162. Synthesis and Evaluation of α-Methylidene-γ-butyrolactone Bearing Flavone and Xanthone Moieties

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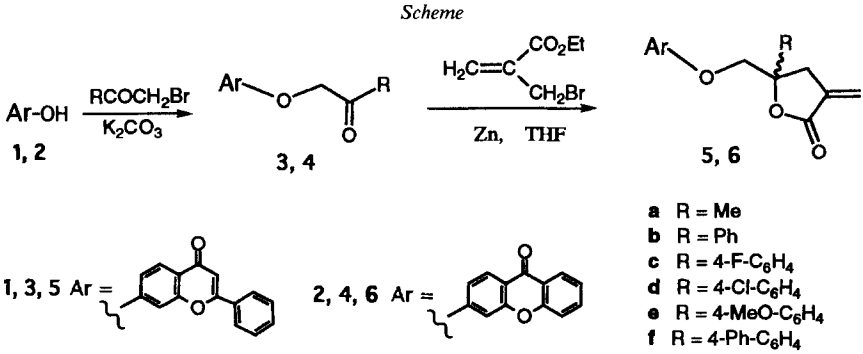
In a search for inhibitors of platelet aggregation, a number of α-methylidene-γ-butyrolactones **5** and **6** bearing flavone or xanthone moieties, respectively, were synthesized and evaluated for their antiplatelet activity against thrombin(Thr)-, arachidonic-acid(AA)-, collagen(Col)-, and platelet-activating-factor(PAF)-induced aggregation in washed rabbit platelets. These compounds were synthesized from 7-hydroxyflavone (**1**) or 3-hydroxyxanthone (**2**) *via* *O*-alkylation (→ **3** and **4**, resp.) and *Reformatsky*-type condensation (*Scheme*). Most of the flavone-containing α-methylidene-γ-butyrolactones **5a–d** showed potent antiplatelet effects on AA- and Col-induced aggregation, while xanthone derivatives **6c–e** were found to have the same pharmacological profile than aspirin in which only AA-induced aggregation was inhibited (*Table 1*). However, **6c–e** were approximately three to ten times more potent than aspirin (*Table 2*). For the vasorelaxing effects, **5a** was the only compound which exhibited significant inhibitory activity on the high-K^+-medium, Ca^{2+}-induced vasoconstriction (*Table 3*). Both **5a** and **6a**, with an aliphatic Me substituent at C(γ) of the lactone, were active against norepinephrine-induced phasic and tonic constrictions while their γ-aryl-substituted counterparts **5b–f** and **6b–f** were inactive.

Introduction. – Coumarin (= 2*H*-1-benzopyran-2-one) derivatives such as bishydroxycoumarin and warfarin have been used as oral anticoagulants. Other clinically useful antiplatelet drugs are aspirin, eicosapentanoic acid (EPA), dipyridamole, and ticlopidine. Their utilization is, however, limited by the potency and the side effects. In our search for effective antiplatelet agents, we have synthesized several coumarin α-methylidene-γ-butyrolactones and evaluated their cardiovascular activities. Among them, 7-[(2-aryl-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)methoxy]-2*H*-1-benzopyran-2-ones and their 4-substituted counterparts have shown potent and broad-spectrum antiplatelet effects, in which thrombin(Thr)-, arachidonic-acid(AA)-, collagen(Col)-, and platelet-activating-factor(PAF)-induced aggregation of rabbit platelets were inhibited [1] [2]. To determine the effect of structural modification with respect to the optimal antiplatelet activity, certain α-methylidene-γ-butyrolactones in which the coumarin moiety was replaced by a quinoline, quinolin-2(1*H*)-one, flavone (= 4*H*-1-benzopyran-4-one), or xanthone (= 9*H*-xanthen-9-one) moiety were synthesized and evaluated [3–5]. The quinoline and quinolin-2(*H*)-one analogs were found to be broad-spectrum but less active in potency than their coumarin counterparts. However, the flavone and

xanthone analogs became more selective antiplatelet agents in which only AA- and Col-induced aggregations were inhibited [3]. Flavones and xanthones are interesting heterocyclic ketones, because they are ubiquitous families of phytochemicals that possess a wide variety of biological activities. A number of natural and synthetic flavones and xanthones were also found to exhibit vasorelaxing and antiplatelet activities [6–10]. In an attempt to better understand their structure-activity relationships, certain α-methylidene-γ-butyrolactones bearing a flavone or xanthone moiety were prepared and evaluated.

Results and Discussion. – 7-Hydroxyflavone (**1**) was treated with potassium carbonate and bromomethyl ketones to provide 7-(2-substituted 2-oxoethoxy)-2-phenyl-4*H*-1-benzopyran-4-ones **3a–f** (*Scheme*). Reaction of **3a–f** with ethyl 2-(bromomethyl)acrylate in dry THF (*Reformatsky*-type condensation) gave the 7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)methoxy]-2-phenyl-4*H*-1-benzopyran-4-ones **5a–f** in 42–62% overall yield. Accordingly, the 3-[(2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)-methoxy]-9*H*-xanthen-9-ones **6a–f** were prepared from 3-(2-substituted 2-oxoethoxy)-9*H*-xanthen-9-ones **4a–f** which were obtained *via* alkylation of 3-hydroxyxanthone (**2**) in an 64–80% overall yield.

Scheme



The antiplatelet activities of α-methylidene-γ-butyrolactones 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 the potential inhibitors was 100 μg/ml. Compound **5b** inhibited AA- and Col-induced platelet aggregation completely (*Table 1*), and those by Thr and PAF partially [3]. When the lactone Ph–C(γ) group of **5b** was replaced by the aliphatic Me group (**5a**) or an electron-withdrawing 4-F- or 4-Cl-substituted phenyl group (**5c, d**), comparable antiplatelet activities were observed. However, when the Ph–C(γ) group was replaced by an electron-donating 4-MeO–C_6H_4 or 4-Ph–C_6H_4 substituent (**5e, f**), the antiplatelet activities were lost completely. Compounds **6b** and **6a** also exhibited good inhibitory activity against the AA- and Col-induced aggregation. However, when the lactone Ph–C(γ) group of **6b** was replaced by a 4-F–C_6H_4, 4-Cl–C_6H_4, or 4-MeO–C_6H_4 substituent (**6c–e**), these compounds became highly selective in which only AA-induced aggregation was inhibited. The antiplatelet activities of

these α-methylidene-γ-butyrolactones were lost when the lactone Ph–C(γ) group was replaced by a bulky 4-Ph–C_6H_4 substituent (**5f** and **6f**). The inhibitory concentrations for 50% aggregation (IC_{50}) induced by AA and PAF are given in *Table 2*. Compound **5a**, with an aliphatic Me substituent at C(γ) of the lactone, was less active against AA-induced aggregation than its γ-aryl-substituted counterparts **5b–d**, but was more active against those induced by PAF. For xanthone derivatives, only **6a** was active against

Table 1. *Effect of α-Methylidene-γ-butyrolactones on the Platelet Aggregation* [%] *Induced by Thrombin* (Thr), *Arachidonic Acid* (AA), *Collagen* (Col), *and Platelet-Activating Factor* (PAF) *in Washed Rabbit Platelets*[a])

	Aggregation [%]			
	Thr (0.1 U/ml)	AA (100 μM)	Col (10 μg/ml)	PAF (2 nM)
Control	92.8 ± 1.5	87.2 ± 1.0	88.8 ± 1.5	90.3 ± 1.6
5a	43.8 ± 10.0[e])	0[b])[c])	0	12.9 ± 7.3[c])
b	65.6 ± 9.3[d])	0	0	36.8 ± 4.2[c])
c	63.0 ± 5.5[c])	0	0	48.1 ± 7.1[c])
d	69.0 ± 8.0[d])	0	0	67.2 ± 8.3[d])
e	73.4 ± 3.6[c])	78.3 ± 4.4[d])	78.0 ± 4.7[e])	68.2 ± 5.9[c])
f	76.5 ± 8.1[e])	82.3 ± 1.7[d])	81.0 ± 4.5[d])	82.0 ± 5.2[d])
6a	70.1 ± 7.1[d])	0	0	28.3 ± 12.6[c])
b	81.7 ± 3.7[d])	0	0	70.3 ± 4.1[c])
c	79.7 ± 2.6[c])	0	81.1 ± 0.8[c])	75.1 ± 3.2[c])
d	81.4 ± 4.1[e])	0	83.6 ± 2.4[e])	77.8 ± 4.7[e])
e	86.4 ± 3.4[d])	0	83.7 ± 3.7[d])	74.8 ± 3.4[c])
f	90.0 ± 3.7[d])	83.5 ± 1.2[d])	80.8 ± 6.0[d])	89.1 ± 1.4[d])
Aspirin	91.9 ± 1.4	0	85.4 ± 3.9	90.5 ± 1.2

[a]) Platelets were preincubated with DMSO (0.5%, control), aspirin (50 μg/ml), or α-methylidene-γ-butyrolactones (100 μg/ml) 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]) Complete inhibition in all experiments. [c]) Significantly different from control value at $p < 0.001$. [d]) Significantly different from control value at $p < 0.01$. [e]) Significantly different from control value at $p < 0.05$.

Table 2. IC_{50} *Values* [μM] *of α-Methylidene-γ-butyrolactones on the Platelet Aggregation Induced by AA and PAF*

	AA	PAF
5a	39.4	101
b	6.1	>150
c	6.8	>150
d	5.8	>150
e	>150	>150
f	>150	>150
6a	18.8	127
b	18.5	>150
c	10.0	>150
d	18.2	>150
e	37.9	>150
f	>150	>150
Aspirin	118	>150

PAF-induced aggregation. Compounds **6c–e** were found to have the same pharmacological profile than aspirin in which only AA-induced aggregation was inhibited. However, **6c–e** were approximately three to ten times more potent than aspirin.

Effects of flavone- and xanthone-containing α-methylidene-γ-butyrolactones on the Ca^{2+}-dependent constriction induced by high K^+ and on the phasic and tonic constrictions induced by norepinephrine (NE) in rat aorta are given in *Table 3*. Compound **5a** was the only compound which exhibited significant inhibitory activity on the high-K^+-medium, Ca^{2+}-induced vasoconstriction. Both **5a** and **6a**, with an aliphatic Me substituent at C(γ) of the lactone, were active against NE-induced phasic and tonic constrictions, while their γ-aryl-substituted counterparts **5b–f** and **6b–f** were inactive. A similar result was obtained with 8-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1*H*)-one bearing an aliphatic Me substituent at C(γ) of the lactone and corresponding γ-aryl-substituted analogs. The former was the only compound which exhibited significant inhibitory activity on the high-K^+-medium, Ca^{2+}-induced vasoconstriction, and was more active than most of its γ-aryl-substituted counterparts against NE-induced phasic and tonic constrictions [4]. This finding is interesting, because γ-phenyl-substituted lactones were found to be better antiplatelet agents than their corresponding γ-methyl-substituted lactone counterparts [1–5].

As a result of these studies, α-methylidene-γ-butyrolactones possess not only antitumor, bactericidal, fungicidal, antibiotic, and anthelmintic activities [11–16] but also antiplatelet and vasorelaxing effects. Although coumarin-containing α-methylidene-γ-butyrolactones and their quinoline analogs inhibited the platelet aggregation caused by four inducers, flavone- and xanthone-containing α-methylidene-γ-butyrolactones exhib-

Table 3. *Effects of α-Methylidene-γ-butyrolactones in High K^+ and Ca^{2+}-Induced and Norepinephrine-Induced Constriction of Rat Thoracic Aorta*[a])

Agonist	K (80 mM) + Ca (1.9 mM)	NE (3 μM), phasic	NE (3 μM) tonic
Control	100 ± 3.8	100 ± 2.9	100 ± 2.1
5a	28.3 ± 3.5	0	24.4 ± 8.7
b	100.1 ± 4.0	90.9 ± 7.7	96.9 ± 3.2
c	98.9 ± 8.6	113.0 ± 5.0	95.0 ± 10.6
d	100.5 ± 6.8	94.7 ± 3.7	86.9 ± 4.9
e	94.1 ± 1.4	81.7 ± 1.2	94.5 ± 2.0
f	97.9 ± 1.5	109.4 ± 5.4	95.5 ± 4.1
6a	94.1 ± 4.2	50.4 ± 3.8	32.2 ± 2.8
b	98.7 ± 3.0	80.2 ± 3.6	87.5 ± 5.1
c	100.3 ± 5.5	85.9 ± 2.5	73.9 ± 9.3
d	98.6 ± 0.9	83.7 ± 3.0	89.6 ± 3.8
e	99.4 ± 4.6	79.3 ± 4.0	88.9 ± 2.2
f	100.1 ± 1.7	83.6 ± 3.3	84.5 ± 1.6
Nifedipine	0	98.7 ± 0.7	96.5 ± 2.1
Prazosin	100 ± 2.0	0	0

[a]) Rat aorta were preincubated with α-methylidene-γ-butyrolactones (100 μg/ml), DMSO (0.5%, control), nifedipine (1 μg/ml), or prazosin (1 μg/ml) at 37° for 15 min; then high K^+ (80 mM) and Ca^{2+} (1.9 mM) or norepinephrine (NE, 3 μM) was added. Percentages of the control constriction were calculated and presented as means ± standard errors of the mean (n = 3).

ited selective antiplatelet activities. An aliphatic Me substituent at C(γ) of the lactone moiety is essential for these α-methylidene-γ-butyrolactones to be active as vasorelaxing agents.

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Experimental Part

General. See [4].

*7-(2-Oxopropoxy)-2-phenyl-4*H*-1-benzopyran-4-one* (**3a**). 7-Hydroxyflavone (**1**; 2.38 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. was added bromoacetone (1.37 g, 10 mmol) in dry DMF (10 ml) in one portion. The resulting mixture was stirred at r.t. for 12 h (TLC monitoring) and then poured into ice-water (100 ml). The pale yellow solid thus obtained was collected and crystallized from CH_2Cl_2/Et_2O 1:10: **3a** (1.65 g, 56%). Pale yellow needles. M.p. 157–158°. ^{1}H-NMR ($CDCl_3$): 2.34 (*s*, Me); 4.69 (*s*, 2H–C(1′)); 6.77 (*s*, H–C(3)); 6.91–8.19 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 26.63 (Me); 73.08 (C(1′)); 101.51, 107.61, 114.37, 118.65, 126.20, 127.55, 129.05, 131.56, 131.68, 157.79, 162.07, 163.25 (arom. C); 177.65 (C(4)); 203.83 (C(2′)). Anal. calc. for $C_{18}H_{14}O_4 \cdot 0.25\ H_2O$: C 72.35, H 4.89; found: C 72.21, H 4.83.

*7-[2-(4-Fluorophenyl)-2-oxoethoxy]-2-phenyl-4*H*-1-benzopyran-4-one* (**3c**). From 2-bromo-4′-fluoroacetophenone as described for **3a**: 91% yield. Pale yellow needles. M.p. 185–186°. ^{1}H-NMR ($CDCl_3$): 5.39 (*s*, 2H–C(1′)); 6.75 (*s*, H–C(3)); 6.96–8.17 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 70.74 (C(1′)); 101.75, 107.56, 114.37, 116.03, 116.47, 118.59, 126.17, 127.43, 128.99, 130.64, 130.87, 131.06, 131.49, 131.69, 157.72, 162.28, 163.19, 163.76, 168.87 (arom. C); 177.66 (C(4)); 191.78 (C(2′)). Anal. calc. for $C_{23}H_{15}FO_4$: C 73.79, H 4.04; found: C 73.64, H 4.05.

*7-[2-(4-Chlorophenyl)-2-oxoethoxy]-2-phenyl-4*H*-1-benzopyran-4-one* (**3d**). From 2-bromo-4′-chloroacetophenone as described for **3a**: 82% yield. M.p. 159–160°. ^{1}H-NMR ($CDCl_3$): 5.38 (*s*, 2H–C(1′)); 6.75 (*s*, H–C(3)); 6.96–8.17 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 70.82 (C(1′)); 101.80, 107.63, 114.37, 118.69, 126.21, 127.49, 129.03, 129.39, 129.63, 131.52, 131.74, 132.50, 140.86, 157.74, 162.25, 163.22 (arom. C); 177.65 (C(4)); 192.28 (C(2′)). Anal. calc. for $C_{23}H_{15}ClO_4$: C 70.68, H 3.87; found: C 70.65, H 3.95.

*7-[2-(4-Methoxyphenyl)-2-oxoethoxy]-2-phenyl-4*H*-1-benzopyran-4-one* (**3e**). From 2-bromo-4′-methoxyacetophenone as described for **3a**: 75% yield. M.p. 172–173.°. ^{1}H-NMR ($CDCl_3$): 3.90 (*s*, MeO); 5.37 (*s*, 2 H–C(1′)); 6.75 (*s*, H–C(3)); 6.96–8.17 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 55.60 (MeO); 70.70 (C(1′)); 101.74, 107.60, 114.21, 114.53, 118.50, 126.21, 127.21, 127.35, 129.00, 130.55, 131.45, 131.80, 157.79, 162.59, 163.16, 164.37 (arom. C); 177.72 (C(4)); 191.65 (C(2′)). Anal. calc. for $C_{24}H_{18}O_5$: C 74.60, H 4.69; found: C 74.34, H 4.78.

*7-{2-{[1,1′-Bi(phenyl)]-4-yl}-2-oxoethoxy}-2-phenyl-4*H*-1-benzopyran-4-one* (**3f**). From 2-bromo-4′-methoxyacetophenone as described for **3a**: 80% yield. M.p. 168–169°. ^{1}H-NMR ($CDCl_3$): 5.46 (*s*, 2H–C(1′)); 6.76 (*s*, H–C(3)); 6.99–8.19 (*m*, 17 arom. H). ^{13}C-NMR ($CDCl_3$): 70.84 (C(1′)); 101.77, 107.60, 114.47, 118.57, 126.20, 127.28, 127.42, 127.59, 128.57, 128.73, 128.99, 129.05, 131.45, 131.76, 132.79, 139.48, 146.99, 157.77, 162.46, 163.19 (arom. C); 177.72 (C(4)); 192.75 (C(2′)). Anal. calc. for $C_{29}H_{20}O_4$: C 80.54, H 4.66; found: C 80.16, H 4.71.

*3-(2-Oxopropoxy)-9*H*-xanthen-9-one* (**4a**). As described for **3a**, from 3-hydroxyxanthone: 98% yields. M.p. 163–164°. ^{1}H-NMR ($CDCl_3$): 2.33 (Me); 4.68 (*s*, 2 H–C(1′)); 6.81–8.34 (*m*, 7 arom. H). ^{13}C-NMR ($CDCl_3$): 26.63 (Me); 73.03 (C(1′)); 101.23, 113.15, 116.59, 117.73, 121.91, 124.04, 126.67, 128.73, 134.50, 156.19, 157.85, 162.89 (arom. C); 176.16 (C(9)); 203.79 (C(2′)). Anal. calc. for $C_{16}H_{12}O_4$: C 71.63, H 4.51; found: C 71.36, H 4.57.

Compounds **4c–f** were prepared from 3-hydroxyxanthone by the same procedures as **3c–f**, resp.

*3-[2-(4-Fluorophenyl)-2-oxoethoxy]-9*H*-xanthen-9-one* (**4c**). Yield 94%. M.p. 204–205°. ^{1}H-NMR ((D_6)DMSO): 5.84 (*s*, 2 H–C(1′)); 7.12–8.20 (*m*, 11 arom. H). ^{13}C-NMR ((D_6)DMSO): 70.67 (C(1′)); 101.60, 113.96, 115.22, 115.68, 116.11, 117.83, 121.17, 124.30, 125.87, 127.56, 130.93, 131.12, 135.04, 155.58, 157.37, 162.88, 163.63, 167.90 (arom. C); 174.86 (C(9)); 192.14 (C(2′)). Anal. calc. for $C_{21}H_{13}FO_4$: C 72.41, H 3.76; found: C 72.30, H 3.76.

*3-[2-(4-Chlorophenyl)-2-oxoethoxy]-9*H*-xanthen-9-one* (**4d**). Yield 82%. M.p. 197–198°. ^{1}H-NMR ($CDCl_3$): 5.37 (*s*, 2 H–C(1′)); 6.86–8.32 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 70.71 (C(1′)); 101.45, 113.15, 116.56, 117.65, 121.85, 123.95, 126.63, 128.64, 129.33, 129.56, 132.45, 134.41, 140.79, 156.13, 157.75, 163.04 (arom. C); 176.12 (C(9)); 192.18 (C(2′)). Anal. calc. for $C_{21}H_{13}ClO_4$: C 69.14, H 3.59; found: C 69.03, H 3.58.

3-[2-(4-Methoxyphenyl)-2-oxoethoxy]-9H-xanthen-9-one (**4e**). Yield 92%. M.p. 188–189°. ^{1}H-NMR ((D$_6$)DMSO): 3.89 (*s*, MeO); 5.78 (*s*, 2 H–C(1')); 7.10–8.20 (*m*, 11 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 55.63 (MeO); 70.45 (C(1')); 101.55, 113.97, 114.06, 115.15, 117.84, 121.17, 124.30, 125.87, 127.03, 127.55, 130.29, 135.03, 155.59, 157.35, 163.69, 163.76 (arom. C); 174.85 (C(9)); 191.78 (C(2')). Anal. calc. for $C_{22}H_{16}O_5 \cdot H_2O$: C 69.83, H 4.79; found: C 69.79, H 4.42.

3-{2-{[1,1'-Bi(phenyl)]-4-yl}-2-oxoethoxy}-9H-xanthen-9-one (**4f**). Yield 94%. M.p. 200–201°. ^{1}H-NMR ((D$_6$)DMSO): 5.89 (*s*, 2 H–C(1')); 7.14–8.21 (*m*, 16 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 70.78 (C(1')); 101.63, 114.00, 115.22, 117.86, 121.18, 124.32, 125.88, 126.96, 127.03, 127.59, 128.51, 128.68, 129.10, 132.93, 135.06, 138.76, 145.26, 155.60, 157.38, 163.70 (arom. C); 174.88 (C(9)); 193.06 (C(2')). Anal. calc. for $C_{27}H_{18}O_4 \cdot 0.25$ H_2O: C 78.91, H 4.54; found: C 79.13, H 4.57.

2-Phenyl-7-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-4H-1-benzopyran-4-one (**5a**). To a soln. of **3a** (0.88 g, 3 mmol) in dry THF (60 ml) were added activated Zn powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and ethyl 2-(bromomethyl)acrylate (0.78 g, 4 mmol). 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 CH_2Cl_2 extracts were combined and washed with H_2O, dried (Na_2SO_4), and evaporated to give a brown solid which was purified by column chromatography (silica gel, CH_2Cl_2) and crystallization from CH_2Cl_2/Et_2O 1:10: **5a** (0.85 g, 78%). M.p. 138–139°. UV (0.1N HCl/MeOH): 251 (4.30), 304 (4.41). UV (MeOH): 250 (4.31), 304 (4.45). UV (0.1N NaOH/MeOH): 305 (4.45). ^{1}H-NMR ($CDCl_3$): 1.60 (*s*, Me); 2.80 (*dt*, *J* = 17.1, 2.8, 1 H–C(3')); 3.21 (*dt*, *J* = 17.1, 2.6, 1 H–C(3')); 4.04, 4.15 (*AB*, *J* = 9.6, CH_2O); 5.70 (*t*, *J* = 2.4, 1 H, CH_2=C(4')); 6.32 (*t*, *J* = 2.6, 1 H, CH_2=C(4')); 6.76 (*s*, H–C(3)); 6.94–8.16 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 24.18 (Me); 36.68 (C(3')); 73.27 (CH_2O); 80.95 (C(2')); 101.51, 107.60, 114.38, 118.49, 122.44, 126.19, 127.36, 129.05, 131.53, 131.75, 135.00, 157.78, 162.51, 163.20 (arom. C); 169.34 (C(5')); 177.72 (C(4)). Anal. calc. for $C_{22}H_{18}O_5$: C 72.91, H 5.01; found: C 72.53, H 5.06.

The same procedure was used to convert **3c–f** to **5c–f** and **4a–f** to **6a–f**, resp.

7-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-2-phenyl-4H-1-benzopyran-4-one (**5c**). Yield 68%. M.p. 182–183°. UV (0.1N HCl/MeOH): 250 (4.20), 305 (4.30). UV (MeOH): 250 (4.17), 304 (4.28). UV (0.1N NaOH/MeOH): 305 (4.31). ^{1}H-NMR ($CDCl_3$): 3.23 (*dt*, *J* = 16.9, 2.9, 1 H–C(3')); 3.67 (*dt*, *J* = 16.9, 2.4, 1 H–C(3')); 4.19, 4.28 (*AB*, *J* = 10.1, CH_2O); 5.74 (*t*, *J* = 2.6, 1 H, CH_2=C(4')); 6.35 (*t*, *J* = 2.7, 1 H, CH_2=C(4')); 6.76 (*s*, H–C(3)); 6.91–8.14 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 37.39 (C(3')); 74.45 (CH_2O); 83.35 (C(2')); 101.63, 107.59, 114.30, 115.70, 116.13, 118.60, 122.38, 126.17, 126.98, 127.14, 127.42, 129.03, 131.54, 131.69, 134.29, 135.75, 157.71, 160.29, 162.25, 163.21, 165.24 (arom. C); 168.83 (C5')); 177.69 (C(4)). Anal. calc. for $C_{27}H_{19}FO_5$: C 73.29, H 4.33; found: C 73.02, H 4.40.

7-{[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-2-phenyl-4H-1-benzopyran-4-one (**5d**). Yield 63%. M.p. 174–175°. UV (0.1N HCl/MeOH): 250 (4.29), 305 (4.38). UV (MeOH): 250 (4.27), 304 (4.38). UV (0.1N NaOH/MeOH): 305 (4.38). ^{1}H-NMR ($CDCl_3$): 3.21 (*dt*, *J* = 16.9, 2.9, 1 H–C(3')); 3.67 (*dt*, *J* = 16.9, 2.5, 1 H–C(3')); 4.19, 4.27 (*AB*, *J* = 10.1, CH_2O); 5.75 (*t*, *J* = 2.6, 1 H, CH_2=C(4')); 6.35 (*t*, *J* = 2.9, 1 H, CH_2=C(4')); 6.75 (*s*, H–C(3)); 6.90–8.14 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 37.27 (C(3')); 74.24 (CH_2O); 83.25 (C(2')); 101.61, 107.54, 114.25, 118.58, 122.49, 126.13, 126.56, 127.38, 129.00, 129.10, 131.51, 131.64, 134.09, 134.84, 138.41, 157.66, 162.17, 163.17 (arom. C); 168.71 (C(5')); 177.64 (C(4)). Anal. calc. for $C_{27}H_{19}ClO_5$: C 70.67, H 4.17; found: C 70.62, H 4.21.

2-Phenyl-7-{[2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-methylidene-5-oxofuran-2-yl]methoxy}-4H-1-benzopyran-4-one (**5e**). Yield 77%. M.p. 184–185°. UV (0.1N HCl/MeOH): 249 (4.29), 305 (4.38). UV (MeOH): 248 (4.27), 304 (4.36). UV (0.1N NaOH/MeOH): 305 (4.42). ^{1}H-NMR ($CDCl_3$): 3.24 (*dt*, *J* = 16.9, 2.9, 1 H–C(3')); 3.65 (*dt*, *J* = 16.9, 2.4, 1 H–C(3')); 3.84 (*s*, MeO); 4.17, 4.28 (*AB*, *J* = 10.1, CH_2O); 5.72 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.33 (*t*, *J* = 2.9, 1 H, CH_2=C(4')); 6.75 (*s*, H–C(3)); 6.91–8.14 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 37.26 (C(3')); 55.38 (MeO); 74.56 (CH_2O); 83.66 (C(2')); 101.58, 107.54, 114.23, 114.35, 118.47, 121.93, 126.15, 126.41, 127.33, 129.00, 131.48, 131.70, 131.82, 134.72, 157.71, 159.81, 162.39, 163.14 (arom. C); 169.12 (C(5')); 177.70 (C(4)). Anal. calc. for $C_{28}H_{22}O_6$: C 74.00, H 4.88; found: C 73.92, H 4.89.

7-{{2-{[1,1'-Bi(phenyl)]-4-yl}-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl}methoxy}-2-phenyl-4H-1-benzopyran-4-one (**5f**). Yield 66%. M.p. 145–146°. UV (0.1N HCl/MeOH): 252 (4.55), 304 (4.33). UV (MeOH): 252 (4.56), 305 (4.33). UV (0.1N NaOH/MeOH): 305 (4.36). ^{1}H-NMR ($CDCl_3$): 3.30 (*dt*, *J* = 16.9, 2.9, 1 H–C(3')); 3.72 (*dt*, *J* = 16.9, 2.4, 1 H–C(3')); 4.26, 4.35 (*AB*, *J* = 10.1, CH_2O); 5.75 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.36 (*t*, *J* = 2.9, 1 H, CH_2=C(4')); 6.75 (*s*, H–C(3)); 6.93–8.15 (*m*, 17 arom. H). ^{13}C-NMR ($CDCl_3$): 37.32 (C(3')); 74.49 (CH_2O); 83.73 (C(2')); 101.64, 107.56, 114.39, 118.54, 122.17, 125.58, 126.17, 127.12, 127.37, 127.60, 127.79, 128.93, 129.02, 131.51, 131.70, 134.53, 138.78, 140.11, 141.78, 157.73, 162.38, 163.17 (arom. C); 169.05 (C(5')); 177.71 (C(4)). Anal. calc. for $C_{33}H_{24}O_5$: C 79.18, H 4.83; found: C 79.05, H 4.92.

3-[(2,3,4,5-Tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-9H-xanthen-9-one (**6a**). Yield 82%. M.p. 118–119°. UV (0.1N HCl/MeOH): 232 (sh, 4.58), 266 (3.98), 297 (4.05). UV (MeOH): 230 (4.67, sh), 266 (4.02), 297 (4.09). UV (0.1N NaOH/MeOH): 265 (4.08), 297 (4.13). ^{1}H-NMR ($CDCl_3$): 1.60 (*s*, Me); 2.80 (*dt*, *J* = 17.2, 2.8, 1 H–C(3')); 3.20 (*dt*, *J* = 17.2, 2.6, 1 H–C(3')); 4.04, 4.14 (*AB*, *J* = 9.7, CH_2O); 5.70 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.31 (*t*, *J* = 2.9, 1 H, CH_2=C(4')); 6.85–8.33 (*m*, 7 arom. H). ^{13}C-NMR ($CDCl_3$): 24.17 (Me); 36.67 (C(3')); 73.17 (CH_2O); 80.96 (C(2')); 101.18, 113.22, 116.39, 117.74, 121.91, 122.43, 124.00, 126.66, 128.51, 134.45, 135.01, 156.19, 157.83, 163.36 (arom. C); 169.35 (C(5')); 176.20 (C(9)). Anal. calc. for $C_{20}H_{16}O_5$: C 71.42, H 4.80; found: C 71.47, H 4.81.

3-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-9H-xanthen-9-one (**6c**). Yield 80%. M.p. 164–165°. UV (0.1N HCl/MeOH): 235 (4.16, sh), 265 (3.61), 297 (3.75). UV (MeOH): 234 (4.13, sh), 265 (3.59), 297 (3.72). UV (0.1N NaOH/MeOH): 265 (3.80), 297 (3.84). ^{1}H-NMR ($CDCl_3$): 3.22 (*dt*, *J* = 16.9, 2.9, 1 H–C(3')); 3.67 (*dt*, *J* = 16.9, 2.4, 1 H–C(3')); 4.18, 4.27 (*AB*, *J* = 10.1, CH_2O); 5.74 (*t*, *J* = 2.6, 1 H, CH_2=C(4')); 6.35 (*t*, *J* = 2.8, 1 H, CH_2=C(4')); 6.81–8.24 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 37.42 (C(3')); 74.38 (CH_2O); 83.38 (C(2')); 101.36, 113.14, 115.71, 116.14, 116.55, 117.73, 121.92, 122.37, 124.04, 126.69, 126.98, 127.15, 128.60, 134.33, 134.48, 135.77, 135.84, 156.19, 157.79, 160.30, 163.12, 165.25 (arom. C); 168.83 (C(5')); 176.18 (C(9)). Anal. calc. for $C_{25}H_{17}FO_5$: C 72.11, H 4.12; found: C 71.82, H 4.12.

3-{[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-9H-xanthen-9-one (**6d**). Yield 81%. M.p. 174–175°. UV (0.1N HCl/MeOH): 235 (4.31, sh), 265 (3.75), 298 (3.90). UV (MeOH): 235 (4.33, sh), 265 (3.77), 298 (3.90). UV (0.1N NaOH/MeOH): 265 (4.00), 297 (4.04). ^{1}H-NMR ($CDCl_3$): 3.20 (*dt*, *J* = 16.9, 2.9, 1 H–C(3')); 3.67 (*dt*, *J* = 16.9, 2.4, 1 H–C(3')); 4.18, 4.27 (*AB*, *J* = 10.1, CH_2O); 5.74 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.25 (*t*, *J* = 2.8, 1 H, CH_2=C(4')); 6.81–8.29 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 37.27 (C(3')); 74.14 (CH_2O); 83.24 (C(2')); 101.30, 113.06, 116.51, 117.68, 121.84, 122.47, 123.99, 126.54, 126.62, 128.54, 129.08, 134.09, 134.44, 134.81, 138.40, 156.12, 157.72, 163.02 (arom. C); 168.70 (C(5')); 176.12 (C(9)). Anal. calc. for $C_{25}H_{17}ClO_5$: C 69.37, H 3.96; found: C 69.09, H 4.03.

3-{[2,3,4,5-Tetrahydro-2-(4-methoxyphenyl)-4-methylidene-5-oxofuran-2-yl]methoxy}-9H-xanthen-9-one (**6e**). Yield 85%. M.p. 173–174°. UV (0.1N HCl/MeOH): 230 (4.12, sh), 266 (3.53), 298 (3.65). UV (MeOH): 230 (4.14, sh), 266 (3.53), 298 (3.64). UV (0.1N NaOH/MeOH): 266 (3.86), 298 (3.83). ^{1}H-NMR ($CDCl_3$): 3.23 (*dt*, *J* = 16.9, 2.9, 1 H–C(3')); 3.64 (*dt*, *J* = 16.9, 2.5, 1 H–C(3')); 3.83 (*s*, MeO); 4.17, 4.27 (*AB*, *J* = 10.2, CH_2O); 5.71 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.32 (*t*, *J* = 2.9, 1 H, CH_2=C(4')); 6.81–8.32 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 37.31 (C(3')); 55.41 (MeO); 74.49 (CH_2O); 83.70 (C(2')); 101.32, 113.21, 114.26, 116.43, 117.72, 121.91, 123.98, 126.43, 126.65, 128.51, 131.86, 134.42, 134.78, 156.17, 157.79, 159.84, 163.28 (arom. C); 169.15 (C(5')); 176.18 (C(9)). Anal. calc. for $C_{26}H_{20}O_6 \cdot 0.25\ H_2O$: C 72.13, H 4.77; found: C 72.15, H 4.67.

3-{{2-{[1,1'-Bi(phenyl)]-4-yl}-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl}methoxy}-9H-xanthen-9-one (**6f**). Yield 68%. M.p. 188–189°. UV (0.1N HCl/MeOH): 237 (4.64, sh), 258 (4.38), 297 (4.16). UV (MeOH): 236 (4.72, sh), 257 (4.46), 297 (4.21). UV (0.1N NaOH/MeOH): 236 (4.75, sh), 257 (4.47), 297 (4.24). ^{1}H-NMR ($CDCl_3$): 3.29 (*dt*, *J* = 17.0, 2.9, 1 H–C(3')); 3.71 (*dt*, *J* = 17.0, 2.4, 1 H–C(3')); 4.25, 4.34 (*AB*, *J* = 10.2, CH_2O); 5.74 (*t*, *J* = 2.5, 1 H, CH_2=C(4')); 6.35 (*t*, *J* = 2.9, 1 H, CH_2=C(4')); 6.84–8.33 (*m*, 16 arom. H). ^{13}C-NMR ($CDCl_3$): 37.33 (C(3')); 74.40 (CH_2O); 83.73 (C(2')); 101.36, 113.20, 116.48, 117.71, 121.91, 122.14, 123.99, 125.57, 126.66, 127.12, 127.59, 127.77, 128.55, 128.91, 134.43, 134.53, 138.79, 140.12, 141.77, 156.17, 157.79, 163.23 (arom. C); 169.04 (C(5')); 176.19 (C(9)). Anal. calc. for $C_{31}H_{22}O_5$: C 78.47, H 4.67; found: C 78.42, H 4.67.

Pharmacological Evaluation. Aortic constriction, antiplatelet evaluation, and platelet aggregation as described in [4].

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