 (sh, 4.50), 334(3.43). UV (0.1N NaOH/MeOH): 252 (sh, 4.55), 336(3.53). ^{1}H-NMR ($CDCl_3$): 3.33 (*dt*, *J* = 17.0, 2.8, 1H–C(3′)); 3.75 (*dt*, *J* = 17.0, 2.2, 1H–C(3′)); 4.29, 4.43(*AB* type, *J* = 10.2, CH_2O); 5.88 (*t*, *J* = 2.6, 1H, CH_2=C(4′)); 6.49 (*t*, *J* = 2.6, 1H, CH_2C=C(4′)); 6.64 (*d*, *J* = 9.6, 1H–C(3)); 6.91–7.70 (*m*, 12 arom. H); 7.68 (*d*, *J* = 9.6, 1H–C(4)); 8.93 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 37.69(C(3′)); 75.29(CH_2O); 84.04(C(2′)); 111.60; 120.32; 120.81; 122.04; 122.81; 122.91; 125.53; 127.15; 127.70; 127.90; 128.63; 128.93; 134.81; 138.46; 140.09; 140.21; 141.89; 143.98(C(8)); 161.78(C(2)); 168.77(C(5′)). Anal. calc. for $C_{27}H_{21}NO_4$: C 76.58, H 5.00, N 3.31; found: C 76.34, H 5.01,N 3.27.

8-{[2,3,4,5-Tetrahydro-4-methylidene-2-(4-methoxyphenyl)-5-oxofuran-2-yl]methoxy}-1H-quinolin-2-one (**7f**). Yield: 62%. M.p. 200–201°. UV (0.1N HCl/MeOH): 253(sh, 4.36), 280(3.89), 334(3.59) UV (MeOH): 253(sh, 4.29), 279(3.93), 334(3.58). UV (0.1N NaOH/MeOH): 252(sh, 4.36), 337(3.64). ^{1}H-NMR ($CDCl_3$): 3.28 (*dt*, *J* = 16.8, 3.0, 1H–C(3')); 3.67 (*dt*, *J* = 16.8, 2.6, 1H–C(3')); 3.84 (*s*, MeO); 4.21, 4.36 (*AB* type, *J* = 10.2, 2H, CH_2O); 5.86 (*t*, *J* = 2.6, 1H, CH_2=C(4')); 6.47 (*t*, *J* = 2.8, 1H, CH_2=C(4')); 6.63 (*d*, *J* = 9.6, 1H–C(3)); 6.89–7.45 (*m*, 7 arom. H); 7.68 (*d*, *J* = 9.6, 1H–C(4)); 8.85 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 37.68(C(3')); 55.42(MeO); 75.35(CH_2O); 83.98(C(2')); 111.53; 114.37; 120.28; 120.72; 122.02; 122.60; 122.89; 126.37; 128.59; 131.48; 135.02; 140.19; 143.98(C(8)); 159.92(C(4")); 161.74(C(2)); 168.84(C(5')). Anal. calc. for $C_{22}H_{19}NO_5$: C 70.02, H 5.09, N 3.71; found: C 69.81, H 5.05, N 3.68.

Pharmacological Evaluation. Aortic Constriction. 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 org. 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 94% 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; constrictions 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 in [23]. 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* [24] 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. at 100% aggregation. The inhibitory concentration for 50% aggregation (IC_{50}) was calculated from computerization of *CA-Cricket Graph III* for the five or six dose-effect levels.

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