J. Pharm. Pharmacol. 1996, 48: 532–538
Received February 28, 1995
Accepted December 11, 1995

Synthesis and Anti-inflammatory Effects of Xanthone Derivatives

CHUN-NAN LIN, MEI-ING CHUNG, SHIOU-JYH LIOU, TAI-HUA LEE AND JIP-PYANG WANG*

*School of Pharmacy, Kaohsiung Medical College, Kaohsiung, Taiwan 807, and *Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan 407, R.O.C.*

Abstract

Eighteen synthetic xanthone derivatives were tested for their inhibitory effects on the activation of mast cells and neutrophils.

1,3- and 3,5-Dihydroxyxanthone showed strong inhibitory effects on the release of β-glucuronidase and histamine from rat peritoneal mast cells stimulated with compound 48/80. 1,6-Dihydroxyxanthone and 1,3,8-trihydroxyxanthone showed strong inhibitory effects on the release of β-glucuronidase, and β-glucuronidase and lysozyme, respectively, from rat neutrophils stimulated with formyl-Met-Leu-Phe (fMLP). 1,3- and 1,6-Dihydroxyxanthone, 1,3,7-trihydroxyxanthone, and 1,3,5,6-, 2,3,6,7-, and 3,4,5,6-tetrahydroxyxanthone showed potent inhibitory effects on superoxide formation of rat neutrophils stimulated with fMLP. 1,6- and 3,5-Dihydroxyxanthone showed remarkable inhibitory effects on hind-paw oedema induced by polymyxin B in normal as well as in adrenalectomized mice.

These data indicated that the anti-inflammatory effect of these compounds is mediated through the suppression of chemical mediators released from mast cell and neutrophil degranulation.

Some natural and synthetic flavonoids which selectively inhibit 5-lipoxygenase have shown anti-inflammatory effects (Koshihara et al 1988; Horie et al 1991). Some xanthone dicarboxylic acids have shown potent inhibition of binding of leukotriene B_4 to receptors on intact neutrophils (Jackson et al 1993). In a previous report (Wang et al 1994), we have shown that a flavonoid-related compound, norathyriol (1,3,6,7-tetrahydroxyxanthone), had anti-inflammatory effects mediated partly through the suppression of mast cell degranulation, and partly through, at least at higher doses, a non-selective blockade of the increase in vascular plasma exudation caused by various mediators. As part of ongoing work on the development of drugs with anti-inflammatory activity, we have synthesized various oxygenated xanthones (Lin et al 1992, 1993; Liou et al 1992) and evaluated their anti-inflammatory activity. In this paper we report the synthesis and structure-activity relationships of various oxygenated xanthones.

Synthesis

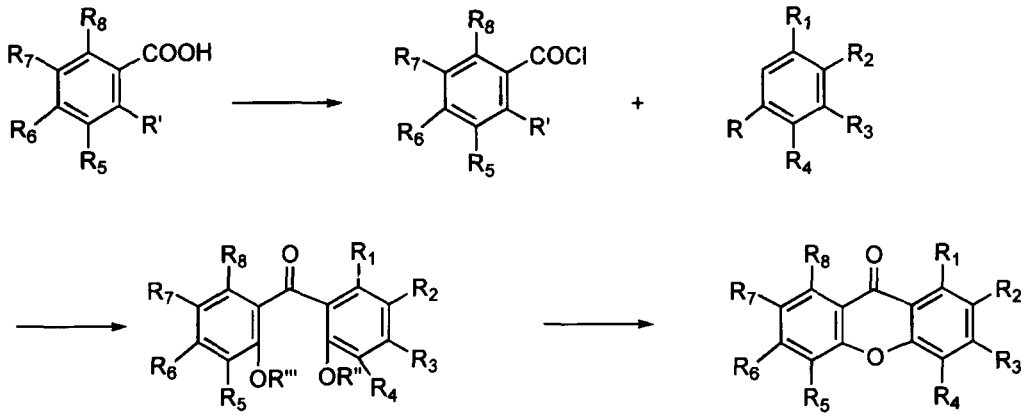
2- and 3-Hydroxyxanthones 2,3-, 3,4-, 1,3-, 1,6-, 1,7-, 2,5-, 2,6-, 3,6-, and 3,5-dihydroxyxanthones; 1,3,6-, 1,3,7-, and 1,3,8-trihydroxyxanthones; and 1,3,5,6-, 2,3,6,7-, 3,4,5,6-, and 3,4,6,7-tetrahydroxyxanthones were synthesized by a previously described method (Lin et al 1992, 1993; Liou et al 1992). Briefly, the above compounds were synthesized (Scheme 1) by Friedel-Crafts acylation of the appropriate trimethoxybenzene with another appropriate trimethoxybenzoyl chloride generated in-situ. These acylated products were refluxed with tetramethylammonium hydroxide in pyridine and demethylated with hydrogen iodide to yield appropriate hydroxylated xanthones.

Results and Discussion

The anti-inflammatory activity of compounds **1-18** (Table 1) were studied as the inhibitory effect on the activation of mast cells and neutrophils. Compound 48/80 (10 $\mu g\ mL^{-1}$) induced the release of histamine and β-glucuronidase from rat peritoneal mast cells. Compounds **2**, **5** and **11** produced strong and dose-dependent inhibition of mast cells degranulation caused by compound 48/80 (Table 2). Compounds **6** (10 $\mu g\ mL^{-1}$) and **7** (30 $\mu g\ mL^{-1}$) showed significant inhibition of mast cell degranulation caused by compound 48/80, while compounds **4** and **8** (each at 30 $\mu g\ mL^{-1}$) only showed significant inhibitory effect on release of histamine and β-glucuronidase, respectively, from mast cell degranulation caused by compound 48/80 (Table 2). The hydroxylation of **1** and **2** at C-1 or C-5 and C-5 or C-8, respectively, enhanced the inhibitory effects on the acti-vation of mast cells caused by compound 48/80. Mepacrine was used in this study as a positive control and produced a dose-dependent inhibition of mast cell degranulation caused by compound 48/80 (Table 2).

fMLP (1 μM) induced the release of β-glucuronidase and lysozyme from rat neutrophils. Compounds **6** and **14** (each at 10 $\mu g\ mL^{-1}$) showed strong and dose-dependent inhibitory effects on the release of β-glucuronidase, and β-glucuronidase and lysozyme, respectively, from rat neutrophils degranulation caused by fMLP (Table 3). Compounds **1**, **3**, **4**, **8**, **15**, and **16** (each at 30 $\mu g\ mL^{-1}$) showed potent inhibition of rat neutrophil degranulation caused by fMLP (Table 3). Compound **12** produced dose-dependent inhibition of neutrophil degranulation caused by fMLP and was a potent inhibitor with minimal-effect concentrations around 0·3 and 1 $\mu g\ mL^{-1}$, and maximal-effect concentrations around 3 $\mu g\ mL^{-1}$ and 3 $\mu g\ mL^{-1}$ for inhibitory effects on release of β-glucuronidase and lysozyme, respectively, from rat neutrophil degranulation caused by fMLP. Compound **2** did not produce potent inhibition of rat neutrophils degranulation caused by fMLP but the hydroxylation of **2** at C-2 or C-1 or C-8 or C-1 and C-6 or C-1 and C-8, respectively, enhanced the inhibitory effects on the activation of neutrophils caused by fMLP. Trifluoperazine was used in this study as a positive control and produced a dose-dependent inhibition of neutrophil degranulation caused by fMLP.

Correspondence: C.-N. Lin, School of Pharmacy, Kaohsiung Medical College, Kaohsiung 807, Taiwan, R.O.C.



SCHEME 1. General synthesis of xanthone derivatives.

Table 1. Oxygenated xanthone derivatives.

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Yield (%)	mp (°C)	Analysis
1	H	OH	H	H	H	H	H	H	53	189–190	$C_{13}H_8O_3$
2[a]	H	H	OH	H	H	H	H	H	93	241–242	$C_{13}H_8O_3$
3[a]	H	OH	OH	H	H	H	H	H	94	293–295	$C_{13}H_8O_4\ \frac{1}{2}H_2O$
4[a]	H	H	OH	OH	H	H	H	H	95	238–240	$C_{13}H_8O_4$
5[a]	OH	H	OH	H	H	H	H	H	95	257–258	$C_{13}H_8O_4$
6[a]	OH	H	H	H	H	OH	H	H	91	242–243	$C_{13}H_8O_4$
7	OH	H	H	H	H	H	OH	H	82	194–195	$C_{13}H_8O_4$
8	H	OH	H	H	OH	H	H	H	75	224–225	$C_{13}H_8O_4$
9[a]	H	OH	H	H	H	OH	H	H	92	> 300	$C_{13}H_8O_4$
10[a]	H	H	OH	H	H	OH	H	H	91	> 300	$C_{13}H_8O_4$
11[a]	H	H	OH	H	OH	H	H	H	89	> 300	$C_{13}H_8O_4$
12	OH	H	OH	H	H	OH	H	H	80	264–265	$C_{13}H_8O_5\ H_2O$
13	OH	H	OH	H	H	H	OH	H	88	264–267	$C_{13}H_8O_5$
14	OH	H	OH	H	H	H	H	OH	88	210–211	$C_{13}H_8O_5$
15[b]	OH	H	OH	H	OH	OH	H	H	94	> 300	$C_{13}H_8O_6$
16[b]	H	OH	OH	H	H	OH	OH	H	96	> 300	$C_{13}H_8O_6$
17[b]	H	H	OH	OH	OH	OH	H	H	95	> 300	$C_{13}H_8O_6$
18[b]	H	H	OH	OH	H	OH	OH	H	95	> 300	$C_{13}H_8O_6$

[a] Data from Lin et al (1993). [b] Data from Lin et al (1992).

fMLP (0·3 μM) also induced the superoxide formation from rat neutrophils caused by fMLP. Compounds **5**, **6**, **7**, **8**, **10**, **13**, **15**, **16** and **17** all showed potent inhibitory effects on superoxide formation from rat neutrophils caused by fMLP (Table 4). All compounds (except **7** and **8**) with a 3-hydroxylated moiety showed significant inhibition of superoxide formation from rat neutrophils caused by fMLP.

The process of subplantar injection of polymyxin B induced hind-paw swelling. Oedematous response was significantly suppressed in mice pretreated with compounds **6** and **11** (Table 5). Polymyxin B-induced paw oedema was inhibited by indomethacin (Table 5). The inhibitory effect of **6** and **11** on polymyxin B-induced oedematous response was demonstrated not only in normal mice but also in adrenalectomized mice (Table 6). Four days after adrenalectomy, mice were fasted for determinination of liver glycogen content. Dexamethasone (1·3 μmol kg^{-1}) greatly increased the liver glycogen content, while **6** and **11** (each at 100 μmol kg^{-1}) was ineffective in this respect (Table 7).

Drugs which possess inhibitory effects on the activation of mast cells and neutrophils will alleviate the inflammatory syndrome. Most of the xanthone derivatives **1**–**18** showed significant inhibition of mast cell and neutrophil degranulation. They showed significant anti-inflammatory effect. The results shown in Tables 2-4 indicate the oxygenated group of C-3 in the xanthone skeleton as the important moiety related to the anti-inflammatory effects in-vitro. The oxygenated group of C-3 in the xanthone skeleton also is the important moiety related to the antiplatelet effects (Lin et al 1993).

Polymyxin B-induced oedema is suppressed by non-steroidal anti-inflammatory drugs such as aspirin and indomethacin, and blockers of histamine and 5-hydroxytryptamine (5-HT) (Bertelli & Soldani 1979). In this study, **6** and **11** significantly reduced the paw swelling in polymyxin B-induced oedema.

Compounds **6** and **11** retain anti-inflammatory activity in adrenalectomized mice, indicating that the action of **6** and **11** does not depend upon direct or indirect stimulation of the adrenal gland. On the administration of glucocorticoid to the adrenalectomized animal, the processes of gluconeogenesis and glycogenesis are enhanced, and the liver glycogen stores are built up (Haynes 1990). Unlike dexamethasone, **6** and **11** did not increase liver glycogen content, suggesting that **6** and **11** do not possess glucocorticoid activity.

The present results demonstrate that **6** and **11** have an anti-inflammatory effect. The inhibitory effects of **6** and **11** on polymyxin B-induced oedema are not mediated by steroid

Table 2. The concentration-dependent inhibition of xanthone derivatives on the release of β-glucuronidase and histamine from rat peritoneal mast cells stimulated with compound 48/80.

Compound[a]	Concn ($\mu g\ mL^{-1}$)	Inhibition of release(%)[b] β-Glucuronidase	Histamine
1	30	33·7 ± 10·3	8·5 ± 8·7
2	10	90·09 ± 11·0	72·8 ± 12·7
3	30	26·3 ± 9·7	20·0 ± 0·5
4	30	33·1 ± 8·2	41·9 ± 2·3
5	10	100·1 ± 12·7	106·9 ± 11·1
6	10	68·1 ± 8·5	52·4 ± 10·1
7	30	39·8 ± 0·2	39·6 ± 1·0
8	30	41·2 ± 14·4	21·7 ± 9·3
9	30	15·5 ± 3·3	0·3 ± 3·7
10	30	17·7 ± 7·5	-
11	10	118·6 ± 10·9	97·9 ± 7·3
12	30	34·9 ± 9·0	25·0 ± 3·4
13	30	24·3 ± 4·9	15·0 ± 6·6
14	30	− 27·3 ± 9·9	17·4 ± 3·1
15	30	18·8 ± 4·1	19·5 ± 5·4
16	30	5·1 ± 1·6	21·3 ± 4·7
17	30	− 0·3 ± 6·8	33·1 ± 1·1
18	10	9·6 ± 1·2	27·9 ± 3·2
Mepacrine	100	91·9 ± 9·5	70·1 ± 5·8

[a] Release was triggered by addition of compound 48/80 (10 $\mu g\ mL^{-1}$) to the mast cell suspension, which was preincubated with dimethylsulphoxide or compounds **1–18**, and mepacrine, respectively, at 37°C for 3 min. After a further 15-min incubation, the reaction was terminated. Histamine and β-glucuronidase in the supernatant were determined as described in Materials and Methods. [b] Numbers are percent inhibition at the highest concentration assayed.

Table 3. The concentration-dependent inhibition of xanthone derivatives on the release of β-glucuronidase and lysozyme from rat neutrophils stimulated with fMLP.

Compound[a]	Concn ($\mu g\ mL^{-1}$)	IC50 ($\mu g\ mL^{-1}$)[b] β-Glucuronidase	Lysozyme
1	30	78·6 ± 12·3	54·9 ± 7·2
2	10	9·0 ± 7·3	37·9 ± 2·8
3	30	106·6 ± 6·2	91·1 ± 1·1
4	30	64·1 ± 11·6	44·6 ± 11·4
5	10	81·0 ± 8·4	46·2 ± 3·8
6	10	102·9 ± 2·6	77·6 ± 2·1
7	30		55·9 ± 14·5
8	30	90·0 ± 2·2	63·8 ± 3·3
9	30	55·8 ± 10·6	17·9 ± 9·1
10	10	36·6 ± 3·1	30·4 ± 7·2
11	10	− 4·2 ± 13·5	2·5 ± 13·2
12		1·56	2·58
13	30	46·0 ± 7·8	51·8 ± 4·2
14		0·61	2·93
15	30	62·7 ± 5·2	70·2 ± 7·0
16	30	35·9 ± 7·9	55·4 ± 10·7
17	30	14·4 ± 1·6	25·0 ± 4·9
18	10	4·3 ± 6·0	23·9 ± 2·6
Trifluoperazine	20	67·0 ± 8·4	99·1 ± 1·7

[a] Release was triggered by the addition of fMLP (1 $\mu g\ mL^{-1}$) to the leucocyte suspension, which was preincubated with dimethylsulphoxide or compounds **1–18**, and trifluoperazine, respectively, at 37°C for 3 min. After a further 45-min incubation, the β-glucuronidase and lysozyme in the supernatant were determined as described in Materials and Methods. [b] Average ± s.e.m. of at least three determinations. Values where the concentration of compound is given are percent inhibition at the highest concentration assayed.

hormones released from the adrenal gland. The anti-inflammatory effects of **6** and **11** are mediated through the suppression of chemical mediators released from mast cell and neutrophil degranulation, and mast cell degranulation, respectively.

Table 4. The concentration-dependent inhibition of xanthone derivatives on superoxide formation from rat neutrophils stimulated with fMLP.

Compound[a]	Concn($\mu g\ mL^{-1}$)	Inhibition of superoxide formation (%)[b] (nmol $O_2^-/10^6$ cells)
1	30	55·1 ± 7·5
2	10	− 15·0 ± 1·2
3	30	81·1 ± 9·9
4	30	77·4 ± 9·4
5	10	62·2 ± 12·2
6	10	70·2 ± 3·2
7	30	63·7 ± 9·4
8	30	73·3 ± 7·9
9	30	29·6 ± 7·8
10	30	64·7 ± 7·2
11	30	− 37·1 ± 13·8
12	30	4·2 ± 9·5
13	30	71·3 ± 7·2
4	30	32·4 ± 6·4
15	10	62·4 ± 15·4
16	10	71·1 ± 10·3
17	1	56·7 ± 12·5
18	30	66·9 ± 2·8

[a] PMN leucocyte suspension was preincubated at 37°C with dimethylsulphoxide or compounds **1–18**, for 3 min; superoxide dismutase and HBSS were added to the blank and test tubes, respectively. After addition of cytochrome c, reaction was initiated by challenge with fMLP (0·3 μM). Ten minutes later, reaction was terminated and the amount of superoxide radical generated was determined as described in Materials and Methods. [b] Values are percent inhibition at the highest concentration assayed.

Table 5. Effects of indomethacin, 1,6- (**6**) and 3,5-dihydroxyxanthone (**11**) on polymyxin B-induced mouse hind-paw oedema.

Compound	Concn ($\mu mol\ kg^{-1}$)	Hind-paw oedema (area under the curve)
Control		147·4 ± 14·1
Indomethacin	3	100·8 ± 7·5*
6	10	121·5 ± 13·6
	30	97·9 ± 14·2*
	100	93·4 ± 11·0*
	300	86·1 ± 9·8*
11	10	115·6 ± 8·8
	30	96·4 ± 8·4*
	100	82·6 ± 4·4*
	300	73·7 ± 7·0**

Mice were pretreated with dimethylsulphoxide or indomethacin or **6** or **11** 1 h before subplantar injection of 10 μg polymyxin B. Values are expressed as the means ± s.e.m. of 4–5 animals. *$P < 0.05$, **$P < 0.01$ compared with control.

Norathyriol (1,3,6,7-tetrahydroxyxanthone), a natural product, widely distributed in Gentianaceous plants, showed an anti-inflammatory effect (Wang et al 1994). The inhibitory effect of norathyriol on local oedema is not due to the release of steroid hormones from the adrenal gland, but is probably partly due to suppression of mast cell degranulation and hence reduction of the release of chemical mediators which increase vascular permeability, and partly, at least in higher doses, due to protection of the vasculature from challenge by various mediators (Wang et al 1994). The above results indicate that the anti-inflammatory effects of **6** (1,6-dihydroxy- or 3,8-dihydroxyxanthone) and **11** may be the same as that of norathyriol. The oxygenated group of C-3 in the xanthone skeleton may also be an important moiety related to anti-inflammatory effects in-vivo.

Table 6. Effects of 1,6- (**6**) and 3,5-dihydroxyxanthone (**11**) on polymyxin B-induced hind-paw oedema in adrenalectomized mice.

Compound	Dose (μmol kg^{-1})	Hind-paw oedema (area under the curve)
Control		156·2 ± 13·0
6	100	90·3 ± 6·5**
11	100	85·0 ± 9·6**

Oedematous response was induced by subplantar injection of 10 μg polymyxin B in control or drug-pretreated mice. Compound **6** or **11** was given intraperitoneally 1 h before the induction of paw swelling. Values are expressed as the means ± s.e.m. of 4–5 animals. **$P < 0.01$ compared with control.

Table 7. Effects of dexamethasone, 1,6- (**6**) and 3,5-dihydroxyxanthone (**11**) on liver glycogen content in adrenalectomized mice.

Compound	Dose (μmol kg^{-1})	Glycogen content (mg (g liver)$^{-1}$)
Control		2·41 ± 0·40
Dexamethasone	1·3	27·03 ± 2·09**
6	100	3·19 ± 0·63
11	100	2·49 ± 0·14

Adrenalectomized mice were deprived of food and saline for 18 h before intraperitoneal injection of dimethylsulphoxide or dexamethasone or **6** or **11**. Eight hours later, the liver glycogen content was determined. Values are expressed as the means ± s.e.m. of 5–9 animals. **$P < 0.01$ compared with control.

Experimental Section

General procedures

Melting points (uncorrected) were determined with a Yanaco Micro-Melting Point apparatus. IR spectra were determined with a Hitachi model 260-30 IR spectrophotometer. ^{1}H and ^{13}CNMR spectra [δ (ppm), J (Hz)] were determined with a Varian Gemini 200 MHz FT-NMR spectrometer. Mass spectra were determined with a Jeol JMS-D-100 mass spectrometer. Elemental analyses were within ±0·4% of the theoretical values, unless otherwise noted. Chromatography was performed using a flash-column technique on silica gel 60 supplied by E. Merck.

3-Hydroxyxanthones

2,3-, 3,4, 1,3-, 1,6-, 2,6-, 3,6-, and 3,5-dihydroxyxanthones; and 1,3,5,6-, 2,3,6,7-, 3,4,5,6-, and 3,4,6,7-tetrahydroxyxanthones were synthesized and identified as previously described (Lin et al 1992, 1993).

*2-Hydroxy-5-methoxy-2′-methoxybenzophenone (**1a**) and 2,5-dimethoxy-2′-hydroxybenzophenone (**1b**)*

o-Methoxybenzoic acid (2·0 g, 13·14 mmol) in dry benzene (60 mL) was treated with 5·0 mL oxalyl chloride under an argon atmosphere and thoroughly stirred at room temperature (21°C) (Quillinan & Scheinmann 1973). After 2 h, the solvent and the excess reagent were removed under reduced pressure. The residue, 2-methoxybenzoyl chloride, was dissolved in anhydrous ether (80 mL) and *p*-dimethoxybenzene (1·8 g, 13·03 mmol) and $AlCl_3$ (5·0 g) were added (Quillinan & Scheinmann 1973). After stirring for 8 h at room temperature, the mixture was hydrolysed with ice-cold H_2O (500 mL) containing concentrated HCl (45 mL) and extracted with $CHCl_3$. Solvent removal gave a crude product that was purified by column chromatography (silica gel-$CHCl_3$) to yield **1a** + **1b** as a yellow oil (2·20 g, 8·53 mmol, 65%); ^{1}H NMR ($CDCl_3$): δ 3·73 (s, 12H, 4 × OCH_3), 6·83–6·89 (m, 2H, H-5′ of **1a** and **1b**), 6·90 (d, J = 2·0 Hz, 2H, H-5 of **1a** and **1b**), 6·97 (dd, J = 2·0; 9·0 Hz, 2H, H-4 of **1a** and **1b**), 7·06 (d, J = 9·0 Hz, 2H, H-3 of **1a** and **1b**), 7·31(dd, J = 1·8; 7·5 Hz, 2H, H-3′ of **1a** and **1b**), 7·37–7·49 (m, 2H, H-4′ of **1a** and **1b**), 7·85 (dd, J = 1·8; 7·9 Hz, 2H, H -6′ of **1a** and **1b**), 10·92 (s, 2H, 2 × OH of **1a** and **1b**, D_2O exchangeable).

*2-Methoxyxanthone (**1M**)*

Compound **1a** + **1b** (2·20 g, 8·53 mmol) was treated with pyridine (100 mL), H_2O (5O mL) and aqueous 25% tetramethylammonium hydroxide (13·6 mL). The mixture was refluxed for 36 h (Quillinan & Scheinmann 1973), poured into ice, acidified with HCl, and extracted with $CHCl_3$. This procedure yielded an oil which, after purification by column chromatography (silica gel – $CHCl_3$) and crystallization from methanol, yielded **1M** as white needles (1·2 g, 5·29 mmol, 62%); mp 128–129°C; EI-MS: m/z (%) 226 (100) (M^+); IR (KBr): cm^{-1} 1650; ^{1}H NMR ($CDCl_3$): δ 3·91(s, 3H, OCH_3), 7·31 (dd, J = 3·1; 9·1 Hz, 1H, H-3), 7·36 (m, 1H, H-7), 7·38 (d, J = 9·1 Hz, 1H, H-4), 7·47 (dd, J = 1·74; 7·90 Hz, 1H, H-5), 7·69 (d, J = 3·1 Hz, 1H, H-1), 7·71 (m, 1H, H-6), 8·34 (dd, J = 1·74; 7·90 Hz, 1H, H-8); ^{13}C NMR($CDCl_3$): δ 55·8 (OCH_3), 105·7 (C-l), 117·9 (C-5), 119·3 (C4), 121·2 (C-8a), 122·0 (C-8b), 123·6 (C-7), 124·8 (C-3), 126·6 (C-8), 134·5 (C-6), 150·9 (C4a), 155·9 (C-2), 156·0 (C-4b), 177·4 (C = O); Anal. ($C_{14}H_{10}O_3$), C, H.

*2-Hydroxyxanthone (**1**)*

A mixture of **1M** (1·2 g, 5·29 mmol), phenol (24 mL) and hydrogen iodide (20 mL) was refluxed at 160°C for 8 h and the reaction mixture was poured into aqueous $NaHSO_3$ solution. The resulting precipitate was collected, purified by silica gel column chromatography($CHCl_3$–CH_3OH, 20 : 1) and crystallized from $CHCl_3$ to give **1** as pale yellow needles (0·59 g, 2·8 mmol, 53%); mp 189–190°C; EI-MS: m/z (%) 212 (100) (M^+); IR (KBr): cm^{-1} 3350, 1655; ^{1}H NMR (CD_3OD): δ 7·31 (dd, J = 3·0; 9·0 Hz, 1H, H-3), 7·41 (m, 1H, H-7), 7·48 (d, J = 9·O Hz, 1H, H-4), 7·55 (d, J = 3·0 Hz, 1H, H-1), 7·56 (d, J = 7·9 Hz, 1H, H-5), 7·78 (m, 1H, H-6), 8·24 (dd, J = 1·72; 7·90 Hz, 1H, H-8); ^{13}C NMR (CD_3OD): δ 108·6 (C-1), 117·7 (C-5), 118·9 (C-4), 120·5 (C-8a), 121·6 (C-8b), 123·3 (C-7), 124·5 (C-3), 125·9 (C-8), 134·5 (C-6), 150·0 (C-4a), 153·3 (C-2), 155·9 (C-4b), 177·8 (C = O) (Chaudhuri et al 1978); Anal. ($C_{13}H_8O_3$), C, H.

*2-Hydroxy-6-methoxy-2′,5′-dimethoxybenzophenone (**7a**) and 2,6-dimethoxy-2′-hydroxy-5′-methoxybenzophenone (**7b**)*

2,6-Dimethoxybenzoic acid (3·00 g, 16·48 mmol) was treated as in **1a** and **1b** and reacted with *p*-dimethoxy benzene (2·20 g, 15·94 mmol) as in **1a** and **1b** to yield **7a** + **7b** as a yellow oil (3·49 g, 12·11 mmol, 76%); ^{1}H NMR ($CDCl_3$): δ 3·62, 3·72, 3·75, 3·83 (4s, 18H, 6 × OCH_3), 6·40 (d, J = 8·4 Hz, 1H, H-3′ of **7a** or **7b**), 6·59 (dd, J = 1·1; 8·4 Hz, 1H, H4′ of **7a** or **7b**), 6·62 (d, J = 8·4 Hz, 1H, H-3′ of **7a** or **7b**), 6·78–6·89 (m, 5H, aromatic H of **7a** and **7b**), 6·97 (d, J = 8·4 Hz, 1H, H-3 of **7a** or **7b**), 7·09 (dd, J = 1·1; 8·4 Hz, 1H, H-3 of **7a** or **7b**), 7·31 (t, J = 8·4 Hz, 1H, H-4 of **7a** or **7b**), 7·36 (t, J = 8·4 Hz, 1H, H-4

of **7a** or **7b**), 11·36, 11·80 (2s, 2 × OH of **7a** and **7b**, D_2O exchangeable).

1,7-Dimethoxyxanthone (7M)

Compound **7a** + **7b** (3·49 g, 12·11 mmol) was treated as in **1M** to yield **7M** as a colourless powder (crystallized from CH_3OH; 2·23 g, 8·72 mmol, 72%); mp 150–151°C; EI-MS: m/z (%) 256 (100) (M^+); IR (KBr): cm^{-1} 1665; ^1H NMR ($CDCl_3$): δ 3·92, 4·40 (2s, 6H, 2 × OCH_3), 6·79 (d, J = 8·5 Hz, 1H, H-4), 7·05 (dd, J = 1·1; 8·5 Hz, 1H, H-2), 7·27 (dd, J = 1·1; 8·5 Hz, 1H, H-6), 7·37 (d, J = 8·5 Hz, 1H, H-5), 7·59 (t, J = 8·5 Hz, 1H, H-3), 7·71 (d, J = 1·1 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$): δ 55·7, 56·3 (2 × OCH_3), 105·0) (C-4), 106·2 (C-2), 109·9 (C-4), 112·0 (C-8b), 118·5 (C-5), 123·2 (C-8a), 123·8 (C-6), 134·5 (C-3), 149·6 (C-4b), 155·9 (C-4a), 158·0 (C-7), 160·6 (C-1), 176·2 (C = O) (Chaudhuri et al 1978); Anal. ($C_{15}H_{12}O_4$), C, H.

1,7-Dihydroxyxanthone (7)

Compound **7M** (2·23 g, 8·72 mmol) was treated as in **1** to yield **7** as a yellow powder (1·63 g, 7·15 mmol, 82%); mp 194–195°C; EI-MS: m/z (%) 228 (100) (M^+); IR (KBr): cm^{-1} 3330, 1640; ^1H NMR (CD_3OD): δ 6·71 (dd, J = 1·1; 8·4 Hz, 1H, H-2), 6·92 (dd, J = 1·1; 8·4 Hz, 1H, H-4), 7·29 (dd, J = 1·1; 8·4 Hz, 1H, H-6), 7·40 (d, J = 8·4 Hz, 1H, H-5), 7·49 (d, J = 1·1 Hz, 1H, H-8), 7·60 (t, J = 8·4 Hz, 1H, H-3); ^{13}C NMR (CD_3OD): δ 108·3 (C-8), 109·5 (C-8b), 109·7 (C-4), 110·9 (C-2), 120·5 (C-8a), 122·4 (C-5), 126·6 (C-6), 138·1 (C-3), 151·7 (C-4b), 155·7 (C-7), 158·0 (C-4a), 163·1 (C-1), 183·7 (C = O); Anal. ($C_{13}H_8O_4$), C, H.

2-Hydroxy-5-methoxy-2′,3′-dimethoxybenzophenone (8a) and 2,5-dimethoxy-2′-hydroxy-3′-methoxybenzophenone (8b)

2,3-Dimethoxybenzoic acid (3·00 g, 16·48 mmol) was treated as in **1a** and **1b** and reacted with *p*-dimethoxybenzene (2·27 g, 15·94 mmol) as in **1a** and **1b** to yield **8a** + **8b** as yellow oil (3·28 g, 11·37 mmol, 69%); ^1H NMR($CDCl_3$): δ 3·70, 3·83 (2s, 18H, 6 × OCH_3), 6·76 (t, J = 8·0 Hz, 2H, H-5′ of **8a** or **8b**), 6·79 (m, 6H, H-3, H-4 and H-6 of **8a** or **8b**), 6·97 (dd, J = 1·5; 8·0 Hz, 2H, H-4′ of **8a** and **8b**), 7·41 (dd, J = 1·5; 8·0 Hz, 2H, H-6′ of **8a** or **8b**), 11·13 (s, 2 × OH of **8a** and **8b**, D_2O exchangeable).

2,5-Dimethoxyxanthone (8M)

Compound **8a** + **8b** (3·28 g, 11·37 mmol) was treated as in **1M** to yield **8M** as a colourless powder (crystallized from CH_3OH; 2·10 g, 8·18 mmol, 72%); mp 178–179°C; EI-MS: m/z (%) 256 (100) (M^+); IR (KBr): cm^{-1} 1660; ^1H NMR ($CDCl_3$): δ 3·92, 4·03 (2s, 6H, 2 × OCH_3), 7·22 (dd, J = 2·0; 7·6 Hz, 1H, H-6), 7·29 (t, J = 7·6 Hz, 1H, H-7), 7·33 (dd, J = 2·0; 7·6 Hz, 1H, H-3), 7·56 (d, J = 7·6 Hz, 1H, H-4), 7·70 (d, J = 2·0 Hz, 1H, H-1), 7·91 (dd, J = 2·0; 7·6 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$): δ 55·8, 56·3 (2 × OCH_3), 105·6 (C-1), 114·9 (C-8), 117·5 (C-6), 119·6 (C4), 121·8 (C-8a), 122·0 (C-8b), 123·1 (C-7), 124·8 (C-3), 146·5 (C-4b), 148·5 (C-5), 150·7 (C-4a), 156·0 (C-2), 176·9 (C = O); Anal. ($C_{15}H_{12}O_4$), C, H.

2,5-Dihydroxyxanthone (8)

Compound **8M** (2·10 g, 8·18 mmol) was treated as in **1** to yield **8** as a pale yellow powder (1·40 g, 6·14 mmol, 75%); mp 224–225°C; EI-MS: m/z (%) 228 (100) (M^+); IR (KBr): cm^{-1} 3150, 1640; ^1H NMR (CD_3OD): δ 7·23 (t, J = 7·2 Hz, 1H, H-7), 7·24 (dd, J = 2·4; 7·2 Hz, 1H, H-6), 7·30 (dd, J = 2·4; 7·2 Hz, 1H, H-3), 7·54 (d, J = 2·4 Hz, 1H, H-1), 7·55 (d, J = 7·2 Hz, 1H, H-4), 7·68 (dd, J = 2·4; 7·2 Hz, 1H, H-8); ^{13}C NMR (CD_3OD): δ 110·0 (C-1), 117·2 (C-8), 120·8 (C-4), 121·2 (C-8b), 123·2 (C-6), 123·3 (C-8a), 124·9 (C-3), 126·0 (C-7), 147·5 (C-4b), 148·0 (C-5), 151·6 (C-2), 155·7 (C-4a), 179·4 (C = O); Anal. ($C_{13}H_8O_4$), C, H.

2-Hydroxy-4,6-dimethoxy-2′,4′-dimethoxybenzophenone (12a) and 2,4,6-trimethoxy-2′-hydroxy-4′-methoxybenzophenone (12b)

2,4-Dimethoxybenzoic acid (5 g, 27·47 mmol) was treated as in **1a** and **1b** and reacted with 1,3, 5-trimethoxybenzene (4·4 g, 26·44 mmol) as in **1a** and **1b** to yield **12a** + **12b** as a colourless powder (crystallized from CH_3OH; 7·84 g, 24·72 mmol, 90%); ^1H NMR ($CDCl_3$): δ 3·64, 3·80 (2s, 24H, 8 × OCH_3), 6·10 (d, J = 2·3 Hz, 4H, H-3 and H-5 of **12a** and **12b**), 6·40 (dd, J = 2·3; 9·0 Hz, 2H, H-5′ of **12a** and **12b**), 6·43 (d, J = 2·3 Hz, 2H, H-3′ of **12a** and **12b**), 7·61(d, J = 9·0 Hz, 2H, H-6′ of **12a** and **12b**).

1,3,6-Trimethoxyxanthone (12M)

Compound **12a** + **12b** (5 g, 15·78 mmol) was treated as in **1M** to yield **12M** as a colourless powder (crystallized from CH_3OH; 3·70 g, 12·94 mmol, 82%); mp 156–157°C; EI-MS: m/z (%) 286 (100) (M^+); IR (KBr): cm^{-1} 1664; ^1H NMR ($CDCl_3$): δ 3·89, 3·96 (2s, 9H, 3 × OCH_3), 6·32 (d, J = 2·3 Hz, 1H, H-2), 6·45 (d, J = 2·3 Hz, 1H, H-4), 6·76 (d, J = 2·3 Hz, 1H, H-5), 6·88 (dd, J = 2·3; 8·9 Hz, 1H, H-7), 8·19 (d, J = 8·9 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$): δ 55·69 (2 × OCH_3), 56·32 (OCH_3), 92·8 (C-4), 95·1 (C-2), 99·6 (C-5), 107·2 (C-8b), 112·6 (C-7), 117·0 (C-8a), 128·3 (C-8), 155·6 (C-4b), 159·9 (C-4a), 162·0 (C-1), 164·3 (C-3 and C-6), 174·9 (C = O); Anal. ($C_{16}H_{14}O_5$), C, H.

1,3,6-Trihydroxyxanthone (12)

Compound **12M** (3·0 g, 10·49 mmol) was treated as in **1** to yield **12** as a yellow powder (crystallized from $CHCl_3$, 2·05 g, 8·39 mmol, 80%); mp 264–265°C, EI-MS: m/z (%) 244 (100) (M^+); IR (KBr): cm^{-1} 3350, 1630; ^1H NMR (CD_3OD): δ 6·16 (d, J = 2·2 Hz, 1H, H-2), 6·30 (d, J = 2·2 Hz, 1H, H-4), 6·76 (d, J = 2·2 Hz, 1H, H-5), 6·84 (dd, J = 2·2; 8·8 Hz, 1H, H-7), 8·19 (d, J = 8·8 Hz, 1H, H-8); ^{13}C NMR (CD_3OD): δ 95·3 (C-4), 99·3 (C-2), 103·4 (C-5), 103·7 (C-8b), 114·5 (C-7), 115·1 (C-8a), 128·6 (C-8), 159·6 (C-4b), 159·7 (C-4a), 165·0 (C-1), 167·0 (C-2 and C-6), 181·5 (C = O); Anal. ($C_{13}H_8O_5 \cdot H_2O$), C, H.

2-Hydroxy-4,6-dimethoxy-2′,5′-dimethoxybenzophenone (13a) and 2,4,6-trimethoxy-2′-hydroxy-5′-methoxybenzophenone (13b)

2,5-Dimethoxy benzoic acid (5 g, 27·47 mmol) was treated as in **1a** and **1b** and reacted with 1,3,5-trimethoxybenzene (4·4 g, 26·44 mmol) as in **1a** and **1b** to yield **13a** + **13b** as a yellow powder (crystallized from CH_3OH; 7·49 g, 23·62 mmol, 86%); ^1H NMR ($CDCl_3$): δ 3·37, 3·66, 3·76, 3·81 (4s, 24H, 8 × OCH_3), 5·81 (d, J = 2·4 Hz, 2H, H-3 or H-5 of **13a** and **13b**), 6·10 (d, J = 2·4 Hz, 2H, H-3 or H-5 of **13a** and **13b**), 6·78 (dd, J = 2·9; 8·6 Hz, 2H, H-4′ of **13a** and **13b**), 6·79 (d, J = 8·6 Hz, 2H, H-3′ of **13a** and **13b**), 6·85 (d, J = 2·9 Hz, 2H, H-6′ of **13a** and **13b**), 11·83(s, 1H, OH, D_2O exchangeable), 13·36 (s, 1H, OH, D_2O exchangeable).

1,3,7-Trimethoxyxanthone (13M)

Compound **13a** + **13b** (5 g, 15·78 mmol) was treated as in **1M** to yield **13M** as colourless needles (crystallized from CH_3OH; 4·06 g, 14·20 mmol, 90%); mp 172–173°C; EI-MS: m/z (%) 286 (100) (M^+); IR(KBr): cm^{-1} 1660; ^1H NMR ($CDCl_3$): δ 3·90, 3·98 (2s, 9H, 3 × OCH_3), 6·34 (d, J = 2·4 Hz, 1H, H-2), 6·49 (d, J = 2·4 Hz, 1H, H-4), 7·22 (dd, J = 3·0; 9·0 Hz, 1H, H-5), 7·31 (dd, J = 3·0; 9·0 Hz, 1H, H-6), 7·60 (d, J = 3·0 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$): δ 55·8, 56·4 (3 × OCH_3), 92·6 (C-4), 95·0 (C-2), 99·6 (C-5), 106·7 (C-8 and C-8b), 118·3 (C-5), 123·4 (C-6 and C-8a), 149·7 (C-4b), 156·0 (C-7), 159·8 (C-4a), 162·0 (C-1), 164·8 (C-3), 175·3 (C = O); Anal. ($C_{16}H_{14}O_5$), C, H.

1,3,7-Trihydroxyxanthone (13)

Compound **13M** (3·0 g, 10·49 mmol) was treated as in **1** to yield **13** as yellow needles (crystallized from $CHCl_3$, 2·26 g, 9·23 mmol, 88%); mp 246–247°C; EI-MS: m/z (%) 244 (100) (M^+); IR (KBr): cm^{-1} 3350, 1640; ^1H NMR (CD_3OD): δ 6·17 (d, J = 2·2 Hz, 1H, H-2), 6·31 (d, J = 2·2 Hz, 1H, H-4), 7·24 (dd, J = 3·0; 9·0 Hz, 1H, H-5), 7·37 (dd, J = 3·0; 9·0 Hz, 1H, H-6), 7·48 (d, J = 3·0 Hz, 1H, H-8); ^{13}C NMR (CD_3OD): δ 95·1 (C-4), 99·2 (C-2), 103·9 (C-8b), 109·7 (C-8), 120·1 (C-5), 122·5 (C-8a), 125·5 (C-8), 151·5 (C-4b), 155·6 (C-7), 159·8 (C-4a), 164·9 (C-1), 167·6 (C-3), 182·0 (C = O); Anal. ($C_{13}H_8O_5$), C, H.

2-Hydroxy-4,6-dimethoxy-2',6'-dimethoxybenzophenone (14a) and 2,4,6-trimethoxy-2'-hydroxy-6'-methoxybenzophenone (14b)

2,6-Dimethoxy benzoic acid (3 g, 16·48 mmol) was treated as in **1a** and **1b** and reacted with 1,3,5-trimethoxybenzene (2·75 g, 16·40 mmol) as in **1a** and **1b** to yield **14a** + **14b** as a pale yellow powder (crystallized from $CHCl_3$, 4·5 g, 14·2 mmol, 86%); ^1H NMR ($CDCl_3$): δ 3·35, 3·71, 3·81 (3s, 24H, 8 × OCH_3), 5·79 (d, J = 2·4 Hz, 2H, H-3 or H-5 of **14a** and **14b**), 6·10 (d, J = 2·4 Hz, 2H, H-3 or H-5 of **14a** and **14b**), 6·54 (d, J = 8·3 Hz, 4H, H-3' or H-5' of **14a** and **14b**), 7·22 (t, J = 8·3 Hz, 2H, H-4' of **14a** and **14b**).

1,3,8-Trimethoxyxanthone (14M)

Compound **14a** + **14b** (4·5 g, 14·2 mmol) was treated as in **1M** to yield **14M** as white needles (crystallized from $CHCl_3$; 4·06 g, 10·2 mmol, 72%); mp 172–173°C; EI-MS: m/z (%) 286 (100)(M^+); IR (KBr): cm^{-1} 1645; ^1H NMR ($CDCl_3$): δ 3·83, 3·89, 3·92 (3s, 9H, 3 × OCH_3), 6·26 (d, J = 2·4 Hz, 1H, H-2), 6·35 (d, J = 2·4 Hz, 1H, H-4), 6·70 (d, J = 8·3 Hz, 1H, H-5), 6·87 (dd, J = 1·5; 8·3 Hz, 1H, H-7), 7·44 (d, J = 8·3 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 55·5, 56·1, 56·2 (3 × OCH_3), 91·9 (C-4), 95·0 (C-2), 105·6 (C-7), 108·3 (C-8b), 108·9 (C-5), 113·6 (C-8a) 133·4 (C-6), 156·8 (C-4b), 158·5 (C-4a), 160·3 (C-8), 161·6 (C-1), 164·1 (C-3), 175·3 (C = O); Anal. ($C_{16}H_{14}O_5$), C, H.

1,3,8-Trihydroxyxanthone (14)

Compound **14M** (32·9 g, 10·2 mmol) was treated as in **1** to yield **14** as pale yellow needles (crystallized from CH_3OH, 2·19 g, 8·98 mmol, 88%); mp 210–211°C; EI-MS: m/z (%) 244 (100) (M^+); IR (KBr): cm^{-1} 3400, 1660; ^1H NMR (CD_3OD): δ 6·15 (d, J = 2·1 Hz, 1H, H-2), 6·25 (d, J = 2·1 Hz, 1H, H-4), 6·67 (dd, J = 1·5; 8·3 Hz, 1H, H-5), 6·81 (dd, J = 1·5; 8·3 Hz, 1H, H-7), 7·55 (t, J = 8·3 Hz, 1H, H-6); ^{13}C NMR (CD_3OD): δ 95·6 (C-4), 99·8 (C-2), 103·2 (C-8b), 108·3 (C-8a), 108·6 (C-5), 111·8 (C-7), 138·2 (C-6), 157·7 (C-4b), 159·7 (C-4a), 162·6 (C-8), 164·5 (C-1), 168·3 (C-3), 185·8 (C = O); Anal. ($C_{13}H_8O_5$), C, H.

According to general procedures for synthesis of **1**, other analogues, **7**, **8**, **12**, **13**, and **14** were prepared as summarized in Table 1.

Pharmacology

Materials

Compound 48/80, histamine, formyl-Met-Leu-Phe (fMLP), cytochalasin B, mepacrine, trifluoperazine, polymyxin B, dexamethasone, indomethacin, heparin, bovine serum albumin, phenolphthalein-β-D-glucuronide, *o*-phthadialdehyde, cytochrome c, sodium pentobarbitone, were obtained from Sigma Chemical Company, St Louis, USA. Hanks balanced salt solution (HBSS) was obtained from Gibco Lab., Grand Island, USA. Dextran T 500 was purchased from Merck Pharmacia LKB, Taipei, R.O.C. Dimethylsulphoxide (DMSO) was obtained from Merck Taiwan Ltd, R.O.C.

Methods

Mast cell degranulation

Heparinized Tyrode solution was injected into the peritoneal cavity of exsanguinated rat (Sprague–Dawley, 250-300 g). After abdominal massage, the cells in the peritoneal fluid were harvested and then separated through 38% bovine serum albumin. The cells were washed and suspended in Tyrode solution. Cell suspension was preincubated at 37°C with DMSO or drugs for 3 min. Fifteen minutes after the addition of compound 48/80 (10 $\mu g\ mL^{-1}$), β-glucuronidase (phenolphthalein-β-D-glucuronide as substrate, 550 nm) and histamine (*o*-phthadialdehyde condensation, 350/450 nm) in the supernatant were determined. The total content was measured after treatment of the cell suspension with Triton X-100. The percent released was determined (Wang et al 1994).

Neutrophil degranulation

Blood was withdrawn from rat and mixed with EDTA. After dextran sedimentation, Ficoll-Hypaque separation and hypotonic lysis of the residual erythrocytes, neutrophils were washed and suspended in Hank's balanced salt solution (HBSS) (Boyum 1968). Cell suspension was preincubated at 37°C with DMSO or drugs for 3 min, then challenged with fMLP (1 μM). Forty-five minutes later, the lysozyme (*Micrococcus lysodeikticus* as substrate, 450 nm) and β-glucuronidase in the supernatant was determined (Smith & Iden 1979).

Superoxide radical formation

Neutrophil suspension was preincubated at 37°C with DMSO or drugs for 3 min, then superoxide dismutase and HBSS were added to the blank and test tubes, respectively. After addition of cytochrome c, reaction was initiated by challenge with fMLP (0·3 μM). Thirty minutes later, reaction was terminated by centrifugation, and supernatant was detected by spectrophotometry at 550 nm (Markert et al 1984).

Phlogist-induced hind-paw oedema

Mice (ICR, 20-25 g) were used. Hind-paw oedema was induced with a single subplantar injection of 5 μL phlogist (0·2%

polymyxin B) in physiological saline or an equal volume of physiological saline in the right and left hind-paw, respectively (Wang et al 1992). The volume of both hind-paws was measured with a plethysmometer. Hind-paw swelling was calculated as following:

$$\text{paw swelling (\%)} = \{[(\text{right paw volume} - \text{initial volume})/(\text{right paw initial volume})] - [(\text{left paw volume} - \text{initial volume})/(\text{left paw initial volume})]\} \times 100 \quad (1)$$

The data were also analysed to compare the area under the time-paw swelling curve (AUC) based on the trapezoidal rule.

Adrenalectomized mouse

Adrenalectomized animal was prepared according to Waynforth (1980), except that mouse was used. Mice were anaesthetized with intraperitoneal sodium pentobarbitone (45 mg kg^{-1}), then adrenalectomized bilaterally from the dorsal region. Sham-operated mice were also prepared concurrently. Adrenalectomized mice had free access to physiological saline as drinking water. On the fourth postoperative day, animals were used for experiments.

Glucocorticoid activity

Four days post-surgery the adrenalectomized mice were deprived of food and saline for 18 h before intraperitoneal administration of the test drugs, and 8 h later the animals were killed (Schiatti et al 1986). Liver glycogen was isolated and the glycogen content was determined (Fong et al 1953; Good et al 1993).

Acknowledgements

This work was supported, in part, by grants from the National Science Council of the Republic of China (NSC 83-0420-037-004-M03 and NSC 83-0420-B037-013-M13) and the National Research Institute of Chinese Medicine, Taipei, Taiwan, R.O.C.

References

Bertelli, A., Soldani, G. (1979) Polymyxin B – induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. Arzneim. Forsch. 29: 777–778

Boyum, A.(1968) Isolation of mononuclear cells and granulocytes from blood. Scand. J. Clin. Invest. 97(Suppl.): 77–89

Chaudhuri, R. K., Zymalkowski, F., Frahm, A. W. (1978) ^{13}CNMR – Spectroscopy of polymethoxyxanthones. Tetrahedron 34: 1837–1840

Fong, J., Schaffer, K. L., Kirk, P. L. (1953) The ultramicrodetermination of glycogen in liver: a comparison of the anthrone and reducing-sugar methods. Arch. Biochem. Biophys. 45: 319–326

Good, C. A., Kramer, H., Somogyi, M. (1993) The determination of glycogen. J. Biol. Chem. 100: 485–491

Haynes, R. C. (1990) Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical steroids. In: Gilman, A. G., Rall, T. W., Nies, A. S., Taylor, P. (eds) The Pharmacological Basis of Therapeutics. Pergamon Press, New York, pp 1431–1462

Horie, T., Tominaga, H., Kawamura, Y., Hada, T., Ueda, N., Amano, Y., Yamamoto, S. (1991) Synthesis of 5,7,8- and 5,6,7-trioxygenated 3-alkyl-3′,4′-dihydroxy flavones and their inhibitory activity against arachidonate 5-lipoxygenase. J. Med. Chem. 34: 2169–2176

Jackson, W. T., Boyd, R. J., Froelich, L. L., Gapinski, D. M. Mallett, B. E., Sawyer, J. S. (1993) Design, synthesis, and pharmacological evaluation of potent xanthone dicarboxylic acid leukotriene B4 receptor antagonists. J. Med. Chem. 36: 1726–1734

Koshihara, Y., Fujimoto, Y., Inoue, H. (1988) A new 5-lipoxygenase selective inhibitor derived from *Artocarpus communis* strongly inhibits arachidonic acid-induced ear edema. Biochem. Pharmacol. 37: 2161–2165

Lin, C. N., Liou, S. S., Ko, F. N., Teng, C. M. (1992) γ-Pyrone compounds. II: 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. IV: synthesis and antiplatelet effects of mono- and dioxygenated xanthones and xanthonoxypropanolamine. J. Pharm. Sci. 82: 11–16

Liou, S. S., Shieh, W. L., Cheng, T. H., Won, S. J., Lin, C. N. (1992) γ-Pyrone compounds as potential anti-cancer drugs. J. Pharm. Pharmacol. 45: 791–794

Markert, M., Andrews, P. C., Babior, B. M. (1984) Measurement of O_2-production by human neutrophils. The preparation and assay of NADPH oxidase-containing particles from human neutrophils. Methods Enzymol. 105: 358–365

Quillinan, A. J., Scheinmann, F. (1973) Studies in the xanthone series. Part II: A general synthesis of polyoxygenated xanthones from benzophenone precursors. J. Chem. Soc. Perkin. Trans. I: 1239–1337

Schiatti, P., Selva, D., Galliani, G., Baldoli, E., Diena, A., Glüsser, A., Leali, M., Toja, E. (1986) High selective anti-inflammatory and analgesic activity of 3-(1-methyl-ethyl)-2-(4-methoxyphenyl)-3H-naphth[11,2-d] imidazole, a new non-acidic molecule. Arzneim. Forsch. 36: 102–109

Smith, R. J., Iden, S. S. (1979) Phorbol myristate acetate-induced release of granule enzymes from human neutrophils: inhibition by the calcium antagonist, 8-(*N,N*-diethylamino)-octyl 3,4,5-trimethoxybenzoate hydrochloride. Biochem. Biophys. Res. Commun. 91: 263–271

Wang, J. P., Hsu, M. F., Raung, S. L., Chen, C. C., Kuo, J. S., Teng, C. M. (1992) Anti-inflammatory and analgesic effects of magnolol. Naunyn Schmiedebergs Arch. Pharmacol. 346: 707–712

Wang, J. P., Raung, S. L., Lin, C. N., Teng, C. M. (1994) Inhibitory effect of norathyriol, a xanthone from *Tripterospermum lanceolatum*, on cutaneous plasma extravasation. Eur. J. Pharmacol. 251: 35–42

Waynforth, H. B. (1980) Specific surgical operations. In.: Waynforth, H. B. (ed.) Experimental and Surgical Technique in the Rat. Academic Press, London, pp 124–208