

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

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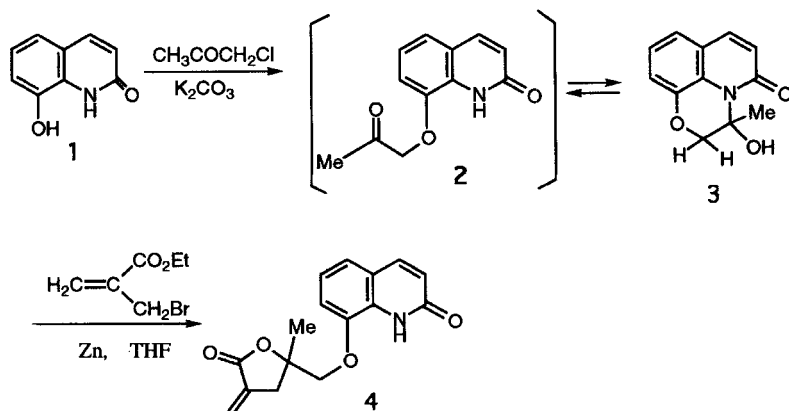
O-Alkylation of 8-hydroxy-1*H*-quinolin-2-one (**1**) afforded 8-(2-oxopropoxy)-1*H*-quinolin-2-one (**2**) which was immediately cyclized to form the tricyclic 2,3-dihydro-3-hydroxy-3-methyl-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-5-one (**3**). The *Reformatsky*-type condensation of **3** furnished 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, Ca²⁺-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 anthelmintic 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**

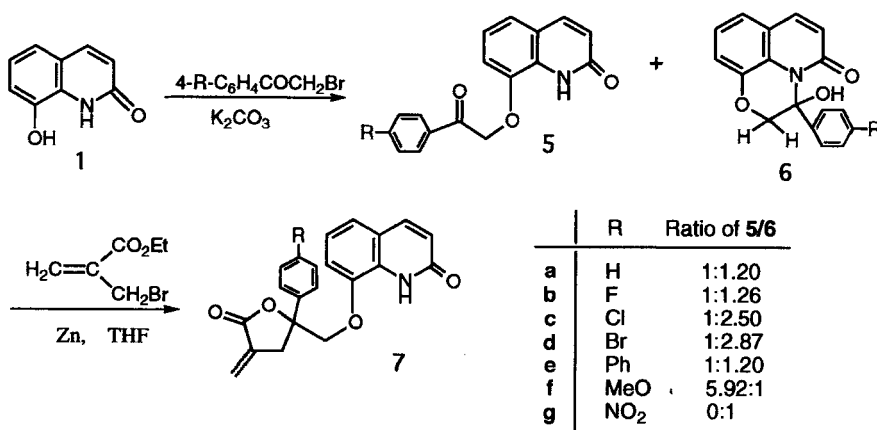
with K_2CO_3 and chloroacetone to afford the expected 8-(2-oxopropoxy)-1*H*-quinolin-2-one (**2**) were obscure. The ^{13}C -NMR of the sole product isolated in this reaction showed a quaternary C resonance at 84.48 ppm, and no peak was observed around 190 ppm, indicating the absence of the carbonyl 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 1H -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 1H , ^{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 interconvertible, 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 1H -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 interconvertible.

Scheme 2



The antiplatelet activities of (oxoquinolinylloxy)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 μ M), collagen (Col, 10 μ g/ml), and platelet-activating factor (PAF, 2 nM). The final concentration of compounds was 100 μ g/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 μ M)	Col (10 μ g/ml)	PAF (2 nM)
Control	91.7 $\pm$ 1.0	86.4 $\pm$ 1.0	89.2 $\pm$ 1.4	88.2 $\pm$ 0.8
4	74.7 $\pm$ 1.4 ^{b)}	0 ^{b)} c)	0	31.2 $\pm$ 11.1 ^{b)}
7a	70.9 $\pm$ 1.8 ^{b)}	0	0	27.8 $\pm$ 1.4 ^{b)}
7b	0	0	0	0
7c	0	0	0	0
7d	24.8 $\pm$ 13.2 ^{b)}	0	0	0
7e	76.7 $\pm$ 3.4 ^{b)}	0	0	66.8 $\pm$ 6.1 ^{b)}
7f	77.4 $\pm$ 0.6 ^{b)}	0	0	26.9 $\pm$ 12.5 ^{b)}
Aspirin	91.9 $\pm$ 1.4	0	85.4 $\pm$ 3.9	90.5 $\pm$ 1.2

^{a)} Platelets were preincubated with 1H-quinolin-2-ones (100 μ M/ml) or DMSO (0.5%, control) at 37° for 3 min, and the inducer was then added. Percentages of aggregation are presented as means $\pm$ 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 1*H*-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 1*H*-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 $\pm$ 5.2	100 $\pm$ 5.0	100 $\pm$ 2.8
4	22.1 $\pm$ 2.7	40.6 $\pm$ 0.4	24.1 $\pm$ 3.7
7a	95.1 $\pm$ 0.1	92.7 $\pm$ 9.2	52.7 $\pm$ 6.9
7b	95.9 $\pm$ 2.9	77.1 $\pm$ 2.1	44.6 $\pm$ 4.8
7c	84.3 $\pm$ 4.0	23.7 $\pm$ 2.8	26.7 $\pm$ 2.1
7d	92.7 $\pm$ 1.6	58.3 $\pm$ 3.7	64.9 $\pm$ 0.9
7e	102.5 $\pm$ 1.8	101.2 $\pm$ 0.8	98.5 $\pm$ 3.3
7f	93.9 $\pm$ 0.9	44.0 $\pm$ 3.1	42.0 $\pm$ 0.9
Nifedipine	0	98.7 $\pm$ 0.7	96.5 $\pm$ 2.1
Prazosin	100 $\pm$ 2.0	0	0

^{a)} Rat aorta were preincubated with 1*H*-quinolin-2-ones (100 $\mu g/ml$), DMSO (0.5%, control), nifedipine (1 $\mu g/ml$), or prazosin (1 $\mu g/ml$) 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 $\pm$ 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. ¹H- and ¹³C-NMR Spectra: Varian-Gemini-200 spectrometer, chemical

shifts δ in ppm with SiMe₄ 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), K₂CO₃ (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 CH₂Cl₂/Et₂O 1:10 to afford **3** (0.91 g, 84%). M.p. 192–193°. ¹H-NMR (CDCl₃): 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). ¹³C-NMR (CDCl₃): 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 C₁₂H₁₁NO₃ · 0.125 H₂O: 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. ¹H-NMR (DMSO): 5.74 (s, CH₂O) (**5a**); 4.19, 4.28 (AB type, $J = 11.4$, 2H–C(2)) (**6a**). ¹³C-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 C₁₇H₁₃NO₃: 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. ¹H-NMR (DMSO): 5.73 (s, CH₂O) (**5b**); 4.18, 4.26 (AB type, $J = 11.6$, 2H–C(2)) (**6b**). ¹³C-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 C₁₇H₁₂FNO₃: 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. ¹H-NMR (DMSO): 5.72 (s, CH₂O) (**5c**); 4.17, 4.24 (AB type, $J = 11.6$, 2H–C(2)) (**6c**). ¹³C-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 C₁₇H₁₂ClNO₃: 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. ¹H-NMR (DMSO): 5.71 (s, CH₂O) (**5d**); 4.16, 4.23 (AB type, $J = 11.6$, 2H–C(2)) (**6d**). ¹³C-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 C₁₇H₁₂BrNO₃: 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'-phenylacetophenone by the same procedure as for **3** in 98% yield. ¹H-NMR (CDCl₃): 5.78 (s, CH₂O) (**5e**); 4.24, 4.32 (AB type, $J = 11.4$, 2H–C(2)) (**6e**). ¹³C-NMR (CDCl₃): 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 C₂₃H₁₇NO₃: 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. ¹H-NMR (CDCl₃): 3.88 (s, MeO); 5.40 (s, CH₂O) (**5f**); 3.76 (s, MeO); 4.31, 4.35 (AB type, $J = 10.8$, 2H–C(2)) (**6f**). ¹³C-NMR (CDCl₃): 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 C₁₈H₁₅NO₄: 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°. ¹H-NMR (CDCl₃): 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). ¹³C-NMR (CDCl₃): 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 C₁₇H₁₂N₂O₅: 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 N₂ 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 $\times$ 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 $\text{CH}_2\text{Cl}_2/\text{acetone}$ 20:1. The proper fractions were combined and evaporated to furnish a residual solid which was crystallized from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 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). $^1\text{H-NMR}$ (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, $\text{CH}_2=\text{C}(4')$); 6.39 (t, $J = 2.8$, 1H, $\text{CH}_2=\text{C}(4')$); 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). $^{13}\text{C-NMR}$ (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 $\text{C}_{16}\text{H}_{15}\text{NO}_4$: 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). $^1\text{H-NMR}$ (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, $\text{CH}_2=\text{C}(4')$); 6.48 (t, $J = 3.0$, 1H, $\text{CH}_2=\text{C}(4')$); 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). $^{13}\text{C-NMR}$ (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 $\text{C}_{21}\text{H}_{17}\text{NO}_4$: 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). $^1\text{H-NMR}$ (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, $\text{CH}_2=\text{C}(4')$); 6.48 (t, $J = 2.6$, 1H, $\text{CH}_2=\text{C}(4')$); 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). $^{13}\text{C-NMR}$ (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 $\text{C}_{21}\text{H}_{16}\text{FNO}_4$: 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). $^1\text{H-NMR}$ (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, $\text{CH}_2=\text{C}(4')$); 6.49 (t, $J = 2.8$, 1H, $\text{CH}_2=\text{C}(4')$); 6.64 (d, $J = 9.6$, 1H–C(3)); 6.89–7.45 (m, 7 arom. H); 7.69 (d, $J = 9.6$, H–C(4)); 8.89 (br. s, NH). $^{13}\text{C-NMR}$ (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 $\text{C}_{21}\text{H}_{16}\text{ClNO}_4$: 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). $^1\text{H-NMR}$ (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, $\text{CH}_2=\text{C}(4')$); 6.48 (t, $J = 2.2$, 1H, $\text{CH}_2=\text{C}(4')$); 6.64 (d, $J = 9.6$, 1H–C(3)); 6.89–7.62 (m, 7 arom. H); 7.69 (d, $J = 9.6$, H–C(4)); 8.90 (br. s, NH). $^{13}\text{C-NMR}$ (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 $\text{C}_{21}\text{H}_{16}\text{BrNO}_4$: 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): 253 (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). $^1\text{H-NMR}$ (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, $\text{CH}_2=\text{C}(4')$); 6.49 (t, $J = 2.6$, 1H, $\text{CH}_2=\text{C}(4')$); 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). $^{13}\text{C-NMR}$ (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 $\text{C}_{27}\text{H}_{21}\text{NO}_4$: C 76.58, H 5.00, N 3.31; found: C 76.34, H 5.01, N 3.27.

8- $\{[2,3,4,5\text{-Tetrahydro-4-methylidene-2-(4-methoxyphenyl)-5-oxofuran-2-yl]methoxy\}$ -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). $^1\text{H-NMR}$ (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, $\text{CH}_2=\text{C}(4'')$); 6.47 (*t*, $J = 2.8$, 1H, $\text{CH}_2=\text{C}(4'')$); 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). $^{13}\text{C-NMR}$ (CDCl_3): 37.68(C(3'')); 55.42(MeOH); 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 $\text{C}_{22}\text{H}_{19}\text{NO}_5$: 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 $90 \times g$ and r.t. Platelet suspension was prepared from this EDTA-anti-coagulated, 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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