α-Methylene-γ-butyrolactones: Synthesis and Vasorelaxing Activity Assay of Coumarin, Naphthalene, and Quinoline Derivatives

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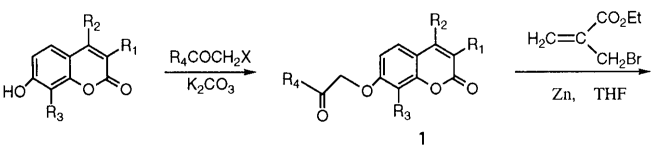
Certain α-methylene-γ-butyrolactone derivatives of coumarin, naphthalene, and quinoline were synthesized and evaluated for vasorelaxing effects on isolated rat thoracic aorta. The 7-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-2*H*-1-benzopyran-2-ones, which have an aliphatic methyl substituent at the lactone C_2, were more active than their C_2-phenyl counterparts against high-K^+ (80 mM) medium, Ca^{2+} (1.9 mM)-induced vasoconstriction and the norepinephrine (NE, 3 μM)-induced phasic and tonic constrictions (2a *vs.* 2b; 2c *vs.* 2d; 2e *vs.* 2f; 2g *vs.* 2h). Although 3-chloro-7-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-4-methyl-2*H*-1-benzopyran-2-one (2g) demonstrated the most potent inhibitory activities on the NE-induced phasic and tonic constrictions at concentrations of as low as 10 μg/ml, it possesses both affinity for NE-receptor and intrinsic activity to trigger the vasoconstriction. However, 8-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)-methoxy]quinoline (10a) and other quinoline derivatives (11a, 12a) are pure irreversible non-competitive blockers of NE-receptor with no intrinsic activity. The aromatic ring played an important role in the vasorelaxing effects of α-methylene-γ-butyrolactones; naphthalene was inactive, quinolines exhibited only affinity to the α-receptor, and coumarins possessed both affinity and intrinsic activity.

Key words α-methylene-γ-butyrolactone; coumarin; naphthalene; quinoline; vasorelaxing effect

Phenoxybenzamine and dibenzamine, which carry a β-chloroethylamine side chain capable of reacting covalently with α-adrenergic receptor, are representative irreversible non-competitive α-blockers.[1-4] The mechanism of receptor inactivation involves the formation of an aziridinium ion, which reacts with a nucleophilic group on the receptor, leading to the formation of a covalent bond between the drugs and the receptor.[5] This alkylation of the receptor leads to a prolonged α-receptor blockade, which is not overcome by norepinephrine. Although phenoxybenzamine is widely used in the treatment of peripheral vascular disease and in the preoperative management of patients with pheochromocytoma, its long duration of action and the lack of specificity for the cardiovascular system restrict its usefulness. As part of our new drug discovery projects, we have synthesized several 4-hydroxycoumarin derivatives with various functional groups, such as 2-hydroxy-3-isopropylaminopropyl, 2,3-epoxypropyl, 2,3-dihydroxypropyl and α-methylene-γ-butyrolactones substituted at the C_4-oxygen, in the hope of discovering new coumarin anticoagulants. The α-methylene-γ-butyrolactone moiety proved to be the best for improvement of the antiplatelet activity of the 4-hydroxycoumarin skeleton.[6] Certain 7-hydroxycoumarin and 8-hydroxyquinoline α-methylene-γ-butyrolactones were also prepared and proved to have significant antiplatelet activities.[7,8] Recent reports have revealed that antiplatelet agents are capable of inhibiting vasoconstriction induced by norepinephrine.[9-11] Since the α-methylene-γ-butyrolactone moiety is a known alkylating agent which undergoes Michael-type addition with biological cellular nucleophiles,[12,13] a reaction which resembles that of phenoxybenzamine and dibenzamine, we set out to study whether this addition occurs between the α-methylene-γ-butyrolactone and the α-adrenergic receptor. We also examined the effect of various aromatic skeletons (carriers) such as coumarin, naphthalene, quinoline, methylquinoline, and hydroxyquinoline on the optimal vasorelaxing activities.

Chemistry

The preparation of 3-chloro-7-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-4-methyl-2*H*-1-benzopyran-2-one (**2g**) and its analogs is illustrated in Chart 1. 3-Chloro-7-hydroxy-4-methylcoumarin was treated with potassium carbonate and chloroacetone to afford 3-chloro-4-methyl-7-(2-oxopropoxy)-2*H*-1-benzopyran-2-one (**1g**), which was then reacted with ethyl 2-(bromomethyl)acrylate in dry tetrahydrofuran (THF) to give **2g** in 64% overall yield. Treatment of 3-chloro-7-hydroxy-4-methylcoumarin with potassium carbonate and



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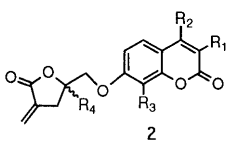

2

	R_1	R_2	R_3	R_4
a	H	H	H	CH_3
b	H	H	H	C_6H_5
c	H	CH_3	H	CH_3
d	H	CH_3	H	C_6H_5
e	CH_3	CH_3	CH_3	CH_3
f	CH_3	CH_3	CH_3	C_6H_5
g	Cl	CH_3	H	CH_3
h	Cl	CH_3	H	C_6H_5

Chart 1

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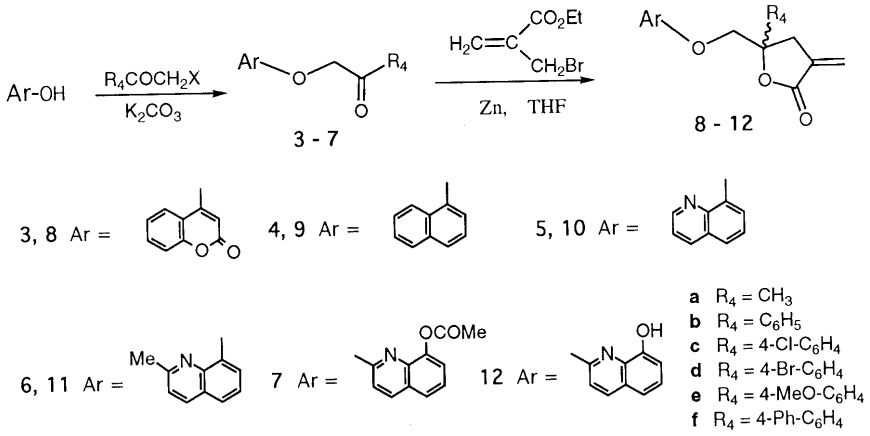

Chart 2

2-bromoacetophenone gave 3-chloro-4-methyl-7-(2-oxo-2-phenylethoxy)-2*H*-1-benzopyran-2-one (**1h**) which was allowed to react with ethyl 2-(bromomethyl)acrylate in THF (Reformatsky-type reaction) to afford 3-chloro-7-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenyl-2-furanyl)methoxy]-4-methyl-2*H*-1-benzopyran-2-one (**2h**) in 47% overall yield. Compounds **2a**—**f** were similarly prepared from their respective 2-substituted 2-oxoethoxy precursors as described previously.[7]

2-[(2,3,4,5-Tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-8-hydroxyquinoline (**12a**) was prepared from 8-acetoxy-2-(2-oxopropoxy)quinoline (**7a**), which was obtained *via* *O*-alkylation of 8-acetoxyquinolin-2(1*H*)-one[14] and chloroacetone. Similarly, Reformatsky-type reaction of 2-methyl-8-(2-oxopropoxy)quinoline (**6a**) gave 8-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-2-methylquinoline (**11a**) (Chart 2). Alkylation of 8-acetoxyquinolin-2(1*H*)-one with 2-bromoacetophenone or its 4′-substituted derivatives, followed by the Reformatsky-type reaction afforded 2-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenyl-2-furanyl)methoxy]-8-hydroxyquinoline (**12b**) or its 4′-substituted counterparts **12c**—**f** respectively.[15] Similarly, compounds **8a**, **b**, **9a**, **b**, **10a**—**f** and **11b**—**f** were prepared from their respective precursors **3a**, **b**, **4a**, **b**, **5a**—**f** and **6b**—**f** as described previously.[6,8]

Results and Discussion

The effects of coumarin (2*H*-1-benzopyran-2-one), naphthalene, and quinoline 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 summarized in Table 1. The 7-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-2*H*-1-benzopyran-2-ones (**2a**, **2c**, **2e**, **2g**), which have an aliphatic methyl substituent at the lactone C_2, were more active against high-K^+ medium, Ca^{2+}-induced and NE-induced vasoconstrictions than their C_2-phenyl counterparts (**2b**, **2d**, **2f**, **2h**). This finding is interesting, because C_2-phenyl lactones were found to be better antiplatelet agents than their respective C_2-methyl counterparts.[6-8] 7-[(2,3,4,5-Tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-2*H*-1-benzopyran-2-one (**2a**) at a concentration of 30 μg/ml strongly inhibited NE-induced phasic and tonic constrictions but did not have a significant effect on the Ca^{2+}-induced constriction. The inhibitory activities for **2c**, **2e**, and **2g** are comparable, indicating that the methyl substitutions on the coumarin did not affect the vasorelaxing activity. Among these coumarin derivatives, 3-chloro-7-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-4-methyl-2*H*-1-benzopyran-2-one (**2g**) exhibited the most potent inhibitory activities on the NE-induced phasic and tonic constrictions with concentrations of as low as 10 μg/ml. The high-K^+ medium, Ca^{2+}-induced vasoconstriction was also inhibited concentration-dependently by **2g**. A comparison of **2a** and **8a** indicates that the 7-substituted coumarins are superior to the 4-substituted counterparts in the inhibition of NE-induced constrictions. Replacement of the coumarin moiety with naphthalene led to complete loss of vasorelaxing effects (**9a** and **9b**). However, the quinoline counterparts **10a**, **10b** and **12a**, showed strong inhibitory activities on the NE-induced constriction and a fairly good activity against the Ca^{2+}-induced constriction. The 2-methylquinoline derivatives **11a** and **11b** were less potent than **10a** and **10b** respectively, on the NE-induced and Ca^{2+}-induced constrictions. Although **11a** inhibited the vasoconstriction induced by NE, it was inactive against Ca^{2+}-induced constriction. The poor inhibitory potency of **10c**—**f**, **11c**—**f**, and **12c**—**f** implies that a substituent on the C_2-phenyl moiety reduced the vasorelaxing effect.

Although the coumarin α-methylene-γ-butyrolactones (**2a**, **2c**, **2e**, **2g**, and **8a**) exhibited potent vasorelaxing effects, these compounds by themselves (without NE as an inducer) caused vasoconstriction. The explanation is that coumarin derivatives possess not only high affinity for the NE receptor, but also intrinsic activity. However, the quinoline derivatives (**10a**, **10b**, **11a**, **11b**, and **12a**) were devoid of self-induced vasoconstriction, indicating that they are pure irreversible non-competitive blockers of the NE-receptor.

In summary, α-methylene-γ-butyrolactones possess not only antitumor, bactericidal, fungicidal, antibiotic and anthelmintic activities,[16-20] but also antiplatelet and vasorelaxing effects. A C_2-phenyl substituent on the lactone ring is required for the optimal antiplatelet activities while a C_2-methyl is neccessary for a superior

Table 1. Effects of α-Methylene-γ-butyrolactones on High K^+ and Ca^{2+}-Induced and Norepinephrine-Induced Constriction of Rat Thoracic Aorta[a]

Agonist (μg/ml)	K^+ (80 mM) + Ca^{2+} (1.9 mM)	NE (3 μM)-phasic	NE (3 μM)-tonic
Control	100±3.8	100±2.9	100±2.1
2a (100)	7.3±3.1	0	0
(30)	82.0±1.4	28.1±2.2	7.7±0.4
(10)	107.4±3.6	96.7±2.4	107.6±3.7
2b (100)	52.7±0.3	23.1±3.9	7.3±2.7
2c (100)	9.2±4.4	7.9±1.5	1.2±0.8
(30)[b]	61.7±3.5	24.4±4.0	7.8±3.7
(10)[b]	98.6±6.6	70.9±5.5	62.6±6.2
2d (100)	98.8±0.9	96.9±2.2	38.9±1.3
2e (100)	13.6±1.3	9.1±6.4	0
(30)[b]	91.4±2.1	30.7±6.6	10.8±1.6
(10)	98.1±0.9	75.4±4.9	71.0±6.0
2f (100)	102.4±6.9	93.8±4.4	98.3±2.9
2g (100)	9.0±1.5	0	0
(30)[b]	31.5±1.3	0	0
(10)[b]	83.3±4.4	16.8±1.0	4.0±0.5
(3)	99.4±2.5	103.3±6.0	109.0±1.2
2h (100)	114.2±5.6	97.2±2.0	82.3±3.9
8a (100)	5.4±0.6	0	0
(30)[b]	81.9±1.3	67.4±3.4	45.5±7.1
(10)	111.9±1.0	94.6±7.7	108.1±5.7
8b (100)	110.7±1.9	50.0±5.9	42.0±5.6
9a (100)	90.9±3.1	90.8±1.9	78.9±1.9
9b (100)	109.4±3.4	112.5±2.9	96.5±5.1
10a (100)	5.9±0.3	0	3.5±1.6
(30)	52.3±4.6	0	39.5±5.6
(10)	85.3±3.7	110.7±2.2	95.2±3.8
10b (100)	21.5±3.0	0	5.1±1.7
(30)	59.7±3.8	61.2±2.9	39.3±1.2
(10)	83.8±3.1	84.5±2.2	64.6±4.9
10c (100)	76.1±7.4	71.6±3.5	62.5±7.2
10d (100)	70.9±6.7	94.1±0.2	76.8±7.6
10e (100)	108.1±3.8	100.0±11.8	82.4±2.5
10f (100)	108.7±2.3	91.2±2.1	100.2±6.6
11a (100)	102.6±1.6	0	11.3±3.4
(30)	—	67.1±10.0	55.0±6.7
(10)	—	93.6±0.8	80.2±2.1
11b (100)	49.6±2.6	24.3±10.1	27.3±9.9
11c (50)	84.1±12.9	95.8±3.8	87.8±2.2
11d (50)	107.1±2.4	112.7±4.9	106.4±4.4
11e (50)	72.3±3.9	73.9±2.2	45.9±6.7
11f (50)	102.5±1.8	108.4±1.2	101.1±2.6
12a (100)	1.6±1.1	0	3.6±2.5
(30)	18.9±2.6	23.4±3.9	16.3±3.1
(10)	78.8±8.6	91.3±1.5	76.3±3.8
12b (100)	97.4±1.9	94.2±2.8	79.8±1.6
12c (100)	100.1±3.0	99.4±5.4	99.7±11.1
12d (100)	93.9±0.3	100.2±4.6	95.4±0.1
12e (100)	91.1±1.8	100.0±4.7	96.3±2.8
12f (100)	93.6±1.1	98.4±1.7	98.9±4.3
Nifedipine	0	98.7±0.7	96.5±2.1
Prazosin	100±2.0	0	0

a) Rat aorta was preincubated with agonists, DMSO (0.5%, control), nifedipine (1 μg/ml), or prazosin (1 μg/ml) at 37 °C for 15 min; then high K^+ (80 mM) and Ca^{2+} (1.9 mM) or norepinephrine (NE, 3 μM) were added. Percentages of the control constriction were calculated and presented as means ± standard errors of the mean ($n=3$). b) Generated vasoconstriction (3—16%) in the absence of norepinephrine.

vasorelaxant. A suitable substituent on the C_2-phenyl moiety enhanced the antiplatelet activity, while all substituents interfered with the vasorelaxing effect. The aromatic ring plays an important role in the vasorelaxing effect of α-methylene-γ-butyrolactones; naphthalene was inactive, quinolines exhibited only α-receptor affinity, and coumarins possessed both affinity and intrinsic activity.

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 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 length 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.

3-Chloro-4-methyl-7-(2-oxopropoxy)-2*H*-1-benzopyran-2-one (1g) To a solution of 3-chloro-7-hydroxy-4-methylcoumarin (2.10 g, 10 mmol) in acetone (20 ml) were added potassium carbonate (5.53 g, 40 mmol) and chloroacetone (1.38 g, 15 mmol). The resulting mixture was refluxed for 4 h (monitored by TLC). Evaporation of the solvent gave a residue, which was poured into ice water (50 ml). The resulting solid was collected and crystallized from ethyl acetate to afford **1g** (2.37 g, 89%). mp 181—183 °C. IR (KBr) ν_{max}: 1714, 1628. UV ($CHCl_3$) λ_{max} (log ε): 311 (4.14), 244 (3.57). ^1H-NMR ($CDCl_3$) δ: 2.31 (3H, s, 3′-CH_3), 2.56 (3H, s, 4-CH_3), 4.65 (2H, s, OCH_2), 6.78 (1H, d, $J=2.5$ Hz, 8-H), 6.94 (1H, dd, $J=8.9$, 2.6 Hz, 6-H), 7.57 (1H, d, $J=8.9$ Hz, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 16.18 (4-Me), 26.55 (C-3′), 72.95 (C-1′), 101.79 (C-8), 112.95 (C-6), 114.18 (C-4a), 118.37 (C-3), 126.23 (C-5), 147.67 (C-4), 152.97 (C-8a), 157.02 (C-7), 160.40 (C-2), 203.28 (C-2′). *Anal.* Calcd for $C_{13}H_{11}ClO_4$: C, 58.55; H, 4.16. Found: C, 58.52; H, 4.20.

3-Chloro-4-methyl-7-(2-oxo-2-phenylethoxy)-2*H*-1-benzopyran-2-one (1h) Compound **1h** was prepared from 2-bromoacetophenone by means of the same procedure as described for **1g**, in 66% yield. mp 196—197 °C. IR (KBr) ν_{max}: 1725, 1702, 1625. UV ($CHCl_3$) λ_{max} (log ε): 310 (4.20), 249 (4.14). ^1H-NMR ($CDCl_3$) δ: 2.55 (3H, s, 4-CH_3), 5.40 (2H, s, OCH_2), 6.81 (1H, d, $J=2.6$ Hz, 8-H), 6.99 (1H, dd, $J=8.9$, 2.6 Hz, 6-H), 7.49—8.02 (6H, m, 5-H and Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 16.19 (4-Me), 70.62 (C-1′), 101.88 (C-8), 113.34 (C-6), 114.07 (C-4a), 118.72 (C-3), 126.12 (C-5), 128.01, 129.07, 134.15, 134.32 (Ar-Cs), 147.76 (C-4), 152.96 (C-8a), 157.22 (C-7), 160.83 (C-2), 193.00 (C-2′). *Anal.* Calcd for $C_{18}H_{13}ClO_4$: C, 65.76; H, 3.98. Found: C, 65.74; H, 4.07.

3-Chloro-7-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-4-methyl-2*H*-1-benzopyran-2-one (2g) 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 **1g** (0.8 g, 3 mmol) in dry THF (60 ml). The mixture was refluxed under a nitrogen atmosphere for 36 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 CH_2Cl_2 extracts were combined, washed with saline, dried over Na_2SO_4, and then evaporated to give a residual solid, which was crystallized from ethyl acetate to afford **2g**. Yield: 72%. mp 137—139 °C. IR (KBr) ν_{max}: 1752, 1715, 1617. UV ($CHCl_3$) λ_{max} (log ε): 326 (4.24), 244 (3.67). ^1H-NMR ($CDCl_3$) δ: 1.58 (3H, s, 2′-CH_3), 2.54 (3H, s, 4-CH_3), 2.80 (1H, dt, $J=17.1$, 2.8 Hz, 3′-H), 3.19 (1H, dt, $J=17.2$, 2.6 Hz, 3′-H), 3.99, 4.10 (2H, AB type, $J=9.8$ Hz, OCH_2), 5.70 (1H, t, $J=2.5$ Hz, $CH_2=C(4')$), 6.30 (1H, t, $J=2.8$ Hz, $CH_2=C(4')$), 6.78 (1H, d, $J=2.5$ Hz, 8-H), 6.88 (1H, dd, $J=8.9$, 2.5 Hz, 6-H), 7.52 (1H, d, $J=8.8$ Hz, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 16.19 (4-Me), 24.12 (2′-Me), 36.59 (C-3′), 73.22 (C-1″), 81.04 (C-2′), 101.59 (C-8), 113.15, 113.92 (C-4a, C-6), 118.26 (C-3), 122.38 (vinylic C), 126.07 (C-5), 135.02 (C-4′), 147.82 (C-4), 152.90 (C-8a), 157.18 (C-7), 160.90 (C-2), 169.37 (C-5′). *Anal.* Calcd for $C_{17}H_{15}ClO_5$: C, 61.00; H, 4.52. Found: C, 61.09; H, 4.57.

3-Chloro-7-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenyl-2-furanyl)methoxy]-4-methyl-2*H*-1-benzopyran-2-one (2h) Compound **2h** was prepared by means of the same procedure as described for **2g**, in 71% yield. mp 149—150 °C. IR (KBr) ν_{max}: 1762, 1724, 1618. UV ($CHCl_3$) λ_{max} (log ε): 328 (4.25), 244 (3.69). ^1H-NMR ($CDCl_3$) δ: 2.52 (3H, s, 4-CH_3), 3.24 (1H, dt, $J=16.9$, 2.9 Hz, 3′-H), 3.68 (1H, dt, $J=16.9$, 2.5 Hz, 3′-H), 4.18, 4.25 (2H, AB type, $J=10.3$ Hz, OCH_2), 5.71 (1H, t, $J=2.5$ Hz, $CH_2=C(4')$), 6.31 (1H, t, $J=2.9$ Hz, $CH_2=C(4')$), 6.73 (1H, d, $J=2.4$ Hz, 8-H), 6.84 (1H, dd, $J=8.9$, 2.5 Hz, 6-H), 7.38—7.52 (6H, m, 5-H, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 16.17 (4-Me), 37.35 (C-3′), 74.47 (C-1″), 83.89 (C-2′), 101.77 (C-8), 113.13, 113.99 (C-4a, C-6), 118.32 (C-3), 122.02

(vinylic C), 126.03 (C-5), 125.04, 128.76, 128.93, 139.83 (Ar-Cs), 134.57 (C-4′), 147.72 (C-4), 152.85 (C-8a), 157.09 (C-7), 160.79 (C-2), 169.08 (C-5′). *Anal.* Calcd for $C_{22}H_{17}ClO_5$: C, 66.59; H, 4.32. Found C, 66.23; H, 4.41.

2-Methyl-8-(2-oxopropoxy)quinoline (6a) A mixture of 2-methyl-8-hydroxyquinoline (0.80 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 chloroacetone (0.46 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), and then poured into ice water (100 ml). The pale yellow solid thus obtained was collected and crystallized from CH_2Cl_2 and Et_2O (1 : 10) to afford **6a** (0.77 g, 72%). mp 99—100 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, 3′-CH_3), 2.79 (3H, s, 2-CH_3), 4.86 (2H, s, OCH_2), 6.88—7.44 (3H, m, Ar-H), 7.33 (1H, d, J=8.4 Hz, 3-H), 8.03 (1H, d, J=8.5 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 25.50 (2-Me), 26.49 (C-3′), 74.53 (C-1′), 110.39, 120.94, 122.72, 125.40, 127.92, 136.14, 139.66, 153.25, 158.35 (Ar-Cs), 206.48 (C-2′). *Anal.* Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.42; H, 6.09; N, 6.49.

8-Acetoxy-2-(2-oxopropoxy)quinoline (7a) Prepared from 8-acetoxyquinolin-2(1*H*)-one,[14] as described for **6a**. Yield: 66%. mp 79—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s, CH_3), 2.42 (3H, s, 3′-CH_3), 4.85 (2H, s, OCH_2), 7.06 (1H, d, J=8.8 Hz, 3-H), 7.26—7.67 (3H, m, Ar-H), 8.08 (1H, d, J=8.9 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 20.72 (Me), 26.07 (C-3′), 70.98 (C-1′), 113.19, 121.99, 124.27, 125.47, 126.69, 138.64, 139.67 (Ar-Cs), 145.95 (C-8), 160.84 (C-2), 169.53 (COMe), 206.15 (C-2′). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.82; H, 5.15; N, 5.44.

8-[(2,3,4,5-Tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-2-methylquinoline (11a) 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 **6a** (0.65 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, washed with water, dried over Na_2SO_4, and then evaporated to give a residual oil, which was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent to afford **11a** (0.6 g, 70%). UV λ_{max} (log ε): 253 (4.42) (0.1 N HCl/MeOH), 238 (4.45) (MeOH), 239 (4.46) (0.1 N NaOH/MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, s, 2′-CH_3), 2.71 (3H, s, 2-CH_3), 2.80 (1H, dt, J=17.2, 2.8 Hz, 3′-H), 3.53 (1H, dt, J=17.2, 2.7 Hz, 3′-H), 4.24, 4.30 (2H, AB type, J=10.3 Hz, OCH_2), 5.67 (1H, t, J=2.5 Hz, CH_2=C(4′)), 6.28 (1H, t, J=2.7 Hz, CH_2=C(4′)), 7.08—7.42 (3H, 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: 23.87 (2′-Me), 25.20 (2-Me), 36.39 (C-3′), 75.07 (OCH_2), 81.89 (C-2′), 112.60, 120.94, 121.41, 122.02, 125.19, 127.49, 135.47, 135.60, 140.07, 153.90, 157.67 (Ar-Cs), 169.53 (C-5′). *Anal.* Calcd for $C_{17}H_{17}NO_3 \cdot 0.125H_2O$: C, 71.50; H, 6.09; N, 4.90. Found: C, 71.26; H, 6.13; N, 4.73.

2-[(2,3,4,5-Tetrahydro-2-methyl-4-methylene-5-oxo-2-furanyl)methoxy]-8-hydroxyquinoline (12a) 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** (0.78 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, 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 **12a** (0.59 g, 60%) as white crystals. mp 99—100 °C. UV λ_{max} (log ε): 258 (4.70) (0.1 N HCl in MeOH), 246 (4.69) (MeOH), 261 (4.59) (0.1 N NaOH in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, s, 2′-CH_3), 2.78 (1H, dt, J=18.0, 2.8 Hz, 3′-H), 3.17 (1H, dt, J=17.0, 2.6 Hz, 3′-H), 4.50 (2H, s, OCH_2), 5.65 (1H, t, J=2.6 Hz, CH_2=C(4′)), 6.29 (1H, t, J=2.8 Hz, CH_2=C(4′)), 6.91 (1H, d, J=8.8 Hz, 3-H), 7.18—7.41 (3H, m, Ar-H), 8.02 (1H, d, J=8.8 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 24.28 (Me), 36.87 (C-3′), 70.49 (OCH_2), 81.33 (C-2′), 111.24, 113.39, 118.03, 122.08, 125.22, 125.28, 135.17, 135.37, 139.67 (Ar-Cs), 150.58 (C-8), 160.54 (C-2), 169.62 (C-5′). *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.38; H, 5.32; N, 5.00.

Pharmacology

Aortic Constriction Wistar rats of either sex, weighing 250 to 300 g, were killed by means of a blow to the head. The thoracic aorta was isolated and excess fat and connective tissue were removed. Vessels were cut into rings of about 5 mm in length and each was mounted in an organ bath containing 5 ml of Krebs solution 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 solution was maintained at 37 °C and bubbled with a 95% 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 solution and maintained under an optimal tension of 1 g before specific experimental protocols were initiated; contractions were recorded isometrically *via* a force displacement transducer connected to a Gould polygraph (Medel 2400). The final concentration of DMSO was fixed at 0.5%.

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