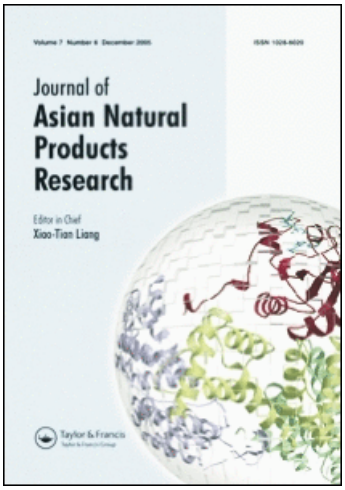

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Paeciloxanthone, a new cytotoxic xanthone from the marine mangrove fungus *Paecilomyces* sp. (Tree1-7)

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The metatrophic fungus *Paecilomyces* sp. (Tree1-7) was isolated from an estuarine mangrove from the Taiwan Strait. The methanol extract of the fungal mycelium exhibited cytotoxicity against hepG2. Paeciloxanthone (**1**), a new xanthone, and the known compounds emodin (**2**) and chrysophanol (**3**), were isolated from the extract. Their structures were elucidated by spectroscopic experiments. Paeciloxanthone (**1**) exhibited *in vitro* cytotoxicity against hepG2 ($IC_{50} = 1.08\ \mu g/mL$), acetylcholineesterase (AChE) inhibitory ($IC_{50} = 2.25\ \mu g/mL$) and antimicrobial activities.

Keywords: *Paecilomyces* sp.; Paeciloxanthone; Marine mangrove fungus; HepG2 toxicity

1. Introduction

A large variety of new bioactive compounds have recently been isolated from different sources of marine organisms [1]. In the course of our ongoing search for natural potent antitumor products from marine mangrove fungi [2–5], the extract of the metatrophic fungus Tree1-7 exhibited good cytotoxicity. The metatrophic strain was collected from the bark of a mangrove from the Taiwan Strait, which had been identified as *Paecilomyces* sp. A new xanthone paeciloxanthone (**1**), together with emodin (**2**) [12,13] and chrysophanol (**3**) [14], were isolated from the methanol extract of the fungal mycelium.

Paeciloxanthone (**1**) is one of the xanthones, which are secondary metabolites commonly occurring in a few higher plant families, fungi and lichens. In general, xanthone derivatives have also shown to be effective as allergy inhibitors and bronchodilators for the treatment of asthma [6]. Their taxonomic importance in such families and pharmacological properties have aroused great interest [7]. Some xanthones possess antidepressant and antitubercular

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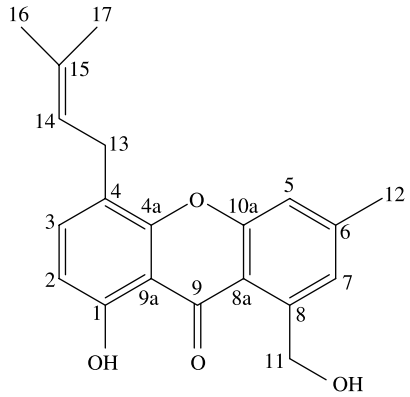

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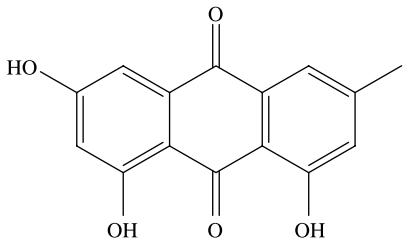

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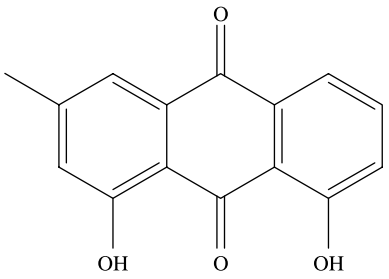

3

Figure 1. Structures of compounds **1**-**3**.

activities, while their glycosides exhibit depressant action. Recently, various bioactivities of xanthones including cytotoxic, antitumor, antiinflammatory, antifungal, choline acetyltransferase enhancement and lipid peroxidase inhibition activities have been described [8].

In the primary bioassay, paeciloxanthone (**1**) exhibited antitumor, AChE inhibition, and antimicrobial activities.

2. Results and discussion

The methanol extract of the fungal mycelium was repeatedly chromatographed on silica gel columns. Paeciloxanthone (**1**) was obtained from the fraction eluted with 10% ethyl acetate/petroleum ether (V/V) as a yellow amorphous solid, mp 137°C , with a molecular formula $C_{20}H_{20}O_4$ determined by FAB mass spectrometry 325 $[M + H]^+$ and elemental

analysis. Its UV (CH_3OH) spectrum showed the absorption bands at λ_{max} 232, 258, 301, and 368 nm, indicating that **1** was a xanthone derivative [9–11]. The IR spectrum displayed characteristic absorption bands for hydroxyl (3423 cm^{-1}), and absorption bands for carbonyl (1577, 1410 cm^{-1}). The ^1H NMR spectrum (table 1) disclosed a chelated phenolic hydroxyl group at δ 12.5, an alcoholic hydroxyl at δ 4.41, two aromatic singlets at δ 7.14 (1H, s) and 7.27 (1H, s), two *ortho* coupled aromatic doublets at δ 6.74 (1H, d, $J = 8.4$ Hz) and 7.45 (1H, d, $J = 8.4$ Hz), an olefinic multiplet at δ 5.32, two methylene doublets at δ 4.95 (2H, t, $J = 7.5$ Hz) and 3.51 (2H, d, $J = 7.5$ Hz), and three methyl singlets at δ 2.51, 1.81, and 1.77. The ^{13}C NMR spectrum revealed 20 signals (table 1).

The final structure was assembled through 2D NMR experiments. The proton and carbon signals in the 1D NMR spectra were assigned by ^1H-^1H COSY and HMQC. In the HMBC experiment (figure 2), the long-range correlations between H-13 (δ 3.51) and C-14 (δ 121.5), C-15 (δ 133.2), between H-14 (δ 5.32) and C-16 (δ 25.9), C-17 (δ 18.0), revealed the presence of a 2-isopentenyl group in **1**. The correlations between the hydroxyl proton at OH-1 (δ 12.50) and C-1 (δ 159.8), C-2 (δ 110.1), C-9a (δ 109.2); H-13 (δ 3.51) and C-3 (δ 136.9), C-4 (δ 118.9), C-4a (δ 152.7); H-11 (δ 4.95) and C-7 (δ 127.0), C-8 (δ 142.5), C-8a (δ 116.4); and H-12 (δ 2.51) and C-5 (δ 117.9), C-6 (δ 147.1), C-7 (δ 127.0), determined the positions of the hydroxyl, 2-isopentenyl, hydroxymethyl, and methyl groups in the xanthone skeleton, respectively. Thus, **1** was determined as 1-hydroxy-4-(2-isopentenyl)-6-methyl-8-hydroxyl-methyl xanthone, named as paeciloxanthone.

Compound **2** (figure 1) was identified as emodin by comparison of its NMR data with those reported in the literature [12,13]. Compound **3** (figure 1) was confirmed as the known compound chrysophanol by NMR data and physical properties [14].

Paeciloxanthone (**1**) was tested cytotoxicity against hepG2 (human liver cancer cell) cell lines, and showed significant activity with IC_{50} value of 1.08 μg/ml. In the standard disk

Table 1. 1D and 2D NMR spectral data of compound **1** ($CDCl_3$).

No.	δ_C	δ_H	*COSY*	*HMBC*
1	159.8			
2	110.1 CH	6.74 (d, 8.4)	H-3	C-1, C-4, C-9a
3	136.9 CH	7.45 (d, 8.4)	H-2	C-1, 4a, C-13
4	118.9			
4a	152.7			
5	117.9 CH	7.27 (br s)	H-12	C-7, C-8, C-10a, C-12
6	147.1			
7	127.0 CH	7.14 (br s)	H-12	C-5, C-8, C-8a, C-11, C-12
8	142.5			
8a	116.4			
9	184.3			
9a	109.2			
10a	157.8			
11	65.2 CH_2	4.95 (t, 7.5)	OH-11	C-7, C-8, C-8a
12	22.0 CH_3	2.51 (br s)	H-5, 7	C-5, C-6, C-7
13	27.5 CH_2	3.51 (d, 7.5)	H-14	C-3, C-4, C-4a, C-14, C-15
14	121.5 CH	5.32 (t, 7.5)	H-13	C-13, C-16, C-17
15	133.2			
16	25.9 CH_3	1.77 (s)		C-14, C-15, C-17
17	18.0 CH_3	1.81 (s)		C-14, C-15, C-16
OH-1		12.50 (s)		C-1, C-2, C-9a
OH-11		4.41 (t, 7.5)	H-11	

(^1H, ^{13}C NMR in 300NB; COSY, HMBC in 500NB).

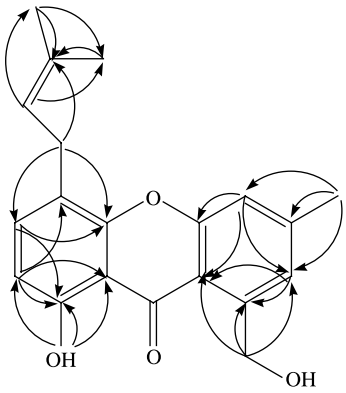

Figure 2. Key HMBC correlations of paeciloxanthone (**1**).

assays at 40 μg/disk, **1** was active against *Curvularia Lunata* (walker) Boedijn, *E. Coli*., and *Candida albicans*, affording inhibitory zones of 6, 12, and 10 mm, respectively. Paeciloxanthone (**1**) also displayed AChE inhibition activity *in vitro* ($IC_{50} = 2.25$ μg/mL).

3. Experimental

3.1 General experimental procedures

The UV spectrum was recorded on a Shimadzu UV-2501PC. The IR spectrum was recorded on a Bruker EQUINOX 55. Optical rotation was recorded on a Horiba SEPA-300 polarimeter. ^{1}H and ^{13}C NMR data, along with 2D-NMR spectra, were obtained on a Varian Inova 500NB NMR spectrometer or a Varian Inova 300NB NMR spectrometer, using TMS as an internal standard. FABMS was measured with a VG ZAB-HS Double Focussing Mass Spectrometer. The elemental analysis was measured on an Elementar Vario EL CHNS instrument. Separation and purification were performed by column chromatography on silica gel (Qingdao Haiyang Chemical Co., Ltd.). TLC was performed on silica gel GF_{254}.

3.2 Fungal strain

Paecilomyces sp. Tree 1-7 was isolated from mangrove saprophytic bark from the Taiwan Strait. The colour of mycelium was yellow, and it was plated on a potato-dextrose agar medium. Tree 1-7 is stored at Xiamen University, Xiamen, and Zhongshan University, Guangzhou, China.

3.3 Culture conditions

Plugs of agar, supporting mycelial growth, were cut from solid culture medium and transferred aseptically to a 250 mL Erlenmeyer flask, containing 100 ml liquid medium (glucose 10 g/L, peptone 2 g/L, yeast extract 1 g/L, sea salt 2 g/L). The fungus was cultured in the medium and incubated at 28°C, placed for thirty days.

3.4 Extraction and isolation

The culture (110L) was filtered through cheesecloth. The mycelium was air-dried and dipped in methanol. The filtrate was concentrated to 5L *in vacuo* below 55°C; and extracted five times by shaking with an equal volume of ethyl acetate. The combined organic extracts were applied to a silica gel column, eluting with a gradient of petroleum ether to ethyl acetate to offer compounds **1** (11 mg), **2** (45 mg), and **3** (14 mg).

Paeciloxanthone (1-hydroxy-4-(2-isopentenyl)-6-methyl-8-hydroxymethyl xanthone, **1**). Yellow amorphous solid, mp 137°C; UV (CH_3OH) λ_{max} (nm) (logϵ): 232 (5.56), 258 (5.49), 301 (5.22), 368 (5.01); IR ν_{max} (KBr) (cm^{-1}): 3423, 1577, 1410; FAB-MS *m/z* 325 (M + 1), 307, 289, 219, 123, 107, 77, 41. Elemental analysis found (%): C 73.75, H 6.21 (for $C_{20}H_{20}O_4$, C 74.07, H 6.17). ^1H and ^{13}C NMR, COSY, and HMBC ($CDCl_3$) spectral data were given in table 1.

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