Synthesis and Antiplatelet-Activity Evaluation of α-Methylidene-γ-butyrolactones Bearing 3,4-Dihydroquinolin-2(1*H*)-one Moieties

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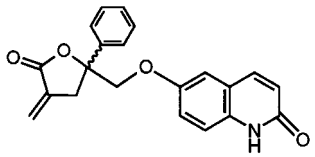
In continuation of our search for potent antiplatelet agents, we have synthesized and evaluated several α-methylidene-γ-butyrolactones bearing 3,4-dihydroquinolin-2(1*H*)-one moieties. *O*-Alkylation of 3,4-dihydro-8-hydroxyquinolin-2(1*H*)-one (**1**) with chloroacetone under basic conditions afforded 3,4-dihydro-8-(2-oxopropoxy)quinolin-2(1*H*)-one (**2a**) and tricyclic 2,3,6,7-tetrahydro-3-hydroxy-3-methyl-5*H*-pyrido[1,2,3-*de*][1,4]-benzoxazin-5-one (**3a**) in a ratio of 1:2.84. Their *Reformatsky*-type condensation with ethyl 2-(bromomethyl)-prop-2-enoate furnished 3,4-dihydro-8-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-quinolin-2(1*H*)-one (**4a**), which shows antiplatelet activity, in 70% yield. Its 2′-Ph derivatives, and 6- and 7-substituted analogs were also obtained from the corresponding 3,4-dihydroquinolin-2(1*H*)-ones *via* alkylation and the *Reformatsky*-type condensation. Of these compounds, 3,4-dihydro-7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinolin-2(1*H*)-one (**10b**) was the most active against arachidonic acid (AA) induced platelet aggregation with an IC_{50} of 0.23 μM. For the inhibition of platelet-activating factor (PAF) induced aggregation, 6-{[2-(4-fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1*H*)-one (**9c**) was the most potent with an IC_{50} value of 1.83 μM.

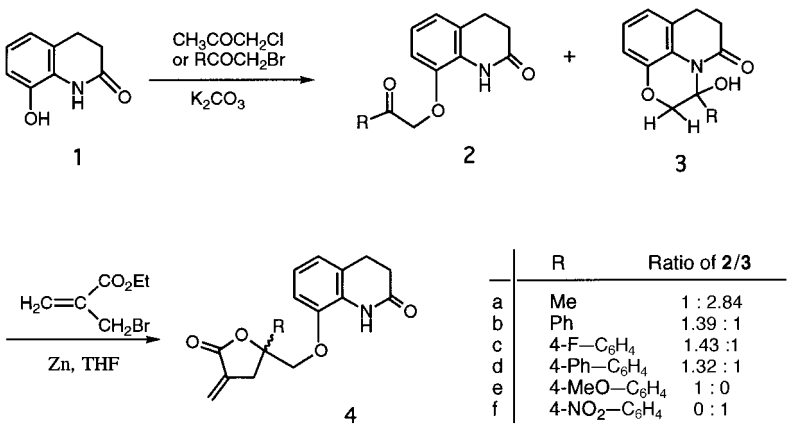
Introduction. – Recently, we have synthesized and evaluated the cardiovascular activities of certain α-methylidene-γ-butyrolactones bearing heterocycles such as coumarins, flavones, xanthones, quinolines, and quinolin-2(1*H*)-ones [1–3]. Among these heterocycles, coumarins exhibited the most potent inhibitory activities on the high-K^+-medium, Ca^{2+}-induced vasoconstriction, and the norepinephrine-induced phasic and tonic vasoconstrictions, while quinolin-2(1*H*)-ones proved to be the most active against platelet aggregation [2][3]. One of the most potent antiplatelet agents, 6-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinolin-2(1*H*)-one (CCT-62), has been proved to be an inhibitor of phosphodiesterases, and its antiplatelet effect is mainly mediated by elevation of cyclic-AMP levels [4]. In the continuation of our search for more potent antiplatelet agents, we report herein the preparation, antiplatelet-activity evaluation, and structure-activity relationships of several α-methylidene-γ-butyrolactones bearing 3,4-dihydroquinolin-2(1*H*)-one moieties, saturated analogs of CCT-62. The cardiovascular and neuroprotective activities of certain quinolin-2(1*H*)-ones and 3,4-dihydroquinolin-2(1*H*)-ones substituted with various side chains have been reported earlier [5–9].



CCT-62

Results and Discussion. – The preparation of 3,4-dihydro-8-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1*H*)-one (**4a**) and its 2′-Ph derivatives is illustrated in *Scheme 1.* 3,4-Dihydro-8-hydroxyquinolin-2(1*H*)-one (**1**)

Scheme 1

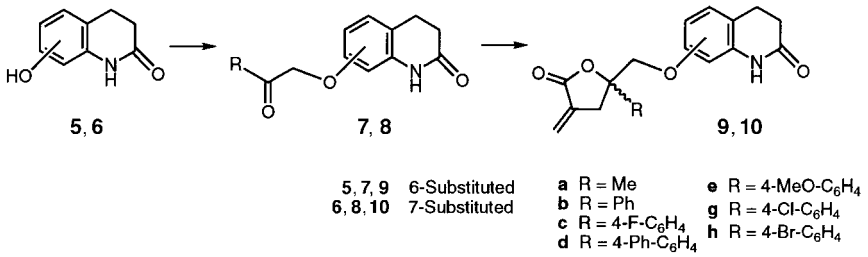


	R	Ratio of **2**/**3**
a	Me	1 : 2.84
b	Ph	1.39 : 1
c	4-F–C_6H_4	1.43 :1
d	4-Ph–C_6H_4	1.32 : 1
e	4-MeO–C_6H_4	1 : 0
f	4-NO_2–C_6H_4	0 : 1

was treated with chloroacetone under basic conditions to afford 3,4-dihydro-8-(2-oxopropoxy)quinolin-2(1*H*)-one (**2a**) and 2,3,6,7-tetrahydro-3-hydroxy-3-methyl-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one (**3a**) in a ratio of 1:2.84 (75% yield). Compounds **2a** and **3a** are interconvertible: when the mixture was subjected to a *Reformatsky*-type condensation, **4a** was obtained in 70% yield. Accordingly, **1** was reacted with 2-bromoacetophenone, 2-bromo-4′-fluoroacetophenone, and 2-bromo-4′-phenylacetophenone, respectively, under the same reaction conditions to give **2b**–**d** and **3b**–**d** in ratios of 1.32:1 to 1.43:1, based on the integration of CH_2O ^{1}H-NMR signals. An electron-donating substituent (R = 4-MeO–C_6H_4) retarded ring cyclization, and only **2e** was isolated, while an electron-withdrawing substituent (R = 4-NO_2–C_6H_4) favored the formation of **3f**. That alkylation of **1** occurred at HO–C(8) rather than at N(1) or C(2)=O was shown by the ^{1}H,^{13}C-HETCOR spectrum, which reveals the correlation of CH_2(1′) protons (5.53 ppm, *singlet*) with C-atoms resonating at 71.50 (^1J) and 144.87 (^3J), corresponding to C(1′) and C(8). The structure of **3f** was confirmed by the ^{1}H-NMR spectrum in which the CH_2(2) protons are magnetically nonequivalent, and two distinct *doublets* (J = 11.4 Hz) at 3.80 and 3.99 ppm (*AB* type) were observed. Furthermore, the ^{1}H,^{13}C-HETCOR spectrum revealed the correlation of CH_2(2) protons with C-atoms resonating at 74.35 (^1J), 83.04 (^2J), and 144.53 (^3J) ppm, corresponding to C(2), C(3), and C(11), respectively. *Reformatsky*-type condensation of **2b**–**d** and **3b**–**d** afforded 3,4-dihydro-8-[(2,3,4,5-tetrahydro-4-meth-

ylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1*H*)-ones **4b**–**d**, respectively, in 65–68% yield, indicating that **2b**–**d** and the corresponding tricyclic counterparts **3b**–**d** are interconvertible. Accordingly, **4e** and **4f** were prepared from **2e** and **3f**, respectively, *via Reformatsky*-type condensation. The 6- and 7-substituted analogs **9a**–**h** and **10a**–**d** were also obtained from the corresponding 3,4-dihydroquinolin-2(1*H*)-ones **5** and **6** [10] *via* alkylation and *Reformatsky*-type condensation (*Scheme 2*).

Scheme 2



The antiplatelet activities of α-methylidene-γ-butyrolactones with 3,4-dihydroquinolin-2(1*H*)-one moieties 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*.

Table 1. *Effect of 3,4-Dihydroquinolin-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	90.5 ± 0.8	87.1 ± 0.1	90.0 ± 0.7	88.7 ± 0.9
4a	69.7 ± 3.5[b])	0[b])	0	68.5 ± 6.3[b])
4b[c])	0	0	0	0
4d	75.7 ± 2.2[b])	0	0	32.6 ± 6.0[b])
9a	2.9 ± 1.2[b])	0	0	0
9d	53.6 ± 4.8[b])	0	5.5 ± 2.3[b])	0
9e	6.2 ± 5.0[b])	0	0	0
10a	8.9 ± 7.2[b])	0	0	7.8 ± 3.6[b])
Aspirin	91.9 ± 1.4	0	85.4 ± 3.9	90.5 ± 1.2

[a]) Platelets were preincubated with 3,4-dihydroquinolin-2(1*H*)-ones (100 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]) Significantly different from control value at $p < 0.001$. [c]) Platelet aggregation induced by the four inducers was completely inhibited by **4b**, **4c**, **4e**, **4f**, **9b**, **9c**, **9g**, **9h**, **10b**–**d**.

All of the tested compounds were found to completely inhibit platelet aggregation induced by AA and Col. Compounds **4b**, **4c**, **4e**, **4f**, **9b**–**c**, **9g**, **9h**, and **10b**–**d** also exhibited good inhibitory activity against Thr- and PAF-induced aggregation. The inhibitory concentrations for 50% aggregation (IC_{50}) induced by AA and PAF are given in *Table 2*.

Table 2. IC_{50} *Values* ([μM]) *of 3,4-Dihydroquinolin-2(1*H*)-ones on the Platelet Aggregation Induced by AA and PAF*

a) *8-Substituted 3,4-dihydroquinolin-2(1*H*)-ones*

	4a	**4b**	**4c**	**4d**	**4e**	**4f**
AA	35.73	4.39	3.75	7.73	8.20	3.40
PAF	> 100	21.7	15.6	78.03	35.46	8.63

b) *6-Substituted 3,4-dihydroquinolin-2(1*H*)-ones*

	9a	**9b**	**9c**	**9d**	**9e**	**9g**	**9h**
AA	1.64	0.57	0.60	3.29	1.01	0.57	0.63
PAF	13.29	2.33	1.83	6.23	7.24	2.30	2.30

c) *7-Substituted 3,4-dihydroquinolin-2(1*H*)-ones*

	10a	**10b**	**10c**	**10d**
AA	2.31	0.23	0.28	1.91
PAF	51.37	6.13	3.54	11.44

Compound **4a**, with a Me substituent at C(2′) of the lactone moiety, was less active against AA- and PAF-induced aggregation than its PhC(2′)-lactone counterparts (**4b**–**f**). Compounds **4c** and **4f**, which possess electron-withdrawing substituents (F and NO_2, resp.), were found to be more potent than that of onyl-Ph-substituted **4b**, while **4d** and **4e**, which possess an electron-donating substituent (Ph and MeO, resp.), were even less active. Comparison of the positional isomers showed that 6- and 7-substituted derivatives **9a**–**d** and **10a**–**d** are more potent than the respective 8-substituted isomers **4a**–**d** in inhibiting both AA- and PAF-induced aggregations.

In summary, the lower inhibitory potency of **4d**, **9d**, and **10d** implies that an electron-donating aryl substituent at C(2′) of the lactone moiety reduces the antiplatelet activity of compounds of this type. For AA-induced platelet aggregation, the inhibitory potency decreases in the order 7-substituted > 6-substituted > 8-substituted. For PAF-induced platelet aggregation, the inhibitory potency decreases in the order 6-substituted > 7-substituted > 8-substituted. All of these α-methylidene-γ-butyrolactones bearing 3,4-dihydroquinolin-2(1*H*)-ones are more potent than their respective unsaturated counterparts [3].

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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.: *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 calc. values.

*3,4-Dihydro-8-(2-oxopropoxy)quinolin-2(1*H*)-one* (**2a**) *and 2,3,6,7-Tetrahydro-3-hydroxy-3-methyl-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one* (**3a**). *3,4-Dihydro-8-hydroxyquinolin-2(1*H*)-one* (**1**, 1.63 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., 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 purified by column chromatography (CC) (silica gel; hexane/AcOEt 1:1), affording a residual solid which was

crystallized from CH_2Cl_2/Et_2O 1:10: **2a** and **3a** (1:2.84; 1.64 g, 75%). ^{1}H-NMR (DMSO): 4.79 (*s*, 2 H–C(1′) of **2a**); 3.78, 3.91 (2*d*, *J* = 11.2, *AB* type, 2 H–C(2) of **3a**). ^{13}C-NMR (DMSO): 73.44 (C(1′)); 169.60 (C(2)); 204.71 (C(2′) of **2a**); 73.51 (C(2)); 82.12 (C(3)); 169.53 (C(5) of **3a**). Anal. calc. for $C_{12}H_{13}NO_3$: C 65.74, H 5.98, N 6.39; found: C 65.73, H 6.02, N 6.42.

*3,4-Dihydro-8-(2-oxo-2-phenylethoxy)quinolin-2(1*H*)-one* (**2b**) *and 2,3,6,7-Tetrahydro-3-hydroxy-3-phenyl-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one* (**3b**). A mixture of **2b** and **3b** (1.39:1) was obtained from **1** and 2-bromoacetophenone, according to the procedure described above, in 74% yield. ^{1}H-NMR (DMSO): 5.60 (*s*, 2 H–C(1′) of **2b**); 3.80, 3.96 (2*d*, *J* = 11.6, *AB* type, 2 H–C(2) of **3b**). ^{13}C-NMR (DMSO): 71.70 (C(1′)); 169.54 (C(2)); 194.98 (C(2′) of **2b**); 74.82 (C(2)); 84.05 (C(3)); 168.74 (C(5) of **3b**). Anal. calc. for $C_{17}H_{15}NO_3$: C 72.58, H 5.38, N 4.98; found: C 72.61, H 5.37, N 4.97.

*8-[2-(4-Fluorophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**2c**) *and 3-(4-Fluorophenyl)-2,3,6,7-tetrahydro-3-hydroxy-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one* (**3c**). A mixture of **2c** and **3c** (1.43:1) was obtained from **1** and 2-bromo-4′-fluoroacetophenone, according to the procedure described above, in 80% yield. ^{1}H-NMR (DMSO): 5.58 (*s*, 2 H–C(1′) of **2c**); 3.80, 3.95 (2*d*, *J* = 11.4, *AB* type, 2 H–C(2) of **3c**). ^{13}C-NMR (DMSO): 71.62 (C(1′)); 169.56 (C(2)); 193.66 (C(2′) of **2c**); 74.75 (C(2)); 83.61 (C(3)); 168.66 (C(5) of **3c**). Anal. calc. for $C_{17}H_{14}FNO_3$: C 68.22, H 4.71, N 4.68; found: C 68.07, H 4.72, N 4.66.

*8-[2-(1,1′-Biphenyl-4-yl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**2d**) *and 3-(1,1′-Biphenyl-4-yl)-2,3,6,7-tetrahydro-3-hydroxy-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one* (**3d**). A mixture of **2d** and **3d** (1.32:1) was obtained from **1** and 2-bromo-4′-phenylacetophenone, according to the procedure described above, in 84% yield. ^{1}H-NMR (DMSO): 5.64 (*s*, 2 H–C(1′) of **2d**); 3.85, 4.00 (2*d*, *J* = 11.2, *AB* type, 2 H–C(2) of **3d**). ^{13}C-NMR (DMSO): 71.72 (C(1′)); 169.51 (C(2)); 194.53 (C(2′) of **2d**); 74.75 (C(2)); 83.89 (C(3)); 168.71 (C(5) of **3d**). Anal. calc. for $C_{23}H_{19}NO_3 \cdot H_2O$: C 73.58, H 5.64, N 3.73; found: C 73.33, H 5.72, N 3.74.

*3,4-Dihydro-8-[2-(4-methoxyphenyl)-2-oxoethoxy]quinolin-2(1*H*)-one* (**2e**). Compound **2e** was obtained from **1** and 2-bromo-4′-methoxyacetophenone, according to the procedure described above, in 77% yield. M.p. 169–170°. ^{1}H-NMR (DMSO): 2.45–2.52 (*m*, 2 H–C(3)); 2.85–2.93 (*m*, 2 H–C(4)); 3.86 (*s*, MeO); 5.53 (*s*, 2 H–C(1′)); 6.84–8.04 (*m*, 7 arom. H); 8.95 (br. *s*, NH). ^{13}C-NMR (DMSO): 24.84 (C(4)); 30.41 (C(3)); 55.61 (MeO); 71.50 (C(1′)); 112.06; 114.07; 120.56; 122.06; 124.68; 127.07; 127.49; 130.28; 144.87 (C(8)); 163.65; 169.51 (C(2)); 193.31 (C(2′)). Anal. calc. for $C_{18}H_{17}NO_4$: C 69.44, H 5.51, N 4.50; found: C 69.11, H 5.48, N 4.48.

*2,3,6,7-Tetrahydro-3-hydroxy-3-(4-nitrophenyl)-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one* (**3f**). Compound **3f** was obtained from **1** and 2-bromo-4′-nitroacetophenone, according to the procedure described above, in 74% yield. M.p. 183–184°. ^{1}H-NMR (DMSO): 2.50–2.56 (*m*, 2 H–C(6)); 2.56–3.08 (*m*, 2 H–C(7)); 3.80, 3.99 (2*d*, *J* = 11.4, *AB* type, 2 H–C(2)); 6.91–8.22 (*m*, 7 arom. H); 7.14 (*s*, OH). ^{13}C-NMR (DMSO): 24.18 (C(7)); 31.86 (C(6)); 74.35 (C(2)); 83.04 (C(3)); 115.41; 121.38; 122.95; 123.24; 125.94; 126.30; 126.52; 144.53 (C(11)); 146.70; 149.44; 168.21 (C(5)). Anal. calc. for $C_{17}H_{14}N_2O_5$: C 62.58, H 4.32, N 8.58; found: C 62.40, H 4.36, N 8.50.

*3,4-Dihydro-6-(2-oxopropoxy)quinolin-2(1*H*)-one* (**7a**). Compound **7a** was obtained from **5a** and chloroacetone, according to the procedure described above, in 78% yield. M.p. 125–126°. ^{1}H-NMR (DMSO): 2.14 (*s*, Me); 2.36–2.44 (*m*, 2 H–C(3)); 2.79–2.86 (*m*, 2 H–C(4)); 4.72 (*s*, 2 H–C(1′)); 6.66–6.79 (*m*, 3 arom. H); 9.92 (br. *s*, NH). ^{13}C-NMR (DMSO): 25.10 (C(4)); 26.27 (Me); 30.35 (C(3)); 72.50 (C(1′)); 113.03; 114.10; 115.81; 124.97; 132.14; 153.02 (C(6)); 169.96 (C(2)); 204.57 (C(2′)). Anal. calc. for $C_{12}H_{13}NO_3$: C 65.74, H 5.98, N 6.39; found: C 65.61, H 5.98, N 6.41.

*3,4-Dihydro-6-(2-oxo-2-phenylethoxy)quinolin-2(1*H*)-one* (**7b**). Compound **7b** was obtained from **5b** and 2-bromoacetophenone, according to the procedure described above, in 85% yield. M.p. 111–112°. ^{1}H-NMR (DMSO): 2.37–2.44 (*m*, 2 H–C(3)); 2.79–2.86 (*m*, 2 H–C(4)); 5.49 (*s*, 2 H–C(1′)); 6.77–8.04 (*m*, 8 arom. H); 9.93 (br. *s*, NH). ^{13}C-NMR (DMSO): 25.14 (C(4)); 30.39 (C(3)); 70.53 (C(1′)); 113.27; 114.27; 115.83; 124.93; 127.94; 128.93; 132.14; 133.87; 134.50; 153.25 (C(6)); 169.99 (C(2)); 194.91 (C(2′)). Anal. calc. for $C_{17}H_{15}NO_3$: C 72.58, H 5.38, N 4.98; found: C 72.44, H 5.42, N 4.98.

*6-[2-(4-Fluorophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**7c**). Compound **7c** was obtained from **5c** and 2-bromo-4′-fluoroacetophenone, according to the procedure described above, in 94% yield. M.p. 214–215°. ^{1}H-NMR (DMSO): 2.35–2.43 (*m*, 2 H–C(3)); 2.78–2.85 (*m*, 2 H–C(4)); 5.46 (*s*, 2 H–C(1′)); 6.75–8.12 (*m*, 7 arom. H); 9.91 (br. *s*, NH). ^{13}C-NMR (DMSO): 25.12 (C(4)); 30.37 (C(3)); 70.47 (C(1′)); 113.27; 114.26; 115.75; 115.81; 116.18; 124.93; 130.93; 131.12; 131.24; 131.29; 132.17; 153.19 (C(6)); 162.87; 167.89; 169.97 (C(2)); 193.57 (C(2′)). Anal. calc. for $C_{17}H_{14}FNO_3$: C 68.22, H 4.71, N 4.68; found: C 68.02, H 4.72, N 4.71.

*6-[2-(1,1′-Biphenyl-4-yl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**7d**). Compound **7d** was obtained from **5d** and 2-bromo-4′-phenylacetophenone, according to the procedure described above, in 87% yield. M.p.

182–183°. ^{1}H-NMR (DMSO): 2.36–2.43 (*m*, 2 H–C(3)); 2.78–2.86 (*m*, 2 H–C(4)); 5.51 (*s*, 2 H–C(1′)); 6.77–8.11 (*m*, 12 arom. H); 9.93 (br. *s*, NH). ^{13}C-NMR (DMSO): 25.14 (C(4)); 30.38 (C(3)); 70.56 (C(1′)); 113.27; 114.26; 115.83; 124.94; 127.07; 127.10; 128.60; 128.71; 129.22; 132.14; 133.29; 138.90; 145.19; 153.25 (C(6)); 169.98 (C(2)); 194.45 (C(2′)). Anal. calc. for $C_{23}H_{19}NO_3$: C 77.29, H 5.36, N 3.92; found: C 77.09, H 5.41, N 3.90.

*3,4-Dihydro-6-[2-(4-methoxyphenyl)-2-oxoethoxy]quinolin-2(1*H*)-one* (**7e**). Compound **7e** was obtained from **5e** and 2-bromo-4′-methoxyacetophenone, according to the procedure described above, in 96% yield. M.p. 179–180°. ^{1}H-NMR (DMSO): 2.38–2.42 (*m*, 2 H–C(3)); 2.80–2.84 (*m*, 2 H–C(4)); 3.86 (MeO); 5.40 (*s*, 2 H–C(1′)); 6.75–8.01 (*m*, 7 arom. H); 9.91 (br. *s*, NH). ^{13}C-NMR (DMSO): 25.11 (C(4)); 30.34 (C(3)); 55.65 (MeO); 70.28 (C(1′)); 113.21; 114.09; 114.23; 115.77; 124.87; 127.41; 130.28; 132.07; 153.29 (C(6)); 163.59; 169.91 (C(2)); 193.18 (C(2′)). Anal. calc. for $C_{18}H_{17}NO_4$: C 69.44, H 5.51, N 4.50; found: C 69.16, H 5.56, N 4.43.

*6-[2-(4-Chlorophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**7g**). Compound **7g** was obtained from **5g** and 2-bromo-4′-chloroacetophenone, according to the procedure described above, in 76% yield. M.p. 212–213°. ^{1}H-NMR (DMSO): 2.37–2.44 (*m*, 2 H–C(3)); 2.79–2.86 (*m*, 2 H–C(4)); 5.48 (*s*, 2 H–C(1′)); 6.77–8.05 (*m*, 7 arom. H); 9.93 (br. *s*, NH). ^{13}C-NMR (DMSO): 25.12 (C(4)); 30.38 (C(3)); 70.53 (C(1′)); 113.27; 114.26; 115.82; 124.94; 129.03; 129.91; 132.19; 133.17; 138.74; 153.15 (C(6)); 169.98 (C(2)); 194.04 (C(2′)). Anal. calc. for $C_{17}H_{14}ClNO_3$: C 64.66, H 4.47, N 4.44; found: C 64.47, H 4.45, N 4.44.

*6-[2-(4-Bromophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**7h**). Compound **7h** was obtained from **5h** and 2-bromo-4′-bromoacetophenone, according to the procedure described above, in 75% yield. M.p. 198–199°. ^{1}H-NMR (DMSO): 2.36–2.44 (*m*, 2 H–C(3)); 2.79–2.86 (*m*, 2 H–C(4)); 5.47 (*s*, 2 H–C(1′)); 6.76–7.97 (*m*, 7 arom. H); 9.92 (br. *s*, NH). ^{13}C-NMR (DMSO): 25.13 (C(4)); 30.38 (C(3)); 70.51 (C(1′)); 113.28; 114.27; 115.83; 124.96; 127.94; 130.00; 131.99; 132.20; 133.49; 153.15 (C(6)); 169.99 (C(2)); 194.27 (C(2′)). Anal. calc. for $C_{17}H_{14}BrNO_3$: C 56.68, H 3.92, N 3.89; found: C 56.48, H 3.92, N 3.87.

*3,4-Dihydro-7-(2-oxopropoxy)quinolin-2(1*H*)-one* (**8a**). Compound **8a** was obtained from **6a** and chloroacetone, according to the procedure described above, in 72% yield. M.p. 136–137°. ^{1}H-NMR (DMSO): 2.14 (*s*, Me); 2.38–2.45 (*m*, 2 H–C(3)); 2.75–2.82 (*m*, 2 H–C(4)); 4.71 (*s*, 2 H–C(1′)); 6.40–7.06 (*m*, 3 arom. H); 9.97 (br. *s*, NH). ^{13}C-NMR (DMSO): 23.97 (C(4)); 26.20 (Me); 30.67 (C(3)); 72.18 (C(1′)); 101.92; 107.30; 116.15; 128.38; 139.21; 156.95 (C(7)); 170.31 (C(2)); 204.19 (C(2′)). Anal. calc. for $C_{12}H_{13}NO_3$: C 65.74, H 5.98, N 6.39; found: C 65.74, H 6.03, N 6.36.

*3,4-Dihydro-7-(2-oxo-2-phenylethoxy)quinolin-2(1*H*)-one* (**8b**). Compound **8b** was obtained from **6b** and 2-bromoacetophenone, according to the procedure described above, in 84% yield. M.p. 181–182°. ^{1}H-NMR (DMSO): 2.37–2.45 (*m*, 2 H–C(3)); 2.75–2.82 (*m*, 2 H–C(4)); 5.50 (*s*, 2 H–C(1′)); 6.45–8.04 (*m*, 8 arom. H); 9.96 (br. *s*, NH). ^{13}C-NMR (DMSO): 23.97 (C(4)); 30.67 (C(3)); 70.18 (C(1′)); 102.01; 107.48; 116.04; 127.81; 128.29; 128.82; 133.77; 134.37; 139.16; 157.14 (C(7)); 170.22 (C(2)); 194.61 (C(2′)). Anal. calc. for $C_{17}H_{15}NO_3 \cdot 0.125\ H_2O$: C 72.01, H 5.42, N 4.94; found: C 72.01, H 5.42, N 4.82.

*7-[2-(4-Fluorophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**8c**). Compound **8c** was obtained from **6c** and 2-bromo-4′-fluoroacetophenone, according to the procedure described above, in 78% yield. M.p. 190–191°. ^{1}H-NMR (DMSO): 2.38–2.45 (*m*, 2 H–C(3)); 2.75–2.82 (*m*, 2 H–C(4)); 5.48 (*s*, 2 H–C(1′)); 6.45–8.14 (*m*, 7 arom. H); 9.96 (br. *s*, NH). ^{13}C-NMR (DMSO): 24.01 (C(4)); 30.71 (C(3)); 70.16 (C(1′)); 102.08; 107.52; 115.72; 116.15; 128.35; 130.87; 131.06; 131.14; 131.20; 139.19; 157.14 (C(7)); 162.84; 167.86; 170.32 (C(2)); 193.36 (C(2′)). Anal. calc. for $C_{17}H_{14}FNO_3$: C 68.22, H 4.71, N 4.68; found: C 68.08, H 4.76, N 4.67.

*7-[2-(1,1′-Biphenyl-4-yl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one* (**8d**). Compound **8d** was obtained from **6d** and 2-bromo-4′-phenylacetophenone, according to the procedure described above, in 80% yield. M.p. 187–188°. ^{1}H-NMR (DMSO): 2.38–2.45 (*m*, 2 H–C(3)); 2.75–2.83 (*m*, 2 H–C(4)); 5.53 (*s*, 2 H–C(1′)); 6.47–8.12 (*m*, 12 arom. H); 9.97 (br. *s*, NH). ^{13}C-NMR (DMSO): 24.01 (C(4)); 30.70 (C(3)); 70.24 (C(1′)); 102.04; 107.56; 116.09; 127.04; 128.35; 128.53; 128.61; 129.14; 133.18; 138.82; 139.19; 145.17; 157.19 (C(7)); 170.30 (C(2)); 194.21 (C(2′)). Anal. calc. for $C_{23}H_{19}NO_3 \cdot 0.125\ H_2O$: C 76.81, H 5.39, N 3.90; found: C 76.75, H 5.43, N 3.89.

*3,4-Dihydro-8-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1*H*)-one* (**4a**). To a soln. of **2a** and **3a** (0.66 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 × 60 ml). The combined CH_2Cl_2 extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give a residual solid which was purified by CC on silica gel using CH_2Cl_2/acetone 5 : 1. The proper fractions were combined and evaporated, furnishing a residual solid, which was crystallized from CH_2Cl_2

to afford **4a** (0.60 g, 70%). Colorless crystals. M.p. 178–179°. UV (0.1N HCl/MeOH): 249 (3.99), 284 (3.63). UV (MeOH): 249 (3.95), 285 (3.58). UV (0.1N NaOH/MeOH): 249 (3.98), 284 (3.63). ^{1}H-NMR ($CDCl_3$): 1.58 (*s*, Me); 2.59–2.63 (*m*, 2 H–C(3)); 2.81 (*dt*, *J* = 17.2, 2.8, 1 H–C(3′)); 2.93–2.97 (*m*, 2 H–C(4)); 3.16 (*dt*, *J* = 16.8, 2.4, 1 H–C(3′)); 3.95, 4.09 (2*d*, *J* = 9.6, *AB* type, CH_2O); 5.75 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.37 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.72–6.94 (*m*, 3 arom. H); 7.55 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 23.95 (Me); 25.36 (C(4)); 30.53 (C(3)); 37.01 (C(3′)); 73.66 (CH_2O); 81.11 (C(2′)); 109.93; 120.88; 122.48; 122.64; 124.48; 126.62; 135.27; 144.32 (C(8)); 169.16 (C(5′)); 170.09 (C(2)). Anal. calc. for $C_{16}H_{17}NO_4$: C 66.88, H 5.92, N 4.88; found: C 66.71, H 6.05, N 4.88.

The same procedure was used to convert each of the compounds **2b–f** and **3b–f** to the follow-up products **4b–f**; **7a–e** and **7g** to **9a–e** and **9g**; and **8a–d** to **10a–d**, resp.

*3,4-Dihydro-8-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinolin-2(1*H*)-one* (**4b**). Yield: 65%. M.p. 212–213°. UV (0.1N HCl/MeOH): 249 (4.00), 284 (3.61). UV (MeOH): 249 (3.97), 285 (3.57). UV (0.1N NaOH/MeOH): 249 (4.00), 284 (3.63). ^{1}H-NMR ($CDCl_3$): 2.54–2.62 (*m*, 2 H–C(3)); 2.89–2.97 (*m*, 2 H–C(4)); 3.25 (*dt*, *J* = 16.8, 3.0, 1 H–C(3′)); 3.64 (*dt*, *J* = 16.8, 2.2, 1 H–C(3′)); 4.13, 4.27 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.82 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.44 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.64–7.49 (*m*, 8 arom. H); 7.45 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.35 (C(4)); 30.51 (C(3)); 37.61 (C(3′)); 75.10 (CH_2O); 84.07 (C(2′)); 110.11; 120.96; 122.33; 122.53; 124.50; 124.93; 126.74; 128.73; 128.79; 128.90; 134.89; 139.65; 144.26 (C(8)); 168.78 (C(5′)); 169.95 (C(2)). Anal. calc. for $C_{21}H_{19}NO_4$: C 72.19, H 5.48, N 4.01; found: C 72.07, H 5.62, N 4.02.

*8-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1*H*)-one* (**4c**). Yield: 66%. M.p. 168–169°. UV (0.1N HCl/MeOH). 249 (4.00), 284 (3.61). UV (MeOH): 249 (4.00), 285 (3.59). UV (0.1N NaOH/MeOH). 249 (4.02), 285 (3.64). ^{1}H-NMR ($CDCl_3$): 2.57–2.62 (*m*, 2 H–C(3)); 2.91–2.96 (*m*, 2 H–C(4)); 3.22 (*dt*, *J* = 16.8, 3.2, 1 H–C(3′)); 3.62 (*dt*, *J* = 16.8, 2.4, 1 H–C(3′)); 4.10, 4.24 (2*d*, *J* = 10.4, *AB* type, CH_2O); 5.83 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.45 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.66–7.49 (*m*, 7 arom. H); 7.45 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.37 (C(4)); 30.51 (C(3)); 37.66 (C(3′)); 75.04 (CH_2O); 83.65 (C(2′)); 110.13; 115.83; 116.04; 121.09; 122.57; 122.63; 124.58; 126.76; 126.87; 126.96; 134.65; 135.53; 135.57; 144.18 (C(8)); 161.49; 163.96; 168.57 (C(5′)); 169.97 (C(2)). Anal. calc. for $C_{21}H_{18}FNO_4$: C 68.65, H 4.94, N 3.81; found: C 68.58, H 5.01, N 3.83.

*8-{[2-(1,1′-Biphenyl-4-yl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1*H*)-one* (**4d**). Yield: 68%. M.p. 162–163°. UV (0.1N HCl/MeOH). 251 (4.66). UV (MeOH): 250 (4.61). UV (0.1N NaOH/MeOH): 250 (4.64). ^{1}H-NMR ($CDCl_3$): 2.57–2.62 (*m*, 2 H–C(3)); 2.91–2.96 (*m*, 2 H–C(4)); 3.29 (*dt*, *J* = 17.2, 2.8, 1 H–C(3′)); 3.66 (*dt*, *J* = 16.8, 2.4, 1 H–C(3′)); 4.16, 4.31 (2*d*, *J* = 10.0, *AB* type, CH_2O); 5.84 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.46 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.68–7.69 (*m*, 12 arom. H); 7.49 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.37 (C(4)); 30.53 (C(3)); 37.62 (C(3′)); 75.07 (CH_2O); 84.03 (C(2′)); 110.18; 121.01; 122.46; 122.56; 124.54; 125.45; 126.79; 127.10; 127.59; 127.72; 128.88; 134.85; 138.55; 140.08; 141.76; 144.29 (C(8)); 168.77 (C(5′)); 169.97 (C(2)). Anal. calc. for $C_{27}H_{23}NO_4$: C 76.22, H 5.45, N 3.29; found: C 75.84, H 5.60, N 3.30.

*3,4-Dihydro-8-{[2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-methylidene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**4e**). Yield: 70%. M.p. 148–149°. UV (0.1N HCl/MeOH): 249 (4.08), 280 (3.77). UV (MeOH): 249 (4.09), 280 (3.76): UV (0.1N NaOH/MeOH): 249 (4.09), 280 (3.78). ^{1}H-NMR ($CDCl_3$): 2.54–2.63 (*m*, 2 H–C(3)); 2.90–2.98 (*m*, 2 H–C(4)); 3.23 (*dt*, *J* = 16.9, 3.1, 1H–C(3′)); 3.59 (*dt*, *J* = 16.8, 2.2, 1 H–C(3′)); 3.83 (*s*, MeO); 4.08, 4.24 (2*d*, *AB* type, *J* = 10.2, CH_2O); 5.81 (*t*, *J* = 2.7, 1 H, CH_2=C(4′)); 6.43 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.64–7.44 (*m*, 7 arom. H); 7.36 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.36 (C(4)); 30.53 (C(3)); 37.61 (C(3′)); 55.36 (MeO); 75.13 (CH_2O); 83.96 (C(2′)); 110.12; 112.28; 114.25; 120.93; 122.24; 122.53; 124.48; 126.30; 126.75; 131.60; 135.07; 144.29 (C(8)); 159.80; 168.87 (C(5′)); 169.95 (C(2)). Anal. calc. for $C_{22}H_{21}NO_5$: C 69.64, H 5.58, N 3.69; found: C 69.49, H 5.68, N 3.69.

*3,4-Dihydro-8-{[2,3,4,5-tetrahydro-4-methylidene-2-(4-nitrophenyl)-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**4f**). Yield: 66%. M.p. 192–193°. UV (0.1N HCl/MeOH): 252 (4.14). UV (MeOH): 252 (4.14). UV (0.1N NaOH/MeOH): 252 (4.14). ^{1}H-NMR ($CDCl_3$): 2.55–2.63 (*m*, 2 H–C(3)); 2.91–2.98 (*m*, 2 H–C(4)); 3.23 (*dt*, *J* = 16.8, 3.0, 1 H–C(3′)); 3.70 (*dt*, *J* = 16.9, 2.2, 1 H–C(3′)); 4.18, 4.29 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.88 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.48 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.65–8.34 (*m*, 7 arom. H); 7.44 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.34 (C(4)); 30.46 (C(3)); 37.52 (C(3′)); 74.60 (CH_2O); 83.37 (C(2′)); 110.20; 121.38; 122.63; 123.46; 124.16; 124.72; 126.23; 126.76; 133.71; 143.97 (C(8)); 146.54; 148.06; 168.05 (C(5′)); 169.98 (C(2)). Anal. calc. for $C_{21}H_{18}N_2O_6$: C 63.96, H 4.60, N 7.10; found: C 63.78, H 4.67, N 7.07.

*3,4-Dihydro-6-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1*H*)-one* (**9a**). Yield: 81%. M.p. 135–136°. UV (0.1N HCl/MeOH): 255 (4.18). UV (MeOH): 255 (4.20). UV (0.1N

NaOH/MeOH): 255 (4.21). ^{1}H-NMR ($CDCl_3$): 1.54 (*s*, Me); 2.56–2.64 (*m*, 2 H–C(3)); 2.73 (*dt*, *J* = 16.1, 2.8, 1 H–C(3′)); 2.88–2.96 (*m*, 2 H–C(4)); 3.17 (*dt*, *J* = 17.0, 2.6, 1 H–C(3′)); 3.88, 3.96 (2*d*, *J* = 9.7, *AB* type, CH_2O); 5.66 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.27 (*t*, *J* = 2.9, 1 H, CH_2=C(4′)); 6.69–6.71 (*m*, 3 arom. H); 8.32 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 24.07 (Me); 25.55 (C(4)); 30.49 (C(3)); 36.61 (C(3′)); 73.42 (CH_2O); 81.41 (C(2′)); 113.23; 114.75; 116.24; 121.95; 125.05; 131.54; 135.35; 154.20 (C(6)); 169.58 (C(5′)); 171.64 (C(2)). Anal. calc. for $C_{16}H_{17}NO_4$; C 66.88, H 5.92, N 4.88; found: C 66.87, H 5.97, N 4.87.

*3,4-Dihydro-6-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinolin-2(1*H*)-one* (**9b**). Yield: 90%. M.p. 113–114°. UV (0.1N HCl/MeOH): 255 (4.21). UV (MeOH): 256 (4.22). UV (0.1N NaOH/MeOH): 255 (4.22). ^{1}H-NMR ($CDCl_3$): 2.54–2.62 (*m*, 2 H–C(3)); 2.85–2.93 (*m*, 2 H–C(4)); 3.19 (*dt*, *J* = 17.0, 2.9, 1 H–C(3′)); 3.65 (*dt*, *J* = 16.8, 2.6, 1 H–C(3′)); 4.06, 4.13 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.68 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.29 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.60–7.47 (*m*, 8 arom. H); 8.91 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.52 (C(4)); 30.46 (C(3)); 37.25 (C(3′)); 74.87 (CH_2O); 84.22 (C(2′)); 113.35; 114.89; 116.17; 121.53; 125.01; 128.47; 128.72; 131.57; 134.91; 140.28; 154.12 (C(6)); 169.29 (C(5′)); 171.56 (C(2)). Anal. calc. for $C_{21}H_{19}NO_4$: C 72.19, H 5.48, N 4.01; found: C 72.01, H 5.58, N 3.97.

*6-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1*H*)-one* (**9c**). Yield: 81%. M.p. 130–131°. UV (0.1N HCl/MeOH): 255 (4.27). UV (MeOH): 255 (4.25). UV (0.1N NaOH/MeOH): 255 (4.27). ^{1}H-NMR ($CDCl_3$): 2.55–2.62 (*m*, 2 H–C(3)); 2.86–2.93 (*m*, 2 H–C(4)); 3.15 (*dt*, *J* = 16.8, 2.9, 1 H–C(3′)); 3.63 (*dt*, *J* = 16.9, 2.4, 1 H–C(3′)); 4.03, 4.10 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.69 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.30 (*t*, *J* = 2.7, 1 H, CH_2=C(4′)); 6.60–7.49 (*m*, 7 arom. H); 8.72 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.56 (C(4)); 30.48 (C(3)); 37.35 (C(3′)); 74.82 (CH_2O); 83.81 (C(2′)); 113.38; 114.93; 115.50; 115.93; 116.19; 121.93; 125.14; 126.91; 127.08; 131.67; 134.66; 136.15; 136.21; 154.04 (C(6)); 160.14; 165.07; 169.10 (C(5′)); 171.49 (C(2)). Anal. calc. for $C_{21}H_{18}FNO_4$: C 68.65, H 4.94, N 3.81; found: C 68.39, H 5.04, N 3.78.

*6-{[(2-(1,1′-Biphenyl-4-yl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1*H*)-one* (**9d**). Yield: 90%. M.p. 206–207°. UV (0.1N HCl/MeOH): 254 (4.35). UV (MeOH): 254 (4.36). UV (0.1N NaOH/MeOH): 254 (4.36). ^{1}H-NMR ($CDCl_3$): 2.54–2.62 (*m*, 2 H–C(3)); 2.86–2.93 (*m*, 2 H–C(4)); 3.22 (*dt*, *J* = 16.9, 2.9, 1 H–C(3′)); 3.67 (*dt*, *J* = 16.8, 2.4, 1 H–C(3′)); 4.10, 4.17 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.69 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.31 (*t*, *J* = 2.7, 1 H, CH_2=C(4′)); 6.63–7.67 (*m*, 12 arom. H); 8.71 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.56 (C(4)); 30.49 (C(3)); 37.27 (C(3′)); 74.84 (CH_2O); 84.17 (C(2′)); 113.42; 114.94; 116.17; 121.68; 125.11; 125.54; 127.07; 127.43; 127.68; 128.87; 131.61; 134.88; 139.21; 140.16; 141.49; 154.15 (C(6)); 169.28 (C(5′)); 171.46 (C(2)). Anal. calc. for $C_{27}H_{23}NO_4$: C 76.22, H 5.45, N 3.29; found: C 75.98, H 5.49, N 3.29.

*3,4-Dihydro-6-{[2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-methylidene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one* (**9e**). Yield: 74%. M.p. 128–129°. UV (0.1N HCl/MeOH): 255 (4.22). UV (MeOH): 256 (4.23). UV (0.1N NaOH/MeOH): 255 (4.22). ^{1}H-NMR ($CDCl_3$): 2.54–2.62 (*m*, 2 H–C(3)); 2.86–2.93 (*m*, 2 H–C(4)); 3.16 (*dt*, *J* = 16.9, 2.9, 1 H–C(3′)); 3.61 (*dt*, *J* = 16.9, 2.4, 1 H–C(3′)); 3.82 (*s*, MeO); 4.02, 4.10 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.67 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.28 (*t*, *J* = 2.7, 1 H, CH_2=C(4′)); 6.61–7.41 (*m*, 7 arom. H); 8.60 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.54 (C(4)); 30.48 (C(3)); 37.22 (C(3′)); 55.32 (MeO); 74.90 (CH_2O); 84.11 (C(2′)); 113.36; 114.06; 114.91; 116.09; 121.43; 125.07; 126.35; 131.51; 132.26; 135.09; 154.15 (C(6)); 159.61; 169.36 (C(5′)); 171.36 (C(2)). Anal. calc. for $C_{22}H_{21}NO_5$: C 69.64, H 5.58, N 3.69; found: C 69.35, H 5.66, N 3.65.

*6-{[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1*H*)-one* (**9g**). Yield: 85%. M.p. 169–170°. UV (0.1N HCl/MeOH): 256 (4.28). UV (MeOH): 255 (4.31). UV (0.1N NaOH/MeOH): 255 (4.29). ^{1}H-NMR ($CDCl_3$): 2.54–2.62 (*m*, 2 H–C(3)); 2.86–2.93 (*m*, 2 H–C(4)); 3.14 (*dt*, *J* = 16.9, 2.9, 1 H–C(3′)); 3.63 (*dt*, *J* = 16.8, 2.4, 1 H–C(3′)); 4.03, 4.10 (2*d*, *J* = 10.1, *AB* type, CH_2O); 5.70 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.30 (*t*, *J* = 2.9, 1 H, CH_2=C(4′)); 6.60–7.41 (*m*, 7 arom. H); 8.65 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.56 (C(4)); 30.48 (C(3)); 37.26 (C(3′)); 74.65 (CH_2O); 83.71 (C(2′)); 113.37; 114.93; 116.16; 122.07; 122.15; 126.55; 128.94; 131.70; 134.46; 134.55; 138.85; 153.99 (C(6)); 168.99 (C(5′)); 171.42 (C(2)). Anal. calc. for $C_{21}H_{18}ClNO_4$: C 65.71, H 4.72, N 3.65; found: C 65.46, H 4.77, N 3.63.

*6-{[2-(4-Bromophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1*H*)-one* (**9h**). Yield: 91%. M.p. 167–168°. UV (0.1N HCl/MeOH): 255 (4.15). UV (MeOH): 255 (4.15). UV (0.1N NaOH/MeOH): 255 (4.15). ^{1}H-NMR ($CDCl_3$): 2.57–2.60 (*m*, 2H–C(3)); 2.87–2.91 (*m*, 2 H–C(4)); 3.14 (*dt*, *J* = 16.8, 2.8, 1 H–C(3′)); 3.62 (*dt*, *J* = 16.8, 2.4, 1 H–C(3′)); 4.04, 4.09 (2*d*, *J* = 10.0, *AB* type, CH_2O); 5.70 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.30 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.61–7.57 (*m*, 7 arom. H); 8.84 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 25.53 (C(4)); 30.46 (C(3)); 37.20 (C(3′)); 74.57 (CH_2O); 83.72 (C(2′)); 113.36; 114.90; 116.19; 122.08; 122.66; 125.12; 126.84; 131.71; 131.88; 134.41; 139.37; 153.97 (C(6)); 168.95 (C(5′)); 171.49 (C(2)). Anal. calc. for $C_{21}H_{18}BrNO_4$: C 58.89, H 4.24, N 3.27; found: C 58.70, H 4.21, N 3.25.

3,4-Dihydro-7-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1H)-one (**10a**). Yield: 77%. M.p. 138–139°. UV (0.1N HCl/MeOH): 251 (4.09). UV (MeOH): 251 (4.06). UV (0.1N NaOH/MeOH): 251 (4.09). ^{1}H-NMR ($CDCl_3$): 1.54 (*s*, Me); 2.58–2.65 (*m*, 2 H–C(3)); 2.73 (*dt*, *J* = 17.2, 2.9, 1 H–C(3′)); 2.86–2.93 (*m*, 2 H–C(4)); 3.16 (*dt*, *J* = 17.1, 2.6, 1 H–C(3′)); 3.89, 3.97 (2*d*, *J* = 9.6, *AB* type, CH_2O); 5.66 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.27 (*t*, *J* = 2.7, 1 H, CH_2=C(4′)); 6.36–7.06 (*m*, 3 arom. H); 8.88 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 24.12 (Me); 24.53 (C(4)); 30.93 (C(3)); 36.62 (C(3′)); 73.00 (CH_2O); 81.37 (C(2′)); 102.46; 108.69; 116.64; 122.13; 128.67; 135.23; 138.29; 157.84 (C(7)); 169.54 (C(5′)); 172.11 (C(2)). Anal. calc. for $C_{16}H_{17}NO_4$: C 66.88, H 5.92, N 4.88; found: C 66.81, H 6.01, N 4.91.

3,4-Dihydro-7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]quinolin-2(1H)-one (**10b**). Yield: 84%. M.p. 70–71°. UV (0.1N HCl/MeOH): 251 (4.01). UV (MeOH): 251 (3.96); UV (0.1N NaOH/MeOH): 251 (4.05). ^{1}H-NMR ($CDCl_3$): 2.55–2.63 (*m*, 2 H–C(3)); 2.84–2.91 (*m*, 2 H–C(4)); 3.18 (*dt*, *J* = 17.0, 2.9, 1 H–C(3′)); 3.64 (*dt*, *J* = 16.9, 2.4, 1 H–C(3′)); 4.07, 4.15 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.67 (*t*, *J* = 2.5, 1 H, CH_2=C(4′)); 6.29 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.43–7.50 (*m*, 8 arom. H); 8.39 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 24.53 (C(4)); 30.91 (C(3)); 37.26 (C(3′)); 74.46 (CH_2O); 84.16 (C(2′)); 102.53; 108.84; 116.80; 121.69; 125.04; 128.50; 128.70; 128.74; 134.81; 138.20; 140.25; 157.76 (C(7)); 169.25 (C(5′)); 171.77 (C(2)). Anal. calc. for $C_{21}H_{19}NO_4$: C 72.19, H 5.48, N 4.01; found: C 72.05, H 5.49, N 4.00.

7-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one (**10c**). Yield: 80%. M.p. 117–118°. UV (0.1N HCl/MeOH): 251 (3.96). UV (MeOH): 252 (3.92). UV (0.1N NaOH/MeOH): 252 (3.98). ^{1}H-NMR ($CDCl_3$): 2.57–2.61 (*m*, 2 H–C(3)); 2.85–2.89 (*m*, 2 H–C(4)); 3.15 (*dt*, *J* = 17.2, 2.8, 1 H–C(3′)); 3.62 (*dt*, *J* = 16.8, 2.8, 1 H–C(3′)); 4.05, 4.11 (2*d*, *J* = 10.4, *AB* type, CH_2O); 5.69 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.30 (*t*, *J* = 2.8, 1 H, CH_2=C(4′)); 6.32–7.47 (*m*, 7 arom. H); 8.77 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 24.50 (C(4)); 30.86 (C(3)); 37.31 (C(3′)); 74.34 (CH_2O); 83.75 (C(2′)); 102.56; 108.88; 115.57; 115.78; 116.18; 116.87; 122.06; 126.96; 127.04; 128.69; 134.52; 136.11; 136.14; 138.25; 157.65 (C(7)); 161.35; 163.81; 169.06 (C(5′)); 172.02 (C(2)). Anal. calc. for $C_{21}H_{18}FNO_4 \cdot H_2O$: C 65.45, H 5.23, N 3.64; found: C 65.75, H 5.26, N 3.65.

7-{[2-(1,1′-Biphenyl-4-yl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one (**10d**). Yield: 83%. M.p. 101–102°. UV (0.1N HCl/MeOH): 251 (4.47). UV (MeOH): 251 (4.49). UV (0.1N NaOH/MeOH): 252 (4.40). ^{1}H-NMR ($CDCl_3$): 2.55–2.58 (*m*, 2 H–C(3)); 2.84–2.88 (*m*, 2 H–C(4)); 3.22 (*dt*, *J* = 16.8, 2.9, 1 H–C(3′)); 3.66 (*dt*, *J* = 16.8, 2.5, 1 H–C(3′)); 4.11, 4.19 (2*d*, *J* = 10.2, *AB* type, CH_2O); 5.69 (*t*, *J* = 2.6, 1 H, CH_2=C(4′)); 6.31 (*t*, *J* = 2.4, 1 H, CH_2=C(4′)); 6.32–7.67 (*m*, 12 arom. H); 8.46 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 24.56 (C(4)); 30.92 (C(3)); 37.27 (C(3′)); 74.39 (CH_2O); 84.12 (C(2′)); 102.56; 108.86; 116.83; 121.85; 125.56; 127.09; 127.43; 127.67; 128.72; 128.87; 134.77; 138.24; 139.17; 140.17; 141.50; 157.77 (C(7)); 169.25 (C(5′)); 171.81 (C(2)). Anal. calc. for $C_{27}H_{23}NO_4$: C 76.22, H 5.45, N 3.29; found: C 76.25, H 5.47, N 3.28.

Antiplatelet-Activity 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* at r.t. A platelet suspension was prepared from this EDTA-anticoagulated, platelet-rich plasma according to the washing procedures described in [11]. 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* [12] with 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 from the absorbance of platelet suspension as 0% aggregation and the absorbance of *Tyrode*'s solution as 100% aggregation. The inhibitory concentration for 50% aggregation (IC_{50}) was calculated with CA Cricket Graph III for five or six dose-effect levels.

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