58. Synthesis of Coumarin Derivatives as Inhibitors of Platelet Aggregation

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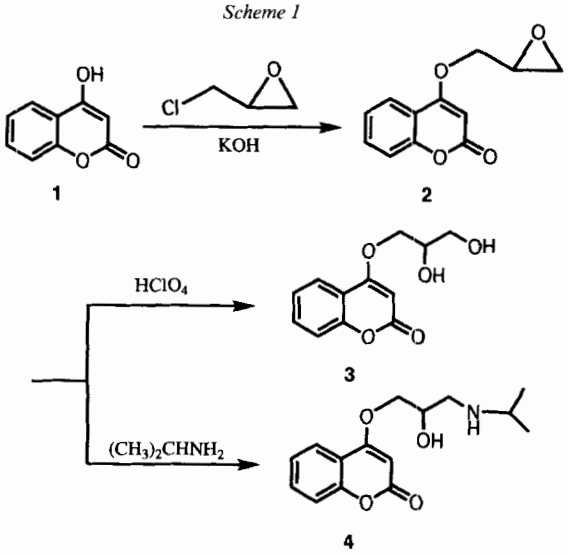
In a search for the inhibitors of platelet aggregation, certain coumarin derivatives were synthesized and evaluated for antiplatelet activity against thrombin(Thr)-, arachidonic acid(AA)-, collagen(Col)-, and platelet-activating-factor(PAF)-induced aggregation in washed rabbit platelets. These compounds were synthesized from 4-hydroxycoumarin (**1**) or naphthalen-1-ol *via* alkylation and *Reformatsky*-type condensation (*Schemes 1–3*). Among them, 4-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**6b**) showed potent antiplatelet effects on AA- and PAF-induced aggregation with IC_{50} values of 8.21 and 103.67 μM, respectively (see *Tables 1* and *2*). The antiplatelet potency of **6b** against PAF-induced aggregation could be further improved by introducing a proper substituent at the 2-phenyl group of the lactone ring.

Introduction. – Coumarin (= 1*H*-2-benzopyran-1-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. As part of our new drug-discovery projects, we have synthesized several coumarin derivatives carrying a side chain at C(4) with various functional groups, such as a 2-hydroxy-3-(isopropylamino)propoxy group (see **4**), the side chain of a potent β-adrenergic blocking propranolol [1–3], and a methoxy group substituted with an α-methylidene-γ-butyrolactone moiety (see **6**), an integral building block of many biologically active natural products [4–6], in a hope of discovering new coumarin anticoagulants. These compounds were synthesized from 4-hydroxycoumarin (**1**) or naphthalen-1-ol *via* alkylation and *Reformatsky*-type condensation. Among them, 4-[2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**6b**) showed potent antiplatelet effects on AA- and PAF-induced aggregation with IC_{50} values of 8.21 and 103.67 μM, respectively. The antiplatelet potency of **6b** against PAF-induced aggregation could be further inproved by introducing a proper substituent at the 2-phenyl group of the lactone ring.

The α-methylidene-γ-butyrolactone moiety seems to play a very important role for the antiplatelet activity, yet the function of coumarin is not clear. Therefore, the 4,5-dihydro-5-methyl-3-methylidenefuran-2(3*H*)-one **8a** and its 5-phenyl counterpart **8b**, possessing the bicyclic naphthalene instead of the coumarin moiety, were prepared for the antiplatelet screening. Their preliminary structure-activity relationships were also discussed.

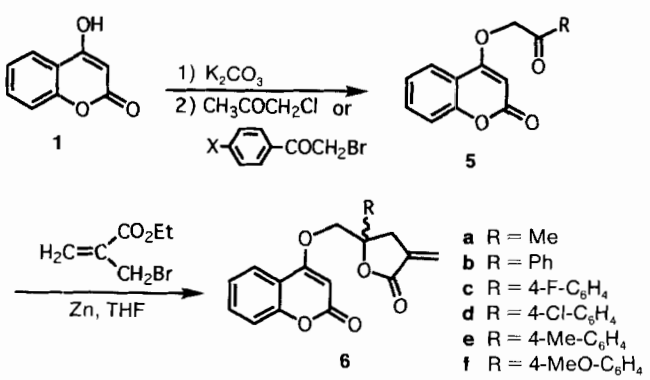
Results and Discussion. – Hydroxycoumarin **1** was treated with KOH and epichlorohydrin to give 4-[(oxiran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**2**) as shown in *Scheme 1*. Reaction of **2** with either perchloric acid or (i-Pr)NH_2 gave 4-(2,3-dihydroxypropoxy)-2*H*-1-benzopyran-2-one (**3**) or 4-[2-hydroxy-3-(isopropylamino)propoxy]-2*H*-1-benzopyran-2-one (**4**), respectively.

Scheme 1



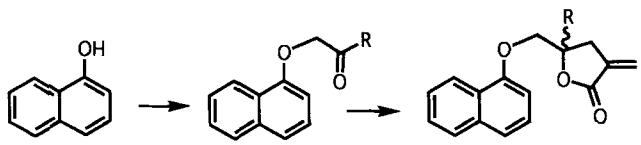
The preparation of 4-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**6a**) is illustrated in *Scheme 2*. Hydroxycoumarin **1** was treated with K_2CO_3 and chloroacetone to provide 4-(2-oxopropoxy)-2*H*-1-benzopyran-2-one (**5a**) which was then reacted with ethyl 2-(bromomethyl)acrylate in tetrahydrofuran (THF; *Reformatsky*-type reaction) to give **6a** in 42% overall yield. Treatment of **1** with K_2CO_3 and 2-bromoacetophenone gave 4-(2-oxo-2-phenylethoxy)-2*H*-1-benzopyran-2-one (**5b**) which was reacted with ethyl 2-(bromomethyl)acrylate in THF

Scheme 2



to afford 4-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**6b**) in 55% overall yield. Accordingly, the 4,5-dihydro-5-methyl-3-methylidene-5-[(naphthalen-1-yloxy)methyl]furan-2(3*H*)-one (**8a**) and its 5-phenyl counterpart **8b** were prepared from 1-(naphthalen-1-yloxy)propan-2-one (**7a**) and 2-(naphthalen-1-yloxy)-1-phenylethan-1-one (**7b**), respectively, which were obtained *via* alkylation of naphthalen-1-ol (*Scheme 3*).

Scheme 3



7a R = Me
b R = Ph

8a R = Me
b R = Ph

The antiplatelet activities of coumarin derivatives 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 results are shown in *Table 1*. Compound **2** was found to have a weak activity against AA-induced aggregation, while compounds **3** and **4** were devoid of activity at the concentration of 100 μg/ml. The 4-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**6a**) exhibited fairly good inhibitory activities on AA-, collagen-, and PAF-induced aggregation but was inactive against thrombin-

Table 1. *Effect of 4-Substituted Coumarins on the Platelet Aggregation* [%] *Induced by Thrombin* (Thr), *Arachidonic Acid* (AA), *Collagen* (Col), *and Platelet-Activating Factor* (PAF) *in Washed Rabbit Platelets*[a])

	Inducer			
	Thr 0.1 U/ml	AA 100 μM	Col 10 μg/ml	PAF 2nM
Control	92.8 ± 1.5(4)	87.2 ± 1.0(6)	88.8 ± 1.5(4)	90.3 ± 1.6(7)
2	87.5 ± 1.8(4)	48.0 ± 15.2(4)[c])	78.3 ± 1.7(3)[b])	69.8 ± 7.3(4)[c])
3	88.7 ± 0.7(3)	81.8 ± 3.6(3)	87.4 ± 1.2(3)	82.7 ± 2.3(3)[d])
4	92.4 ± 0.5(4)	86.3 ± 4.0(3)	84.7 ± 1.5(3)	83.1 ± 3.2(3)[d])
6a	74.4 ± 9.6(4)	23.3 ± 12.6(4)[b])	8.5 ± 6.9(3)[b])	33.6 ± 16.6(5)[b])
b	0.0 ± 0.0(4)	0.0 ± 0.0(3)	0.0 ± 0.0(3)	0.0 ± 0.0(4)[b])
c	0.0 ± 0.0(3)[b])	0.0 ± 0.0(4)[b])	0.0 ± 0.0(3)[b])	0.0 ± 0.0(3)[b])
d	0.0 ± 0.0(3)[b])	0.0 ± 0.0(4)[b])	6.0 ± 5.2(4)[b])	0.0 ± 0.0(3)[b])
e	7.9 ± 3.6(3)[b])	0.0 ± 0.0(4)[b])	0.0 ± 0.0(3)[b])	0.0 ± 0.0(4)[b])
f	36.3 ± 6.8(3)[b])	0.0 ± 0.0(4)[b])	0.0 ± 0.0(3)[b])	0.0 ± 0.0(4)[b])
8a	79.9 ± 4.0(4)[c])	0.0 ± 0.0(3)[b])	0.0 ± 0.0(3)[b])	76.8 ± 3.4(3)[d])
b	89.5 ± 1.0(3)	0.0 ± 0.0(3)[b])	0.0 ± 0.0(3)[b])	73.1 ± 5.6(3)[d])
Aspirin	91.9 ± 1.4(3)	0.0 ± 0.0(3)[c])	85.4 ± 3.9(4)	90.5 ± 1.2(3)

[a]) Platelets were preincubated with DMSO (0.5%, control), aspirin (10 μg/ml), or 4-substituted coumarins (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*).

[b]) Significantly different from control value at $p < 0.001$.

[c]) Significantly different from control value at $p < 0.01$.

[d]) Significantly different from control value at $p < 0.05$.

induced aggregation. Its 2-phenyl counterpart **6b** demonstrated potent and broad-spectrum antiplatelet effects in which thrombin-induced aggregation was also inhibited. Significant antiplatelet activities were also observed, when the 2-phenyl group of **6b** was replaced by a 4-halogen-, 4-Me-, or 4-MeO-substituted phenyl group (see **6c–f**), and the less electron-donating substituent the stronger activity against thrombin-induced aggregation. Compounds **8a** and **8b** exhibited good inhibitory activities on AA- and collagen-induced aggregation but was inactive against either thrombin- or PAF-induced aggregation indicating that both coumarin and α-methylidene-γ-butyrolactone moieties are required for the compounds to be broad-spectrum antiplatelet agents.

The inhibitory concentration for 50% aggregation (IC_{50}) induced by AA and PAF was expressed in *Table 2*. The 4-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**6a**), with Me substituent at C(2) of the lactone moiety, was shown to be less active than its Ph–C(2) counterpart **6b**. Compounds **6c–f**, possessing a substituted phenyl group at C(2), were found to have broad antiplatelet activities in which both AA- and PAF-induced aggregation were strongly inhibited. This finding is especially important for most of the antiplatelet agents are either narrow-spectrum or specific. *E.g.*, aspirin inhibits AA-induced platelet aggregation but not those induced by thrombin, collagen, and PAF. Further studies on methoxy-substituted coumarins with an α-methylidene-γ-butyrolactone moiety as candidates for potent and versatile antiplatelet agents are undergoing.

Table 2. IC_{50} *Values* (μM) *of 4-Substituted Coumarins on the Platelet Aggregation Induced by AA and PAF*

	AA	PAF		AA	PAF
6a	191.21	278.67	**8a**	34.90	> 500
b	8.21	103.67	**b**	22.26	> 500
c	14.14	14.58			
d	8.99	22.92			
e	10.02	10.02			
f	12.08	12.77			

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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.: *YANACO* micromelting-point apparatus; uncorrected. UV Spectra (λ_{max} (log ε) in nm): *Beckman* UV/VIS spectrophotometer. IR Spectra (cm^{-1}): *Hitachi-260-30* spectrophotometer. ^1H- and ^{13}C-NMR Spectra: *Varian-Gemini-200* spectrometer, chemical shifts δ in ppm with $SiMe_4$ as an internal standard. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer, and results were within ±0.4% of theoretical values.

*4-[(Oxiran-2-yl)methoxy]-2*H*-1-benzopyran-2-one* (**2**). To a stirred soln. of 4-hydroxycoumarin (**1**; 3.24 g, 20 mmol) in EtOH (100 ml) was added an aq. soln. of KOH (1.25 g in 5 ml H_2O). The soln. was stirred at r.t. for 30 min, and then epichlorohydrin (20 ml) was added. The mixture was heated at reflux for 2.5 h (TLC monitoring). Evaporation gave a residue which was partitioned between H_2O (80 ml) and $CHCl_3$ (100 ml). The org. phase was washed with H_2O (80 ml), dried (Na_2SO_4), and evaporated. Crystallization of the residue from EtOH gave **2** (3.28 g, 80%). White solid. M.p. 114–116°. ^1H-NMR ($CDCl_3$): 2.83 (*dd*, *J* = 4.7, 2.7, 1 H–C(3′)); 3.00 (*dd*, *J* = 4.6, 4.2, 1 H–C(3′)); 3.48 (*m*, H–C(2′)); 4.03 (*dd*, *J* = 11.3, 6.4, 1 H, CH_2O); 4.49 (*dd*, *J* = 11.2, 2.6, 1 H, CH_2O); 5.71 (*s*, H–C(3)); 7.30 (*m*, H–C(6), H–C(8)); 7.57 (*m*, H–C(7)); 7.87 (*dd*, *J* = 7.9, 1.3, H–C(5)). ^{13}C-NMR ($CDCl_3$):

44.42 (C(3')); 49.17 (C(2')); 70.00 (CH_2O); 90.95 (C(3)); 115.41 (C(4a)); 116.81 (C(8)); 123.14 (C(5)); 124.06 (C(6)); 132.66 (C(7)); 153.33 (C(8a)); 162.80 (C(4)); 165.32 (C(2)). Anal. calc. for $C_{12}H_{10}O_4$: C 66.05, H 4.62; found: C 65.96, H 4.66.

*4-(2,3-Dihydroxypropoxy)-2*H*-1-benzopyran-2-one* (**3**). A soln. of **2** (2.06 g, 10 mmol) in 6% perchloric acid (50 ml) was stirred at r.t. for 16 h. Then, the pH was adjusted to **8** with $NaHCO_3$, and the soln. was extracted continuously with CH_2Cl_2 for 24 h. Removal of the solvent gave **3** (1.48 g, 63%) as a viscous liquid which solidified upon standing. M.p. 145–147°. ^{1}H-NMR (DMSO): 3.51 (*m*, 2 H–C(3')); 3.90 (*m*, H–C(2')); 4.18 (*m*, 2 H–C(1')); 4.77 (*t*, *J* = 4.7, OH–C(3')); 5.18 (*d*, *J* = 5.2, OH–C(2')); 5.88 (*s*, H–C(3)); 7.39 (*m*, H–C(6), H–C(8)); 7.66 (*m*, H–C(7)); 7.90 (*dd*, *J* = 8.2, 1.6, H–C(5)). ^{13}C-NMR (DMSO): 62.24 (C(3')); 69.40 (C(2')); 71.20 (C(1')); 90.52 (C(3)); 115.51 (C(4a)); 116.54 (C(8)); 123.34 (C(5)); 124.27 (C(6)); 132.94 (C(7)); 153.03 (C(8a)); 161.95 (C(4)); 165.54 (C(2)). Anal. calc. for $C_{12}H_{12}O_5$: C 61.05, H 5.12; found: C 60.80, H 5.18.

*4-[2-Hydroxy-3-(isopropylamino)propoxy]-2*H*-1-benzopyran-2-one* (**4**). To a soln. of **2** (1.03 g, 5 mmol) in EtOH (15 ml) was added isopropylamine (0.61 g, 10 mmol) and the mixture heated under reflux for 2 h (TLC monitoring). After evaporation the residue was crystallized from EtOH: **4** (0.94 g, 68%). Pale yellow powder. M.p. 103–105°. ^{1}H-NMR ($CDCl_3$):1.12 (*d*, *J* = 6.2, Me_2CH); 2.58 (br. *s*, OH, NH); 2.87 (*m*, 2 H–C(3'), Me_2CH); 4.14 (*m*, 2 H–C(1'), H–C(2')); 5.71 (*s*, H–C(3)); 7.28 (*m*, H–C(6), H–C(8)); 7.54 (*m*, H–C(7)); 7.83 (*dd*, *J* = 8.6, 1.6, H–C(5)). ^{13}C-NMR ($CDCl_3$): 22.99, 23.19 (Me_2CH); 48.95 (C(3'), Me_2CH); 67.67 (C(2')); 71.59 (C(1')); 90.80 (C(3)); 115.59 (C(4a)); 116.80 (C(8)); 123.02 (C(5)); 123.93 (C(6)); 132.49 (C(7)); 153.31 (C(8a)); 162.87 (C(4)); 165.56 (C(2)). Anal. calc. for $C_{15}H_{18}NO_4$: C 65.20, H 6.56, N 5.07; found: C 64.83, H 6.91, N 5.12.

*4-(2-Oxopropoxy)-2*H*-1-benzopyran-2-one* (**5a**). To a soln. of **1** (1.62 g, 10 mmol) in acetone (20 ml) were added K_2CO_3 (5.53 g, 40 mmol) and chloroacetone (1.38 g, 15 mmol). The resulting mixture was refluxed for 4 h (TLC monitoring). Evaporation of the solvent gave a residue which was poured into ice water (50 ml). The resulting solid was collected and crystallized from AcOEt: **5a** (1.28 g, 55%). White crystalline needles. 163–165°. IR (KBr): 1716, 1625. UV ($CHCl_3$): 305 (3.83), 266 (4.05). ^{1}H-NMR ($CDCl_3$): 2.36 (*s*, Me–C(3')); 4.77 (*s*, 2 H–C(1')); 5.57 (*s*, H–C(3)); 7.32 (*m*, H–C(6), H–C(8)); 7.59 (*m*, H–C(7)); 7.91 (*dd*, *J* = 8.2, 1.8, H–C(5)). ^{13}C-NMR ($CDCl_3$): 26.06 (C(3')); 72.69 (C(1')); 91.34 (C(3)); 115.20 (C(4a)); 116.88 (C(8)); 123.09 (C(5)); 124.18 (C(6)); 132.83 (C(7)); 153.41 (C(8a)); 162.38 (C(4)); 164.60 (C(2)); 200.91 (C(2')). Anal. calc. for $C_{12}H_{10}O_4$: C 66.05, H 4.62; found: C 66.01, H 4.64.

*4-(2-Oxo-2-phenylethoxy)-2*H*-1-benzopyran-2-one* (**5b**). From 2-bromoacetophenone as described for **5a**: 63% yield. M.p. 183–184°. IR (KBr): 1721, 1703, 1626. UV ($CHCl_3$): 306 (3.79), 253 (4.28). ^{1}H-NMR ($CDCl_3$): 5.50 (*s*, 2 H–C(1')); 5.61 (*s*, H–C(3)); 7.30 (*m*, H–C(6), H–C(8)); 7.60 (*m*, H–C(5), H–C(7), 2 arom. H); 7.98 (*m*, 3 arom. H). ^{13}C-NMR ($CDCl_3$): 70.44 (C(1')); 91.37 (C(3)); 115.37 (C(4a)); 116.75 (C(8)); 123.33 (C(5)); 124.10 (C(6)); 132.68 (C(7)); 127.92, 129.13, 133.81, 134.51 (arom. C); 153.37 (C(8a)); 162.52 (C(4)); 164.94 (C(2)); 190.92 (C(2')). Anal. calc. for $C_{17}H_{12}O_4$: C 72.85, H 4.32; found: C 72.85, H 4.72.

*4-[2-(4-Fluorophenyl)-2-oxoethoxy]-2*H*-1-benzopyran-2-one* (**5c**). From 2-chloro-4'-fluoroacetophenone as described for **5a**: 57% yield. M.p. 205–206°. ^{1}H-NMR ($CDCl_3$): 5.44 (*s*, 2 H–C(1')); 5.60 (*s*, H–C(3)); 7.26 (*m*, H–C(6), H–C(8), 2 arom. H); 7.59 (*m*, H–C(7)); 7.99 (*m*, H–C(5), 2 arom. H). ^{13}C-NMR ($CDCl_3$): 70.32 (C(1')); 91.43 (C(3)); 115.29 (C(4a)); 116.68 (C(8)); 123.24 (C(5)); 124.14 (C(6)); 116.52 (*J* = 28.6), 130.29 (*J* = 3.3), 130.76 (*J* = 9.4), 166.46 (*J* = 257.4, arom. C); 132.75 (C(7)); 153.39 (C(8a)); 162.40 (C(4)); 164.83 (C(2)); 189.44 (C(2')). Anal. calc. for $C_{17}H_{11}FO_4$: C 68.46, H 3.72; found: C 68.52, H 3.86.

*4-[2-(4-Chlorophenyl)-2-oxoethoxy]-2*H*-1-benzopyran-2-one* (**5d**). From 2-bromo-4'-chloroacetophenone as described for **5a**: 63% yield. M.p. 220–221°. ^{1}H-NMR ((D_6)DMSO): 5.88 (*s*, 2 H–C(1')); 6.09 (*s*, H–C(3)); 7.41 (*m*, H–C(6), H–C(8)); 7.68 (*m*, H–C(7), 2 arom. H); 7.93 (*dd*, *J* = 8.4, 1.4, H–C(5)); 8.08 (*m*, 2 arom. H). ^{13}C-NMR ((D_6)DMSO): 71.24 (C(1')); 91.56 (C(3)); 115.08 (C(4a)); 116.40 (C(8)); 122.88 (C(5)); 124.19 (C(6)); 128.87, 129.86, 132.58, 138.94 (arom. C); 132.74 (C(7)); 152.76 (C(8a)); 161.50 (C(4)); 164.30 (C(2)); 191.16 (C(2')). Anal. calc. for $C_{17}H_{11}ClO_4$: C 64.88, H 3.52; found: C 64.76, H 3.61.

*4-[2-(4-Methylphenyl)-2-oxoethoxy]-2*H*-1-benzopyran-2-one* (**5e**). From 2-bromo-4'-methylacetophenone as described for **5a**: 51% yield. M.p. 168–170°. ^{1}H-NMR ($CDCl_3$): 2.46 (*s*, MeO); 5.45 (*s*, 2 H–C(1')); 5.59 (*s*, H–C(3)); 7.31 (*m*, H–C(6), H–C(8), 2 arom. H); 7.58 (*m*, H–C(7)); 7.88 (*m*, 2 arom. H); 7.97 (*dd*, *J* = 8.0, 1.4, H–C(5)). ^{13}C-NMR ($CDCl_3$): 21.84 (Me); 70.37 (C(1')); 91.34 (C(3)); 115.41 (C(4a)); 116.74 (C(8)); 123.34 (C(5)); 124.07 (C(6)); 128.01, 129.79, 131.34, 145.66 (arom. C); 132.64 (C(7)); 153.38 (C(8a)); 162.51 (C(4)); 164.97 (C(2)); 190.43 (C(2')). Anal. calc. for $C_{18}H_{14}O_4$: C 73.46, H 4.80; found: C 73.51, H 4.92.

*4-[2-(4-Methoxyphenyl)-2-oxoethoxy]-2*H*-1-benzopyran-2-one* (**5f**). From 2-bromo-4'-methoxyacetophenone as described for **5a**: 58% yield. M.p. 167–169°. ^{1}H-NMR ($CDCl_3$): 3.91 (*s*, Me); 5.43 (*s*, 2 H–C(1')); 5.60 (*s*, H–C(3)); 7.00 (*m*, 2 arom. H); 7.31 (*m*, H–C(6), H–C(8)); 7.58 (*m*, H–C(7)); 7.96 (*m*, H–C(5), 2 arom. H). ^{13}C-NMR ($CDCl_3$): 55.59 (MeO); 70.25 (C(1')); 91.34 (C(3)); 115.40 (C(4a)); 116.73 (C(8)); 123.32 (C(5)); 124.06

(C(6)); 114.31, 126.80, 130.31, 164.51 (arom. C); 132.62 (C(7)); 153.36 (C(8a)); 162.55 (C(4)); 165.01 (C(2)); 189.30 (C(2')). Anal. calc. for $C_{18}H_{14}O_5 \cdot 0.5\ H_2O$: C 67.71, H 4.74; found: C 67.62, H 4.78.

*4-[(2,3,4,5-Tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one* (**6a**). To a soln. of **5a** (0.66 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 heated under refluxed under N_2 for 36 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl soln. (300 ml) and extracted with CH_2Cl_2 (3 × 75 ml). The CH_2Cl_2 extract was washed with brine, dried (Na_2SO_4), and evaporated and the residual solid crystallized from AcOEt to afford **6a** (0.66 g, 77%). Pale yellow crystals. M.p. 161–162°. IR (KBr): 1766, 1703, 1627. UV ($CHCl_3$): 306 (3.79), 276 (4.01), 266 (4.05). ^{1}H-NMR ($CDCl_3$): 1.64 (*s*, Me–C(2')); 2.88 (*dt*, J = 17.4, 2.9, 1 H–C(3')); 3.19 (*dt*, J = 17.3, 2.5, 1 H–C(3')); 4.18 (A_2B_2, CH_2O); 5.67 (*s*, H–C(3)); 5.75 (*t*, J = 2.5, 1 H, CH_2=C(4')); 6.38 (*t*, J = 2.9, 1 H, CH_2=C(4')); 7.22 (*m*, H–C(6), H–C(8)); 7.58 (*m*, H–C(5), H–C(7)). ^{13}C-NMR ($CDCl_3$): 24.11 (*Me*–C(2')); 36.77 (C(3')); 73.67 (CH_2O); 80.43 (C(2')); 91.11 (C(3)); 115.15 (C(4a)); 116.86 (C(8)); 122.61 (C(5)); 122.86 (C(6)); 124.17 (CH_2=C(4')); 132.75 (C(7)); 134.94 (C(4')); 153.32 (C(8a)); 162.34 (C(4)); 164.90 (C(2)); 169.10 (C(5')). Anal. calc. for $C_{16}H_{14}O_5$: C 67.13, H 4.93; found: C 67.14, H 5.01.

The same procedure was used to convert each of the compounds **5b–f** to **6b–f**, respectively.

*4-[(2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one* (**6b**). Yield 87%. M.p. 212–214°. IR (KBr): 1766, 1717, 1620. UV ($CHCl_3$): 306 (3.89), 277 (4.10), 266 (4.14). ^{1}H-NMR ($CDCl_3$): 3.33 (*dt*, J = 17.2, 3.0, 1 H–C(3')); 3.66 (*dt*, J = 17.1, 2.4, 1 H–C(3')); 4.29 (A_2B_2, CH_2O); 5.60 (*s*, H–C(3)); 5.79 (*t*, J = 2.4, 1 H, CH_2=C(4')); 6.42 (*t*, J = 3.0, 1 H, CH_2=C(4')); 7.40 (*m*, H–C(5), H–C(6), H–C(7), H–C(8), 5 arom. H). ^{13}C-NMR ($CDCl_3$): 37.59 (C(3')); 74.75 (CH_2O); 83.32 (C(2')); 91.19 (C(3)); 115.13 (C(4a)); 116.83 (C(8)); 122.48 (C(5)); 122.88 (C(6)); 124.17 (CH_2=C(4')); 124.94, 129.06, 129.11, 139.20 (arom. C); 132.72 (C(7)); 134.42 (C(4')); 153.30 (C(8a)); 162.21 (C(4)); 164.81 (C(2)); 168.76 (C(5')). Anal. calc. for $C_{21}H_{16}O_5 \cdot 0.25\ H_2O$: C 71.48, H 4.71; found: C 71.37, H 4.67.

*4-{[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-2*H*-1-benzopyran-2-one* (**6c**). Yield 93%. M.p. 192–195°. IR (KBr): 1777, 1708, 1621. UV ($CHCl_3$): 306 (3.77), 277 (3.98), 266 (4.04). ^{1}H-NMR ($CDCl_3$): 3.30 (*dt*, J = 17.1, 3.0, 1 H–C(3')); 3.65 (*dt*, J = 17.1, 2.3, 1 H–C(3')); 4.26 (A_2B_2, CH_2O); 5.60 (*s*, H–C(3)); 5.80 (*t*, J = 2.4, 1 H, CH_2=C(4')); 6.43 (*t*, J = 2.6, 1 H, CH_2=C(4')); 7.24 (*m*, H–C(5), H–C(7), 2 arom. H). ^{13}C-NMR ($CDCl_3$): 37.60 (C(3')); 74.60 (CH_2O); 82.89 (C(2')); 91.20 (C(3)); 115.01 (C(4a)); 116.83 (C(8)); 112.77 (C(5), C(6)); 124.17 (CH_2=C(4')); 116.12 (J = 24.5), 126.94 (J = 8.3), 135.04 (J = 3.5), 162.85 (J = 248.7, arom. C); 132.75 (C(7)); 134.13 (C(4')); 153.26 (C(8a)); 162.14 (C(4)); 164.70 (C(2)); 168.53 (C(5')). Anal. calc. for $C_{21}H_{15}FO_5 \cdot 0.25\ H_2O$: C 68.01, H 4.21; found: C 68.18, H 4.30.

*4-{[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl]methoxy}-2*H*-1-benzopyran-2-one* (**6d**). Yield 89%. M.p. 178–180°. IR (KBr): 1765, 1712, 1619. UV ($CHCl_3$): 306 (3.80), 277 (4.02), 266 (4.07). ^{1}H-NMR ($CDCl_3$): 3.28 (*dt*, J = 17.1, 3.0, 1 H–C(3')); 3.63 (*dt*, J = 17.1, 2.4, 1 H–C(3')); 4.26 (A_2B_2, CH_2O); 5.60 (*s*, H–C(3)); 5.80 (*t*, J = 2.5, 1 H, CH_2=C(4')); 6.44 (*t*, J = 3.0, 1 H, CH_2=C(4)); 7.26 (*m*, H–C(6), H–C(8)); 7.45 (*s*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 37.52 (C(3')); 74.43 (CH_2O): 83.82 (C(2')); 91.22 (C(3)); 115.00 (C(4a)); 116.86 (C(8)); 122.76 (C(5)); 122.92 (C(6)); 124.18 (CH_2=C(4')); 126.42, 129.32, 135.17, 137.70 (arom. C); 132.77 (C(7)); 133.93 (C(4')); 153.27 (C(8a)); 162.10 (C(4)); 164.67 (C(2)); 168.43 (C(5')). Anal. calc. for $C_{21}H_{15}ClO_5 \cdot 0.5\ H_2O$: C 64.38, H 4.12; found: C 64.12, H 4.14.

*4-{[2,3,4,5-Tetrahydro-4-methylidene-2-(4-methylphenyl)-5-oxofuran-2-yl]methoxy}-2*H*-1-benzopyran-2-one* (**6e**). Yield 75%. M.p. 155–157°. IR (KBr): 1769, 1714, 1623. UV ($CHCl_3$): 306 (3.77), 277 (3.98), 266 (4.02). ^{1}H-NMR ($CDCl_3$): 2.39 (*s*, Me); 3.31 (*dt*, J = 17.1, 3.0, 1 H–C(3')); 3.62 (*dt*, J = 17.1, 2.4, 1 H–C(3')); 4.26 (A_2B_2, CH_2O); 5.60 (*s*, H–C(3)); 5.78 (*t*, J = 2.3, 1 H, CH_2=C(4')); 6.42 (*t*, J = 2.6, 1 H, CH_2=C(4')); 7.33 (*m*, H–C(6), H–C(8), 4 arom. H); 7.58 (*m*, H–C(5), H–C(7)). ^{13}C-NMR ($CDCl_3$): 21.09 (Me); 37.54 (C(3')); 74.74 (CH_2O); 83.31 (C(2')); 91.13 (C(3)); 115.12 (C(4a)); 116.82 (C(8)); 122.35 (C(5)); 122.87 (C(6)); 124.14 (CH_2=C(4')); 124.84, 129.71, 136.14, 139.03 (arom. C); 132.69 (C(7)); 134.51 (C(4')); 153.28 (C(8a)); 162.23 (C(4)); 164.81 (C(2)); 168.82 (C(5')). Anal. calc. for $C_{22}H_{18}O_5 \cdot 0.25\ H_2O$: C 72.22, H 5.10; found: C 72.24, H 4.91.

*4-{[2,3,4,5-Tetrahydro-2-(4-methoxyphenyl)-4-methylidene-5-oxofuran-2-yl]methoxy}-2*H*-1-benzopyran-2-one* (**6f**). Yield 67%. M.p. 189–192°. IR (KBr): 1771, 1702, 1622. UV ($CHCl_3$): 306 (3.83), 277 (4.12), 267 (4.13). ^{1}H-NMR ($CDCl_3$): 3.32 (*dt*, J = 17.2, 2.8, 1 H–C(3')); 3.61 (*dt*, J = 17.2, 2.4, 1 H–C(3')); 3.84 (*s*, MeO); 4.24 (A_2B_2, CH_2O); 5.60 (*s*, H–C(3)); 5.78 (*t*, J = 2.4, 1 H, CH_2=C(4')); 6.41 (*t*, J = 2.8, 1 H, CH_2=C(4')); 6.98 (*m*, 2 arom. H); 7.27 (*m*, H–C(6), H–C(8)); 7.42 (*m*, 2 arom. H); 7.57 (*m*, H–C(5), H–C(7)). ^{13}C-NMR ($CDCl_3$): 37.50 (C(3')); 55.40 (MeO); 74.76 (CH_2O); 83.19 (C(2')); 91.13 (C(3)); 115.12 (C(4a)); 116.81 (C(8)); 122.34 (C(5)); 122.85 (C(6)); 124.14 (CH_2=C(4')); 114.41, 126.30, 131.02, 160.00 (arom. C); 132.68 (C(7)); 134.58 (C(4')); 153.28 (C(8a)); 162.22 (C(4)); 164.79 (C(2)); 168.82 (C(5')). Anal. calc. for $C_{22}H_{18}O_6 \cdot 0.75\ H_2O$: C 67.60, H 5.03; found: C 67.54, H 4.71.

1-(Naphthalen-1-yloxy)propan-2-one (**7a**). A mixture of naphthalen-1-ol (1.44 g, 10 mmol) and K_2CO_3 (1.52 g, 11 mmol) in dry DMF (20 ml) was stirred at r.t. under N_2 for 30 min, and then a soln. of chloroacetone (1.01 g, 11 mmol) in dry DMF (10 ml) was added. The mixture was stirred for 24 h (monitored by TLC), then poured into ice-water (100 ml), and extracted with $CHCl_3$ (20 ml × 3). The org. phase was washed with H_2O, dried, and evaporated and the crude oil submitted to column chromatography (silica gel, $MeOH/CH_2Cl_2$ 1:40 (*v/v*)): **7a** (1.66 g, 83%). Brown syrup. ^{1}H-NMR ($CDCl_3$): 2.38 (*s*, Me–C(3)); 4.67 (*s*, 2 H–C(1)); 6.64–8.38 (*m*, 7 arom H). ^{13}C-NMR ($CDCl_3$): 26.66 (C(3)); 73.09 (C(1)); 104.76, 121.28, 121.76, 125.29, 125.50, 126.60, 127.48, 134.52, 153.32 (arom. C); 205.80 (C(2)). Anal. calc. for $C_{13}H_{12}O_2 \cdot 0.5\ H_2O$: C 74.62, H 6.26; found: C 74.84, H 6.21.

2-(Naphthalen-1-yloxy)-1-phenylethan-1-one (**7b**). As described for **7a**, except that the desired product was recrystallized from $MeOH/H_2O$: white crystals in 78% yield. M.p. 64–67°. ^{1}H-NMR ($CDCl_3$): 5.42 (*s*, CH_2); 6.76–8.39 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 71.29 (C(2)); 105.28, 121.33, 122.16, 125.53, 125.64, 126.59, 127.42, 128.31, 128.80, 133.83, 134.61, 134.77, 153.83 (arom. C); 194.59 (C(1)). Anal. calc. for $C_{18}H_{14}O_2$: C 82.42, H 5.38; found: C 82.63, H 5.46.

4,5-Dihydro-5-methyl-3-methylidene-5-[(naphthalen-1-yloxy)methyl]furan-2(3H)-one (**8a**). From **7a**, as described for **6a**: 69% yield. M.p. 117–119°. UV (MeOH): 271 (3.98), 247 (3.76). ^{1}H-NMR ($CDCl_3$): 1.65 (*s*, Me–C(5)); 2.85 (*dt*, *J* = 17.2, 2.9, 1 H–C(4)); 3.31 (*dt*, *J* = 17.2, 2.5, 1 H–C(4)); 4.13 (A_2B_2, CH_2O); 5.72 (*t*, *J* = 2.5, 1 H, CH_2=C(3)); 6.37 (*t*, *J* = 2.9, 1 H, CH_2=C(3)); 6.75–8.12 (*m*, 7 arom. H). ^{13}C-NMR ($CDCl_3$): 24.35 *Me*–C(5)); 36.98 (C(4)); 73.01 (CH_2O); 81.46 (C(5)); 127.48 (CH_2=C(3)); 135.59 (C(3)); 169.62 (C(2)); 104.71, 121.15, 121.76, 122.06, 125.37, 125.48, 125.58, 126.56, 134.50, 153.90 (arom. C). Anal. calc. for $C_{17}H_{16}O_3$: C 76.10, H 6.01; found: C 75.75, H 6.01.

4,5-Dihydro-3-methylidene-5-[(naphthalen-1-yloxy)methyl]-5-phenylfuran-2(3H)-one (**8b**). From **7b**, as described for **6a**: 72% yield. M.p. 154–156°. UV (MeOH): 291 (3.71). ^{1}H-NMR ($CDCl_3$): 3.30 (*dt*, *J* = 17.0, 3.0, 1 H–C(4)); 3.78 (*dt*, *J* = 17.0, 2.4, 1 H–C(4)); 4.32 (A_2B_2, CH_2O); 5.77 (*t*, *J* = 2.5, 1 H, CH_2=C(3)); 6.44 (*t*, *J* = 3.1, 1 H, CH_2=C(3)); 6.70–8.10 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 37.59 (C(4)); 74.40 (CH_2O); 84.29 (C(5)); 125.11 (CH_2=C(3)); 135.19 (C(3)); 169.26 (C(2)); 104.84, 121.25, 121.78, 121.85, 125.38, 125.50, 126.56, 127.45, 128.57, 128.82, 134.52, 135.20, 140.45, 153.85 (arom. C). Anal. calc. for $C_{22}H_{18}O_3$: C 79.98, H 5.49; found: C 79.77, H 5.65.

Pharmacological 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 and r.t. Platelet suspension was prepared from this EDTA-anticoagulated platelet-rich plasma according to the washing procedures described previously [7]. Platelet numbers were counted with a *Coulter* counter (model *ZM*) and adjusted to $4.5 \cdot 10^8$ platelet/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* [8] using a *Chrono-Log Lumiaggregometer*. To eliminate the effect of the solvent on the aggregation, the final concentration of dimethylsulfoxide (DMSO) was fixed at 0.5%. Percentage of aggregation was calculated using the absorbance of platelet suspension as 0% aggregation and the absorbance of *Tyrode*'s soln. as 100% aggregation. The inhibitory concentration for 50% aggregation (IC_{50}) was calculated from computerization of CA-Cricket Graph III for five to six dose-effect levels.

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