γ-Pyrone Compounds. 5. Synthesis and Antiplatelet Effects of Xanthonoxypropanolamines and Related Compounds

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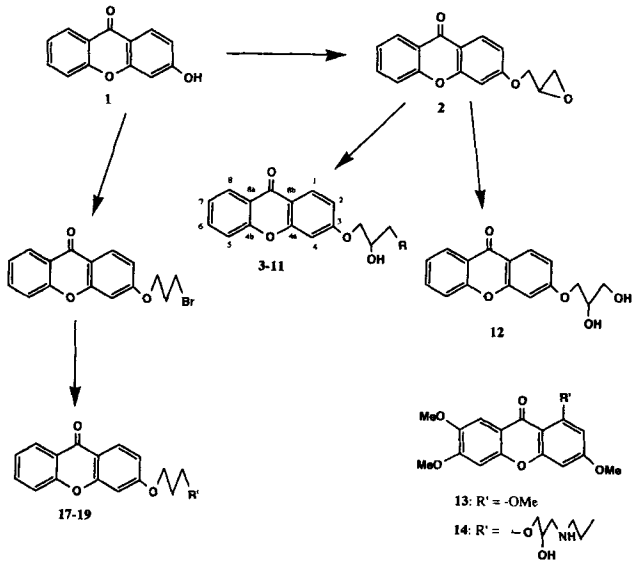
Abstract □ A series of simple xanthonoxypropanolamines and related compounds were synthesized. 3-[3-(Cyclopropylamino)propoxy]-xanthone showed same potent antiplatelet effects as norathyriol tetraacetate on arachidonate-induced aggregation. 3-[3-(Cyclohexylamino)-2-hydroxypropoxy]xanthone showed more potent antiplatelet effects than norathyriol tetraacetate on collagen-induced aggregation. The various amino groups of the oxypropanolamine or oxypropylamine side chains of the synthesized compounds regulated the antiplatelet effects.

Xanthonoids are a group of natural substances which are widely distributed in the families Gentianaceae and Guttiferae. Among their various biological properties, they have been shown to be potent as inhibitors of platelet aggregation[1] and as vasorelaxing agents.[2]

In a study of structure–activity relationships of various natural and synthetic xanthones, we found that the oxygenated group of C-3 in the xanthone skeleton was an important moiety related to the antiplatelet effects; that a 3-(propylamino)-2-hydroxypropoxyl] group substituted at C-3 of 3-methoxy or -hydroxyxanthone enhanced the antiplatelet effects when collagen (10 μg/mL) was used as an aggregation agent;[1,3,4] and that the mechanisms of action of 1,3,6,7-tetraoxygenated xanthone is due to both inhibition of thromboxane formation and phosphoinositide breakdown and of 3,4-dihydroxyxanthone is due to inhibition of thromboxane formation.[1,5] A series of xanthone-related γ-pyrone compounds, the flavonoxypropanolamines, showed potent antihypertensive activity.[6] In a continued study of the structure–activity relationships of various xanthone derivatives and their design as antithrombotic or/and antihypertensive agents, we synthesized further xanthonoxypropanolamines and their related compounds. Since one of the initial triggers of platelet aggregation in vivo is the activation by collagen of subendothelial tissues, we focused on an agent which would inhibit collagen-induced platelet aggregation.

Chemistry

Compounds 3–12 and 14 were synthesized (Scheme 1) by the method described in the previous report.[4] Briefly, 3-hydroxyxanthone (1)[4] was allowed to react with 1 equiv of sodium hydroxide in aqueous 2-propanol and excess of epichlorohydrin to yield the epoxide 3-(2,3-epoxypropoxy)xanthone (2) as the major product. Ring opening of 2 with appropriate amines in refluxing absolute EtOH afforded various xanthonoxypropanolamines. 2 was allowed to react with 1 equiv of aqueous 10% sodium hydroxide in 2-propanol to afford 3-(2,3-dihydroxypropoxy)xanthone (12) (Scheme 1). Compounds 17–19 were obtained by the reaction of the potassium salts of 1 with 1,3-dibromopropane in t-BuOH and then aminated with the appropriate amines to give the final products (Scheme 1).[7]



Scheme 1

The physical, spectral, and analytical data for the synthesized products and their derivatives are given in the Experimental Section and Table 1.

Results and Discussion

The antiplatelet effects of 3–14 and 17–19 were studied in the aggregation of washed rabbit platelets induced by thrombin (0.1 unit/mL), arachidonic acid (AA, 100 μM), collagen (10 μg/mL), and PAF (2 ng/mL). As shown in Table 2, 5, 10, 11, and 17–19 (each 300 μM) showed potent antiplatelet effects on thrombin-, AA-, collagen-, and PAF-induced aggregation. Compounds 4–9, 14, and 15 (each 300 μM) all showed potent antiplatelet effects on AA-, collagen-, and PAF-induced aggregation. Compound 3 (300 μM) showed potent antiplatelet effect on collagen- and PAF-induced aggregation, while compound 12 (300 μM) showed potent and significant effects on AA- and collagen-induced aggregation. On the basis of the above evidence, these compounds showed different mechanisms of action from 1,3,6,7-tetraoxygenated and 3,4-dihydroxyxanthone,[1,5] and the various amino groups of the oxypropanolamine or oxypropylamine side chains of these compounds regulated the antiplatelet effects. Further experiments are required to elucidate the differences in the mechanisms of action.

As shown in Table 2, an increase of the length of the N-substituted alkyl straight chain from three carbons (15) to four carbon atoms (6) did not enchance the antiplatelet effects on AA-, collagen-, and PAF-induced aggregation, while the N-substitution with a more bulky group of four carbons, such as in 7 or 8, caused an increase of antiplatelet effects on AA-, collagen-, and PAF-induced aggregation, suggesting some steric or ionic effects around this position. N-substitution with a

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Table 1—Physical Data of Xanthonoxypropanolamines and Related Compounds

Compd	R or R′	% Yield	Mp, °C	Recrystn solvent	Formula	Anal.
3	$NHCH(CH_3)_2$	61	114–115	CH_2Cl_2	$C_{19}H_{21}O_4N$	C,H,N
4	NH-c-C_3H_5	60	118–119	CH_3COCH_3	$C_{19}H_{19}O_4N$	C,H,N
5	$NHCH_2CH{=}CH_2$	70	129–131	CH_3COCH_3	$C_{19}H_{19}O_4N$	C,H,N
6	$NH(CH_2)_3CH_3$	61	131–132	CH_3COCH_3	$C_{20}H_{23}O_4N$	C,H,N
7	$NHCH_2CH(CH_3)_2$	59	107–108	CH_3COCH_3	$C_{20}H_{23}O_4N$	C,H,N
8	$NHC(CH_3)_3$	54	86–87	CH_3COCH_3	$C_{20}H_{23}O_4N$	C,H,N
9	$NHCH(CH_3)(CH_2)_2CH_3$	48	104–106	CH_3COCH_3	$C_{21}H_{25}O_4N$	C,H,N
10	$NHCH(CH_2CH_3)_2$	46	89–91	CH_3COCH_3	$C_{21}H_{25}O_4N$	C,H,N
11	NH-c-C_6H_{11}	66	136–138	CH_3COCH_3	$C_{22}H_{25}O_4N$	C,H,N
12	OH	88	135–136	CH_2Cl_2	$C_{16}H_{14}O_5$	C,H
14	$OCH_2CHOHCH_2NH(CH_2)_2CH_3$	15	230–231	CH_2Cl_2	$C_{22}H_{27}O_7N$	C,H,N
17	$NH(CH_2)_2CH_3$	56	162–163	$CHCl_3$	$C_{19}H_{21}O_3N$	C,H,N
18	NH-c-C_3H_5	41	170–172	$CH_3OH + CHCl_3$	$C_{19}H_{19}O_3N$	C,H,N
19	NH-c-C_6H_{11}	52	179–180	$CH_3OH + CHCl_3$	$C_{22}H_{25}O_3N$	C,H,N

Table 2—Effect of Various Xanthone Derivatives on the Platelet Aggregation Induced by Thrombin, Arachidonic Acid, Collagen, and Platelet-Activating Factor (PAF)[a]

Compound	Platelet Aggregation (% of control) Induced by			
	Thrombin	Arachidonic Acid	Collagen	PAF
DMSO (control)	97.6 ± 4.0(4)	92.7 ± 0.9(5)	91.7 ± 0.8(5)	93.7 ± 1.2(5)
3		73.4 ± 4.1(3)	0.0 ± 0.0(3)***	28.0 ± 4.3(3)***
4		0.0 ± 0.0(3)***	0.0 ± 0.0(3)***	53.9 ± 6.9(4)***
5	36.6 ± 2.2(4)***	0.0 ± 0.0(4)***	0.0 ± 0.0(4)***	16.0 ± 6.6(4)***
6		84.2 ± 1.3(3)	70.0 ± 8.3(3)	70.0 ± 8.3(3)*
7		9.3 ± 4.5(3)***	0.0 ± 0.0(3)***	35.7 ± 9.4(4)***
8		0.0 ± 0.0(3)***	0.0 ± 0.0(3)***	11.3 ± 1.9(3)***
9	90.8 ± 3.9(4)	40.9 ± 13.6(4)***	5.7 ± 3.8(4)***	35.9 ± 13.6(3)***
10	26.5 ± 7.5(4)***	13.5 ± 5.2(5)***	2.1 ± 1.8(4)***	0.0 ± 0.0(4)***
11	19.1 ± 4.4(3)***	0.0 ± 0.0(4)***	19.0 ± 5.5(3)***	9.9 ± 5.0(3)***
12		86.3 ± 0.4(3)***	42.2 ± 13.5(4)**	89.1 ± 0.3(3)
13[b]		67.9 ± 7.0(3)**	55.7 ± 5.0(3)***	86.3 ± 0.4(3)***
14		0.0 ± 0.0(3)***	0.0 ± 0.0(3)***	0.0 ± 0.0(3)***
15[c]		0.0 ± 0.0(3)***	2.8 ± 2.3(3)***	33.5 ± 12.6(4)**
16[c]		29.5 ± 9.9(3)***	44.5 ± 5.0(3)***	90.1 ± 2.2(3)
17	51.0 ± 11.0(3)***	5.4 ± 2.8(3)***	0.0 ± 0.0(3)***	6.4 ± 3.8(3)***
18	20.2 ± 1.0(3)***	0.0 ± 0.0(3)***	0.0 ± 0.0(3)***	0.0 ± 0.0(3)***
19	66.0 ± 7.9(3)***	2.2 ± 1.1(4)***	0.0 ± 0.0(3)***	4.2 ± 3.4(3)***
Aspirin	91.9 ± 2.5(3)	0.0 ± 0.0(5)***	85.4 ± 3.9(3)	90.5 ± 1.2(3)

[a] Platelets were preincubated with **3**–**19** (each at 300 μM), aspirin (50 μM), or DMSO (0.5%, control) at 37 °C for 3 min, then, thrombin (0.1 unit/mL), arachidonic acid (AA, 100 μM), collagen (10 μg/mL), or PAF (2 ng/mL) was added, respectively. Percentages of aggregation are presented as means ± SEM (*n*). $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ as compared with the respective control values. [b] Data from ref 8. [c] Data from ref 4.

more bulky group of three carbons did not significantly affect the antiplatelet effects on AA-, collagen-, and PAF-induced aggregation, but N-substitution with an unsaturated alkyl or a compound with a 3-aminopropoxyl side chain of three carbons, such as **5** or **18**, showed potent inhibition of AA-, collagen-, and PAF-induced aggregation.

An oxypropanolamine side chain substituted at position of C-1 of 1,3,6,7-tetramethoxyxanthone (**13**),[8] such as in **14**, exhibited stronger enhancement of antiplatelet effects on AA-, collagen-, and PAF-induced aggregation than that of an oxypropanolamine side chain substituted at the position C-3 with 3-methoxyxanthone such as in **15**.[4] This suggests that an oxypropanolamine side chain substituted at C-1 of the xanthone possesses much stronger antiplatelet effects.

Aspirin was used in this study as a positive control. It was found (Table 2) that aspirin (50 μM) completely inhibited the platelet aggregation induced by AA but not that induced by thrombin, collagen, or PAF.

Additional experiments were performed to study the effects of xanthonoxypropanolamines and their related compounds in AA- or collagen-induced platelet aggregation. In comparison with data previously reported for **15**,[4] norathyriol tetraacetate (**20**),[1,3] and norathyriol (**21**),[3] **14** and **18** had almost the same potent antiplatelet effects as **15** and **20**, respectively, but **3**, **8**–**10**, and **12** all had less potent antiplatelet effects than **15**, **20**, and **21**, when AA was used as the aggregation agent (Figure 1). In collagen-induced platelet aggregation, **11** was more potent than **15**, **20**, and **21**; **14** had almost the same antiplatelet effects as **20**; but **3**, **4**, **7**–**10**, **12**, and **17**–**19** all had less potent effects than **15** and **20**.

Flavonoxypropanolamines and [2-(ω-aminoalkoxy)phenyl]-ethyl]benzene have shown potent antihypertensive activity and antiplatelet effects in collagen-induced aggregation, respectively.[6,7] To design potential antithrombotic or/and antihypertensive agents, further synthesis of various xanthonoxyalkanolamines is now in progress.

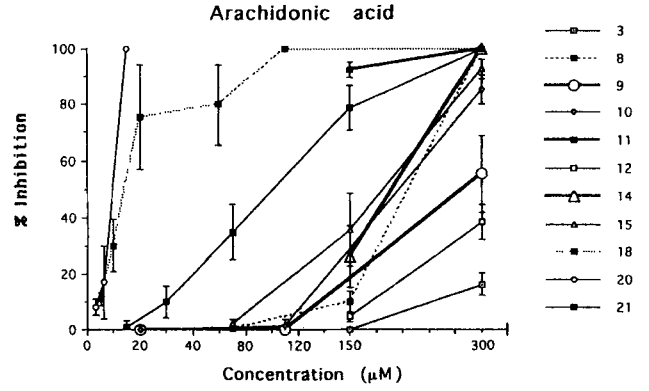

Figure 1—Effect of xanthone derivatives on the platelet aggregation induced by arachidonic acid. Washed rabbit platelets were incubated with various concentrations of **3**, **8–12**, **14**, **15**, **18**, **20**, and **21**, and then arachidonic acid (100 mM) was added to trigger the aggregation. Percent inhibitions are presented as means ± SE (n = 3–5).

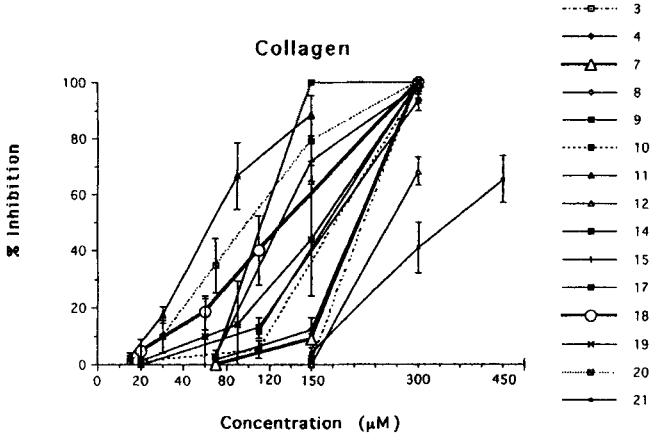

Figure 2—Effect of xanthone derivatives on the platelet aggregation induced by collagen. Washed rabbit platelets were incubated with various concentrations of **3**, **4**, **7–12**, **14**, **15**, and **17–21**, and then collagen (10 μg/mL) was added to trigger the aggregation. Percent inhibitions are presented as means ± SE (n = 3–5).

Experimental Section

All melting points were uncorrected. IR spectra were recorded on a Hitachi Model 260-30 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra [δ (ppm), J (Hz)] were run on a Bruker 100-MHz FT-NMR spectrometer. Mass spectra were determined on a JEOL JMS-D-100 mass spectrometer. Elemental analyses were within ±0.4% the theoretical values, unless otherwise noted.

Procedure I—*Synthesis of (2,3-Epoxypropoxy)xanthone*[4]—To a solution of 0.19 g (4.71 mmol) sodium hydroxide in water were added 2-propanol and the appropriate **1** or 1-hydroxy-3,6,7-trimethoxyxanthone.[8] To the above mixture was then added excess of the appropriate epichlorohydrin, and the mixture was heated at 70 °C for 2 h with stirring. The hot reaction mixture was filtered to remove a dimeric byproduct (a glycidyl ether[6]). The clear filtrate, on cooling, yielded a solid.

Procedure II—*Synthesis of Xanthonoxypropanolamines*[4]—To the former solid were added various appropriate amines and absolute ethanol. The mixture was heated at 50–55 °C for 1.5 h, with stirring. The reaction mixture was clarified by filtration, and the filtrate was concentrated under reduced pressure. The product was filtered, washed with absolute ethanol, purified by column chromatography, and crystallized from appropriate solvents,[5] yielding various xanthonoxypropanolamines. Treatment of **1** (2.00 g, 9.43 mmol) by procedures I and II yielded various xanthonoxypropanolamines: **3** (1.10 g, 3.36 mmol), **4** (1.06 g, 3.26 mmol), **5** (1.20 g, 3.69 mmol), **6** (1.15 g, 3.36 mmol), **7** (1.13 g, 3.30 mmol), **8** (1.02 g, 3.00 mmol), **9** (1.00 g, 2.80 mmol), **10** (1.00 g, 2.80 mmol), **11** (1.25 g, 3.40 mmol), and **14** (0.35 g, 0.84 mmol) (Table 1).

3-[3-(Isopropylamino)-2-hydroxypropoxy]xanthone (3)—IR (KBr): 3450, 3275, 1650, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.11 (d, J = 6.2 Hz, 6 H, 2 × CH_3), 2.81 (dd, J = 12.2, 7.0 Hz, 1 H, *H*CHCHOH), 2.93 (dd, J = 12.2, 3.5 Hz, 1 H, HC*H*CHOH), 4.10 (s, 3 H, C*H*OH and CH_2O), 6.90 (d, J = 2.2 Hz, 1 H, H-4), 6.96 (dd, J = 9.0, 2.2 Hz, 1 H, H-2), 7.28–7.47 (m, 2 H, H-6 and H-7), 7.69 (m, 1 H, H-5), 8.24 (d, J = 9.0 Hz, 1 H, H-1), and 8.32 (dd, J = 9.0, 1.6 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$): δ 23.0 (CH_3), 23.1 (CH_3), 48.9 ($CH(CH_3)_2$), 49.1 (CH_2CHOH), 68.2 (OCH_2), 71.1 (CHOH), 100.9 (C-4), 113.4 (C-2), 115.9 (C-8b), 117.7 (C-5), 121.9 (C-8a), 123.8 (C-7), 126.6 (C-8), 128.3 (C-1), 134.3 (C-6), 156.1 (C-4b), 158.0 (C-4a), 164.1 (C-3), and 176.2 (C=O).[9–11] EI-MS: m/z (rel int) 325 (15) (M^+).

3-[3-(Cyclopropylamino)-2-hydroxypropoxy]xanthone (4)—IR (KBr): 3400, 3275, 1640, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.38–0.51 (m, 4 H, 2 × CH_2 in the cyclopropyl ring), 2.20 (m, 1 H, CH in the cyclopropyl ring), 2.50 (s, 2 H, NH and OH), 2.87 (dd, J = 12.4, 7.4 Hz, 1 H, *H*CHCHOH), 3.02 (dd, J = 12.4, 3.0 Hz, 1 H, HC*H*CHOH), 4.13 (s, 3 H, C*H*OH and CH_2O), 6.92 (dd, J = 8.5, 2.2 Hz, 1 H, H-2), 6.98 (d, J = 2.2 Hz, 1 H, H-4), 7.37 (m, 2 H, H-6 and H-7), 7.66 (m, 1 H, H-5), 8.24 (d, J = 8.5 Hz, 1 H, H-1), and 8.32 (dd, J = 8.0, 1.4 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$): δ 6.17, 6.83 (2 × CH_2 in the cyclopropyl ring), 30.5 (CH in the cyclopropyl ring), 51.6 (CH_2CHOH), 67.8 (OCH_2), 71.1 (CHOH), 100.9 (C-4), 113.5 (C-2), 116.0 (C-8b), 117.7 (C-5), 121.9 (C-8a), 123.9 (C-7), 126.6 (C-8), 128.3 (C-1), 134.3 (C-6), 156.2 (C-4b), 157.9 (C-4a), 164.1 (C-3), and 176.2 (C=O).[9–11] EI-MS: m/z (rel int) 325 (17) (M^+).

3-[3-(Allylamino)-2-hydroxypropoxy]xanthone (5)—IR (KBr): 3450, 3300, 1660, 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.83 (dd, J = 12, 7.5 Hz, 1 H, *H*CHCHOH), 2.95 (dd, J = 12, 3.5 Hz, 1 H, HC*H*CHOH), 3.36 (d, J = 6.2 Hz, 2 H, CH_2NH), 4.11 (m, 3 H, CH_2O and C*H*OH), 5.14–5.30 (m, 2 H, CH=CH_2), 5.84–6.04 (m, 1 H, C*H*=CH_2), 6.86 (d, J = 2.2 Hz, 1 H, H-4), 6.94 (dd, J = 9.0, 2.2 Hz, 1 H, H-2), 7.36 (m, 2 H, H-6 and H-7), 7.68 (m, 1 H, H-5), 8.21 (d, J = 8.8 Hz, 1 H, H-1), and 8.29 (dd, J = 8.0, 1.6 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$): δ 50.8 (CH_2NH), 52.1 (CH_2CHOH), 67.9 (OCH_2), 71.0 (CHOH), 100.9 (C-4), 113.4 (C-2), 116.0 (C-8b), 117.1 (CH=CH_2), 117.7 (C-5), 121.9 (C-8a), 123.9 (C-7), 126.6 (C-8), 128.3 (C-1), 134.3 (C-6), 135.6 (C*H*=CH_2), 156.1 (C-4b), 157.9 (C-4a), 164.0 (C-3), and 176.2 (C=O).[9–11] EI-MS: m/z (rel int) 325 (21) (M^+).

3-[3-(Butylamino)-2-hydroxypropoxy]xanthone (6)—IR (KBr): 3450, 3270, 1660, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.88 (t, J = 7.2 Hz, 3 H, CH_3), 1.37 (m, 4 H, (CH_2)$_2$$CH_3$), 2.57–2.81 (m, 4 H, C$H_2$NH and ($CH_2$CHOH), 4.09 (m, 3 H, C*H*(OH) and CH_2O), 7.07 (dd, J = 8.5, 2.2 Hz, 1 H, H-2), 7.16 (d, J = 2.2 Hz, H-4), 7.54 (m, 2 H, H-6 and H-7), 7.85 (m, 1 H, H-5), 8.11 (d, J = 8.5 Hz, 1 H, H-1), and 8.18 (dd, J = 8.0, 1.6 Hz, 1 H, H-8).[6] ^{13}C NMR (DMSO-d_6): δ 14.1 (CH_3), 20.0 (CH_2), 31.3 (CH_2), 49.0 (CH_2NH), 52.0 (CH_2CHOH), 67.6 (OCH_2), 71.7 (CHOH), 101.3 (C-4), 114.2 (C-2), 115.1 (C-8b), 118.1 (C-5), 121.4 (C-8a), 124.5 (C-7), 126.1 (C-8), 127.7 (C-1), 135.2 (C-6), 155.8 (C-4b), 157.7 (C-4a), 164.6 (C-3), and 175.1 (C=O).[9–11] EI-MS: m/z (rel int) 342 (8) (M + 1)$^+$.

3-[3-[(2-Methylpropyl)amino]-2-hydroxypropoxy]xanthone (7)—IR (KBr): 3400, 3300, 1670, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.88 (d, J = 6.6 Hz, 6 H, 2 × CH_3), 1.69 (m, 1 H, C*H*CH_3), 2.38 (d, 6.6 Hz, 2 H, CH_2CH(CH_3)$_2$), 2.66 (m, 2 H, CH_2CHOH), 4.09 (m, 3 H, C*H*(OH) and CH_2O), 7.07 (dd, J = 9.0, 2.4 Hz, 1 H, H-2), 7.17 (d, J = 2.4 Hz, 1 H, H-4), 7.55 (m, 2 H, H-6 and H-7), 7.85 (m, 1 H, H-5), 7.85 (m, 1 H, H-6), 8.10 (d, J = 9.0 Hz, 1 H, H-1), and 8.18 (dd, J = 8.0, 1.4 Hz, 1 H, H-8).[6] ^{13}C NMR (DMSO-d_6): δ 20.8 (2 × CH_3), 28.0 ($CH(CH_3)_2$), 52.5 (CH_2NH), 57.7 (CH_2CHOH), 68.0 (OCH_2), 71.9 (CHOH), 101.2 (C-4), 114.2 (C-2), 115.0 (C-8b), 118.1 (C-5), 121.4 (C-8a), 124.5 (C-7), 126.0 (C-8), 127.7 (C-1), 135.2 (C-6), 155.8 (C-4b), 157.7 (C-4a), 164.6 (C-3), and 175.0 (C=O).[9–11] EI-MS: m/z (rel int) 342 (2) (M + 1)$^+$.

3-[3-(*tert*-Butylamino)-2-hydroxypropoxy]xanthone (8)—IR (KBr): 3250, 1660, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.15 (s, 9 H, 3 × CH_3), 2.71 (dd, J = 12.0, 7.5 Hz, 1 H, *H*CHNH), 2.91 (dd, J = 12.0, 3.8 Hz, 1 H, HC*H*NH), 4.03 (m, 1 H, C*H*OH), 4.12 (m, 2 H, CH_2OH), 6.91 (d, J = 2.2 Hz, 1 H, H-4), 6.97 (dd, J = 9.0, 2.2 Hz, 1 H, H-2), 7.40 (m, 2 H, H-6 and H-7), 7.70 (m, 1 H, H-5), 8.25 (d, J = 9.0 Hz, 1 H, H-1), and 8.32 (dd, J = 8.0, 1.6 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$): δ 28.8 (3 × CH_3), 45.3 (CH_2CHOH), 51.1 (NHC(CH_3)$_3$), 69.1 (OCH_2), 71.9 (CHOH), 101.9 (C-4), 114.8 (C-2), 116.8 (C-8b), 118.9 (C-5), 122.8 (C-8a), 125.2 (C-7), 127.6 (C-8), 129.3 (C-1), 135.8 (C-6), 157.7 (C-4b), 159.5 (C-4a), 165.9 (C-3), and 178.5 (C=O).[9–11] FAB-MS: m/z (rel int) 342 (M + 1)$^+$.

3-[3-[(1-Methylbutyl)amino]-2-hydroxypropoxy]xanthone (9)—IR (KBr): 3375, 3300, 1660, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J =

6.6 Hz, 3 H, CH_3), 1.16 (d, J = 6.4 Hz, 3 H, CH_3), 1.40 (m, 4 H, 2 × CH_2), 2.91 (m, 3 H, C*H*NH and C*H*$_2$NH), 4.13 (m, 3 H, C*H*(OH) and CH_2O), 6.89 (d, J = 2.2 Hz, 1 H, H-4), 6.96 (dd, J = 9.0, 2.2 Hz, 1 H, H-2), 7.36 (m, 2 H, H-6 and H-7), 7.69 (m, 1 H, H-5), 8.24 (d, J = 9.0 Hz, 1 H, H-1), and 8.31 (dd, J = 8.0, 1.6 Hz, 1 H, H-8).[6] ^{13}CMR ($CDCl_3$): δ 14.1 (CH_3), 19.1 (CH_2), 19.8 (CH_3), 38.6 (CH_2), 48.5 (*C*H$_2$CHOH), 53.3 (NH*C*HCH$_3$), 67.5 (OCH_2), 70.9 (CHOH), 101.0 (C-4), 113.4 (C-2), 116.0 (C-8b), 117.7 (C-5), 121.9 (C-8a), 123.9 (C-7), 126.6 (C-8), 128.3 (C-1), 134.3 (C-6), 156.2 (C-4b), 157.9 (C-4a), 164.0 (C-3), and 176.2 (C=O).[9-11] EI-MS: m/z (rel int) 355 (3) $(M)^+$.

3-[3-[(1-Ethylpropyl)amino]-2-hydroxypropoxy]xanthone (10)—IR (KBr): 3450, 3300, 1670, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.91 (t, J = 7.4 Hz, 6 H, 2 × CH_3), 1.46 (m, 4 H, 2 × CH_2), 2.42 (m, 1 H, C*H*NH), 2.73 (dd, J = 12.2, 7.5 Hz, 1 H, *H*CHOH), 2.93 (dd, J = 12.2, 3.5 Hz, 1 H, HC*H*CHOH), 4.10 (m, 3 H, C*H*(OH) and CH_2O), 6.91 (dd, J = 9.0, 2.2 Hz, 1 H, H-2), 6.98 (d, J = 2.2 Hz, 1 H, H-4), 7.37 (m, 2 H, H-6 and H-7), 7.69 (m, 1 H, H-5), 8.23 (d, J = 9.0 Hz, 1 H, H-1), and 8.31 (dd, J = 8.0, 1.6 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$): δ 9.8, 9.9 (2 × CH_3), 25.9, 26.2 (2 × CH_2), 48.6 (*C*H$_2$CHOH), 60.1 (NHCH), 68.1 (OCH_2), 71.1 (CHOH), 100.9 (C-4), 113.5 (C-2), 115.9 (C-8b), 117.6 (C-5), 121.9 (C-8a), 123.8 (C-7), 126.6 (C-8), 128.2 (C-1), 134.2 (C-6), 156.1 (C-4b), 157.9 (C-4a), 164.2 (C-3), and 176.2 (C=O).[9-11] EI-MS: m/z (rel int) 356 (3) $(M + 1)^+$.

3-[3-(Cyclohexylamino)-2-hydroxypropoxy]xanthone (11)—IR (KBr): 3450, 3275, 1670, 1650, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.18 (m, 5 H), 1.96 (m, 5 H), 2.46 (m, 1 H, CH in the cyclohexyl), 2.77 (dd, J = 12.2, 7.2 Hz, 1 H, *H*CHCHOH), 2.97 (dd, J = 12.2, 3.5 Hz, 1 H, HC*H*CHOH), 4.10 (m, 3 H, CH_2O and C*H*OH), 6.92 (d, J = 2.4 Hz, 1 H, H-4), 6.97 (dd, J = 9.0, 2.2 Hz, 1 H, H-2), 7.41 (m, 2 H, H-6 and H-7), 7.70 (m, 1 H, H-5), 8.26 (d, J = 8.8 Hz, 1 H, H-1), and 8.33 (dd, J = 8.0, 1.6 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$): δ 25.0 (CH_2), 26.0 (CH_2), 33.7 (CH_2), 34.0 (CH_2), 48.6 (*C*H$_2$CHOH), 56.8 (CH in the cyclohexyl), 68.1 (OCH_2), 71.1 (CHOH), 101.6 (C-4), 114.7 (C-2), 115.4 (C-8b), 118.6 (C-5), 121.7 (C-8a), 125.1 (C-7), 126.5 (C-8), 128.3 (C-1), 135.8 (C-6), 156.2 (C-4b), 158.2 (C-4a), 165.2 (C-3), and 175.9 (C=O).[9-11] EI-MS: m/z (rel int) 367 (3) $(M)^+$.

3-(2,3-Dihydroxypropoxy)xanthone (12)—Treatment of compound **1** (2.00 g, 9.43 mmol) by procedure I yielded colorless **2** (1.60 g, 5.97 mmol). The former compound (1.00 g, 3.73 mmol) was refluxed with aqueous 10% NaOH (0.1 g, 4.00 mmol) in 100 mL of 2-propanol to yield a yellow powder, which after purification by column chromatography (silica gel; CH_2Cl_2/MeOH, 4:1) yielded colorless powder **14** (0.94 g, 3.29 mmol); physical data may be found in Table 1. IR (KBr): 3425, 1660, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.48 (d, J = 5.6 Hz, 2 H, C*H*$_2$OH), 3.85 (m, 1 H, C*H*OH), 4.06 (dd, J = 10.0, 6.0 Hz, 1 H, *H*CHCHOH), 4.20 (dd, J = 10.0, 4.0 Hz, 1 H, HC*H*CHOH), 4.80 (s, 1 H, CH_2OH, D_2O exchangeable), 5.12 (s, 1 H, CHO*H*, D_2O exchangeable), 7.04 (dd, J = 9.0, 2.2 Hz, 1 H, H-2), 7.14 (d, J = 2.2 Hz, 1 H, H-4), 7.52 (m, 2 H, H-6 and H-7), 7.84 (m, 1 H, H-5), 8.09 (d, J = 9.0 Hz, 1 H, H-1), and 8.16 (dd, J = 8.0, 1.6 Hz, 1 H, H-8).[6] ^{13}C NMR (DMSO-d_6): δ 62.9 (CH_2-OH), 70.2 (OCH_2), 71.0 (CHOH), 101.6 (C-4), 114.7 (C-2), 115.4 (C-8b), 118.6 (C-5), 121.7 (C-8a), 125.1 (C-7), 126.5 (C-8), 128.3 (C-1), 135.8 (C-6), 156.2 (C-4b), 158.2 (C-4a), 165.2 (C-3), and 175.9 (C=O).[9-11] EI-MS: m/z (rel int) 286 (35) $(M)^+$.

3,6,7-Trimethoxy-1-[3-(propylamino)-2-hydroxypropoxy]xanthone (14)—IR (KBr): 3400, 1630, 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.95 (t, 7.6 Hz, 3 H, CH_3), 1.83 (m, 2 H, CH_2), 3.01 (t, J = 8.2 Hz, 2 H, CH_2), 3.31 (bs, 2 H, C*H*$_2$CHOH), 3.83, 3.91 (3 × OCH_3), 4.00–4.37 (m, 3 H, C*H*OH and CH_2O), 6.52 (d, J = 2.2 Hz, 1 H, H-2), 6.68 (d, J = 2.2 Hz, 1 H, H-4), 7.07 (s, 1 H, H-5), and 7.36 (s, 1 H, H-8).[6] ^{13}C NMR (DMSO-d_6): δ 11.5 (CH_3), 20.4 (CH_2), 51.8 (2 × CH_2NH), 57.0, 57.1, 57.5 (3 × OCH_3), 65.8 (OCH_2), 75.2 (CHOH), 95.6 (C-4), 97.8 (C-2), 101.3 (C-5), 107.8 (C-8b), 116.9 (C-8a), 149.7 (C-7), 154.2 (C-4b), 158.6 (C-6), 162.5 (C-4a), 168.2 (C-3), and 178.1 (C=O).[9-11] EI-MS: m/z (rel int) 413 (9) $(M)^+$.

Procedure III—*Synthesis of (3-Aminopropoxy)xanthone*—To a solution of NaOH (0.2 g, 5.00 mmol) in H_2O (1 mL) were added *n*-BuOH (60 mL), **1** (1.0 g, 4.72 mmol), and 1,3-dibromopropane (1 mL, 9.85 mmol), and the mixture was stirred for 5 h under reflux. The reaction mixture was evaporated, and the organic material was extracted with $CHCl_3$. Extracts were washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residual oil was dissolved in absolute EtOH (100 mL) and *n*-propylamine (15 mL, mmol) or cyclopropylamine (1.5 mL, 21.84 mmol) or cyclohexylamine (2.0 mL, 17.50 mmol), and the mixture was stirred at 60–70 °C for 5 h. The organic material was extracted with $CHCl_3$, and the extracts were washed with brine, dried (Na_2SO_4), and evaporated to a syrup, which was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 9:1) and yielded colorless **17** (0.85 g, 2.62 mmol) or colorless powder **18** (0.63 g, 1.95 mmol) or colorless powder **19** (0.89 g, 2.44 mmol) (Table 1).

3-[3-(Propylamino)propoxy]xanthone (17)—Physical data: see Table 1. IR (KBr): 1660, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 1.00 (t, J = 7.4 Hz, 3 H, CH_3), 1.79 (m, 2 H, CH_2), 2.33 (m, 2 H, CH_2), 2.95 (t, J = 8.0 Hz, 2 H, NHC*H*$_2$), 3.20 (t, J = 7.8 Hz, 2 H, NHC*H*$_2$), 4.02 (t, J = 5.8 Hz, 2 H, OC*H*$_2$), 6.90 (d, J = 2.2 Hz, 1 H, H-4), 6.93 (dd, J = 8.5, 2.2 Hz, 1 H, H-2), 7.39 (m, 2 H, H-6 and H-7), 7.71 (m, 1 H, H-5), 8.16 (d, J = 8.5 Hz, 1 H, H-1), and 8.23 (dd, J = 8.0, 1.4 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 10.5 (CH_3), 19.2 (*C*H$_2$CH$_3$), 25.4 (CH_2), 45.0 (NHC*H*$_2$), 65.3 (OCH_2), 100.6 (C-4), 113.3 (C-2), 115.5 (C-8b), 117.6 (C-5), 121.3 (C-8a), 123.9 (C-7), 126.1 (C-8), 127.9 (C-1), 134.5 (C-6), 156.0 (C-4b), 157.9 (C-4a), 163.8 (C-3), and 176.7 (C=O).[9-11] EI-MS: m/z (rel int) 311 (3) $(M)^+$.

3-[3-(Cyclopropylamino)propoxy]xanthone (18)—Physical data: see Table 1. IR (KBr): 1650, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 0.82 (m, 2 H, CH_2 in the cyclopropyl ring), 1.07 (m, 2 H, CH_2 in the cyclopropyl ring), 2.31 (m, 2 H, CH_2), 2.61 (m, 1 H, CH in the cyclopropyl ring), 3.64 (bs, 2 H, CH_2), 4.14 (t, J = 5.7 Hz, 2 H, OCH_2), 6.83 (d, J = 2.2, 1 H, H-4), 6.85 (dd, J = 8.5, 2.2 Hz, 1 H, H-2), 7.33 (m, 2 H, H-6 and H-7), 7.63 (m, 1 H, H-5), 8.10 (d, J = 8.5 Hz, 1 H, H-1), and 8.18 (dd, J = 8.0, 1.4 Hz, 1 H, H-8).[6] ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 3.39 (2 × CH_2 in the cyclopropyl ring), 25.3 (CH_2), 30.4 (CH in the cyclopropyl ring), 45.8 (NHC*H*$_2$), 65.3 (OCH_2), 65.3 (OCH_2), 100.7 (C-4), 113.4 (C-2), 115.6 (C-8b), 117.6 (C-5), 121.4 (C-8a), 123.9 (C-7), 126.2 (C-8), 128.0 (C-1), 134.5 (C-6), 156.1 (C-4b), 157.9 (C-4a), 163.8 (C-3), and 176.7 (C=O).[9-11] EI-MS: m/z (rel int) 309 (8) $(M)^+$.

3-[3-(Cyclohexylamino)propoxy]xanthone (19)—Physical data: see Table 1. IR (KBr): 1660, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 1.12–2.34 (m, 10 H, 5 × CH_2 in the cyclohexyl ring), 2.95 (m, 1 H, CH in the cyclohexyl ring), 3.12 (t, J = 7.4 Hz, 2 H, NHC*H*$_2$), 3.78 (s, 2 H, CH_2), 4.12 (t, J = 5.6 Hz, 2 H, OCH_2), 6.82 (d, J = 2.2 Hz, 1 H, H-4), 6.84 (dd, J = 8.5, 2.2 Hz, 1 H, H-2), 7.32 (m, 2 H, H-6 and H-7), 7.62 (m, 1 H, H-5), 8.09 (d, J = 8.5 Hz, 1 H, H-1), and 8.17 (dd, J = 8.0, 1.4 Hz, H-8).[6] ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 24.2 (CH_2), 24.6 (CH_2), 25.6 (CH_2), 28.9 (CH_2), 41.8 ($NHCH_2$), 57.4 (CH in the cyclohexyl ring), 65.4 (OCH_2), 100.7 (C-4), 113.4 (C-2), 115.6 (C-8b), 117.6 (C-5), 121.4 (C-8a), 123.9 (C-7), 126.2 (C-8), 128.0 (C-1), 134.6 (C-6), 156.1 (C-4b), 157.9 (C-4a), 163.8 (C-3), and 176.7 (C=O).[9-11] EI-MS: m/z (rel int) 351 (29) $(M)^+$.

Platelet Aggregation—Washed rabbit platelets were obtained from EDTA-anticoagulated platelet-rich plasma according to the washing procedures described previously.[12] Platelet numbers were counted by a Coulter Counter (Model ZM) and adjusted to 4.5 × 10^8 platelets/mL. The platelet pellets were finally suspended in Tyrode's solution containing (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) with bovine serum albumin (0.35%). Aggregation was measured by the turbidimetric method;[13] the absorbance of platelet suspension was assigned as 0% aggregation and the absorbance of platelet-free Tyrode's solution as 100% aggregation. The aggregation was measured by a Lumi-aggregometer (Chrono-Log Co., USA) connected to dual channel recorders. The platelet suspension was stirred at 1200 rpm. To eliminate the effect of the solvent on the aggregation, the final concentration of dimethyl sulfoxide (DMSO) was fixed at 0.5%.

References and Notes

1. Teng, C. M.; Lin, C. N.; Ko, F. N.; Cheng, K. L. *Biochem. Pharmacol.* **1989**, *38*, 3791.
2. Ko, F. N.; Lin, C. N.; Huang, T. F.; Teng, C. M. *Eur. J. Pharmacol.* **1991**, *192*, 133.
3. Lin, C. N.; Liou, S. S.; Ko, F. N.; Teng, C. M. *J. Pharm. Sci.* **1992**, *81*, 1109.
4. Lin, C. N.; Liou, S. S.; Ko, F. N.; Teng, C. M. *J. Pharm. Sci.* **1993**, *82*, 11.
5. Lin, C. N.; Liu, H. W.; Lin, C. N.; Teng, C. M. *Kaohsiung, J. Med. Sci.* **1991**, *7*, 505.
6. Wu, E. S. C.; Cole, T. E.; Davidson, T. A.; Dailey, M. A.; Doring, K. G.; Fedorchuk, M.; Loch, J. T.; Thomas, T. L.; Blosser, J. C.; Borreli, A. R.; Kinsolving, C. R.; Parker, R. B.; Strand, J. C.; Watkins, B. E. *J. Med. Chem.* **1989**, *32*, 183.

7. Kikumoto, R.; Hara, H.; Ninomiya, K.; Osakabe, M.; Sugano, M.; Fukami, H.; Tamao, Y. *J. Med. Chem.* **1990**, *33*, 1818.
8. Lin, C. N.; Ko, F. N.; Liou, S. S.; Teng, C. M. *J. Chin. Med.* **1990**, *1*, 120.
9. Frahm, A. W.; Chaudhuri, R. K. *Tetrahedron* **1979**, *35*, 2035.
10. Chaudhuri, R. K.; Eymalkowski, F.; Frahm, A. W. *Tetrahedron* **1978**, *34*, 1837.
11. Biemann, K. In *Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: New York, 1989; p c 173.
12. Teng, C. M.; Chen, W. Y.; Ko, W. C.; Ouyang, C. *Biochem. Biophys. Acta* **1987**, *924*, 375.
13. O'Brien, J. R. *J. Clin. Pathol.* **1962**, *15*, 452.

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