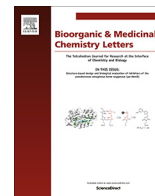




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Marine bis- γ -pyrone polypropionates of onchidione family and their effects on the XBP1 gene expression

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ABSTRACT

Two additional new members of the onchidione family, 16-*epi*-onchidione (**1**) and 4-*epi*-onchidione (**2**), co-occurring with six previously reported bis- γ -pyrone polypropionates including onchidione (**3**), were isolated from the marine pulmonate *Onchidium* sp. Their structures were determined by extensive spectroscopic analysis and by comparison with **3** and onchidione-related derivatives. The absolute configuration of **1** was established by X-ray diffraction analysis employing graphite monochromated Cu K α radiation ($\lambda = 0.71073 \text{ \AA}$) with small Flack parameter 0.08. In addition, the absolute stereochemistry of previously reported onchidionol (**6**) was confirmed by the X-ray diffraction analysis. Some of the isolated compounds showed significant activation effects on the splicing of XBP1 mRNA as ER stress modulators to inhibit the growth of tumors.

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Marine pulmonate mollusks belonging to the family Onchidiidae are a prolific source of polypropionates possessing a C₃₂ carbon skeleton with two γ -pyrone rings and several contiguous stereogenic centers.¹ These polypropionates include either linear members (i.e. ilikonapyrones)^{2–4} or compounds exhibiting an additional hemiketal pyrone ring in the middle part of the polypropionate chain (i.e. onchidione and onchidionols).^{4–6} Promising *in vitro* growth-inhibitory activity against cancer cell lines have been reported for a series of these polypropionates.^{4,7,8}

XBP1 (X-box binding protein-1) is a key transcription factor that regulates ER (endoplasmic reticulum) homeostasis, it is essential for the anti-oxidant defense and cell survival and is required for tumor growth.⁹ High expression of XBP1 has been reported for many kinds of cancers, such as breast neoplasms, pancreatic cancers and so on. Due to this, XBP1 is considered a new target for molecular treatment of cancers.¹⁰

In the framework of our ongoing research on marine organisms focused on the search of new anticancer compounds,^{11–15} we recently investigated pulmonate mollusks of the genus *Onchidium* sp.^{4–6} Due to the interesting bioactivity showed by *Onchidium* polypropionates, we have examined a further population of the mollusk collected from the intertidal zone along the coast of Hainan situated in the South China Sea, with the aim of isolating

new structural analogs to be evaluated for the effects on the splicing of XBP1 gene.

The chemical analysis of the lipophilic extract of external parts of the mollusk led to the isolation of two new members of the onchidione family, 16-*epi*-onchidione (**1**) and 4-*epi*-onchidione (**2**), together with previously reported compounds **3–8** (Fig. 1). In this paper, we describe the chemical characterization of compounds **1** and **2**, the assignment of the absolute configuration of compound **6**, and the bioactivity evaluation of all isolated metabolites.

The extraction of *Onchidium* sp. specimens was performed according to our previous work.^{4–6} Silica gel column and HPLC purification of selected fractions from the Et₂O-soluble portion of the acetone extract yielded the polypropionate derivatives **1–8**. Among them, the known compounds were readily identified by spectroscopic data as onchidione (**3**),^{5,6} 13-propanoyl-onchidiol (**4**),⁴ onchidiol (**5**),⁵ onchidionol (**6**),⁴ 3-acetylonchidionol (**7**),⁴ and 3-propanoylonchidionol (**8**).⁴

16-*Epi*-onchidione (**1**) was isolated as a colorless crystal. The molecular formula C₃₇H₅₄O₉, the same as onchidione (**3**), was deduced by HRESIMS data. Analysis of NMR spectra (Table 1) clearly indicated the same polypropionate nature as the co-occurring known metabolites. In particular, the ¹H NMR spectrum contained thirteen signals due to methyl groups, four singlets at δ 1.96 (H₃-25), 1.98 (H₃-32), 1.99 (H₃-31), and 2.15 (H₃-26), which were attributed to the methyls in β position of γ -pyrone rings, two triplets due to terminal methyls at δ 1.00 ($J = 7.2 \text{ Hz}$, H₃-1)

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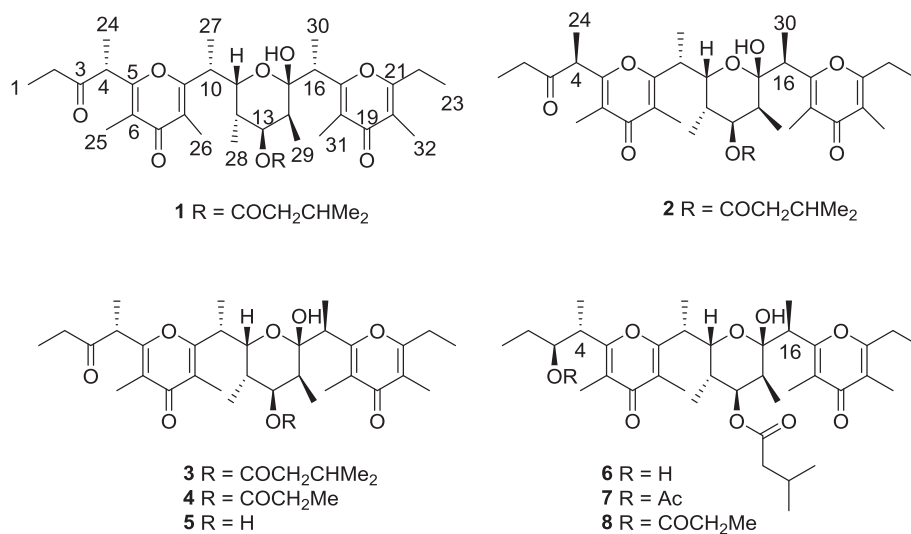


Fig. 1. Structures of compounds 1–8.

Table 1
¹³C and ¹H NMR data of compound **1** in C₆D₆.

Position	$\delta^{13}\text{C}$	$\delta^1\text{H}$	m (J in Hz)	Long range correlations	Position	$\delta^{13}\text{C}$	$\delta^1\text{H}$	m (J in Hz)	Long range correlations
1	7.8	1.00	t, 7.2	–	20	118.3	–	–	–
2a	34.7	2.34	m	–	21	163.9	–	–	H-22, H-23, H-32
2b		2.03	m	–	22a	25.0	2.24	m	–
3	207.7	–	–	H ₃ -1, H ₂ -2, H ₃ -24, H ₄ -4	22b		2.11	m	–
4	48.1	3.33	q, 7.2	–	23	11.8	0.92	t, 7.2	–
5	159.4	–	–	H ₃ -24, H ₃ -25	24	13.1	1.16	d, 7.2	–
6	119.6	–	–	–	25	10.8,	1.96	s	–
7	178.7	–	–	–	26	9.8	2.15	s	–
8	119.4	–	–	–	27	13.4	0.75	d, 6.6	–
9	164.1	–	–	H-11, H ₃ -27	28	9.3	0.61	d, 7.2	–
10	37.1	2.89	dq, 7.2, 10.8	–	29	12.4	0.80	d, 7.2	–
11	68.2	4.22	dd, 2.4, 10.8	H-10, H-13, H ₃ -27, H ₃ -28	30	11.2	1.07	d, 6.6	–
12	33.5	1.87	m	H-11	31	9.9	1.99	s	–
13	77.5	4.82	dd, 3.0, 3.0	H-10, H ₃ -28, H ₃ -29	32	10.2	1.98	s	–
14	33.4	1.61	dq, 3.0, 7.2	–	1'	171.5	–	–	H-13, H-2'
15	99.6	–	–	H-11, H-13, H-16, H-29, H-30	2'a	43.7	2.25	m	–
16	43.7	3.10	q, 6.6	–	2'b		3.10	m	–
17	162.5	–	–	H-16, H-30, H-31	3'	26.4	2.24	m	–
18	120.2	–	–	–	4'	22.4	1.02	d, 6.6	–
19	179.1	–	–	–	5'	22.4	0.98	d, 6.6	–
15-OH		4.09	s	–					

Bruker-DRX-600 spectrometer (600 MHz for ¹H and 150 MHz for ¹³C NMR) in C₆D₆, chemical shifts (ppm) referred to C₆H₆ (δ_{H} 7.16) and to C₆D₆ (δ_{C} 128.1). The assignments were based on ¹H–¹H COSY, HSQC, HMBC experiments

and 0.92 ($J = 7.2$ Hz, H₃–23), and the remaining seven doublets resonating between δ 0.61 and δ 1.16, assigned to five methyls of the polypropionate chain and to the isopropyl methyls of the acyl residue at C-13 (Table 1). The ¹³C NMR spectrum displayed carbon resonances consistent with the C₃₂ polypropionate onchidione-like skeleton^{4–6} containing two substituted γ -pyrone rings, a ketone, a hemiketal oxane ring and a 3-methyl butanoyl residue esterifying 13-OH (Table 1). Detailed analysis of 2D NMR experiments, which were recorded in C₆D₆ (Table 1) and CDCl₃ (Suppl. Material) revealed that compound **1** had the same planar structure as onchidione^{5,6} and differed with the latter one only in their stereochemical aspects. Analysis of the proton coupling constants and NOE effects of **1** indicated that the relative configuration of the substituents at the hemiketal oxane ring was the same as **3**^{5,6} and related derivatives.⁴ In particular, the esterified hydroxyl group at C-13 was deduced to be axial by the coupling constants of the geminal proton H-13 (dd, $J = 3.0$ and 3.0 Hz) which was equatorial. Significant steric effects were observed between the

methyl at C-12 and H-14, and between 15-OH and H-11 thus suggesting for all the axial orientation. Thus, differences were assumed to be in the configuration of one or more stereogenic centers in the chain.

In order to clarify these stereochemical aspects and determine the absolute configuration of **1**, a suitable crystal of **1**, which was obtained by careful crystallization from *n*-hexane/H₂O, was submitted to X-ray diffraction analysis. On the basis of the eight oxygen atoms, the final refinement on the Cu K α data resulted in a Flack parameter of 0.08, allowing unambiguous assignment of the absolute configuration of **1** as shown in Fig. 2. Thus, compound **1** was determined to be the C-16 epimer of onchidione (**3**).

Compound **2** was isolated as a colorless gum. The molecular formula, C₃₇H₅₄O₉, the same as **1** and **3**, was established by HRESIMS. The ¹H and ¹³C NMR spectra (C₆D₆ data in Table 2, CDCl₃ data in Suppl. Material) showed great similarities with those of co-occurring **1** and **3**, indicating they shared the same planar structure. Again, the relative orientation of the substituents in the hemiketal

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