Synthesis and Antiplatelet Evaluation of α-Methylene-γ-butyrolactone Bearing 2-Methylquinoline and 8-Hydroxyquinoline Moieties

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In a search for inhibitors of platelet aggregation, some α-methylene-γ-butyrolactones bearing 2-methylquinoline and 8-hydroxyquinoline moieties were synthesized and evaluated for antiplatelet activities against thrombin (Thr)-, arachidonic acid (AA)-, collagen (Col)-, and platelet-activating factor (PAF)- induced aggregation in washed rabbit platelets. With the exception of 2-[[2,3,4,5-tetrahydro-4-methylene-5-oxo-2-(4-phenylphenyl)-2-furanyl]methoxy]-8-hydroxyquinoline (8f), these α-methylene-γ-butyrolactones completely inhibited the platelet aggregation induced by AA and Col. The 2-methylquinoline derivatives were also active against Thr- and PAF-induced aggregation, while their 8-hydroxyquinoline counterparts were relatively inactive.

Key words α-methylene-γ-butyrolactone; antiplatelet aggregation; 8-hydroxyquinoline; 2-methylquinoline

A number of natural products bearing an α-methylene-γ-butyrolactone functionality exhibit wide-ranging biological activities, which include antitumor, bactericidal, fungicidal and anthelmintic properties.[1-3] Because of their broad range of biological activities and their interesting structural features, α-methylene-γ-butyrolactones present a scientific challenge which is reflected in an increasing number of investigations and syntheses of these heterocycles.[4-10] Recently, several 4-hydroxycoumarin derivatives with various functional groups, such as 2-hydroxy-3-isopropylaminopropyl, 2,3-epoxypropyl, 2,3-dihydroxypropyl and α-methylene-γ-butyrolactone were synthesized and evaluated for antiplatelet activity. The α-methylene-γ-butyrolactone moiety proved to be the best for improvement of the antiplatelet activity of the coumarin skeleton.[11] 3-[(2,3,4,5-Tetrahydro-4-methylene-5-oxo-2-phenylfuranyl)methoxy]xanthone[12] also exhibited higher antiplatelet potency than that of 3-[3-(propylamino)-2-hydroxypropoxy]xanthones[13,14] or ω-aminoalkoxylxanthones[15] against arachidonic acid (AA)- and collagen (Col)-induced aggregation. As a part of our new drug discovery projects, we have synthesized certain α-methylene-γ-butyrolactones for antiplatelet screening. Certain quinoline derivatives such as 8-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenyl-2-furanyl)methoxy]-quinoline and 8-[[(2-chlorophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]quinoline proved to possess a broad spectrum of antiplatelet activities.[12] This finding is important, because most of the antiplatelet agents are rather specific. For example, aspirin inhibits platelet aggregation induced by AA, but not that induced by thrombin (Thr), Col, or platelet-activating factor (PAF). To establish further the antiplatelet structure–activity relationships of various quinoline derivatives, several α-methylene-γ-butyrolactones bearing 2-methylquinoline and 8-hydroxyquinoline have been prepared and evaluated.

Chemistry

The preparation of 8-[(2-aryl-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl)methoxy]-2-methylquinolines (**3a—f**) is illustrated in Chart 1. 2-Methyl-8-hydroxyquinoline was treated with haloketones and potassium carbonate to afford 8-(2-aryl-2-oxoethoxy)-2-methylquinolines (**2a—f**), which were then reacted with ethyl 2-(bromomethyl)acrylate and zinc powder in dry THF to afford the target **3a—f** in a good overall yield. To optimize the antiplatelet effect, we also prepared certain analogues of **3a—f**. 8-Hydroxyquinoline 1-oxide (**4**),[16] obtained by the oxidation of 8-hydroxyquinoline, was treated with acetic anhydride to generate 2,8-diacetoxyquinoline (**5**) as an intermediate. Due to aza-activation, the 2-acetate is more electron-deficient than the 8-acetate and therefore, is more susceptible to electrophilic attack during the work-up process in water, leading to the formation of **6**, which is in equilibrium with its lactam tautomer. Treatment of **6** with haloketones and potassium carbonate should provide either 8-acetoxy-2-(2-aryl-2-oxoethoxy)quinolines (**7a—f**) or their *N*-alkylated counterparts depending on the site of alkylation. Therefore, an X-ray crystallographic analysis of **7a** was carried out. A view of a single molecule of **7a** is given in Fig. 1. As can be seen in the Figure, the hydrolysis occurred at the 2-acetate, and *O*- rather than *N*-alkylation occurred. Reformatsky-type condensation of **7a—f** gave the target **8a—f** in a good overall yield (Chart 2).

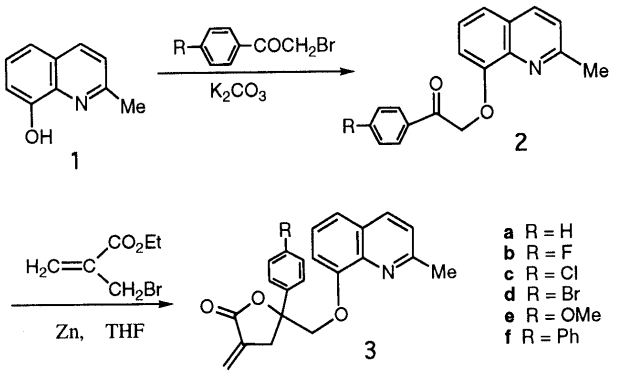

Chart 1

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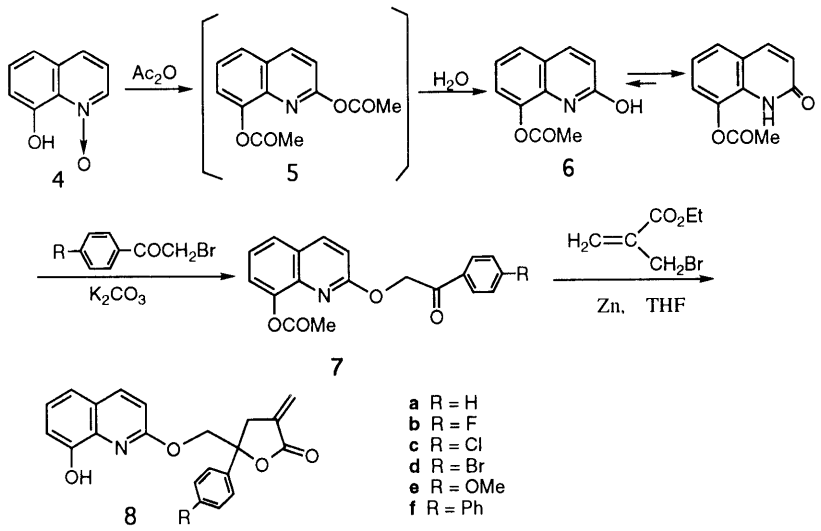

Chart 2

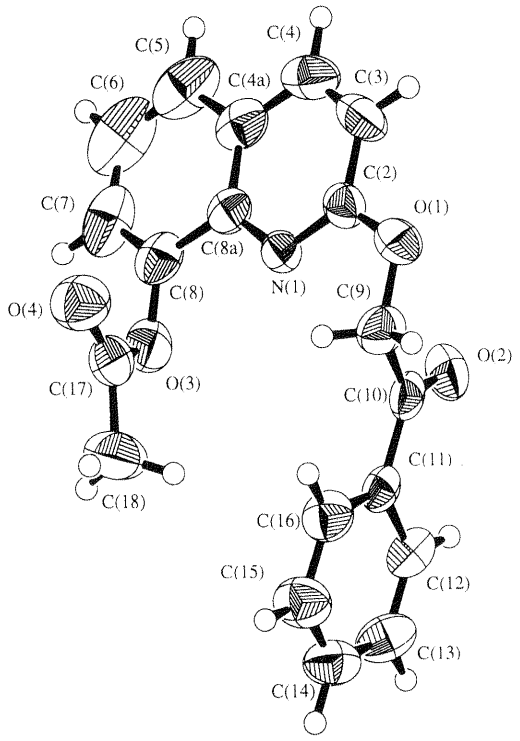

Fig. 1. X-Ray Crystallographic Structure of **7a**

Results and Discussion

The antiplatelet activities of the α-methylene-γ-butyrolactones bearing 2-methylquinoline and 8-hydroxyquinoline moieties were evaluated in washed rabbit platelets. Platelet aggregation was induced by Thr (0.1 U/ml), AA (100 μM), Col (10 μg/ml), and PAF (2 nM). The final concentration of compounds was 100 μg/ml and the results are summarized in Table 1. With the exception of 2-[[2,3,4,5-tetrahydro-4-methylene-5-oxo-2-(4-phenylphenyl)-2-furanyl]methoxy]-8-hydroxyquinoline (**8f**), these α-methylene-γ-butyrolactones were found to inhibit completely the platelet aggregation induced by AA and Col. The 2-methylquinoline derivatives were also active against Thr- and PAF-induced aggregation while their 8-hydroxyquinoline counterparts were relatively inactive.

Table 1. Effect of α-Methylene-γ-butyrolactones on the Aggregation (%) of Washed Rabbit Plateletsa Induced by Thr, AA, Col and PAF

Compd	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
3a	0[b,c]	0	0	0
3b	38.8±18.3[d]	0	0	33.2±16.6[c]
3c	0	0	0	0
3d	0	0	0	0
3e	0	0	0	0
3f	78.9±0.8[c]	0	0	84.9±0.9[c]
8a	54.3±1.3[c]	0	0	42.2±1.3[c]
8b	25.9±0.7[c]	0	0	31.8±1.7[c]
8c	72.3±0.9[c]	0	0	72.6±1.4[c]
8d	76.2±0.6[c]	0	0	78.1±0.8[c]
8e	69.4±0.5[c]	0	0	65.6±1.2[c]
8f	90.7±2.5	63.0±2.0[c]	59.5±1.2[c]	86.3±0.7[d]
Aspirin	91.9±1.4	0	85.4±3.9	90.5±1.2

a) Platelets were preincubated with DMSO (0.5%, control) or an α-methylene-γ-butyrolactone (100 mg/ml) or aspirin (50 μM) at 37 °C for 3 min, and then the inducer was added. Percentages of aggregation are presented as means±S.D. errors of the mean ($n=3-7$). *b*) Complete inhibition in all experiments. *c*) Significantly different from the control value at $p<0.001$. *d*) Significantly different from the control value at $p<0.01$.

Table 2. IC_{50} Values (μM) of α-Methylene-γ-butyrolactones on Platelet Aggregation Induced by AA (100 μg/ml) and PAF (2 nM)

Compd	Inducer	
	AA	PAF
3a	12.9	30.6
3b	11.4	>200
3c	11.0	28.5
3d	10.5	59.1
3e	21.3	58.9
3f	47.8	>200
8a	23.9	>200
8b	11.9	>200
8c	13.5	>200
8d	20.8	>200
8e	25.1	>200
8f	>200	>200

The inhibitory concentrations for 50% aggregation (IC_{50}) induced by AA and PAF are given in Table 2. The IC_{50} values of **3a**, **3b**, **3c**, and **3d** against AA-induced aggregation are comparable, indicating that the halogen substitutions at C-2 of the phenyl group do not affect the antiplatelet activity. However, the potency was decreased when C-2 was substituted with an electron-donating methoxy or phenyl group (**3e**, **3f**). Besides **3b** and **3f**, all the 2-methylquinoline derivatives exhibited fairly good activity against PAF-induced aggregation. In contrast, all the 8-hydroxyquinoline derivatives (**8a**—**f**) were inactive. The poor inhibitory activity of **3f** and **8f** implies that a bulky substituent at aromatic benzene reduced the antiplatelet potency.

In summary, 8-[(2-aryl-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl)methoxy]-2-methylquinolines (**3a**—**f**) exhibited comparable antiplatelet effects to their quinoline counterparts,[12] indicating that the methyl substitution on the quinoline did not affect the antiplatelet activity of these compounds. However, 8-hydroxyquinoline derivatives (**8a**—**f**) became narrow-spectrum antiplatelet agents which inhibited only AA- and Col-induced platelet aggregation.

Experimental

Melting points were determined on a Yanaco micromelting point apparatus and are uncorrected. The ultraviolet (UV) absorption spectra were obtained on a Beckman UV-Visible spectrophotometer. Infrared (IR) spectra were recorded on a Hitachi 260-30 spectrophotometer. Nuclear magnetic resonance (NMR) (^1H and ^{13}C) spectra were obtained with a Varian Gemini-200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was run on precoated (0.2 mm) Silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave UV light (254 nm) was used to detect the UV-absorbing spots. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer.

2-Methyl-8-(2-oxo-2-phenylethoxy)quinoline (2a) 2-Methyl-8-hydroxyquinoline (0.80 g, 5 mmol), potassium carbonate (0.69 g, 5 mmol) and dry dimethylformamide (DMF) (40 ml) were stirred at room temperature for 30 min. To this solution was added 2-bromoacetophenone (1.0 g, 5 mmol) in dry DMF (10 ml) in one portion. The resulting mixture was stirred at room temperature for 24 h (monitored by TLC) and then poured into ice water (100 ml). The pale yellow solid thus obtained was collected and crystallized from dichloromethane and ether (1 : 10) to afford **2a** (1.0 g, 72%). mp 70—71 °C. ^1H-NMR ($CDCl_3$) δ: 2.77 (3H, s, 2-CH_3), 5.63 (2H, s, OCH_2), 6.94—8.10 (8H, m, Ar-H), 7.29 (1H, d, J=8.4 Hz, 3-H), 7.99 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.41 (2-Me), 71.89 (C-1′), 110.63, 120.67, 122.55, 125.30, 127.78, 128.07, 128.72, 133.70, 134.59, 136.04, 139.67, 153.20, 158.16 (Ar-Cs), 194.32 (C-2′). *Anal.* Calcd for $C_{18}H_{15}NO_2$ 0.125 H_2O: C, 77.33; H, 5.50; N, 5.01. Found: C, 77.16; H, 5.65; N, 4.95.

8-[2-(4-Fluorophenyl)-2-oxoethoxy]-2-methylquinoline (**2b**): Compound **2b** was prepared from 2-bromo-4′-fluoroacetophenone by the same procedure as described for **2a** in 74% yield. mp 119—120 °C. ^1H-NMR ($CDCl_3$) δ: 2.77 (3H, s, 2-CH_3), 5.57 (2H, s, OCH_2), 6.94—8.23 (7H, m, Ar-H), 7.30 (1H, d, J=8.4 Hz, 3-H), 8.00 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.66 (2-Me), 72.41 (C-1′), 110.92, 115.72, 116.16, 120.96, 122.67, 125.38, 127.89, 131.15, 131.24, 131.33, 136.10, 139.86, 153.26, 158.30, 163.56, 168.64 (Ar-Cs), 193.44 (C-2′). *Anal.* Calcd for $C_{18}H_{14}FNO_2$: C, 73.21; H, 4.78; N, 4.74. Found: C, 73.02; H, 4.85; N, 4.78.

8-[2-(4-Chlorophenyl)-2-oxoethoxy]-2-methylquinoline (**2c**): Compound **2c** was prepared from 2-bromo-4′-chloroacetophenone by the same procedure as described for 2a in 64% yield. mp 112—113 °C. ^1H-NMR ($CDCl_3$) δ: 2.77 (3H, s, 2-CH_3), 5.56 (2H, s, OCH_2), 6.94—8.12 (7H, m, Ar-H), 7.31 (1H, d, J=8.4 Hz, 3-H), 8.00 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.66 (2-Me), 72.47 (C-1′), 110.99, 121.01, 122.68, 125.37, 127.90, 129.10, 129.92, 133.05, 136.11, 139.84, 140.24, 153.20, 158.31 (Ar-Cs), 193.93 (C-2′). *Anal.* Calcd for $C_{18}H_{14}ClNO_2$ 0.5 H_2O: C, 67.40; H, 4.71; N, 4.37. Found: C, 67.05; H, 4.60; N, 4.38.

8-[2-(4-Bromophenyl)-2-oxoethoxy]-2-methylquinoline (**2d**): Compound **2d** was prepared from 2-bromo-4′-bromoacetophenone by the same procedure as described for **2a** in 74% yield. mp 141—142 °C. ^1H-NMR ($CDCl_3$) δ: 2.77 (3H, s, 2-CH_3), 5.55 (2H, s, OCH_2), 6.94—8.05 (7H, m, Ar-H), 7.30 (1H, d, J=8.4 Hz, 3-H), 8.00 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.63 (2-Me), 72.50 (C-1′), 111.05, 121.03, 122.68, 125.37, 127.90, 129.01, 130.00, 132.09, 133.46, 136.11, 139.85, 153.20, 158.31 (Ar-Cs), 194.16 (C-2′). *Anal.* Calcd for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96; N, 3.93. Found: C, 60.52; H, 4.06; N, 3.96.

8-[2-(4-Methoxyphenyl)-2-oxoethoxy]-2-methylquinoline (**2e**): Compound **2e** was prepared from 2-bromo-4′-methoxyacetophenone by the same procedure as described for **2a** in 77% yield. mp 78—79 °C. ^1H-NMR ($CDCl_3$) δ: 2.79 (3H, s, 2-CH_3), 3.87 (3H, s, OCH_3), 5.57 (2H, s, OCH_2), 6.93—8.15 (7H, m, Ar-H), 7.31 (1H, d, J=8.4 Hz, 3-H), 8.00 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.65 (2-Me), 55.51 (OCH_3), 71.92 (C-1′), 110.50, 113.99, 120.61, 122.63, 125.41, 127.77, 127.85, 130.65, 136.07, 139.83, 153.43, 158.24, 164.01 (Ar-Cs), 193.06 (C-2′). *Anal.* Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.01; H, 5.60; N, 4.61.

2-Methyl-8-[2-oxo-2-(4-phenylphenyl)ethoxy]quinoline (**2f**): Compound **2f** was prepared from 2-bromo-4′-phenylacetophenone by the same procedure as described for **2a** in 73% yield. mp 73—74 °C. ^1H-NMR ($CDCl_3$) δ: 2.79 (3H, s, 2-CH_3), 5.66 (2H, s, OCH_2), 6.96—8.21 (12H, m, Ar-H), 7.30 (1H, d, J=8.4 Hz, 3-H), 8.01 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.62 (2-Me), 72.13 (C-1′), 110.68, 120.79, 122.68, 125.41, 127.29, 127.43, 127.90, 128.38, 128.86, 128.99, 133.37, 136.12, 139.75, 139.84, 146.49, 153.36, 158.31 (Ar-Cs), 194.14 (C-2′). *Anal.* Calcd for $C_{24}H_{19}NO_2$ H_2O: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.39; H, 5.63; N, 3.77.

8-[(2,3,4,5-Tetrahydro-4-methylene-5-oxo-2-phenyl-2-furanyl)methoxy]-2-methylquinoline (3a) Activated zinc powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and ethyl 2-(bromomethyl)acrylate (0.78 g, 4 mmol) were added to a solution of **2a** (0.83 g, 3 mmol) in dry THF (60 ml). The mixture was refluxed under a nitrogen atmosphere for 6 h (monitored by TLC). After cooling, it was poured into an ice-cold 5% HCl solution (300 ml), neutralized with 1.0 N $NaHCO_3$, and extracted with CH_2Cl_2 (60 ml × 3). The CH_2Cl_2 extracts were combined and washed with water, dried over Na_2SO_4, and then evaporated to give a residual solid, which was crystallized from a mixed solvent of dichloromethane and ether (1 : 10) to afford **3a** (0.64 g, 61%). mp 108—109 °C. UV λ_{max} (log ε): 253 (4.53) (0.1 N HCl in MeOH), 239 (4.46) (MeOH), 240 (4.51) (0.1 N NaOH in MeOH). ^1H-NMR ($CDCl_3$) δ: 2.74 (3H, s, CH_3), 3.25 (1H, dt, J=16.9, 2.9 Hz, 3′-H), 4.12 (1H, dt, J=16.9, 2.6 Hz, 3′-H), 4.41, 4.56 (2H, AB type, J=10.8 Hz, OCH_2), 5.71 (1H, t, J=2.6 Hz, CH_2=C(4′)), 6.31 (1H, t, J=2.8 Hz, CH_2=C(4′)), 7.06—7.60 (8H, m, Ar-H), 7.27 (1H, d, J=8.4 Hz, 3-H), 7.98 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.51 (Me), 37.44 (C-3′), 76.76 (OCH_2), 84.97 (C-2′), 113.45, 121.40, 121.48, 122.25, 125.22, 125.46, 127.82, 128.25, 128.60, 135.17, 135.88, 140.51, 140.82, 154.23, 157.98 (Ar-Cs), 169.53 (C-5′). *Anal.* Calcd for $C_{22}H_{19}NO_3$: C, 76.51; H, 5.54; N, 4.06. Found: C, 76.52; H, 5.55; N, 4.15.

The same procedure was used to convert each of compounds **2b**—**f** to the corresponding **3b**—**f**.

8-[[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-2-methylquinoline (**3b**): Yield: 61%. mp 100—101 °C. UV λ_{max} (log ε): 253 (4.60) (0.1 N HCl in MeOH), 238 (4.57) (MeOH), 240 (4.56) (0.1 N NaOH in MeOH). ^1H-NMR ($CDCl_3$) δ: 2.74 (3H, s, CH_3), 3.21 (1H, dt, J=16.9, 2.9 Hz, 3′-H), 4.09 (1H, dt, J=16.9, 2.5 Hz, 3′-H), 4.38, 4.50 (2H, AB type, J=10.5 Hz, OCH_2), 5.72 (1H, t, J=2.6 Hz, CH_2=C(4′)), 6.32 (1H, t, J=2.8 Hz, CH_2=C(4′)), 7.05—7.62 (7H, m, Ar-H), 7.27 (1H, d, J=8.4 Hz, 3-H), 7.98 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.60 (Me), 37.62 (C-3′), 76.59 (OCH_2), 84.47 (C-2′), 113.38, 115.30, 115.74, 121.52, 121.98, 122.33, 125.49, 127.16, 127.33, 127.86, 134.88, 135.93, 136.69, 136.75, 141.51, 154.13, 158.05, 160.09, 165.00 (Ar-Cs), 169.40 (C-5′). *Anal.* Calcd for $C_{22}H_{18}FNO_3$: C, 72.71; H, 4.99; N, 3.85. Found: C, 72.79; H, 5.04; N, 3.91.

8-[[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-2-methylquinoline (**3c**): Yield: 68%. mp 129—130 °C. UV λ_{max} (log ε): 253 (4.62) (0.1 N HCl in MeOH), 238 (4.60) (MeOH), 240 (4.61) (0.1 N NaOH in MeOH). ^1H-NMR ($CDCl_3$) δ: 2.74 (3H, s, CH_3), 3.20 (1H, dt, J=16.9, 2.8 Hz, 3′-H), 4.08 (1H, dt, J=16.9, 2.6 Hz, 3′-H), 4.37, 4.50 (2H, AB type, J=10.5 Hz, OCH_2), 5.72 (1H, t, J=2.5 Hz, CH_2=C(4′)), 6.32 (1H, t, J=2.9 Hz, CH_2=C(4′)), 7.04—7.58 (7H, m,

Ar-H), 7.27 (1H, d, J=8.4 Hz, 3-H), 7.98 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.60 (Me), 37.55 (C-3′), 76.39 (OCH_2), 84.36 (C-2′), 113.40, 121.56, 122.12, 122.34, 125.49, 126.85, 127.85, 128.77, 134.29, 134.70, 135.93, 139.41, 140.48, 154.08, 158.06 (Ar-Cs), 169.31 (C-5′). *Anal.* Calcd for $C_{22}H_{18}ClNO_3$: C, 69.56; H, 4.78; N, 3.69. Found: C, 69.51; H, 4.79; N, 3.75.

8-[[2-(4-Bromophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-2-methylquinoline (**3d**): Yield: 63%. mp 139—140 °C. UV λ_{max} (log ε): 253 (4.63) (0.1 N HCl in MeOH), 237 (4.68) (MeOH), 239 (4.65) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.74 (3H, s, CH_3), 3.19 (1H, dt, J=17.0, 2.8 Hz, 3′-H), 4.08 (1H, dt, J=16.9, 2.6 Hz, 3′-H), 4.37, 4.50 (2H, AB type, J=10.5 Hz, OCH_2), 5.72 (1H, t, J=2.4 Hz, CH_2=C(4′)), 6.32 (1H, t, J=2.9 Hz, CH_2=C(4′)), 7.05—7.52 (7H, m, Ar-H), 7.28 (1H, d, J=8.4 Hz, 3-H), 7.98 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.63 (Me), 37.53 (C-3′), 76.39 (OCH_2), 84.38 (C-2′), 113.43, 121.58, 122.15, 122.34, 122.46, 125.49, 127.17, 127.86, 131.74, 134.67, 135.94, 139.97, 154.08, 158.06 (Ar-Cs), 169.28 (C-5′). *Anal.* Calcd for $C_{22}H_{18}BrNO_3$: C, 62.28; H, 4.28; N, 3.30. Found: C, 62.31; H, 4.31; N, 3.34.

8-[[2,3,4,5-Tetrahydro-2-(4-methoxyphenyl)-4-methylene-5-oxo-2-furanyl]methoxy]-2-methylquinoline (**3e**): Yield: 64%. mp 113—114 °C. UV λ_{max} (log ε): 253 (4.69) (0.1 N HCl in MeOH), 237 (4.78) (MeOH), 237 (4.77) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.73 (3H, s, CH_3), 3.22 (1H, dt, J=16.9, 2.8 Hz, 3′-H), 3.81 (3H, s, OCH_3), 4.07 (1H, dt, J=16.9, 2.6 Hz, 3′-H), 4.38, 4.51 (2H, AB type, J=10.7 Hz, OCH_2), 5.70 (1H, t, J=2.5 Hz, CH_2=C(4′)), 6.30 (1H, t, J=2.8 Hz, CH_2=C(4′)), 6.91—7.51 (7H, m, Ar-H), 7.26 (1H, d, J=8.4 Hz, 3-H), 7.97 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.59 (Me), 37.48 (C-3′), 55.33 (OMe), 76.80 (OCH_2), 84.88 (C-2′), 113.34, 113.97, 121.36, 121.47, 122.27, 125.49, 126.59, 127.83, 132.87, 135.36, 135.88, 140.56, 154.30, 158.00, 159.50 (Ar-Cs), 169.69 (C-5′). *Anal.* Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.66; H, 5.70; N, 3.83.

8-[[2,3,4,5-Tetrahydro-4-methylene-5-oxo-2-(4-phenylphenyl)-2-furanyl]methoxy]-2-methylquinoline (**3f**): Yield: 69%. mp 140—141 °C. UV λ_{max} (log ε): 253 (4.78) (0.1 N HCl in MeOH), 240 (4.68) (MeOH), 241 (4.69) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.75 (3H, s, CH_3), 3.28 (1H, dt, J=16.9, 2.8 Hz, 3′-H), 4.14 (1H, dt, J=16.9, 2.5 Hz, 3′-H), 4.45, 4.59 (2H, AB type, J=10.7 Hz, OCH_2), 5.73 (1H, t, J=2.5 Hz, CH_2=C(4′)), 6.33 (1H, t, J=2.8 Hz, CH_2=C(4′)), 7.11—7.64 (12H, m, Ar-H), 7.27 (1H, d, J=8.4 Hz, 3-H), 7.98 (1H, d, J=8.4 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.62 (Me), 37.50 (C-3′), 76.72 (OCH_2), 84.92 (C-2′), 113.46, 121.45, 121.68, 122.29, 125.50, 125.75, 127.11, 127.33, 127.57, 127.84, 128.84, 135.13, 135.90, 139.78, 140.35, 140.56, 141.24, 154.27, 158.03 (Ar-Cs), 169.59 (C-5′). *Anal.* Calcd for $C_{28}H_{23}NO_3$: C, 79.79; H, 5.50; N, 3.32. Found: C, 79.78; H, 5.53; N, 3.44.

8-Acetoxy-2(1*H*)-quinolinone (6) A mixture of 8-hydroxyquinoline 1-oxide (0.81 g, 5 mmol) in acetic anhydride (20 ml) was heated at reflux for 2 h (monitored by TLC). After cooling, it was poured into ice water (100 ml). The resulting solid was collected and crystallized from dichloromethane to give **6** (0.85 g, 84%) as white crystals. mp 240—241 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.55 (3H, s, CH_3), 6.66 (1H, d, J=9.5 Hz, 3-H), 7.15—7.23 (3H, m, Ar-H), 7.78 (1H, d, J=9.5 Hz, 4-H), 11.31 (1H, br s, OH). ^{13}C-NMR (DMSO-d_6) δ: 21.28 (Me), 121.18, 122.05, 122.43, 123.51, 125.19, 131.04, 136.87, 140.53 (Ar-Cs), 163.21 (C-2), 169.11 (COMe). *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.89; H, 4.46; N, 6.84.

8-Acetoxy-2-(2-oxo-2-phenylethoxy)quinoline (7a) A mixture of **6** (1.02 g, 5 mmol), potassium carbonate (0.69 g, 5 mmol) and dry DMF (40 ml) was stirred at room temperature for 30 min and then 2-bromoacetophenone (1.0 g, 5 mmol) in dry DMF (10 ml) was added in one portion. The resulting mixture was further stirred at room temperature for 24 h (monitored by TLC), then poured into ice water (100 ml) and the pale yellow solid thus obtained was crystallized from dichloromethane and ether (1 : 10) to afford **7a** (1.19 g, 74%). mp 141—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, s, CH_3), 5.66 (2H, s, OCH_2), 7.11 (1H, d, J=8.9 Hz, 3-H), 7.25—8.04 (8H, m, Ar-H), 8.05 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 20.02 (Me), 68.03 (C-1′), 113.35, 121.71, 123.88, 125.40, 126.64, 127.82, 128.76, 133.53, 134.82, 138.59, 139.34, 145.70 (Ar-Cs), 160.58 (C-2), 169.01 (COMe), 193.75 (C-2′). *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.92; H, 4.75; N, 4.36.

8-Acetoxy-2-[2-(4-fluorophenyl)-2-oxoethoxy]quinoline (**7b**): Compound **7b** was prepared from 2-bromo-4′-fluoroacetophenone by the same procedure as described for **7a** in 73% yield. mp 140—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, CH_3), 5.59 (2H, s, OCH_2), 7.09 (1H, d, J=8.9 Hz, 3-H), 7.12—8.09 (7H, m, Ar-H), 8.05 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 20.24 (Me), 68.13 (C-1′), 113.30, 115.74, 116.18, 121.84, 124.04, 125.48, 126.70, 130.53, 130.71, 131.32, 138.61, 139.49, 145.74, 160.55, 163.37, 168.45 (Ar-Cs), 169.02 (COMe), 192.67 (C-2′). *Anal.* Calcd for $C_{19}H_{14}FNO_4$: C, 67.25; H, 4.16; N, 4.13. Found: C, 67.14; H, 4.21; N, 4.10.

8-Acetoxy-2-[2-(4-chlorophenyl)-2-oxoethoxy]quinoline (**7c**): Compound **7c** was prepared from 2-bromo-4′-chloroacetophenone by the same procedure as described for **7a** in 67% yield. mp 154—155 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, CH_3), 5.57 (2H, s, OCH_2), 7.08 (1H, d, J=8.8 Hz, 3-H), 7.26—7.97 (7H, m, Ar-H), 8.05 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 20.28 (Me), 68.22 (C-1′), 113.25, 121.87, 124.05, 125.47, 126.71, 129.09, 129.36, 133.24, 138.59, 139.52, 139.93, 145.73 (Ar-Cs), 160.50 (C-2), 169.03 (COMe), 193.25 (C-2′). *Anal.* Calcd for $C_{19}H_{14}ClNO_4$: C, 64.14; H, 3.97; N, 3.94. Found: C, 64.04; H, 4.01; N, 3.92.

8-Acetoxy-2-[2-(4-bromophenyl)-2-oxoethoxy]quinoline (**7d**): Compound **7d** was prepared from 2-bromo-4′-bromoacetophenone by the same procedure as described for **7a** in 65% yield. mp 158—159 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, CH_3), 5.56 (2H, s, OCH_2), 7.08 (1H, d, J=8.9 Hz, 3-H), 7.26—7.90 (7H, m, Ar-H), 8.05 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 20.31 (Me), 68.21 (C-1′), 113.25, 121.89, 124.07, 125.49, 126.70, 128.64, 129.46, 132.08, 133.62, 138.58, 139.54, 145.72 (Ar-Cs), 160.49 (C-2), 169.05 (COMe), 193.50 (C-2′). *Anal.* Calcd for $C_{19}H_{14}BrNO_4$: C, 57.02; H, 3.53; N, 3.50. Found: C, 56.83; H, 3.59; N, 3.50.

8-Acetoxy-2-[2-(4-methoxyphenyl)-2-oxoethoxy]quinoline (**7e**): Compound **7e** was prepared from 2-bromo-4′-methoxyacetophenone by the same procedure as described for **7a** in 69% yield. mp 130—131 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 5.61 (2H, s, OCH_2), 7.10 (1H, d, J=8.8 Hz, 3-H), 6.95—8.07 (7H, m, Ar-H), 8.01 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 20.22 (Me), 55.52 (OMe), 67.92 (C-1′), 113.47, 113.97, 121.69, 123.88, 125.43, 126.67, 127.88, 130.17, 138.66, 139.32, 145.78, 160.73, 163.82 (Ar-Cs), 169.11 (COMe), 192.27 (C-2′). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 67.99; H, 4.89; N, 3.98.

8-Acetoxy-2-[2-(4-phenylphenyl)-2-oxoethoxy]quinoline (**7f**): Compound **7f** was prepared from 2-bromo-4′-phenylacetophenone by the same procedure as described for **7a** in 64% yield. mp 173—174 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s, CH_3), 5.68 (2H, s, OCH_2), 7.12 (1H, d, J=8.9 Hz, 3-H), 7.25—8.12 (12H, m, Ar-H), 8.06 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 20.16 (Me), 68.15 (C-1′), 113.41, 121.77, 123.94, 125.45, 126.69, 127.23, 127.37, 128.38, 128.49, 129.00, 133.53, 138.64, 139.40, 139.68, 145.75, 146.23 (Ar-Cs), 160.64 (C-2), 169.08 (COMe), 193.49 (C-2′). *Anal.* Calcd for $C_{25}H_{19}NO_4$: C, 75.55; H, 4.82; N, 3.52. Found: C, 75.75; H, 4.82; N, 3.58.

2-[(2,3,4,5-Tetrahydro-4-methylene-5-oxo-2-phenyl-2-furanyl)methoxy]-8-hydroxyquinoline (8a) Activated zinc powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and ethyl 2-(bromomethyl)acrylate (0.78 g, 4 mmol) were added to a solution of **7a** (0.96 g, 3 mmol) in dry THF (60 ml). The mixture was refluxed under a nitrogen atmosphere for 6 h (monitored by TLC). After cooling, it was poured into an ice-cold 5% HCl solution (300 ml) and extracted with CH_2Cl_2 (75 ml × 3). The dichloromethane extracts were combined and washed with water, dried over Na_2SO_4, and then evaporated to give a brown solid which was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent. The appropriate fractions were combined and evaporated to furnish a residual solid which was crystallized from dichloromethane and ether (1 : 10) to afford **8a** (0.6 g, 57%). mp 145—146 °C. UV λ_{max} (log ε): 260 (4.69) (0.1 N HCl in MeOH), 247 (4.73) (MeOH), 261 (4.61) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.23 (1H, dt, J=17.0, 2.8 Hz, 3′-H), 3.63 (1H, dt, J=16.8, 2.6 Hz, 3′-H), 4.63, 4.71 (2H, AB type, J=11.6 Hz, OCH_2), 5.66 (1H, t, J=2.6 Hz, CH_2=C(4′)), 6.30 (1H, t, J=2.9 Hz, CH_2=C(4′)), 6.88 (1H, d, J=8.8 Hz, 3-H), 7.15—7.52 (8H, m, Ar-H), 8.00 (1H, d, J=8.8 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 37.63 (C-3′), 71.65 (OCH_2), 84.12 (C-2′), 111.26, 113.35, 118.02, 121.72, 125.14, 125.25, 125.31, 128.61, 128.87, 134.86, 135.13, 139.69, 140.37, 150.56 (Ar-Cs), 160.44 (C-2), 169.34 (C-5′). *Anal.* Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.69; H, 4.94; N, 4.11.

The same procedure was used to convert each of compounds **7b—f** to the corresponding **8b—f**.

2-[[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-8-hydroxyquinoline (**8b**): Yield: 65%. mp 149—150 °C.

UV λ_{max} (log ε): 260 (4.59) (0.1 N HCl in MeOH), 247 (4.60) (MeOH), 262 (4.54) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.20 (1H, dt, J=16.9, 2.9 Hz, 3′-H), 3.62 (1H, dt, J=16.9, 2.5 Hz, 3′-H), 4.60, 4.67 (2H, AB type, J=11.6 Hz, OCH_2), 5.68 (1H, t, J=2.6 Hz, CH_2=C(4′)), 6.32 (1H, t, J=2.8 Hz, CH2=C(4′)), 6.88 (1H, d, J=8.8 Hz, 3-H), 7.14—7.50 (7H, m, Ar-H), 8.01 (1H, d, J=8.8 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 37.66 (C-3′), 71.52 (OCH_2), 83.71 (C-2′), 111.31, 113.25, 115.61, 116.04, 118.04, 122.06, 125.30, 126.99, 127.15, 134.58, 135.07, 136.16, 136.22, 139.75, 150.53, 160.33, 165.14 (Ar-Cs), 169.13 (C-5′). *Anal.* Calcd for $C_{21}H_{16}FNO_4$: C, 69.03; H, 4.41; N, 3.83. Found: C, 68.95; H, 4.37; N, 3.94.

2-[[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-8-hydroxyquinoline (**8c**): Yield: 74%. mp 163—164 °C. UV λ_{max} (log ε): 260 (4.57) (0.1 N HCl in MeOH), 247 (4.65) (MeOH), 262 (4.53) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.18 (1H, dt, J=16.9, 2.9 Hz, 3′-H), 3.61 (1H, dt, J=16.9, 2.5 Hz, 3′-H), 4.60, 4.67 (2H, AB type, J=11.6 Hz, OCH_2), 5.68 (1H, t, J=2.5 Hz, CH_2=C(4′)), 6.32 (1H, t, J=2.8 Hz, CH_2=C(4′)), 6.88 (1H, d, J=8.8 Hz, 3-H), 7.16—7.45 (7H, m, Ar-H), 8.01 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 37.59 (C-3′), 71.37 (OCH_2), 83.62 (C-2′), 111.34, 113.23, 118.04, 122.20, 125.33, 126.63, 129.06, 134.39, 134.65, 135.07, 138.87, 139.78, 150.53 (Ar-Cs), 160.30 (C-2), 169.03 (C-5′). *Anal.* Calcd for $C_{21}H_{16}ClNO_4$: C, 66.06; H, 4.22; N, 3.67. Found: C, 65.93; H, 4.30; N, 3.74.

2-[[2-(4-Bromophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-8-hydroxyquinoline (**8d**): Yield: 62%. mp 172—173 °C. UV λ_{max} (log ε): 260 (4.78) (0.1 N HCl in MeOH), 246 (4.84) (MeOH), 262 (4.74) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.18 (1H, dt, J=16.9, 2.4 Hz, 3′-H), 3.61 (1H, dt, J=16.9, 2.4 Hz, 3′-H), 4.60, 4.67 (2H, AB type, J=11.6 Hz, OCH_2), 5.68 (1H, t, J=2.6 Hz, CH_2=C(4′)), 6.32 (1H, t, J=2.8 Hz, CH_2=C(4′)), 6.87 (1H, d, J=8.8 Hz, 3-H), 7.16—7.60 (7H, m, Ar-H), 8.01 (1H, d, J=8.8 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 37.54 (C-3′), 71.30 (OCH_2), 83.65 (C-2′), 111.34, 113.23, 118.05, 122.25, 122.78, 125.33, 126.93, 134.39, 132.02, 134.36, 135.07, 139.41, 139.78, 150.53 (Ar-Cs), 160.29 (C-2), 169.02 (C-5′). *Anal.* Calcd for $C_{21}H_{16}BrNO_4$: C, 59.17; H, 3.78; N, 3.29. Found: C, 58.90; H, 3.78; N, 3.39.

2-[[2,3,4,5-Tetrahydro-2-(4-methoxyphenyl)-4-methylene-5-oxo-2-furanyl]methoxy]-8-hydroxyquinoline (**8e**): Yield: 56%. mp 139—140 °C. UV λ_{max} (log ε): 259 (4.73) (0.1 N HCl in MeOH), 247 (4.72) (MeOH), 262 (4.62) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.21 (1H, dt, J=16.9, 2.8 Hz, 3′-H), 3.59 (1H, dt, J=16.9, 2.5 Hz, 3′-H), 3.83 (3H, s, OMe), 4.60, 4.67 (2H, AB type, J=11.6 Hz, OCH_2), 5.65 (1H, t, J=2.5 Hz, CH_2=C(4′)), 6.29 (1H, t, J=2.9 Hz, CH_2=C(4′)), 6.88 (1H, d, J=8.8 Hz, 3-H), 6.95—7.46 (7H, m, Ar-H), 8.00 (1H, d, J=8.8 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 37.57 (C-3′), 55.39 (OMe), 71.68 (OCH_2), 84.03 (C-2′), 111.23, 113.37, 114.21, 118.00, 121.62, 125.21, 125.29, 126.48, 132.30, 135.05, 135.13, 139.66, 150.56, 159.73, 160.46 (Ar-Cs), 169.43 (C-5′). *Anal.* Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.09; N, 3.71. Found: C, 70.04; H, 5.04; N, 3.79.

2-[[2,3,4,5-Tetrahydro-4-methylene-5-oxo-2-(4-phenylphenyl)-2-furanyl]methoxy]-8-hydroxyquinoline (**8f**): Yield: 58%. mp 183—184 °C. UV λ_{max} (log ε): 259 (4.84) (0.1 N HCl in MeOH), 247 (4.84) (MeOH), 260 (4.77) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.27 (1H, dt, J=16.9, 2.8 Hz, 3′-H), 3.66 (1H, dt, J=16.9, 2.5 Hz, 3′-H), 4.68, 4.75 (2H, AB type, J=11.7 Hz, OCH_2), 5.68 (1H, t, J=2.5 Hz, CH_2=C(4′)), 6.32 (1H, t, J=2.8 Hz, CH_2=C(4′)), 6.90 (1H, d, J=8.8 Hz, 3-H), 7.25—7.70 (12H, m, Ar-H), 8.01 (1H, d, J=8.8 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 37.62 (C-3′), 71.59 (OCH_2), 84.07 (C-2′), 111.28, 113.35, 118.02, 121.85, 125.25, 125.32, 125.64, 127.15, 127.57, 127.70, 128.90, 134.81, 135.12, 139.25, 139.71, 140.23, 141.62, 150.57 (Ar-Cs), 160.44 (C-2), 169.32 (C-5′). *Anal.* Calcd for $C_{27}H_{21}NO_4$: C, 76.58; H, 5.00; N, 3.31. Found: C, 76.52; H, 5.05; N, 3.38.

X-Ray Structural Determination of 7a[17] Crystallographic details: $C_{19}H_{15}NO_4$, M=321.33, Monoclinic, space group $P2_{1/n}$ (#14), a=11.175(2) Å, b=9.972(2) Å, c=15.204(2) Å, V=1630.6(5) Å^3, Z=4. D_{calc}=1.309 g/cm^3. Crystal dimensions 0.35×0.42×0.47 mm. F_{000}=672.00. μ(Mo$K\alpha$)=0.93 cm^{-1}. Radiation: Mo$K\alpha$ (λ=0.71069 Å), ω–2θ scanning technique. The crystal structure was solved by direct methods (SIR92). Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, N, O; fixed H contributions) converged at R=0.043 (R_w=0.027) for 2744 reflections.

Antiplatelet Evaluation A) Preparation of Platelet Aggregation Inducers: 1) Bovine thrombin, obtained from Parke Davis Co., was dissolved in 50% (v/v) glycerol to give a stock solution of 100 NIH units/ml. 2) Collagen (type I, bovine Achilles tendon), obtained from Sigma Chemical Co., was homogenized in 25 mM acetic acid and stored at −70 °C. 3) PAF (1-O-alkyl-2-acetyl-sn-glycerol-3-phosphorylcholine), purchased from Sigma, was dissolved in chloroform and diluted into 0.1% bovine serum albumin in saline solution immediately prior to use. 4) Arachidonic acid, purchased from Sigma, was dissolved in deionized water.

B) Preparation of Platelets: Platelet suspension was prepared from EDTA-anticoagulated platelet-rich plasma according to the washing procedures described previously.[18] Platelets were counted by a Hemalaser 2 (Sebia, France) and adjusted to a concentration of 4.5×10^8 platelets/ml. Platelet pellets were finally suspended in Tyrode's buffer (pH 7.4) of the following composition: NaCl (136.8 mM), KCl (2.8 mM), $NaHCO_3$ (11.9 mM), $MgCl_2$ (2.1 mM), NaH_2PO_4 (0.33 mM), $CaCl_2$ (1 mM), glucose (11.2 mM) containing 0.35% bovine serum albumin.

C) Platelet Aggregation and ATP Release Reaction: Aggregation was measured by the turbidimetry method as described by O'Brien.[19] ATP released from platelets was detected by the bioluminescence method of DeLuca and McElory.[20] Aggregation and ATP release were measured simultaneously in a Lumi-aggregometer (model 1020B, Payton, Canada) connected to two dual-channel recorders. Platelet preparations were stirred at 900 rpm. When dimethyl sulfoxide (DMSO) was used as the solvent, its final concentration was fixed at 0.5% (v/v). For the calculation of percentage aggregation, the absorbance of the platelet suspension was designated as 0% aggregation and the absorbance of platelet-free Tyrode's solution as 100% aggregation. The 50%-inhibitory concentration (IC_{50}) for aggregation was calculated using a CA-Cricket Graph III for five or six dose-effect levels.

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References and Notes

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