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Synthesis and Antiplatelet Effects of ω-Aminoalkoxylxanthones

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Abstract

A series of ω-aminoalkoxylxanthones were synthesized and tested in-vitro for their ability to inhibit aggregation of rabbit washed platelets and human platelet-rich plasma (PRP) induced by various inducers. Nine of these compounds showed more potent antiplatelet effects than natural norathyriol tetraacetate on collagen-induced aggregation. The various ω-aminoalkoxyl side chains of the synthesized compounds modified the antiplatelet effects. All the compounds tested in human PRP showed significant inhibition of secondary aggregation induced by adrenaline, suggesting that the antiplatelet effects of these compounds is mainly due to an inhibitory effect on thromboxane formation. These compounds at high concentration also cause vasorelaxing action in rat thoracic aorta.

Xanthones isolated from natural sources have been shown to be potent inhibitors of platelet aggregation (Teng et al 1989) and also vasorelaxing agents (Ko et al 1991a). Synthetic xanthones showed antiplatelet effects, reduced the blood pressure and heart rate, and attenuated isoprenaline-induced tachycardia in rats (Chen et al 1993). In the study of structure-activity relationships of various natural and synthetic xanthones, we found that some xanthonoxypropanolamines and related compounds had at least the same antiplatelet effects as natural norathyriol tetraacetate Lin et al 1990, 1992, 1993, 1994; Liou et al 1994). A series of [2-[(ω-aminoalkoxy)phenyl]-ethyl]benzenes has shown potent antiplatelet effects on collagen-induced aggregation (Kikumoto et al 1990). For the study of structure-activity relationships of various xanthone derivatives and their design as antithrombotic or antihypertensive agents, we have synthesized further ω-aminoalkoxylxanthones.

Materials and Methods

Platelet aggregation

Washed rabbit platelets were obtained from ethylene diamine tetraacetic acid (EDTA)-anticoagulated, platelet-rich plasma (PRP) according to the washing procedures described previously (Teng et al 1987). Human PRP was obtained from the supernatant after the centrifugation of blood mixed with 3·8% sodium citrate (1:9 to blood). Platelet numbers were counted by a Coulter Counter (model ZM) and adjusted to $4{\cdot}5 \times 10^8$ platelets mL^{-1}. The platelet pellets were finally suspended in Tyrode solution containing (mM): NaCl 136·8; KCl 2·8; $NaHCO_3$ 1·9; $MgCl_2$ 2·1; NaH_2PO_4 0·33; $CaCl_2$ 1·0 and glucose 11·2, with bovine serum albumin 0·35%. All glassware was siliconized. One minute before the addition of the aggregation inducer, PRP or the platelet suspension was stirred at 1200 rev min^{-1}. Aggregation was measured by the turbidimetric method (O'Brien 1962). The absorbance of PRP or the platelet suspension was taken as 0% aggregation and the absorbance of platelet-poor plasma or platelet-free Tyrode solution taken as 100% aggregation. The aggregation was measured by a Lumi-aggregometer (Chrono-Log Co., USA) connected to dual channel recorders. To eliminate the effect of the solvent on the aggregation, the final concentration of dimethylsulphoxide (DMSO) was fixed at 0·5%.

Aortic contraction

Wistar rats of either sex, 250–300 g, were killed by 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, mounted in organ baths containing 5 mL Krebs solution, maintained at 37° C, and bubbled with a 95% O_2–5% 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 (Model 2400). The final concentration of DMSO was fixed at 0·1%.

Chemistry: synthetic methods

All melting points were uncorrected. IR spectra were recorded on a Hitachi model 260-30 IR spectrophotometer. ^1H and ^{13}C NMR spectra [δ (ppm), J (Hz)] were obtained on a Varian Gemini 200 MHz FT-NMR spectrometer. Mass spectra were determined on a Jeol JMS-D-100 mass spectrometer. Elemental analyses were within ± 0·4% of the theoretical values, unless otherwise noted.

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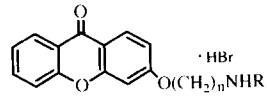
Table 1. Physical data of ω-aminoalkoxylxanthones.



Compound	n	R	Yield (%)	mp (°C)	Recrystallized solvent	Formula	Analysis
1	2		67	225–227	$CH_3COOC_2H_5$	$C_{18}H_{17}O_3N.HBr$	C, H, N
2[a]	3	$-(CH_2)_2CH_3$	56	162–163	$CHCl_3$	$C_{19}H_{21}O_3N.HBr$	C, H, N
3	3	$-CH(CH_3)_2$	65	232–233	$CH_3COOC_2H_5$	$C_{19}H_{21}O_3N.HBr$	C, H, N
4[a]	3		41	170–172	$CHCl_3$–MeOH	$C_{19}H_{19}O_3N.HBr$	C, H, N
5[a]	3		52	179–180	$CHCl_3$–MeOH	$C_{22}H_{25}O_3N.HBr$	C, H, N
6	4	$-(CH_2)_2CH_3$	66	162–163	$CH_3COOC_2H_5$	$C_{20}H_{23}O_3N.HBr$	C, H, N
7	4	$-CH(CH_3)_2$	68	188–189	$CH_3COOC_2H_5$	$C_{20}H_{23}O_3N.HBr$	C, H, N
8	4		61	170–172	$CH_3COOC_2H_5$	$C_{20}H_{21}O_3N.HBr$	C, H, N
9	4		63	179–181	$CH_3COOC_2H_5$	$C_{23}H_{28}O_3N.HBr$	C, H, N
10	5	$-(CH_2)_2CH_3$	64	162–163	$CH_3COOC_2H_5$	$C_{21}H_{25}O_3N.HBr$	C, H, N
11	5	$-(CH(CH_3)_2$	68	168–169	$CH_3COOC_2H_5$	$C_{21}H_{25}O_3N.HBr$	C, H, N
12	5		53	159–161	$CH_3COOC_2H_5$	$C_{21}H_{23}O_3N.HBr$	C, H, N
13	5		72	183–184	$CH_3COOC_2H_5$	$C_{24}H_{30}O_3N.HBr$	C, H, N
14	6	$-(CH_2)_2CH_3$	61	191–192	$CH_3COOC_2H_5$	$C_{22}H_{27}O_3N.HBr$	C, H, N
15	6	$-CH(CH_3)_2$	53	131–132	$CH_3COOC_2H_5$	$C_{22}H_{27}O_3N.HBr$	C, H, N
16	6		53	190–191	$CH_3COOC_2H_5$	$C_{22}H_{25}O_3N.HBr$	C, H, N
17	6		62	191–192	$CH_3COOC_2H_5$	$C_{25}H_{32}O_3N.HBr$	C, H, N

[a]Data from reference 4.

Procedure I

Preparation of 3-[2-(alkylamino)ethoxy]xanthone. To a solution of NaOH (0·20 g, 5·00 mmol) in H_2O (1 mL) was added *n*-butanol (60 mL), 3-hydroxyxanthone (1·00 g, 4·72 mmol), and 1,2-dibromoethane (1·00 mL, 11·60 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 saline, and dried over Na_2SO_4. After evaporation of the solvent, the residual oil was dissolved in absolute ethanol (100 mL) and *n*-propylamine (1·50 mL, 18·25 mmol), isopropylamine (2·00 mL, 23·35 mmol), cyclopropylamine (1·50 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 saline, dried over Na_2SO_4, and evaporated to a syrup, which was purified by column chromatography (silical gel; CH_2Cl_2–methanol, 9 : 1), for the cyclopropylamine derivatives a colourless powder **1** (0·79 g, 2·10 mmol) was obtained (Table 1).

3-[2-(Cyclopropylamino)ethoxy]xanthone (1). Physical data: see Table 1. IR (KBr): 3450, 1660, 1625 cm^{-1}. ^1H NMR ($CDCl_3$-CD_3OD): δ 0·83 (m, 2H, CH_2 in the cyclopropyl ring), 1·10 (m, 2H, CH_2 in the cyclopropyl ring), 2·69 (m, 1H, CH in the cyclopropyl ring), 3·51 (t, J = 4·8 Hz, 2H, $NHCH_2$), 4·43 (t, J = 5·2 Hz, 2H, OCH_2), 6·90 (d, J = 2·4 Hz, 1H, H-4), 6·93 (dd, J = 8·5, 2·4 Hz, 1H, H-2), 7·29 (m, 2H, H-6 and H-7), 7·63 (m, 1H, H-5), 8·10 (d, J = 8·5 Hz, 1H, H-1), 8·18 (dd, J = 8·0, 1·6 Hz, 1HH-8). ^{13}C NMR ($CDCl_3$-CD_3OD): δ 4·1 (2 × CH_2 in the cyclopropyl ring), 31·1 (CH in the cyclopropyl ring), 47·9 ($NHCH_2$), 63·7 (OCH_2), 101·7 (C-4), 113·9 (C-2), 116·7 (C-9a), 118·2 (C-5), 122·0 (C-8a), 124·6 (C-7), 126·8 (C-8), 128·8 (C-1), 135·2) (C-6), 156·6 (C-10a), 158·4 (C-4a), 163·5 (C-3), 177·2 (C=O). EI-MS: m/z (%) 295 (5) (M^+).

Procedure II

Preparation of 3-[3-(alkylamino)propoxy]xanthone. To a solution of NaOH was added *n*-butanol, 3-hydroxyxanthone as in procedure I, and 1,3-dibromopropane (1 mL, 9·85 mmol), and the mixture was treated as in procedure I with isopropylamine to yield a colourless powder, **3** (0·484 g, 2·15 mmol) (Table 1).

3[3-(Isopropylamino)propoxy]xanthone (3). Physical data: see Table 1. IR (KBr): 3450, 1660, 1620 cm^{-1}. ^1H NMR ($CDCl_3$ CD_3OD): δ 1·35 (d, J = 6·6 Hz, 6H, 2 × CH_3), 2·30

(m, 2H, CH_2), 3·10 (t, J = 8·0 Hz, 2H $NHCH_2$), 3·28 (m, 1H, CH), 4·14 (t, J = 5·8 Hz, 2H, OCH_2), 6·83 (d, J = 2·2 Hz, 1H, H-4), 6·86 (dd, J = 8·5, 2·2 Hz, 1H, H-2), 7·33 (m, 2H, H-6 and H-7), 7·63 (m, 1H, H-5), 8·03 (d, J = 8·5 Hz, 1H, H-1), 8·16 (dd, J = 8·0, 1·4 Hz, 1H, H-8), ^{13}C NMR ($CDCl_3$-CD_3OD): δ 18·5 (2 × CH_3), 25·6 (CH_2), 42·0 ($NHCH_2$), 50·7 (CH), 65·3 (OCH_2), 100·6 (C-4), 113·3 (C-2), 115·5 (C-9a), 117·5 (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-10a), 157·9 (C-4a), 163·8 (C-3), 176·7 (C=O). EI-MS: m/z (%) 311 (7) (M^+).

Procedure III

Preparation of 3-[4-(alkylamino)butoxy]xanthone. To a solution of NaOH was added *n*-butanol, 3-hydroxyxanthone as in procedure I, and 1,4-dibromobutane (1·50 mL, 12·71 mmol), and the mixture was treated as in procedure I with the appropriate amine to yield **6**, a colourless powder (0·93 g, 2·28 mmol); **7**, a colourless powder (0·95 g, 2·35 mmol); **8**, a colourless powder (0·85 g, 2·11 mmol); and **9**, a colourless powder (0·97 g, 2·18 mmol) (Table 1).

*3-[4-(Propylamino)butoxy]xanthone (**6**).* Physical data: see Table 1. IR (KBr): 3400, 1620 cm^{-1}. ^1H NMR ($CDCl_3$-CD_3OD): δ 0·92 (t, J = 7·4 Hz, 3H, CH_3), 1·73 (m, 2H, CH_2CH_3), 1·89 (m, 4H, 2 × CH_2), 2·85 (t, J = 8·2 Hz, 2H, NCH_2), 2·98 (t, J = 7·8 Hz, 2H, $NHCH_2$), 4·04 (t, J = 5·6 Hz, 2H, OCH_2), 6·79 (d, J = 2·2 Hz, 1H, H-4), 6·82 (dd, J = 8·5, 2·2 Hz, 1H H-2), 7·34 (m, 2H, H-6 and H-7), 7·62 (m, 1H, H-5), 8·09 (d, J = 8·6 Hz, 1H, H-1), 8·17 (dd, J = 8·0, 1·6 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$-CD_3OD): δ 10·8 (CH_3), 19·2(CH_2CH_3), 22·9 (CH_2), 26·0 (CH_2), 47·2 ($NHCH_2$), 67·5 (OCH_2), 100·6 (C-4), 113·5 (C-2), 115·4 (C-9a), 117·6 (C-5), 121·5 (C-8a), 123·9 (C-7), 126·2 (C-8), 128·0 (C-1), 134·5 (C-6), 156·1 (C-10a), 158·0 (C-4a), 164·2 (C-3), 176·7 (C=O). EI-MS: m/z (%) 325 (5) (M^+).

*3-[4-(Isopropylamino)butoxy]xanthone (**7**).* Physical data: see Table 1. IR (KBr): 3400, 1600 cm^{-1}. ^1H NMR ($CDCl_3$-CD_3OD): δ 1·37 (d, J = 6·6 Hz, 2 × CH_3), 1·95 (m, 4H, 2 × CH_2), 3·00 (t, J = 8·0 Hz, $NHCH_2$), 3·33 (m, 1H, CH), 4·11 (t, J = 5·8 Hz, 2H, OCH_2), 6·87 (d, J = 2·2 Hz, 1H, H-4), 6·90 (dd, J = 8·5, 2·2 Hz, 1H, H-2), 7·30 (m, 2H, H-6 and H-7), 7·70 (m, 1H, H-5), 8·16 (d, J = 8·5 Hz, 1H, H-1), 8·25 (dd, J = 8·0, 1·4 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$-CD_3OD): δ 18·5 (2 × CH_3), 22·8 (CH_2), 25·9 (CH_2), 44·3 ($NHCH_2$), 50·4 (CH), 67·5 (OCH_2), 100·5 (C-4), 113·5 (C-2), 115·3 (C-9a), 117·6 (C-5), 121·4 (C-8a), 123·8 (C-7), 126·1 (C-8), 127·9) (C-1), 134·5 (C-6), 156·0 (C-10a), 158·0 (C-4a), 164·2 (C-3), 176·7 (C=O). EI-MS: m/z (%) 325 (5) (M^+).

*3-[4(-Cyclopropylamino)butoxy]xanthone (**8**).* Physical data: see Table 1. IR (KBr): 3400, 1620 cm^{-1}. ^1H NMR (CD_3OD): δ 0·94 (m, 4H, 2 × CH_2 in the cyclopropyl ring), 1·96 (m, 4H, 2 × CH_2), 2·82 (m, 1H, CH in the cyclopropyl ring), 3·25 (m, 2H, $NHCH_2$), 4·19 (bs, 2H, OCH_2), 6·97 (dd, J = 8·6, 2·2 Hz, 1H, H−2), 7·00(d, J = 2·2 Hz, 1H, H-4), 7·46 (m, 2H, H-6 and H-7), 7·79 (m, 1H, H-5), 8·11 (d, J = 8·6 Hz, 1H, H-1), 8·20 (dd, 8·0, 1·6 H, 1H H-8). ^{13}C NMR (CD_3OD): δ 4·1 (2 × CH_2 in the cyclopropyl ring), 23·9 (CH_2), 26·9 (CH_2), 31·1 (CH in the cyclopropyl ring), 68·8 (OCH_2), 101·8 (C-4), 114·8 (C-2), 116·3 (C-9a), 118·8 (C-5), 122·5 (C-8a), 125·1 (C-7), 127·0 (C-8), 128·8 (C-1), 135·9 (C-6), 157·4 (C-10a), 159·4 (C-4a), 165·9 (C-3), 177·9 (C=O). EI-MS: m/z (%) 323 (5) (M^+).

*3-[4-(Cyclohexylamino)butoxy]xanthone (**9**).* Physical data: see Table 1. IR (KBr): 3450, 1650, 1620, 1600 cm^{-1}. ^1H NMR ($CDCl_3$-CD_3OD): δ 1·14–2·12 (m, 14H, 5 × CH_2 in the cyclohexyl ring and 2 × CH_2), 2·95 (m, 3H, CH in the cyclohexyl ring and $NHCH_2$), 4·06 (t, J = 5·6 Hz, 2H, OCH_2), 6·82 (d, J = 2·2 Hz, 1H, H-4), 6·84 (dd, J = 9·0, 2·4 Hz, 1H, H-2), 7·32 (m, 2H, H-6 and H-7), 7·64 (m, 1H, H-5), 8·12 (d, J = 9·0 Hz, 1H, H-1), 8·19 (dd, J = 8·6, 1·6 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$-CD_3OD): δ 22·9 (CH_2), 24·3 (CH_2), 24·7 CH_2), 26·1 (CH_2), 28·9 (CH_2), 44·0 ($NHCH_2$), 57·1 (CH in the cyclohexyl ring), 67·6 (OCH_2), 100·6 (C-4), 113·5 (C-2), 115·5 (C-9a), 117·6 (C-5), 121·6 (C-8a), 123·9 (C-7), 126·3 (C-8), 128·1 (C-1), 134·5 (C-6), 156·1 (C-10a), 158·0 (C-4a), 164·2 (C-3), 176·6 (C=O). EI-MS: m/z (%) 365 (16) (M^+).

Procedure IV

Preparation of 3-[5-(alkylamino)pentoxy]xanthone. To a solution of NaOH was added *n*-butanol, 3-hydroxyxanthone as in procedure I, and 1,5-dibromopentane (1·50 mL, 11·09 mmol), and the mixture was treated as in procedure I to yield **10**, a colourless powder (0·85 g, 2·03 mmol); **11**, a colourless powder (0·91 g, 2·16 mmol); **12** a colourless powder (0·70 g, 1·68 mmol); and **13**, a colourless powder (1·05 g, 2·28 mmol) (Table 1).

*3-[5-(Propylamino)pentoxy]xanthone (**10**).* Physical data see Table 1. IR (KBr): 3350, 1660, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1·02 (t, J = 7·4 Hz, 3H, CH_3), 1·63 (m, 2H, CH_2CH_3), 1·99 (m, 6H, 3 × CH_2), 2·99 (m, 4H, 2 × $NHCH_2$), 4·04 (t, J = 6·2 Hz, 2H, OCH_2), 6·79 (d, J = 2·4 Hz, 1H, H-4), 6·90 (dd, J = 8·8, 2·4 Hz, 1H, H-2), 7·34 (m, 2H, H-6 and H-7), 7·65 (m, 1H, H-5), 8·20 (d, J = 8·8 Hz, 1H, H-1), 8·27 (dd, J = 8·0, 1·6 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ 11·4 (CH_3), 19·4 (CH_2CH_3), 23·4 (CH_2), 25·5 (CH_2), 28·4 (CH_2), 47·5 ($NHCH_2$), 49·4 ($NHCH_2$), 68·0 (OCH_2), 100·7 (C-4), 113·4 (C-2), 117·7 (C-5), 115·8 (C-9a), 121·9 (C-8a), 123·8 (C-7), 126·6 (C-8), 128·3 (C-1), 134·2 (C-6), 156·1 (C-10a), 158·0 (C-4a), 164·3 (C-3), 176·2 (C=O). EI-MS: m/z (%) 339 (6) (M^+).

*3-[5-(Isopropylamino)pentoxy]xanthone (**11**).* Physical data: see Table 1. IR (KBr): 3450, 1660, 1630, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1·51 (d, J = 6·6 Hz, 6H, 2 × CH_3), 1·60 (m, 2H, CH_2), 1·85 (m, 2H, CH_2), 2·10 (m, 2H, CH_2), 2·99 (m, 2H, $NHCH_2$), 3·43 (m, 1H, CH), 4·02 (t, J = 6·2 Hz, 2H, OCH_2), 6·77 (d, J = 2·2Hz, 1H, H-4), 6·89 (dd, J = 9·0, 2·2 Hz, 1H, H-2), 7·26–7·40 (m, 2H, H-6 and H-7), 7·63 (m, 1H, H-5), 8·16 (d, J = 9·0 Hz, 1H, H-1), 8·25 (dd, J = 8·0, 1·8 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ 19·1 (2 × CH_3), 23·5 (CH_2), 25·7 (CH_2), 28·4 (CH_2), 44·5 ($NHCH_2$), 50·8 (CH), 68·0 (OCH_2), 100·7 (C-4), 113·4 (C-2), 115·7 (C-9a), 117·6 (C-5), 121·9 (C-8a), 123·8 (C-7), 126·5 (C-8), 128·2 (C-1), 134·2 (C-6), 156·1 (C-10a), 158·0 (C-4a), 164·3 (C-3), 176·2 (C=O). EI-MS: m/z (%) 339 (14) (M^+).

*3-[5-(Cyclopropylamino)pentoxy]xanthone (**12**).* Physical data: see Table 1. IR (KBr): 3450, 1660, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0·87 (m, 2H, CH_2 in the cyclopropyl ring), 1·33 (m, 2H, CH_2 in the cyclopropyl ring), 1·63 (m, 2H, CH_2), 1·92 (m, 2H, CH_2), 2·07 (m, 2H, CH_2), 2·63 (m, 1H, CH in the cyclopropyl ring), 3·12 (t, J = 7·8 Hz, 2H, $NHCH_2$), 4·04 (t, J = 6·2 Hz, 2H, OCH_2), 6·80 (d, J = 2·3 Hz, 1H, H-4), 6·90 (dd, J = 8·8, 2·3 Hz, 1H, H-2), 7·37 (m, 2H, H-6 and H-7), 7·65 m, 1H, H-5), 8·19 (d, J = 8·8 Hz, 1H, H-1), 8·15 (dd, J = 8·0, 1·6 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ 4·2 (2 × CH_2 in the cyclopropyl ring), 23·9 (CH_2), 25·9 (CH_2), 28·9 (CH_2), 31·0 (CH in the cyclopropyl ring), 49·1 ($NHCH_2$), 68·5 (OCH_2), 101·2 (C-4), 114·0 (C-2), 116·2 (C-9a), 118·1 (C-5), 122·4 (C-8a), 124·3 (C-7), 127·1 (C-8), 128·7 (C-1), 134·8 (C-6), 156·6 (C-10a), 158·5 (C-4a), 164·8 (C-3), 176·7 (C=O), EI-MS: m/z (%) 337 (9) (M^+).

*3-[5-(Cyclohexylamino)pentoxy]xanthone (**13**).* Physical data: see Table 1. IR (KBr): 3450, 1660, 1630 cm^{-1}. ^1H NMR, ($CDCl_3$): δ 1·20–2·31 (m, 16H, 5 × CH_2 in the cyclohexyl ring and 3 × CH_2), 3·02 (m, 3H, CH in the cyclohexyl ring and $NHCH_2$), 4·03 (t, J = 6·0 Hz, 2H, OCH_2), 6·79 (d, J = 2·4 Hz, 1H, H-4), 6·90 (dd, J = 9·0, 2·4 H, 1H, H-2), 7·33 (m, 2H, H-6 and H-7), 7·64 (m, 1H, H-5), 8·19 (d, J = 9·0 Hz, 1H, H-1), 8·26 (dd, J = 8·0, 1·8 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$). δ 23·5 (CH_2), 24·5 (CH_2), 24·7 (CH_2), 25·7 (CH_2), 28·4 (CH_2), 29·1 (CH_2), 44·4 ($NHCH_2$), 57·7 (CH in the cyclohexyl ring), 68·0 (OCH_2)), 100·7 (C-4), 113·4 (C-2), 115·7 (C-9a), 117·6 (C-5), 121·9 (C-8a), 123·8 (C-7), 126·5 (C-8), 128·2 (C-1), 134·2 (C-6), 156·1 (C-10a), 157·9 (C-4a), 164·3 (C-3), 176·2 (C=O). EI-MS: m/z (%) 379 (10) (M^+).

Procedure V

Preparation of 3-[6-(alkylamino)hexoxy]xanthone. To a solution of NaOH was added *n*-butanol, 3-hydroxyxanthone as in procedure I, and 1,6-dibromohexane (2·00 mL, 13·20 mmol), and the mixture was treated as in procedure I to yield **14**, a colourless powder (0·78 g, 1·79 mmol); **15**, a colourless powder (0·67 g, 1·55 mmol); **16**, a colourless powder (0·67 g, 1·55 mmol); and **17**, a colourless powder (0·86 g, 1·82 mmol) (Table 1).

*3-[6-(Propylamino)hexoxy]xanthone (**14**).* Physical data: see Table 1. IR (KBr): 3450, 1660, 1630 cm^{-1}. ^1H NMR ($CDCl_3$-CD_3OD): δ 0·92 (t, J = 7·5 Hz, 3H, CH_3), 1·43 (m, 4H, 2 × CH_2), 1·75 (m, 6H, CH_2CH_3 and 2 × CH_2), 2·85 (m, 4H, 2 × $NHCH_2$), 4·00 (t, J = 6·2 Hz, 2H, OCH_2), 6·80 (d, J = 2·2 Hz, 1H, H-4), 6·84 (dd, J = 8·8, 2·2 Hz, 1H, H-2), 7·32 (m, 2H, H-6 and H-7), 7·62 (m, 1H, H-5), 8·10 d, J = 8·8 Hz, 1H, H-1), 8·19 (dd, J = 8·0, 1·6 Hz, 1H, H-8), ^{13}C NMR ($CDCl_3$-CD_3OD): δ 10·8 (CH_3), 19·2 (CH_2CH_3), 25·3 (CH_2), 25·6 (CH_2), 26·2 (CH_2), 28·5 (CH_2), 47·4 ($NHCH_2$), 68·2 (OCH_2), 100·5 (C-4), 113·6 (C-2), 115·3 (C-9a), 117·6 (C-5), 121·5 (C-8a), 123·8 (C-7), 126·3 (C-8), 127·9 (C-1), 134·4 (C-6), 156·1 (C-10a), 158·0 (C-4a), 164·6 (C-3), 176·7 (C=O). EI-MS: m/z (%) 353 (8) (M^+).

*3-[6-(Isopropylamino)hexoxy]xanthone (**15**).* Physical data: see Table 1. IR (KBr): 3450, 1650, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1·52 (m, 10H, 2 × CH_3 and 2 × CH_2), 1·82 (m, 2H, CH_2), 2·04 (m, 2H, CH_2), 2·96 (m, 2H, $NHCH_2$), 3·38 (m, 1H, CH), 4·02 (t, J = 6·2 Hz, 2H, OCH_2), 6·79 (d, J = 2·4 Hz, 1H, H-4), 6·89 (dd, J = 8·9, 2·4 Hz, H-2), 7·34 (m, 2H, H-6 and H-7), 7·65 (m, 1H, H-5), 8·20 (d, J = 8·9 Hz, 1H, H-1), 8·27 (dd, J = 8·0, 1·7 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ 19·0 (2 × CH_3), 25·5 (CH_2), 25·8 (CH_2), 26·7 (CH_2), 28·8 (CH_2), 44·6 ($NHCH_2$), 50·7 (CH), 68·3 (OCH_2), 100·6 (C-4), 113·5 (C-2), 115·6 (C-9a), 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-10a), 158·0 (C-4a), 164·4 (C-3), 176·2 (C=O). EI-MS: m/z (%) 353 (27) (M^+).

*3-[6-(Cyclopropylamino)hexoxy]xanthone (**16**).* Physical data: see Table 1. IR (KBr): 3450, 1660, 1630 cm^{-1}. ^1H NMR ($CDCl_3$-CD_3OD): δ 0·75 (m, 2H, CH_2 in the cyclopropyl ring), 0·92 (m, 2H, CH_2 in the cyclopropyl ring), 1·39 (m, 4H, 2 × CH_2), 1·71 (m, 4H, 2 × CH_2), 2·50 (m, 1H, CH in the cyclopropyl ring), 2·94 (m, 2H, $NHCH_2$), 3·99 (bs, 2H, OCH_2), 6·79 (d, J = 2·2 Hz, 1H, H-4), 6·82 (dd, J = 8·7, 2·2 Hz, 1H, H-2), 7·30 (m, 2H, H-6 and H-7), 7·60 (m, 1H, H-5), 8·08 (d, J = 8·7 Hz, 1H, H-1), 8·13 (dd, J = 8·0, 1·6 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$-CD_3OD): δ 3·18 (CH_2 in the cyclopropyl ring), 3·22 (CH_2 in the cyclopropyl ring), 24·8 (CH_2), 25·1 (CH_2), 25·2 (CH_2), 25·5 (CH_2), 30·1 (CH in the cyclopropyl ring), 68·1 (OCH_2), 100·4 (C-4), 113·6 (C-2), 115·1 (C-9a), 117·5 (C-5), 121·3 (C-8a), 123·8 (C-7) 126·1 (C-8), 127·7 (C-1), 134·4 (C-6), 156·0 (C-10a), 158·0 (C-4a), 164·6 (C-3), 176·8 (C=O). EI-MS: m/z (%) 351 (7) (M^+).

*3-[6-(Cyclohexylamino)hexoxy]xanthone (**17**).* Physical data: see Table 1. IR (KBr): 3450, 1660, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1·21–2·31 (m, 18H, 5 × CH_2 in the cyclohexyl ring and 4 × CH_2), 2·98 (m, 3H, CH in the cyclohexyl ring and $NHCH_2$), 4·01 (t, J = 6·2 Hz, 2H, OCH_2), 6·79 (d, J = 2·3 Hz, 1H, H-4), 6·89 (dd, J = 8·9, 2·3 Hz, 1H, H-2), 7·34 (m, 2H, H-6 and H-7), 7·65 (m, 1H, H-5), 8·20 (d, J = 8·9 Hz, 1H, H-1), 8·27 (dd, J = 7·9, 1·5 Hz, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ 24·5 (CH_2), 24·7 (CH_2), 25·6 (CH_2), 25·8 (CH_2), 26·7 (CH_2), 28·8 (CH_2), 29·1 (CH_2), 44·5 ($NHCH_2$), 57·6 (CH in the cyclohexyl ring), 68·3 (OCH_2), 100·6 (C-4), 113·5 (C-2), 115·6 (C-9a), 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-10a), 158·0 (C-4a), 164·4 (C-3), 176·2 (C=O). EI-MS: m/z (%) (9) 393 (M^+).

Results and Discussions

Compounds **2**, **4**, and **5** have been synthesized and reported (Liou et al 1994). Compounds **1**, **3**, **6**–**17** were synthesized (Scheme 1) by the method described in the previous report (Liou et al 1994). Briefly, these compounds were obtained by the reaction of the potassium salts of 3-hydroxyxanthone with 1, ω-dibromoalkane in t-butanol, then aminated with appropriate amines to give the final products (Scheme 1) (Kikumoto et al 1990).

The antiplatelet effects of **1**, **3**, and **6**–**17** were studied in the aggregation of washed rabbit platelets induced by thrombin (0·1 units mL^{-1}), arachidonic acid (100 μM), collagen (10 $\mu g\,mL^{-1}$) and platlet-activating factor (PAF) (2 $ng\,mL^{-1}$). As shown in Table 2, compounds **6**, **7** (each

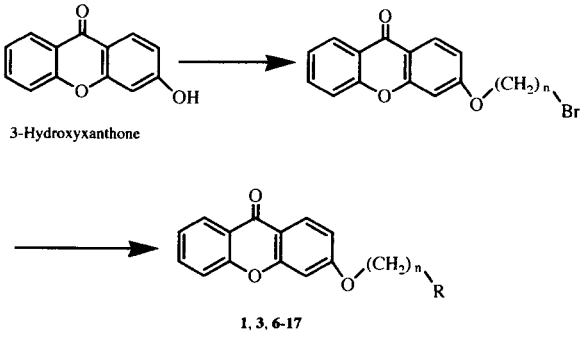
Table 2. Effect of ω-aminoalkoxylxanthones on the platelet aggregation induced by thrombin, arachidonic acid, collagen and platelet-activating factor (PAF).

Compound	Platelet aggregation (%)			
	Thrombin	Arachidonic acid	Collagen	PAF
DMSO (control)	90·6 ± 2·7	88·7 ± 0·8	89·6 ± 0·8	90·3 ± 0.5
1	90·6 ± 0·1	0·0 ± 0·0[d]	17·9 ± 14·6[d]	83·4 ± 1·4[d]
2[a]	51·0 ± 11·0[c]	5·4 ± 2·8[d]	0·0 ± 0·0[d]	6·4 ± 3·8[d]
3	90·0 ± 2·1	83·4 ± 2·5	84·6 ± 1·7	83·3 ± 0·9
4[a]	20·2 ± 1·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]
5[a]	66·0 ± 7·9[c]	2·2 ± 1·1[d]	0·0 ± 0·0[d]	4·2 ± 3·4[d]
6	0·0 ± 0·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]
7	11·3 ± 4·2[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]
8	92.3 ± 0.7	30.8 ± 6·7[d]	71·2 ± 8·6[b]	89·4 ± 0·8
9	12·2 ± 10·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]
10	84·5 ± 0·3[d]	46·3 ± 13·0[d]	19·3 ± 12·2[d]	58·3 ± 11·9[c]
11	24.8 ± 2.6[d]	0.0 ± 0·0[d]	0·0 ± 0·0[d]	2·8 ± 2·3[d]
12	97·2 ± 2·3	0·0 ± 0·0[d]	51.6 ± 7.8[d]	89·3 ± 1·9
13	7·1 ± 5·8[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]
14	17·5 ± 7·2[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]	20·6 ± 10·6[d]
15	ND	ND	72·1 ± 1·6	ND
16	21·3 ± 1·9[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]	2·2 ± 1·5[d]
17	92·1 ± 1·9	71·8 ± 4·5[c]	49·6 ± 8·8[c]	65·2 ± 3·6[d]
Aspirin	91·9 ± 2·5	0·0 ± 0·0[d]	85·4 ± 3·9	90·5 ± 1·2

Platelets were preincubated with **1**, **9** (each at 120 μM), **4–7**, **12**, **14–17** (each at 240 μM), **3** (< 25 μM), **4** (240 μM), **8** (75 μM), **10** (50 μM), **11**, **13** (each 150 μM), aspirin (50 μM) or DMSO (0·5%, control) at 37°C for 3 min, then thrombin (0·1 units mL^{-1}), arachidonic acid (100 μM), collagen (10 μg mL^{-1}) or PAF (2 ng mL^{-1}) was added. Percentages of aggregation are presented as means ± s.e.m. (n = 3–6), $^{b}P < 0.05$, $^{c}P < 0.01$, $^{d}P < 0.001$ as compared with the respective control value. ND = not determined.

[a]Data from Liou et al (1994).

240 μM), **9** (120 μM), **11**, **13** (each 150 μM), and **14**, **16** (each 240 μM) all showed potent antiplatelet effects on the aggregation induced by thrombin, arachidonic acid, collagen, and PAF. Compound **1** (120 μM) showed potent antiplatelet effects on arachidonic acid- and collagen-induced aggregation, while compound **10** (50 μM) showed potent antiplatelet effect on collagen-induced aggregation. Compound **12** (240 μM) only showed potent antiplatelet effect on arachidonic acid-induced aggregation. In comparison with data previously reported for **4** (Liou et al 1994), norathyriol (**18**) (Lin et al 1992), and norathyriol tetraacetate (**18 A**) (Teng et al 1989; Lin et al 1992), **6**, **12**, **13**, and **14** all had less potent antiplatelet effects than **4** and **18 A**, when arachidonic acid was used as the aggregating agent (Table 3). This indicates that the increasing carbon number of oxyalkyl side chain does not enhance the antiplatelet effects when arachidonic acid is used as the aggregating agent. In collagen-induced platelet aggregation, increasing the length of oxyalkyl side chain of cyclopropylaminoalkoxylxanthones to six carbon atoms showed enhancement of antiplatelet effects, but increasing the length of oxyalkyl side chain of propylaminoalkoxylxanthones (from three carbon atoms to five carbon atoms) did not enhance the antiplatelet effects (Table 3). The oxyalkyl side chains with four and



SCHEME 1.

Table 3. IC50 values of ω-aminoalkoxylxanthones on the platelet aggregation induced by arachidonic acid, collagen and adrenaline.

Reagent	IC50 (μM)		
	Arachidonic acid	Collagen	Adrenaline
1	ND	37·0	196·1
2	ND	193·3	281·3
3	ND	ND	66·1
4	13·0	83·3	284·5
5	ND	116·4	65·5
6	90·0	87·4	156·1
7	ND	68·7	28·1
8	ND	ND	71·1
9	ND	35·7	70·5
10	ND	38·5	208·8
11	ND	43·7	57·5
12	77·4	>100	28·5
13	96·5	75·9	45·8
14	169·7	44·7	40·2
15	Agonist[b]	ND	26·9
16	ND	28·6	250·4
17	ND	ND	115·6

[b]Marked agonist activity was observed at 300 μM. ND = not determined.

Table 4. Effect of ω-aminoalkoxylxanthones on aggregation of human platelet-rich plasma (PRP) induced by ADP, collagen or adrenaline.

Compound	Platelet aggregation (%)		
	ADP	Collagen	Adrenaline
DMSO (control)	97·3 ± 1·9	97·7 ± 1·6	95·6 ± 2·0
1	ND	ND	21·8 ± 3·3[c]
2	ND	ND	24·3 ± 6·0[c]
3	22·6 ± 5·4[c]	ND	0·0 ± 0·0[c]
4	ND	ND	0·0 ± 0·0[c]
5	68·7 ± 1·8[c]	0·0 ± 0·0[c]	18·9 ± 5·3[c]
6	ND	ND	11·9 ± 2·0[c]
7	44·4 ± 8·6[b]	ND	45·1 ± 1·7[c]
8	ND	ND	0·0 ± 0·0[c]
9	ND	20·2 ± 10·3[b]	8·1 ± 5·7[c]
10	55·8 ± 2·8[c]	0·0 ± 0·0[c]	0·0 ± 0·0[c]
11	72·5 ± 7·4[a]	35·4 ± 25·0[a]	19·4 ± 4·3[c]
12	ND	81·5 ± 6·8	16·0 ± 1·2[c]
13	11·0 ± 4·6[c]	0·0 ± 0·0[c]	0·0 ± 0·0[c]
14	55·8 ± 3·7[b]	0·0 ± 0·0[c]	0·0 ± 0·0[c]
15	2·8 ± 2·8[c]	0·0 ± 0·0[c]	0·0 ± 0·0[c]
16	77·1 ± 1·5[b]	23·0 ± 7·8[c]	35·8 ± 2·0[c]
17	46·9 ± 4·8[c]	0·0 ± 0·0[c]	0·0 ± 0·0[c]
Aspirin	84·4 ± 1·2	39·6 ± 15·4[a]	74·0 ± 3·2

Platelets were preincubated with **1–4**, **7**, **10**, **12**, **14–17** (each at 300 μM), **5**, **6**, **8**, **9**, **11**, **13** (each at 150 μM), aspirin (50 μM), or DMSO (0·5%, control) at 37°C for 3 min, then ADP (20 μM), collagen (10 μg mL^{-1}) or adrenaline (5 μM) was added. Percentages of aggregation are presented as means ± s.e.m. (n = 3–5). ND = not determined. [a]$P < 0·05$, [b]$P < 0·01$, [c]$P < 0·001$ as compared with the respective control value.

five carbon atoms of cyclohexylaminoalkoxylxanthones and isopropylaminoalkoxylxanthones showed more potent antiplatelet effects, when collagen was used as the aggregating agent (Table 3). Aspirin was used in this study as positive control.

It was found that aspirin (50 μM) inhibited completely the platelet aggregation induced by arachidonic acid but not that induced by thrombin, collagen, or PAF (Table 2).

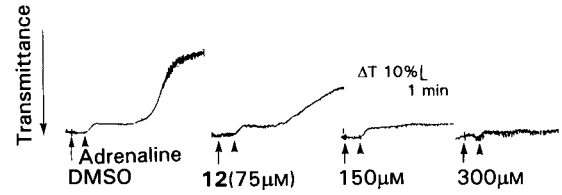


FIG. 1. Effect of **12** on aggregation of human platelet-rich plasma (PRP) induced by adrenaline. PRP was incubated with **12** at various concentrations or DMSO (0·5%) for 1 min, then adrenaline (5 μM) was added to trigger the aggregation.

The antiplatelet effects of these compounds were also studied on the aggregation of human PRP induced by ADP (20 μM), collagen (10 μg mL^{-1}), and adrenaline (5 μM). As shown in Table 4, all compounds showed potent antiplatelet effects on adrenaline-induced aggregation; **5**, **9**, **10**, **11**, **13**, **14**, **15**, **16**, and **17** showed potent antiplatelet effects on collagen-induced aggregation and **3**, **13**, and **15** showed potent antiplatelet effects on ADP-induced aggregation. More experiments were performed to study the effects of these compounds on adrenaline-induced human platelet aggregation at various concentrations. Compounds **12** and **15** showed the most potent antiplatelet effects when adrenaline was used as the aggregation agent (Table 3).

Aspirin was also used in this study as a positive control. It was found (Table 4) that aspirin (50 μM) strongly inhibited the platelet aggregation induced by adrenaline but not that induced by ADP and collagen. In human PRP, these compounds prevented secondary aggregation induced by adrenaline (Fig. 1). This suggests that their mechanism of

Table 5. Effect of various ω-aminoalkoxylxanthones on high K^+- and Ca^{2+}-induced and noradrenaline-induced contraction of rat thoracic aorta.[a]

Compound	K^+ (80 mM) + Ca^{2+} (1·9 mM)	Noradrenaline	
		(3 μM) Phasic	(3 μM) Tonic
Control	100 ± 8·6	100 ± 12·2	100 ± 7·9
1 (30 μM)	104·5 ± 0·6	73·9 ± 3·3	73·7 ± 7·1
2 (300 μM)	17·9 ± 0·0[d]	6·8 ± 0·6[d]	2·8 ± 0·3[d]
3 (30 μM)	103·3 ± 0·1	98·5 ± 2·9	102·8 ± 0·4
4 (60 μM)	77·1 ± 8·8	100 ± 0·0	111·4 ± 8·0
5 (100 μM)	13·7 ± 2·4[d]	37·5 ± 8·8[c]	35·8 ± 0·6[d]
6 (300 μM	3·7 ± 2·6[d]	0·0 ± 0·0[d]	0·0 ± 0·0[d]
7 (300 μM)	5·6 ± 0·7[d]	6·9 ± 0·2[d]	2·8 ± 0·1[d]
8 (60 μM)	72·9 ± 1·5	77·0 ± 4·5	62·7 ± 3·9
9 (30 μM)	37·4 ± 3·8[c]	88·5 ± 8·2	90·1 ± 8·7
10 (50 μM)	38·8 ± 2·3[c]	42·9 ± 10·1[c]	27·4 ± 7·6[d]
11 (150 μM)	29·3 ± 16·5[c]	7·1 ± 5·1[d]	4·1 ± 2·9[d]
12 (30 μM)	61·1 ± 7·9	101·7 ± 8·2	85·0 ± 7·1
13	ND	ND	ND
14 (30 μM)	76·1 ± 4·6	81·3 ± 0·0	103·4 ± 5·6
15 (60 μM)	45·3 ± 5·9[c]	76·3 ± 8·9[b]	77·5 ± 12·4[b]
16 (120 μM)	11·1 ± 5·0[d]	26·7 ± 2·4[c]	13·7 ± 0·2[d]
17 (100 μM)	68·5 ± 4·6	79·9 ± 2·4	86·8 ± 3·3

[a]Rat aorta was preincubated with various ω-aminoalkoxylxanthones or DMSO (0·1%, control) at 37°C for 15 min; then high K^+ (80 mM) and Ca^{2+} (1·9 mM) or noradrenaline (3 μM) was added. Percentages of the contraction were calculated and presented as means ± s.e.m. (n = 3), ND = not determined. [b]$P < 0·05$, [c]$P < 0·01$, [d]$P < 0·001$ as compared with the respective control values.

action is chiefly by the inhibition of thromboxane formation (Weiss 1983). In the rat thoracic aorta, most of these compounds at high concentrations depressed markedly the contractions induced by Ca^{2+} (1·9 mM) in high-K^+ (80 mM) medium and by noradrenaline (3 μM) (Table 5). Norathyriol and apigenin, a natural xanthone and a flavonoid, respectively, markedly inhibited arachidonic acid- and collagen-induced aggregation by inhibiting thromboxane A_2 formation in rabbit washed platelets (Teng et al 1988, 1989). In rat thoracic aorta, they also inhibited K^+- and noradrenaline-induced contractions by suppression of Ca^{2+} influx (Ko et al 1991a, b). Thus, these compounds possess antiplatelet and vasorelaxing actions similar to those of natural norathyriol and apigenin. The activity in PRP represents the functional antagonist property in a physiologically relevant medium and the activity in the rat thoracic aorta represents antagonism on a non-platelet site of the vascular system. These dual activities show that these compounds may be developed as antithrombotic agents.

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References

Chen, I. J., Liou, S. J., Liou, S. S., Lin, C. N. (1993) Xanthonol: a calcium channel and β-adrenoceptor. Gen. Pharmacol. 24: 1425–1433

Kikumoto, R., Hara, H., Ninomiya, K., Osakabe, M., Sugano, M., Fukami, H., Tamao, Y. (1990) Synthesis and platelet aggregation inhibitory and antithrombotic properties of [2[[ω-aminoalkoxyphenyl]ethyl]benzenes. J. Med. Chem. 33: 1818–1823

Ko, F. N., Lin, C. N., Liou, S. S., Huang, T. F., Teng, C. M. (1991a) Vasorelaxation of rat thoracic aorta caused by norathyriol isolated from Gentianaceae. Eur. J. Pharmacol. 192: 133–139

Ko, F. N., Huang, T. F., Teng, C. M. (1991b) Vasodilatory action mechanisms of apigenin isolated from *Apium graveolens* in rat thoracic aorta. Biochim. Biophys. Acta 1115: 69–74

Lin, C. N., Teng, C. M., Liou, S. S., Ko, F. N. (1990) γ-Pyrone compounds. 3. Synthesis and antiplatelet effects of norathyriol derivatives. J. Chin. Med. 1: 120–128

Lin, C. N., Liou, S. S., Ko, F. N., Teng, C. M. (1992) γ-Pyrone compounds. 2. Synthesis and antiplatelet effects of tetraoxygenated xanthones. J. Pharm. Sci. 81: 1109–1112

Lin, C. N., Liou, S. S., Ko, F. N., Teng, C. M. (1993) γ-Pyrone compounds. 4. Synthesis and antiplatelet effects of monooxygenated and dioxygenated xanthones and xanthonoxypropanolamines. J. Pharm. Sci. 82: 11–16

Lin, C.-N., Fang, S.-C., Lin, H.-C., Ko, F.-N., Shieh, B.-J., Liu, H.-W., Teng, C.-M. (1994) Studies on the synthesis of some xanthonoid derivatives possessing antiplatelet effect. J. Pharm. Pharmacol. 46: 917–927

Liou, S. S., Teng, C. M., Ko, F. N., Lin, C. N. (1994) γ-Pyrone compounds. 5. Synthesis and antiplatelet effects of xanthonoxypropanolamines and related compounds. J. Pharm. Sci. 83: 391–395

O'Brien, J. R. (1962) Platelet aggregation. II. Some results from a new method of study. J. Clin. Pathol. (London) 15: 452–455

Teng, C. M., Chen, W. Y., Ko, W. C., Ouyang, C. (1987) Antiplatelet effect of butylidenephthalide. Biochim. Biophys. Acta 924: 375–382

Teng, C. M., Lee, L. G., Ko, F. N., Huang, T. F. (1988) Inhibition of platelet aggregation by apigenin from *Apium graveolens*. Asia Pacific J. Pharmacol. 3: 85–89

Teng, C. M., Lin, C. N., Ko, F. N., Cheng, K. L., Hung, T. F. (1989) Novel inhibitory actions on platelet thromboxane and inositol phosphate formation by xanthone and their glycoside. Biochem. Pharmacol. 38: 3791–3795

Weiss, H. J. (1983) Antiplatelet drugs: pharmacological aspects, In: Platelets: Pathophysiology and Antiplatelet Drug Therapy. Alan R Liss, Inc., New York, p. 46