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γ-Pyrone Compounds as Potential Anti-cancer Drugs

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Abstract—The γ-pyrones, artomunoxanthotrione epoxide, cyclocommunol, cyclomulberrin, and cyclocommunin exhibited potent inhibition of human PLC/PRF/5 and KB cells in-vitro. Dihydroisocycloartomunin showed significant and potent inhibition of human PLC/PRF/5 and KB cells in-vitro, respectively. Cyclomorusin, dihydrocycloartomunin and artomunoxanthone showed significant inhibition of KB cells in-vitro. Based on the above finding and the reported antileukaemic activity of xanthone psorospermin, a series of natural γ-pyrones was prepared and the inhibition of human PLC/PRF/5 and KB cells in-vitro was measured. Structure-activity analysis indicated the epoxide group substituted at 3-hydroxyl and 2,6-; 3,6-; and 3,5-dihydroxyl xanthone enhanced the anti-tumour activity. The epoxide group substituted at the 6-hydroxyl group of 1,6-dihydroxyxanthone did not show anti-tumour activity.

The natural γ-pyrones, prenylflavones and xanthone psorospermin (**1**) exhibit strong cytotoxic activity against leukaemia cells (Habib et al 1987; Fujimoto et al 1990). Recently Cushman & Nagarathnam (1991) reported the cytotoxicity of some flavonoid analogues. Our interest in finding more potent and selective anti-tumour derivatives of γ-pyrone prompted us to study the cytotoxicity of prenylflavonoids, cyclomorusin (**2**), cycloartomunin (**3**), dihydrocycloartomunin (**4**), dihydroisocycloartomunin (**5**), artomunoxanthone (**6**), artomunoxanthotrione epoxide (**7**), cyclocommunol (**8**), cyclomulberrin (**9**) and cyclocommunin (**10**), recently isolated from Formosan *Artocarpus communis* (Lin & Shieh 1991, 1992; Shieh & Lin 1992), against human hepatoma PLC/PRF/5 and KB cells in-vitro. The cytotoxic effects and structure-activity relationships of various prenylflavonoids, isolated from *Artocarpus communis* and natural γ-pyrone compound analogues, xanthones and xanthone epoxides, against human hepatoma PLC/PRF/5 and KB cells in-vitro are also described.

Materials and Methods

Biological assay

PLC/PRF/5 cells were established from human hepatoma and are known to produce HBs Ag continuously in culture fluids (Nakajima et al 1982). The cells were grown as continuous cultures in a growth medium consisting of Dulbecco's modified Eagle medium (MEM, Gibco, Grand Island, NY), 10% foetal bovine serum (FBS, Gibco), 100 int. units mL^{-1} penicillin, 100 μg mL^{-1} streptomycin and 2 mM L-glutamine. The KB cells were maintained on MEM containing 10% FBS, L-glutamine and antibiotics. For microassay, the growth medium was supplemented further with 10 mM HEPES buffer, pH 7·3.

The microassay for anticellular effect was performed as previously (Ito 1984; Lin et al 1991). The ED50 values were calculated from a semilog plot of the drug concentration vs the percentage of viable cells on day 4.

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Chemistry

Compounds **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10** (see Fig. 1) were isolated and identified from the root bark of Formosan *Artocarpus communis* (Lin & Shieh 1991; Shieh & Lin 1992; Lin et al 1993).

Synthetic methods

IR spectra were recorded on a Hitachi model 260-30 infrared spectrophotometer. ^1H and ^{13}CNMR spectra [σ (ppm), J (Hz)] were obtained on a VXR-300 MHz FT-NMR. Mass spectra were determined on a Jeol JMS-D-100 mass spectrometer. Elemental analyses were within ± 0·4% of the theoretical value when indicated by symbols of the element unless otherwise noted.

*Preparation of 1, 3, 6, 7-(**11**) and 3, 4, 6, 7-tetrahydroxyxanthone (**12**), 3-hydroxyxanthone (**13**), 3-(2, 3-epoxy propoxy)xanthone (**14**), 1, 6-, 2, 6- and 3, 6-dihydroxyxanthone*

The above compounds were synthesized and identified as previously (Lin et al 1992a, b).

*Preparation of 6- (2, 3-epoxypropoxy)-1-hydroxyxanthone (**15**)*

To a solution of 0·42 g (10·5 mmol) of sodium hydroxide in 3 mL water was added 50 mL 2-propanol and then 1·2 g (5·26 mmol) of 1,6-dihydroxyxanthone. To the above mixture was added 10 mL (124·63 mmol) epichlorohydrin, and the mixture was heated at 70°C for 3 h with stirring.

The hot reaction mixture was filtered to remove a dimeric byproduct (a glycidyl ether (Wu et al 1989)). The filtrate was concentrated under reduced pressure at 50–60°C. The semi-solid residue was treated with 20 mL of refluxing 2-propanol and more of the dimer was filtered off from the hot mixture. The clear filtrate, on cooling, yielded a solid. This was collected, washed with 3 mL 2-propanol, air-dried and yielded a tan-coloured product (Wu et al 1989), which was purified by column chromatography (silica gel-CH_2Cl_2) and

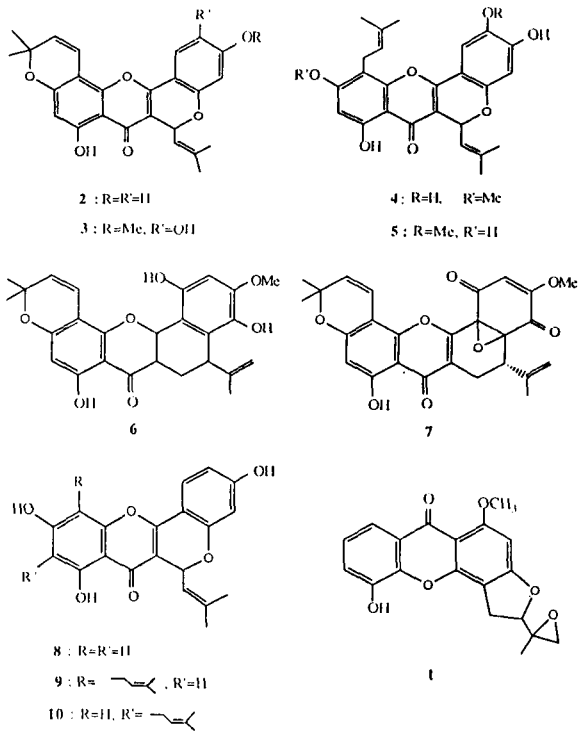
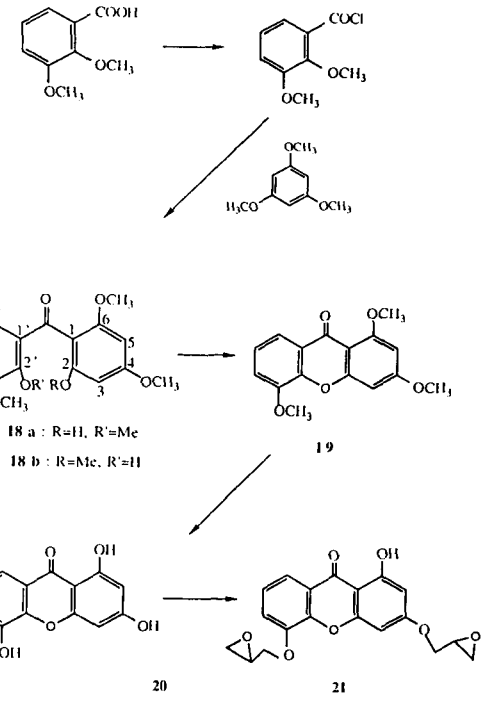


FIG. 1. Structures of compounds.



SCHEME 1.

crystallized from CH_2Cl_2 to give yellow powder (**15**), 1·4 g (4·93 mmol, 94%); MS, m/z (%) 284 (100) (M^+); IR (KBr) 3450, 1650, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): σ 2·81 (1H, dd, J = 11, 6 Hz, CH_2 in the epoxide ring), 2·91 (1H, t, J = 5 Hz, CH_2 in the epoxide ring), 3·42 (1H, m, CH in the epoxide ring), 4·04 (1H, dd, J = 11, 6 Hz, OC*H*H), 4·43 (1H, dd, J = 11, 3 Hz, OCH*H*), 6·78 (1H, dd, J = 9·0, 1·0 Hz, H-2), 6·88 (2 H, m, H-4 and H-5), 6·97 (1H, dd, J = 9·0, 2·5 Hz, H-7), 7·55 (1H, t, J = 9·0 Hz, H-3), 8·16 (1H, d, J = 9·0 Hz, H-8), 12·75 (1H, s, 1-OH, exchangeable with D_2O) (Wu et al 1989); ^{13}C NMR ($CDCl_3$): σ 44·5 (CH_2 in the epoxide ring), 49·7 (CH in the epoxide ring), 69·4 (OCH_2), 100·9 (C-5), 106·8 (C-4), 108·4 (C-8b), 110·2 (C-2), 113·7 (C-7), 114·7 (C-8a), 127·6 (C-8), 136·2 (C-3), 156·3 (C-4a), 158·0 (C-4b), 161·9 (C-1), 164·4 (C-6), 181·3 (CO) (Chaudhuri et al 1978; Frahm & Chaudhuri 1979; Biemann 1989); Anal ($C_{16}H_{12}O_5$) C, H.

Preparation of 2,6-di (2,3-epoxypropoxy) xanthone (16)

To a solution of 0·42 g (10·5 mmol) of sodium hydroxide in 3 mL water was added 50 mL 2-propanol and then 1·2 g (5·26 mmol) of 2,6-dihydroxyxanthone. To the above mixture was then added 10 mL (124·63 mmol) of epichlorohydrin, and the mixture was treated as for **15** to yield a colourless powder (CH_2Cl_2) (**16**), 1·2 g (3·85 mmol, 73%); MS, m/z (%) 340 (100) (M^+); IR (KBr) 1655, 1620 cm^{-1}: ^1H NMR ($CDCl_3$): σ 2·81 (2H, m, CH_2 in the epoxide ring), 2·96 (2H, dd, J = 10, 4·5 Hz, CH_2 in the epoxide ring). 3·42 (2H, m, 2 × CH in the epoxide ring) 4·01 (1H, dd, J = 11, 6·0 Hz, OC*H*H), 4·05 (1H, dd, J = 11, 6·0 Hz, OC*H*H), 4·38 (1H, t, J = 3 Hz, OCH*H*), 4·43 (1H, t, J = 3 Hz, OCH*H*), 6·91 (1H, d, J = 2·5 Hz, H-5), 6·97 (1H, dd, J = 9·0, 2·5 Hz, H-3), 7·35 (1H, dd, J = 9·0, 2·5 Hz, H-7), 7·41 (1H, d, J = 9·0 Hz, H-4), 7·68 (1H, d, J = 2·5 Hz, H-1), 8·26 (1H, d, J = 9·0 Hz, H-8)

Table 1. Cytotoxicity[a] of γ-pyrones isolated from *Artocarpus communis* (ED50 values in μg mL^{-1}).

	Cell line	
Prenylflavonoid	PLC/PRF/5	KB
2	6·51	3·67
3	11·64	10·30
4	5·59	2·82
5	3·67	1·28
6	5·74	3·47
7	1·06	2·09
8	2·03	2·11
9	2·50	0·73
10	2·05	0·71
Cisplatin	5·29	0·16

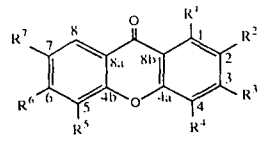
[a] For significant activity of the pure compound, an ED50 < 4·0 μg mL^{-1} is required; n = 8.

(Wu et al 1989); ^{13}C NMR ($CDCl_3$): σ 44·5, 44·6 (CH_2 in the epoxide ring), 49·8, 50·0 (CH in the epoxide ring), 69·3, 69·4 (OCH_2), 100·9 (C-5), 106·9 (C-1), 113·5 (C-7), 115·6 (C-8a), 119·3 (C-4), 122·2 (C-8b), 124·6 (C-3), 128·3 (C-8), 151·2 (C-4a), 154·8 (C-2), 157·8 (C-4b), 163·7 (C-5), 176·0 (CO) (Chaudhuri et al 1978; Frahm & Chaudhuri 1979; Biemann 1989); Anal ($C_{19}H_{16}O_6$) C, H.

Preparation of 3,6- di(2,3-epoxypropxy)xanthone (17)

To a solution of 0·42 g (10·5 mmol) sodium hydroxide in 3 mL water was added 50 mL 2-propanol and then 1·2 g (5·26 mmol) of 3,6-dihydroxyxanthone. To the above mixture was then added 10 mL (124·63 mmol) of epichlorohydrin, and the mixture was treated as for **15** to yield a colourless powder (CH_2Cl_2) (**17**), 1·4 g (4·49 mmol, 85%); MS, m/z (%)

Table 2. Chemical data and cytotoxicity (ED50 values, $\mu g\ mL^{-1}$) of xanthones.



Compound	R1	R2	R3	R4	R5	R6	R7	mp(°C)	Cell line PLC/PRF/5	Cell line KB
11	OH	H	OH	H	H	OH	OH	>300	NS	NS
12	H	H	OH	OH	H	OH	OH	>300	NS	NS
13	H	H	OH	H	H	H	H	241–242	3·75	0·77
14	H	H	[a]	H	H	H	H	157–158	1·43	0·85
15	OH	H	H	H	H	[a]	H	153–154	d	d
16	H	[a]	H	H	H	[a]	H	170–171	0·23	0·0043
17	H	H	[a]	H	H	[a]	H	187–188	0·24	0·11
21	OH	H	[a]	H	[a]	H	H	180–182	0·061	0·089
Cisplatin									5·29	0·16

NS = no significant activity. For significant activity of the pure compound, an ED50 < 4·0 $\mu g\ mL^{-1}$ is required; n = 8.
[a] 2,3-epoxypropoxy-.

340 (100) (M^+); IR (KBr) 1650, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): σ 2·81 (2 H, dd, J = 4·8, 2·5 Hz, CH_2 in the epoxide ring), 2·97 (2 H, t, J = 4·8 Hz, CH_2 in the epoxide ring), 3·42 (2 H, m, 2 × CH in the epoxide ring), 4·05 (2H, dd, J = 11, 6·0 Hz, 2 × OC*H*H), 4·39 (2H, dd, J = 11, 3·0 Hz, 2 × OCH*H*), 6·89 (2 H, d, J = 2·5 Hz, H-4 and H-5), 6·97 (2H, dd, J = 9·0, 2·5 Hz, H-2 and H-7), 8·24 (2H, d, J = 9·0 Hz, H-1 and H-8 (Wu et al 1989); ^{13}C NMR ($CDCl_3$): σ 44·6 ($2CH_2$ in the epoxide ring), 49·8 (2CH in the epoxide ring), 69·3 (2 OCH_2), 101·2 (C-4 and C-5), 113·1 (C-2 and C-7), 116·2 (C-8a and C-8b), 128·3 (C-1 and C-8), 157·9 (C-4a and C-4b), 163·4 (C-3 and C-6), 175·4 (CO) (Chaudhuri et al 1978; Frahm & Chaudhuri 1979; Biemann 1989); Anal ($C_{19}H_{16}O_6$) C, H.

*Preparation of 2-hydroxy-4,6-dimethoxy-2′,3′-dimethoxybenzophenone (**18a**) and 2,4,6-trimethoxy-2′-hydroxy-3′-methoxybenzophenone (**18b**) (scheme 1)*

2,3-Dimethoxybenzoic acid (1·8 g, 9·89 mmol) in dry C_6H_6 (25 mL) was treated with 3·5 mL oxalyl chloride under an argon atmosphere and thorough stirring at room temperature (21°C) (Quillinan & Scheinmann 1973). After 5 h the solvent and the excess reagent were removed under reduced pressure. The residue, 2,3-dimethoxybenzoyl chloride was dissolved in anhydrous Et_2O (40 mL) and 1,3,5-trimethoxybenzene (1·6 g, 9·52 mmol) and $AlCl_3$ (4·0 g) were added (Quillinan & Scheinmann 1973). After stirring for 15 h at room temperature (21°C), the mixture was hydrolysed with ice-cold H_2O (300 mL) containing concentrated HCl (35 mL), and extracted with CH_2Cl_2. Solvent removal gave a crude product that was purified by column chromatography (silica gel-CH_2Cl_2) to a yield pale yellow oil (MeOH) (**18**) (2·9 g, 9·15 mmol, 92%); ^1H NMR ($CDCl_3$): σ 3·70 (12 H, s, 4 OMe), 3·86 (6 H, s, 2 OMe), 3·91 (6 H, s, 2 OMe), 6·16 (4 H, s, H-3 and H-5 of **18a** and **18b**), 6·72 (2H, t, J = 8·0 Hz, H-4′ of **18a** and **18b**), 6·91–7·06 (4H, m, H-5′ and H-6′ of **18a** and **18b**), 12·51 (2 H, s, 2 OH of **18a** and **18b**, D_2O exchangeable).

*Preparation of 1,3,5-trimethoxyxanthone (**19**)*

18 (2·9 g, 9·15 mmol) was treated with pyridine (52·8 mL), H_2O (26·4 mL) and aqueous 10% tetramethylammonium hydroxide (18 mL). The mixture was refluxed for 34 h (Quillinan & Scheinmann 1973), poured into ice, acidified with HCl, and extracted with Et_2O, yielding an oil which, after purification by column chromatography (silica gel—CH_2Cl_2) and crystallization from MeOH, yielded a colourless powder **19**, 2·03 g (7·10 mmol, 78%), mp 233–235°C; ^1H NMR ($CDCl_3$): σ 3·89, 3·96, 4·00 (9H, 3s, 3 OMe), 6·34 (1H, d, J = 2·5 Hz, H-2), 6·62 (1H, d, J = 2·5Hz, H-4), 7·13–7·28 (2H, m, H-6 and H-7), 7·86 (1H, dd, J = 9·0, 2·5 Hz, H-8).

*Preparation of 1,3,5-trihydroxyxanthone (**20**)*

A mixture of **19** (1·9 g, 6·64 mmol), phenol (42 mL) and HI (35 mL) was refluxed at 160°C for 8 h and the reaction mixture was poured into aqueous $NaHSO_3$ solution. The resulting yellow precipitate was collected, purified by silica gel column chromatography (CH_2Cl_2-MeOH, 4:1), and crystallized from MeOH to give pale yellow needles **20**, 1·41 g (5·78 mmol, 87%), mp 211–213°C; ^1H NMR ($CDCl_3 + CD_3OD$): σ 6·19 (1H, d, J = 2·0 Hz, H-2), 6·39 (1H,d, J = 2·0 Hz, H-4), 7·07–7·19 (2 H, m, H-6 and H-7), 7·62 (1H, dd, J = 9·0, 2·5 Hz, H-8).

*Preparation of 3,5-di(2,3-epoxypropoxy)-1-hydroxyxanthone (**21**)*

To a solution of 0·28 g (5·0 mmol) potassium hydroxide in 3 mL water was added 25 mL 2-propanol and then 1·3 g (5·33 mmol) 1,3,5-trihydroxyxanthone. To the above mixture was then added 7·5 mL (93·47 mmol) epichlorohydrin, and the mixture was treated as for **15** to a yield a pale yellow powder (MeOH) (**21**), 0·45 g (1·26 mmol, 35%); MS, m/z (%) 356 (100) (M^+); IR (KBr) 3500, 1670, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): σ 1·61–2·78 (2H, m, CH_2 in the epoxide ring), 2·94–3·01 (2H, m, CH_2 in the epoxide ring), 3·41 (1H, m, CH in the epoxide ring), 3·50 (1H, m, CH in the epoxide ring), 4·03 (1H, dd, J = 11, 6·0 Hz, OC*H*H), 4·11 (1H, dd, J = 11, 6·0 Hz, OC*H*H), 4·35 (1H, dd, J = 11, 3·0 Hz, OCH*H*), 4·48 (1H, dd, J = 11, 3·0 Hz, OCH*H*), 6·38 (1H,d, J = 2·5 Hz, H-2), 6·57 (1H, d, J = 2·5 Hz, H-4), 7·30 (2H, m, H-6 and H-7), 7·85 (1H, dd, J = 9·0, 2·5 Hz, H-8) (Wu et al 1989); ^{13}C NMR ($CDCl_3$): σ 44·6 ($2CH_2$ in the epoxide ring), 49·7 and 50·1 (2 CH in the epoxide ring), 69·2 and 70·6 (2 OCH_2), 93·5 (C-4), 97·9 (C-2), 104·2 (C-8b), 117·7 (C-8), 118·0 (C-6), 122·0 (C-8a), 123·6 (C-

7), 147·2 (C-4b and C-5), 157·5 (C-4a), 163·4 (C-1), 165·4 (C-3), 180·8 (CO) (Chaudhuri et al 1978; Frahm & Chaudhuri 1979; Biemann 1989); Anal ($C_{19}H_{16}O_7$) C, H.

Results and Discussion

Since the natural γ-pyrone compound, prenylflavones and psorospermin (**1**) exhibited strong cytotoxic activities against leukaemia cells (Habib et al 1987; Fujimoto et al 1990), the inhibitory activity of prenylflavonoids **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9** and **10** against human hepatoma PLC/PRF/5 and KB cells in-vitro were studied (Nakajima et al 1982; Ito 1984). The results are listed in Table 1. Compounds **7**, **8**, **9** and **10** showed strong cytotoxic activities against human hepatoma PLC/PRF/5 and KB cells in-vitro. It was clear that a prenyl group substituted at C-6 of **8** did not enhance the cytotoxic activity against human hepatoma PLC/PRF/5 cells in-vitro but substitution at C-8 of **8** decreased the cytotoxic activity against human hepatoma PLC/PRF/5 cells in-vitro. A prenyl group substituted at C-6 or C-8 of **8** greatly enhanced the cytotoxic effect against KB cells in-vitro. Based on the above results, compounds **8**, **9** and **10** may have different selectivities. Further experiments are required to elucidate the differences in the selectivities of action. Compounds **2** and **3** did not show cytotoxic effects against human hepatoma PLC/PRF/5 and KB cells in-vitro except for **2** against KB cells in-vitro. This indicated a chromene ring substituted at C-7 and C-8 of prenylflavonoids decreased the cytotoxic effects but the cleavage of the chromene ring at the ether linkage greatly enhanced the cytotoxic effects against human hepatoma PLC/PRF/5 and KB cells in-vitro. Compound **7** showed strong cytotoxic effects against human hepatoma PLC/PRF/5 and KB cells in-vitro, but **6** only showed significant cytotoxic effect against KB cells in-vitro, indicating that a xanthone with an epoxide ring greatly enhanced the cytotoxic effects.

Based on the above results, compounds **11**, **12**, **13**, **14**, **15**, **16**, **17** and **21** were synthesized, and inhibitory activity of these compounds against human hepatoma PLC/PRF/5 and KB cells in-vitro was studied (Nakajima et al 1982). The results are listed in Table 2. Although **13** showed significant and potent inhibitory activity against human hepatoma PLC/PRF/5 and KB cells in-vitro, respectively, the epoxidation of **13** (**14**) enhanced only very markedly the inhibitory effects against human hepatoma PLC/PRF/5 cells in-vitro. Although the epoxide of 6-OH of 1,6-dihydroxyxanthone (**15**) showed insignificant inhibitory effects against human hepatoma PLC/PRF/5 and KB cells in-vitro, the epoxides of 2-; 6-OH (**16**), 3-; 6-OH (**17**) and 3-; 5-OH (**21**) of 2,6- and 3,6-dihydroxyxanthone and 1,3,5-trihydroxyxanthone, respectively, had novel inhibitory effects against human hepatoma PLC/PRF/5 and KB cells in-vitro. Based on the above results, it is clearly indicated that an additional epoxide group substituted at 5-OH of 3-(2,3-epoxypropoxy)-1-hydroxyxanthone or 6-OH of 2-(2,3-epoxypropoxy)- and 3-(2,3-epoxypropoxy) xanthones showed novel inhibitory activity.

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