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Prenylated xanthones with NGF-potentiating activity from *Garcinia xanthochymus*

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Abstract

Two prenylated xanthones, 1,4,5,6-tetrahydroxy-7,8-di(3-methylbut-2-enyl)xanthone (**1**) and 1,2,6-trihydroxy-5-methoxy-7-(3-methylbut-2-enyl)xanthone (**2**), were isolated from the wood of *Garcinia xanthochymus* along with a known xanthone, 12b-hydroxy-des-D-garcigerrin A (**3**). Their structures were elucidated by spectroscopic analysis. Compound **1** (10 μM), **2** (10–30 μM) and **3** (10 μM) showed a markedly enchancing activity of nerve growth factor (NGF)-mediated neurite outgrowth on PC12D cells.

Keywords: *Garcinia xanthochymus*; Guttiferae; Xanthone; NGF-potentiating activity; PC12D cell

1. Introduction

Garcinia xanthochymus Hook. f. (Guttiferae) is a perennial medicinal plant native to the north of Thailand and Myanmar. The fruit of *G. xanthochymus* has been used widely as a traditional folk medicine for bilious condition, diarrhea, and dysentery in Thailand (Perry, 1980). Plants in the Guttiferae are rich sources of xanthones, biflavonoids and benzophenones (Sordat-Diserens et al., 1989). Previous investigations on *G. xanthochymus* have resulted in the isolation of agathisflavone, 7-*O*-methylamentoflavone, vitexin, friedelin, betulin, β-sitosterol and canophyllol from the leaves (Singh et al., 1991; Parveen et al., 1994), xanthochymol, isoxanthochymol, volkensiflavone, morelloflavone, 1,5-dihydroxyxanthone and 1,7-dihydroxyxanthone from the fruits (Karanjgoakar et al., 1973; Baslas and Kumar, 1979). However, there is no report on the constituents of the wood and the isolation of prenylated xanthone from this plant. In the course of our search for the natural products that possess NGF-potentiating activity or neurotrophic activity from medicinal plants (Li et al., 2001a,b,c), we found that the methanol extract of *G. xanthochymus* exhibited a significant activity enhancing nerve growth factor (NGF)-mediated neurite outgrowth from PC12D cells. Bioassay-guided fractionation by monitoring the potentiation of NGF's action in PC12D cells led to the isolation of two new prenylated xanthones, 1,4,5,6-tetrahydroxy-7,8-di(3-methylbut-2-enyl)xanthone (**1**) and 1,2,6-trihydroxy-5-methoxy-7-(3-methylbut-2-enyl)xanthone (**2**), together with a known xanthone, 12b-hydroxy-des-D-garcigerrin A (**3**) from the most active ethyl acetate-soluble portion of the methanol extract of the wood of *G. xanthochymus*. Here we report the isolation, structure elucidation and biological activities of these compounds.

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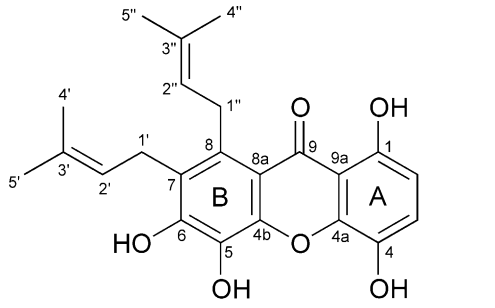

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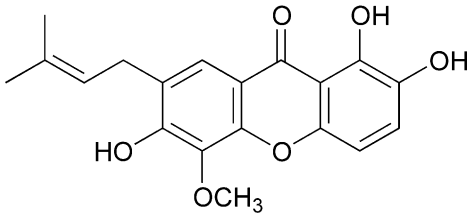

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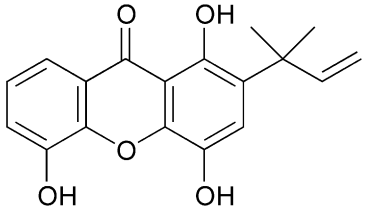

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Table 1
^{1}H and ^{13}C NMR spectral data of **1** and **2**[a]

	1[b]		**2**[c]	
Position	δ_C	δ_H (J = Hz)	δ_C	δ_H (J = Hz)
1	155.1 (*s*)		146.4 (*s*)	
2	109.8 (*d*)	6.53 (1H, *d*, 8.8)	139.4 (*s*)	
3	122.6 (*d*)	7.11 (1H, *d*, 8.8)	124.8 (*d*)	7.17 (1H, *d*, 9.0)
4	137.2 (*s*)		110.6 (*d*)	6.56 (1H, *d*, 9.0)
4a	143.8 (*s*)		155.6 (*s*)	
4b	146.3 (*s*)		151.3 (*s*)	
5	131.6 (*s*)		136.2 (*s*)	
6	151.1 (*s*)		157.1 (*s*)	
7	135.1 (*s*)		129.1 (*s*)	
8	127.1 (*s*)		121.6 (*d*)	7.64 (1H, *s*)
8a	112.2 (*s*)		115.1 (*s*)	
9	184.5 (*s*)		183.5 (*s*)	
9a	110.1 (*s*)		110.5 (*s*)	
1′	25.6 (*t*)	3.41 (2H, *d*, 6.4)	29.9 (*t*)	3.36 (2H, *d*, 7.2)
2′	124.0 (*d*)	5.03 (1H, *t*, 6.4)	123.4 (*d*)	5.35 (1H, *t*, 7.2)
3′	131.2 (*s*)		135.1 (*s*)	
4′	25.9 (*q*)	1.67 (3H, *s*)	26.8 (*q*)	1.78 (3H, *s*)
5′	18.4 (*q*)[d]	1.78 (3H, *s*)[d]	18.7 (*q*)	1.74 (3H, *s*)
1″	29.5 (*t*)	4.01 (2H, *d*, 5.6)		
2″	125.4 (*d*)	5.03 (1H, *t*, 5.6)		
3″	132.2 (*s*)			
4″	25.9 (*q*)	1.67 (3H, *s*)		
5″	18.2 (*q*)[d]	1.77 (3H, *s*)[d]		
5-OCH_3			62.8 (*q*)	4.07 (3H, *s*)

[a] Data reported in ppm. All protons and carbons were assigned by ^{1}H–^{1}H COSY, DEPT, HMQC, and HMBC spectra.
[b] Spectra determined in CD_3OD, ^{1}H NMR 400 MHz, ^{13}C NMR 100 MHz.
[c] Spectra determined in CD_3OD, ^{1}H NMR 600 MHz, ^{13}C NMR 150 MHz.
[d] Signals may be interchangeable.

2. Results and discussion

The wood of *G. xanthochymus* was extracted at room temperature with MeOH and the MeOH extract was partitioned with EtOAc, BuOH and water. The potentiating activity of NGF action was observed in the ethyl acetate fraction. The EtOAc-soluble materials were subjected to a series of bioassay-directed chromatographic separations including silica gel vacuum liquid chromatography and column chromatography, followed by Sephadex LH-20 column and reversed-phase YMC-ODS semipreparative HPLC chromatography to give **1**–**3**.

Compound **1** was obtained as yellow needles and its molecular formula was determined to be $C_{23}H_{24}O_6$ by HREIMS spectrum of **1** [m/z 396.1548, Δ−2.5 mmu]. The IR spectrum of **1** exhibited strong bands due to a phenolic hydroxyl (3400 cm^{-1}) and a chelated carbonyl (1650 cm^{-1}) group. The UV absorptions (204, 229, 256, 283, 335 nm) indicated **1** to be a hydroxyl xanthone derivative (Nkengfack et al., 2002). ^{1}H and ^{13}C NMR spectroscopic data (Table 1) aided by DEPT and HMQC experiments disclosed the presence of one carbonyl and twelve sp^2 quaternary carbons (six of which were oxygen-bearing), four sp^2 methine, two sp^3 methylene, and four methyl carbons. The initial analysis of the NMR spectral data of **1** indicated that the molecule consisted of a xanthone skeleton and two prenyl moieties.

The ^{1}H NMR spectrum of 1 (Table 1) showed a pair of *ortho*-coupled aromatic proton signals at δ 7.11 (1H, *d*, J = 8.8 Hz, H-3) and 6.53 (1H, *d*, J = 8.8 Hz, H-2) as well as the presence of two prenyl moieties, the one of which has a pair of *gem*-dimethyl signals at δ 1.78 (3H, *s*, H_3-5′) and 1.67 (3H, *s*, H_3-4′), a methine signal at δ 5.03 (1H, *t*, J = 6.4 Hz, H-2′), and a methylene signal at δ 3.41 (2H, *d*, J = 6.4 Hz, H_2-1′) and the other of which has a pair of *gem*-dimethyl signals at δ 1.77 (3H, *s*, H_3-5″) and 1.67 (3H, *s*, H_3-4″), a methine signal at δ 5.03 (1H, *t*, J = 5.6 Hz, H-2″), and a methylene signal at δ 4.01 (2H, *d*, J = 5.6 Hz, H_2-1″). The locations of two prenyl moieties were placed at the C-7 (δ_C 135.1) and C-8 (δ_C 127.1) positions by the HMBC correlations of H_2-1′/C-6 (δ_C 151.1), H_2-1′/C-7, and H_2-1′/C-8, and H_2-1″/C-7, H_2-1″/C-8 and H_2-1″/C-8a (δ_C 112.2) in the HMBC spectrum of **1** (Fig. 1), respectively. The substitution pattern of ring A was elucidated by the interrelated peaks of H-2/

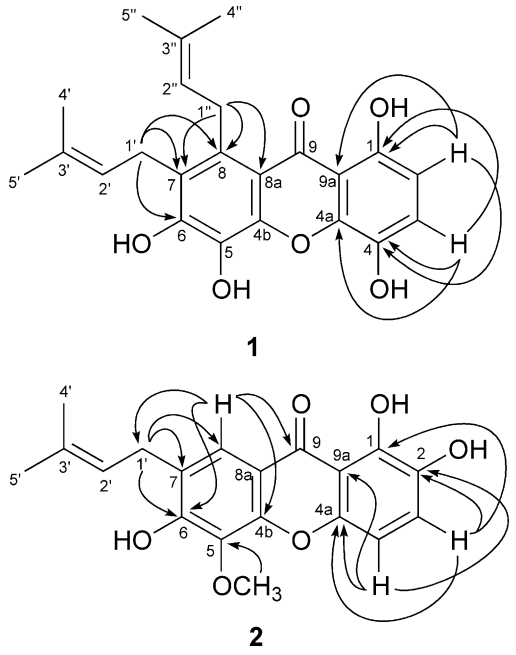

Fig. 1. Selected HMBC correlations of compounds **1** and **2** in CD_3OD.

C-1 (δ_C 155.1), H-2/C-4 (δ_C 137.2), H-2/C-9a (δ_C 110.1), H-3/C-1, H-3/C-4, and H-3/C-4a (δ_C 143.8) in the HMBC spectrum of **1** (Fig. 1), and comparing the ^{13}C NMR spectral data of **1** with those of gartanin (Hano et al., 1990), which has the same substructure as **1**. Comparison of their ^1H and ^{13}C NMR spectral data of **1** with those of subelliptinone A indicated that the substituent pattern of the ring B was similar to that of subelliptinone A (Iinuma et al., 1994). Therefore, four hydroxyl groups were positioned to the C-1, C-4, C-5 (δ_C 131.6), and C-6 positions, and the remaining two oxygen-bearing quaternary carbons were assigned to the C-4a and C-4b (δ_C 146.3) positions, correspondingly. Full analysis of the ^1H–^1H COSY, DEPT, HMQC and HMBC data enabled the complete assignment of all protons and carbons. Thus, compound **1** was determined to be 1,4,5,6-tetrahydroxy-7,8-di(3-methylbut-2-enyl)xanthone.

Compound **2** was obtained as yellow needles. Its molecular formula $C_{19}H_{18}O_6$ was determined by HREIMS spectrum [m/z 342.1117, Δ +1.4 mmu). The IR spectrum of **2** exhibited bands due to a phenolic hydroxyl (3350 cm^{-1}) and a chelated carbonyl (1650 cm^{-1}) group. The UV spectrum of **2** revealed the maximum absorptions at 204, 236, 249, 284, 315, and 385 nm. The UV and IR spectral features of **2** were similar to those of **1**, suggesting that it is a xanthone derivative. In the ^1H NMR spectrum of **2**, a group of signals at δ 5.35 (1H, *t*, J=7.2 Hz, H-2′), 3.36 (2H, *d*, J=7.2 Hz, H_2-1′), 1.78 (3H, *s*, H_3-4′), and 1.74 (3H, *s*, H_3-5′) suggested the presence of a prenyl moiety, which was connected to C-7 (δ_C 129.1) on the basis of the HMBC correlations of H_2-1′ with C-6 (δ_C 157.1), C-7, and C-8 (δ_C 121.6) (Fig. 1). A singlet aromatic proton signal at δ 7.64 (1H, *s*, H-8) was attached to the C-8 position, because H-8 correlated with C-4b (δ_C 151.3), C-6, C-9 (δ_C 183.5), and C-1′ (δ_C 29.9) in the HMBC spectrum of **2**. A methoxyl signal at δ 4.07 (3H, *s*, 5-OCH_3) showed a C–H long-range correlation with C-5 (δ_C 136.2), therefore, this methoxyl position can be assigned. The substitution pattern of the ring B was further verified by comparison of ^1H and ^{13}C NMR spectral data of **2** with literature values of globulixanthone D (Nkengfack et al., 2002), which has the same partial structure. In addition, a pair of *ortho*-coupled aromatic protons at δ 7.17 (H-3) and 6.56 (H-4) were located to the C-3 (δ_C 124.8) and C-4 (δ_C 110.6) positions of the ring A, respectively, on the basis of comparison of the ^1H and ^{13}C NMR data of **2** with those of globulixanthone C (Nkengfack et al., 2002), which has the same partial structure as **2**. Furthermore, the HMBC correlations of H-3/C-1 (δ_C 146.4), H-3/C-2 (δ_C 139.4), H3/C-4a (δ_C 155.6), H-4/C-2, H-4/C-4a, and H-4/C-9a (δ_C 110.5) confirmed this assignment. The remaining protons and carbons could all be assigned by analysis of the 2D NMR spectral data of **2** including ^1H–^1H COSY, HMQC, HMBC and NOESY spectra of **2**. These results suggested that **2** was 1,2,6-trihydroxy-5-methoxy-7-(3-methylbut-2-enyl)xanthone.

Compound **3** was identified by comparison of their spectral data with the literature values as 12b-hydroxy-des-D-garcigerrin A (Sordat-Diserens et al., 1989; Iinuma et al., 1995).

The ability of **1–3** to enhance NGF's effects for stimulating neurite outgrowths from PC12D cells was assessed utilizing previously reported methodology (Li et al., 1999). In control experiments, the percentage of neurite-bearing cells was 23.3% following incubation with 2 ng/ml NGF and 94.8% with 30 ng/ml NGF after 48 h. As shown in Figs. 2 and 3, compounds **1**, **2** and **3** (10 μM) did not induce neurite outgrowth from PC12D cells in the absence of NGF, but increased the NGF-induced (2 ng/ml) proportion of neurite-bearing cells by 23.5, 27.4 and 28.8%, respectively. Increasing concentration of **2** to 30 μM further enhanced the NGF action, whereas **1** and **3** at the concentration of 30 μM showed cytotoxicity on PC12D cells.

Compounds which enhance nerve growth factor's ability to stimulate neurite outgrowths from PC12D cells may be useful in the treatment of neurological disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and human immunodeficiency virus associate dementia (HAD) (Connor and Dragunow, 1998; Helfti, 1994; Siegel and Chauhan, 2000). Although it has been reported that garciniaxanthone B, isolated from *Garcinia subelliptica*, enhanced choline acetyltranferase activity in a cultured neuronal cell of

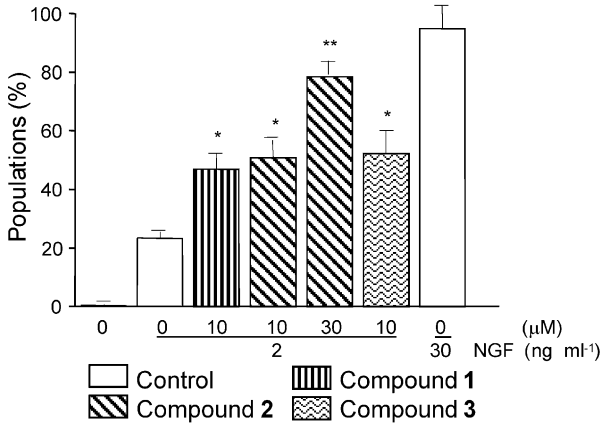

Fig. 2. Enhancement of NGF's effects for stimulating neurite outgrowths in PC12D cells with compounds **1**–**3**. Cells were incubated in the presence of NGF (2 or 30 ng/ml) alone and in the presence of compounds **1**–**3** plus NGF (2 ng/ml) for 48 h before fixed with 2% glutaraldehyde (37 °C, 1 h). The ratio of neurite-bearing cells was determined and expressed as a mean ± S.E. ($N = 12$). A statistically significant difference (*$P < 0.01$ or **$P < 0.001$) from the control (2 ng/ml NGF) in the absence of compounds **1**–**3** were apparent.

fetal rat brain hemisphere (Fukuyama et al., 1991), the prenylated xanthones **1**–**3** were reported to have the NGF-potentiating activity in this paper for the first time.

3. Experimental

3.1. General experimental procedures

Melting points were determined on a Yanaco micro-melting point apparatus and were uncorrected. IR spectra were measured on an IR-408 Shimadzu spectrophotometer. UV spectra were recorded on a UV-260 Shimadzu spectrophotometer. 1D and 2D NMR spectra were run on a INOVA-600 and JEOL GX-400 instruments. Chemical shifts were measured using residual MeOH (δ_H 3.35 and δ_C 49.0) as internal standard. LREIMS and HREIMS were recorded on a Jeol JMS AX500 and a Jeol JMS DX303 spectrometer.

3.2. Plant material

Stem of *Garcinia xanthochymus* Hook. f. was collected at Chiangmai, Thailand in July 1999. Authentication was achieved by comparison with the specimen at the Royal Forest Department, Ministry of Agriculture and Cooperation of Thailand. A voucher specimen (NSR 092513) has been deposited in the herbarium, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

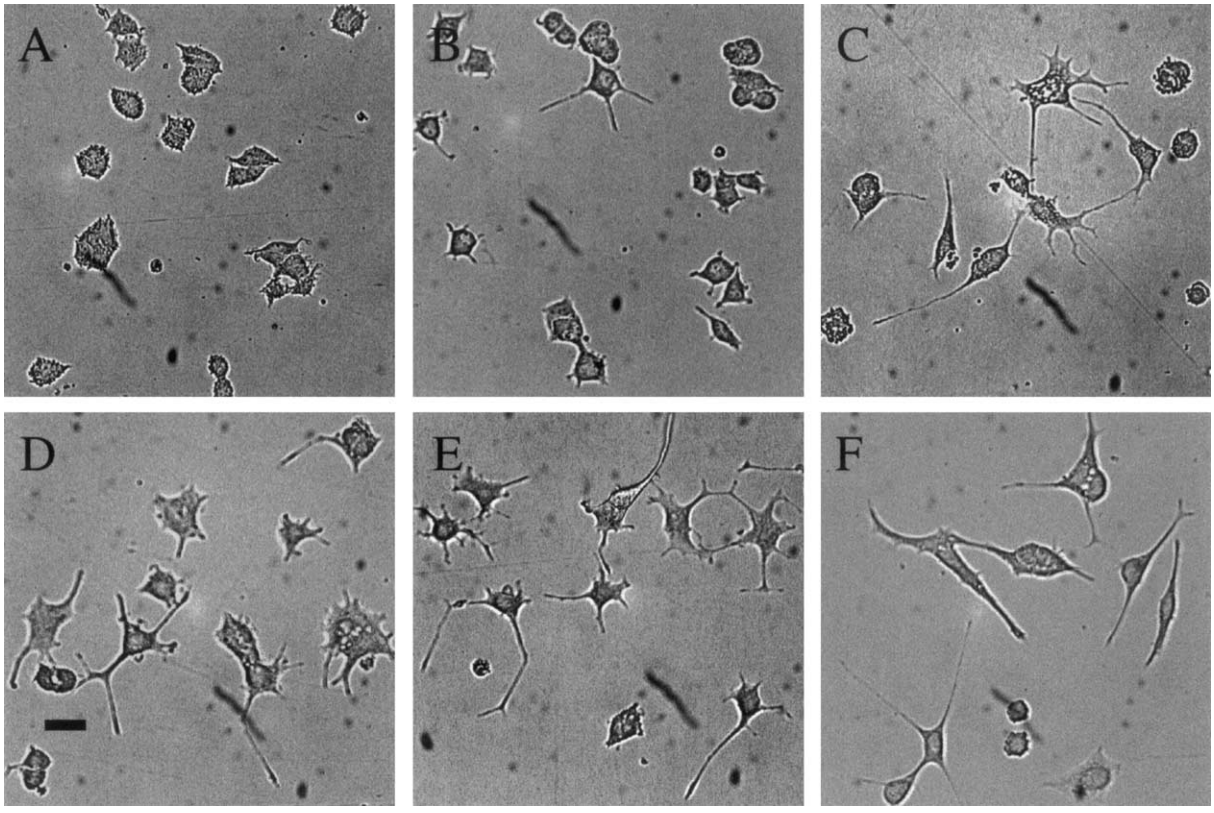

Fig. 3. Effects of compounds **1**–**3** and NGF on the morphology of PC12D cells. The cells were treated for 48 h without (A) or with **1** (10 μM) (C), **2** (10 μM) (D), **2** (30 μM) (E), and **3** (10 μM) (F) in the absence (A) or the presence (B–F) of NGF (2 ng ml^{-1}). Scale bar indicates 50 μm.

3.3. Extraction and isolation

The dried powdered stem of *Garcinia xanthochymus* (10 kg) was macerated with MeOH (4×9 l) at room temperature for 3-day periods. The extracted solution was evaporated under reduced pressure to yield a brown gummy extract (694 g). An aqueous suspension (800 ml) of this extract was extracted successively with EtOAc (3×800 ml), and then with BuOH (3×800 ml). The respective extracts were evaporated to give EtOAc-soluble materials (386 g), BuOH-soluble materials (153 g) and H_2O-soluble materials (124 g). The EtOAc-soluble materials (24 g) were subjected to vacuum liquid chromatography on silica gel eluted with *n*-hexane–EtOAc (50: 50→0:100) system and MeOH to give seven fractions: fr. I 4.8 g, fr. II 3.1 g, fr. III 0.5 g, fr. IV 4.1 g, fr.V 0.6 g, fr. VI 1.2 g and fr. VII 4.7 g. Fr. III (0.5 g) was further subjected to a silica gel column eluted with *n*-hexane–EtOAc (2:1) system to give compound **1** (15 mg, 0.0024%) and **3** (6 mg, 0.0010%). Fr. II (3.1 g) was further purified on a Sephadex LH-20 column (MeOH) to give five fractions. The fourth fr. was repeatedly purified by reversed-phase semipreparative HPLC (YMC-AM 324 ODS, i.d. 10×300 mm, 87% MeOH in H_2O) to yield compound **2** (20 mg, 0.0032%).

3.4. 1,4,5,6-Tetrahydroxy-7,8-di(3-methylbut-2-enyl)-xanthone (1)

Yellow needles, mp 188–190 °C; UV λ_{max} (MeOH) nm (log ε): 204 (4.32), 229 (4.24), 256 (4.28), 283 (3.98), 335 (3.92); IR ν_{max} (neat) cm^{-1}: 3400, 2900, 1650, 1580, 1490, 1260, 1095; for ^1H NMR (CD_3OD) and; ^{13}C NMR (CD_3OD), see Table 1; EIMS *m*/*z* (rel. int.): 396 [M^+] (100), 378 (16), 353 (92), 340 (45), 325 (94), 311 (21), 299 (56), 162 (11); HREIMS *m*/*z* 396.1548 (calcd for $C_{23}H_{24}O_6$: 396.1571).

3.5. 1,2,6-Trihydroxy-5-methoxy-7-(3-methylbut-2-enyl)xanthone (2)

Yellow needles, mp 220–222 °C; UV λ_{max} (MeOH) nm (log ε): 204 (4.20), 236 (4.21), 249 (4.19), 284 (3.99), 315 (3.82), 385 (3.52); IR ν_{max} (neat) cm^{-1}: 3350, 2950, 1650, 1580, 1480, 1370, 1230, 1090; for ^1H NMR (CD_3OD) and ^{13}C NMR (CD_3OD), see Table 1; EIMS *m*/*z* (rel. int.): 342 [M^+] (100), 327 (19), 311 (9), 287 (91), 268 (23); HREIMS *m*/*z* 342.1117 (calcd for $C_{19}H_{18}O_6$: 342.1102).

3.6. Bioassay procedure

The enhancing activity of NGF-mediated neurite outgrowth on PC12D cells was examined by a reported method (Li et al., 1999). PC12D cells were dissociated by incubation with 1 mM ethylene glycol-bis-(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA) in phosphate-buffered saline (PBS) for 30 min and then were seeded in 24-well culture plates (2×10^4 cells/well) coated with poly-L-lysine. After 24 h, the medium was changed to test medium containing various concentrations of NGF (30 ng/ml for control and 2 ng/ml for test samples), 1% fetal calf serum, 2% horse serum, and various concentrations of test compounds (10, 30 μM). All test compound stock solutions were prepared at 100 mM in DMSO. After 48 h the cells were fixed with 2% glutaraldehyde at 37 °C for 1 h. The neurite outgrowth was assessed under a phase-contrast microscope. Neurite processes with a length equal to or greater than the diameter of the neuron cell body were scored as a neurite-bearing cell. The ratio of the neurite-bearing cells to total cells (with at least 100 cells examined/viewing area; 3 viewing areas/well; 6 wells/sample) was determined and expressed as a percentage. The data were analyzed by Student *t*-test.

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