Cytotoxic Dihydrothiophene-Condensed Chromones from the Marine-Derived Fungus *Penicillium oxalicum*

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Abstract

Two new dihydrothiophene-condensed chromones and a new natural chromone, namely oxalicumones A–C (**1**–**3**), respectively, were isolated from a culture broth of a marine-derived fungus, *Penicillium oxalicum*. The structures of **1**–**3** and acetylated derivatives of **1** (**4**–**7**) were elucidated on the basis of spectroscopic methods and chemical reactions. The absolute configuration of **1** and **2** were established by using the modified Mosher ester method and circular dichroism data of an *in situ* formed [$Rh_2(OCOCF_3)_4$] and [$Mo_2(OAc)_4$] complex. (R)-MTPA ester of **1** showed cytotoxicity against A375, SW-620, and HeLa carcinoma cell lines with IC_{50} values of 8.9, 7.8, and 18.4 µM, respectively. Compound **1** displayed cytotoxicity against A375 and SW-620 cell lines with IC_{50} values of 11.7 and 22.6 µM, respectively. The structure–biological activity relationship of **1** was discussed.

Key words

Penicillium oxalicum · Trichocomaceae · dihydrothiophene-condensed chromone · cytotoxicity

Supporting information available online at http://www.thieme-connect.de/ejournals/toc/plantamedica

Gorgonian corals are known to produce novel acetogenins, sesquiterpenoids, diterpenoids, prostanoids, and steroids with various bioactivities such as antitumor, antituberculosis, anti-inflammation, and antioxidant effects [1,2]. It is thought that maybe gorgonian-associated microorganisms are the true producers of some of their host-derived compounds [3]. Recently, there were a few reports about the secondary metabolites of gorgonian-associated microorganisms [4–9]. The fungus *Penicillium oxalicum* SCSGAF 0023 strain (Trichocomaceae) was isolated from the South China Sea gorgonian *Muricella flexuosa*, and identified by Zhang et al. [10]. Previous chemical investigations on *P. oxalicum* led to the isolation of some biologically active and structurally novel secondary metabolites [11–14]. During the course of our investigation on the secondary metabolites of the *P. oxalicum* SCSGAF 0023 strain, two new dihydrothiophene-condensed chromones, oxalicumones A and B (**1, 2**), and a new natural chromone (**3**) [15] (**Fig. 1**) were isolated from a culture broth of the fungal strain. Although chromones are naturally occurring compounds (polyketides) widely found in plants and fungi [16], a dihydrothiophene-condensed chromone core is rare in natural products or synthetic compounds [17].

The molecular formula of **1** was determined to be $C_{19}H_{20}O_9S$ by HRESIMS (*m/z* 447.0693 $[M + Na]^+$) and NMR spectra. The ^1H NMR spectrum (**Table 1**) showed characteristic signals for two aromatic protons at δ_H 6.63 (s), 6.72 (s), two methoxy groups at δ_H 3.84 (s), 3.89 (s), one tertiary methyl at δ_H 2.39 (s), two methylenes at δ_H 2.94, 3.04, 3.14, 3.38 (each 1H), two methines at δ_H 4.45, 4.13, and one phenolic hydroxyl proton at δ_H 12.06. The ^{13}C and DEPT NMR spectral data (**Table 2**) indicated that **1** con-

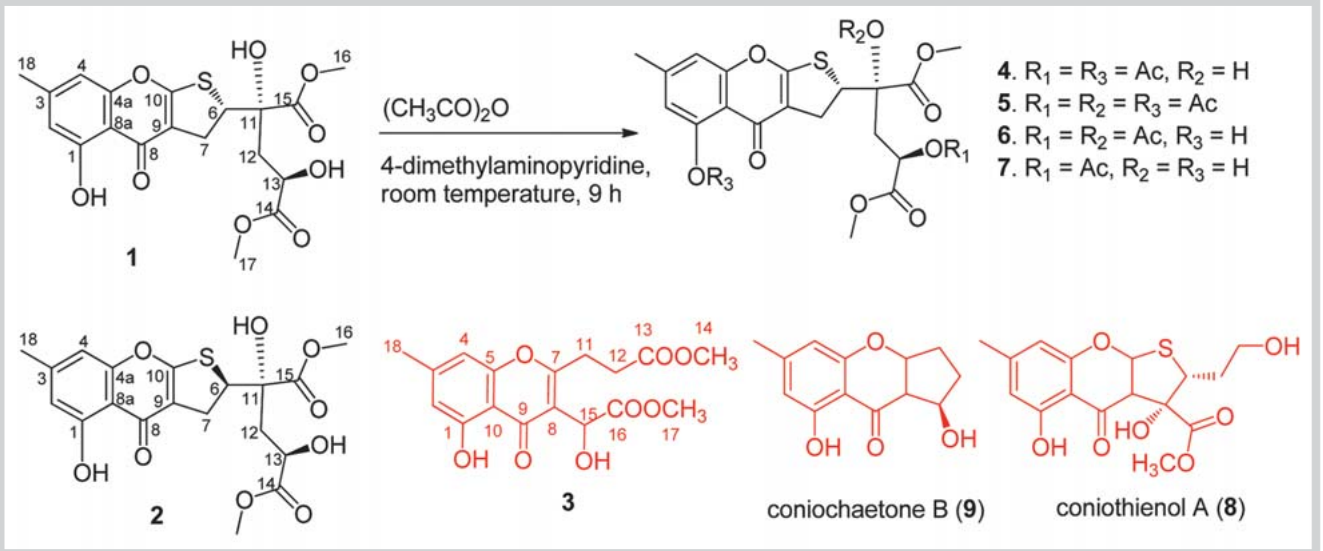

Fig. 1 Structures of **1**–**9**. (Color figure available online only.)

Table 1 ^{1}H NMR data of compounds **1, 2**, and **4–7** in $CDCl_3$.

no.	δ,[a] mult (J[b])					
	1	**2**	**4**	**5**	**6**	**7**
2	6.63, s	6.64, s	7.17, s	7.16, s	6.66, s	6.64, s
4	6.72, s	6.73, s	6.84, s	6.84, s	6.73, s	6.73, s
6	4.13, dd (8.0, 9.0)	3.91, dd (9.5, 9.2)	3.96, dd (8.3, 8.4)	4.33, dd (4.6, 7.8)	4.42, dd (4.3, 7.8)	4.01, dd (8.3, 8.6)
7	3.14, dd (9.0, 17.5)	2.93, dd (9.8, 17.3)	3.12, dd (8.6, 17.2)	3.17, dd (4.6, 17.4)	3.20, dd (4.3, 17.7)	3.13, dd (8.3, 17.7)
	3.38, dd (8.0, 17.5)	3.34, dd (9.2, 17.3)	3.17, dd (8.1, 17.2)	3.57, dd (7.8, 17.4)	3.63, dd (7.8, 17.7)	3.35, dd (8.6, 17.7)
12	2.94, dd (6.0, 14.5)	3.00, dd (5.5, 14.0)	3.01, dd (7.6, 14.5)	2.99, d (5.7)	3.02, d (6.0)	3.02, d (7.5)
	3.04, dd (3.5, 14.5)	3.36, dd (3.8, 14.1)	3.08, dd (4.3, 14.5)	3.00, d (6.6)	3.04, d (6.0)	3.07, d (4.5)
13	4.45, dd (3.0, 6.0)	4.53, dd (5.5, 3.9)	5.22, dd (4.3, 7.6)	5.18, dd (5.6, 6.6)	5.21, dd (5.8, 6.2)	5.24, dd (4.5, 7.5)
Me-16	3.84, s	3.81, s	3.78, s	3.78, s	3.77, s	3.79, s
Me-17	3.89, s	3.84, s	3.86, s	3.80, s	3.84, s	3.90, s
Me-18	2.39, s	2.40, s	2.45, s	2.45, s	2.41, s	2.40, s
-OOC*Me*	–	–	2.18, s	2.17, S	2.19, s	2.19, s
			2.38, s	2.19, S	2.23, s	
				2.40, S		
13-OH	–	4.33, br s	–	–	–	–
11-OH	–	–	4.06, br s	–	–	4.09, br s
1-OH	12.06, s	12.02, s	–	–	12.21, s	12.04, s

[a] 500 M Hz; [b] coupling constants in Hz

Table 2 ^{13}C NMR data of compounds **1, 2, 4**, and **5** in $CDCl_3$.

No.	δ,[a] C[b]			
	1	**2**	**4**	**5**
1	160.8, C	160.8, C	149.3, C	149.3, C
2	113.0, CH	113.0, CH	121.1, CH	121.3, CH
3	147.2, C	147.2, C	145.1, C	145.1, C
4	107.8, CH	107.9, CH	117.5, CH	115.5, CH
4a	157.1, C	157.1, C	158.0, C	157.7, C
6	50.7, CH	52.1, CH	50.2, CH	49.9, CH
7	37.9, CH_2	37.1, CH_2	37.6, CH_2	39.7, CH_2
8	178.8, C	179.5, C	173.3, C	174.7, C
8a	109.1, C	109.0, C	116.3, C	115.5, C
9	120.5, C	119.9, C	117.5, C	117.6, C
10	171.0, C	169.6, C	167.2, C	168.7, C
11	79.6, C	86.2, C	80.0, C	86.2, C
12	35.4, CH_2	36.8, CH_2	32.2, CH_2	29.7, CH_2
13	71.2, CH	70.7, CH	72.0, CH	72.1, CH
14	173.1, C	172.2, C	168.7, C	169.6, C
15	173.4, C	173.3, C	172.4, C	169.8, C
16	53.0, CH_3	52.9, CH_3	52.7, CH_3	52.7, CH_3
17	53.7, CH_3	53.1, CH_3	53.8, CH_3	53.4, CH_3
18	22.3, CH_3	22.3, CH_3	20.6, CH_3	20.5, CH_3
-OOC*Me*			21.1, 21.7	21.6, 21.4, 21.2
-OOCMe			170.0, 171.8	170.0, 170.1, 170.1

[a] 125 M Hz; [b] Assignments by edited gs-HSQC experiments

tained 19 carbons, including three methyls, two methylenes, four methines, and ten quaternary carbons. These data suggested that **1** contained a 1-hydroxy-3-methylchromone core [18–20].

This suggestion was proved by the HMBC spectrum (**Fig. 2**), which showed correlations from H-2 to C-1/C-3/C-4/C-8a/C-18, from H-4 to C-2/C-3/C-4a/C-8a/C-18, and from Me-18 to C-2/C-3/C-4. In addition, correlations from H-7 [δ_H 3.14 (1H, dd, J = 9.0, 17.5 Hz), 3.38 (1H, dd, J = 8.0, 17.5 Hz)] to C-6 (δ_C 52.1)/C-10 (δ_C 171.0)/C-9 (δ_C 120.5) in the HMBC spectrum and a correlation from H-7 to H-6 [δ_H 4.13 (1H, dd, J = 8.0, 9.0 Hz)] in the ^{1}H-^{1}H COSY spectrum (**Fig. 2**), combined with the molecular formula $C_{19}H_{20}O_9S$ and chemical shifts of H-7, H-6, C-7 (δ_C 37.9), and C-6, indicated the presence of a five-membered ring containing a sul-

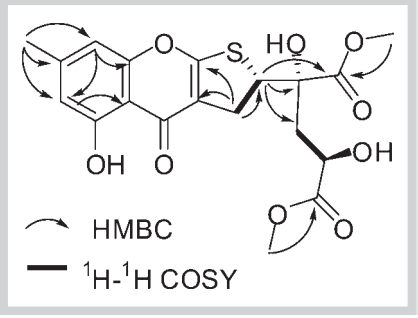

Fig. 2 Key HMBC and ^{1}H-^{1}H COSY correlations for **1**.

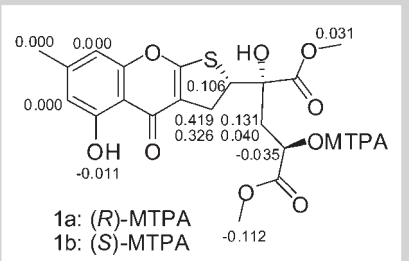

Fig. 3 $\Delta\delta$ ($\delta_S - \delta_R$) values in ppm for MTPA esters of **1**.

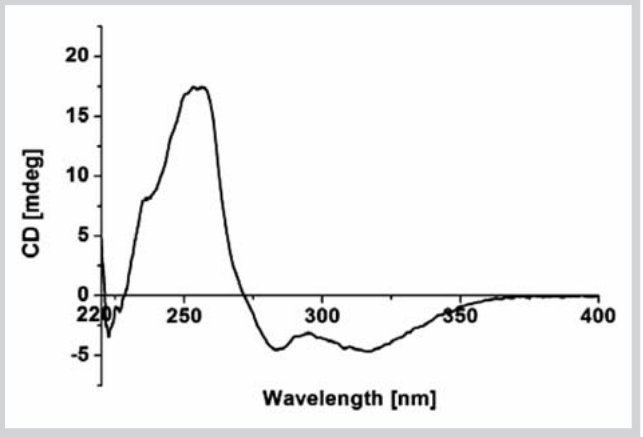

Fig. 4 CD spectrum of **1** in CH_2Cl_2.

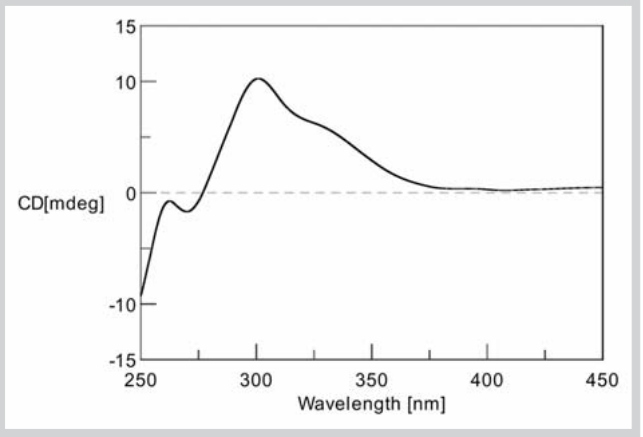

Fig. 5 CD spectrum of Rh-complex of **1b** with the inherent CD spectrum subtracted.

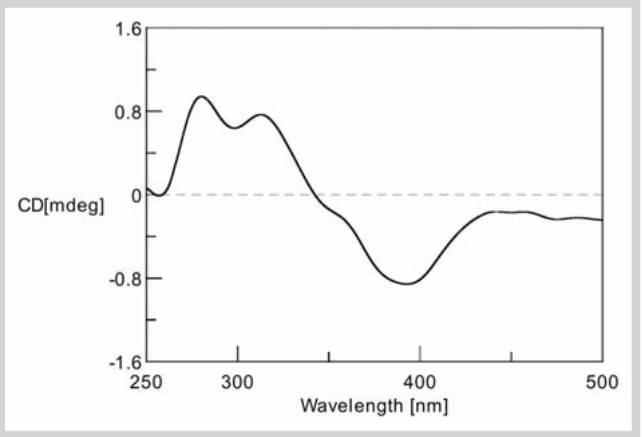

Fig. 6 CD spectrum of **1** in DMSO containing $Mo_2(OAc)_4$ with the inherent CD spectrum subtracted.

fur atom (2,3-dihydrothiophene unit) connected with the 1-hydroxy-3-methylchromone core. Further comparison of the ^1H and ^{13}C NMR data of **1** with those of coniothienol A [17] suggested that **1** had the same dihydrothiophene-condensed chromone skeleton. Coniothienol A (**8**), preussochromone A [21], and coniothiepinols A and B [17] were isolated from fungi and have similar chromone structures with a sulfur atom placed at the same position. In this study, we also obtained coniochaetone B (**9**) [22] (a known chromone) and oxalicumone C (**3**) (a new natural chromone) [15]. From their structural analysis, we conjectured that coniochaetone B derived from **3**, and preussochromone A, coniothiepinols A and B, coniothienol A, and **1** had similar biogenetic pathways to form the thiophene-condensed chromone, thiopyran-condensed chromone, or thiepinol skeletons. So, we inferred that the sulfur atom in **1** should be located at position-5 instead of position-7. X-ray data would be strong evidence for the structure inferred, but unfortunately we failed to obtain a crystal of **1**. Furthermore, HMBC correlations from H-6 to C-7/C-11/C-12/C-15, from H-7 to C-6/C-11, from H-12 to C-6/C-11/C-13/C-14/C-15, from H-13 to C-11/C-12/C-14, from Me-16 to C-15, from Me-17 to C-14, and ^1H-^1H COSY correlation of H-12 with H-13, suggested a 2,4-dihydroxy-1,5-pentanedioic acid dimethyl ester unit connected with the dihydrothiophene unit by a C6-C11 bond.

The absolute stereochemistry of **1** was further determined using a modified Mosher ester NMR method [23]. Compound **1** was treated separately with (*S*)-(+)- and (*R*)-(−)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride (MTPA-Cl) in dry pyridine to yield the (*R*)- and (*S*)-MTPA ester derivatives **1a** and **1b**, respectively. The shifted signals (H-6, H-7, H-12, and H-17) of the diastereomeric MTPA esters (**1a** and **1b**) were clearly different, and the observed chemical shift differences ($\Delta\delta_{S\text{-}R}$, ▶ **Fig. 3**) unambiguously indicated the absolute configuration of C-13 in **1** to be *R*. The 6*S* absolute configuration was proved by the CD data of **1** (▶ **Fig. 4**) that showed negative Cotton effects at around 300 to 350 nm, similar to those of coniothienol A [17]. The absolute configuration of C-11 tertiary alcohol in **1** was assigned via the CD data of the *in situ* formed $[Rh_2(OCOCF_3)_4]$ complex of **1b** (MTPA ester of **1**), with the inherent contribution subtracted. According to the bulkiness rule [24,25], the Rh-complex of **1b** showed a positive E band at ca. 350 nm (▶ **Fig. 5**), revealing the 11*S* absolute configuration in **1b** and **1**. In order to further verify the result, the absolute configuration of the tert/sec 11,13-diol moiety in **1** was assigned using the *in situ* dimolybdenum CD method [26, 27]. Upon addition of dimolybdenum tetraacteate $[Mo_2(OAc)_4]$ to **1** in DMSO solution, a metal complex was generated as an auxiliary chromophore. The observed sign of the Cotton effect in the induced spectrum originated solely from the chirality of the 1,3-diol moiety expressed by the sign of the O–C–C–C–O torsion angle. In the experiment (▶ **Fig. 6**), the negative Cotton effect was observed at around 400 nm. Based on the empirical rule proposed by Frelek [26,27], two absolute configurations of (11*S*,13*R*) and (11*R*,13*S*) could be deduced. Because the 13*R* abso-

Table 3 Cytotoxicity of **1**–**7** and **1a** against several cell lines.

Compound	Cell-lines (IC_{50} μM)					
	A375	A549	HeLa	HepG2	SW-620	L-02
1	11.7 ± 0.9	41.9 ± 2.8	46.2 ± 3.4	77.8 ± 4.5	22.6 ± 1.5	99.0 ± 4.2
2	27.8 ± 2.2	149.3 ± 7.8	60.9 ± 6.1	–	40.6 ± 3.2	> 442.0
3	> 571.0	> 571.0	> 571.0	–	423 ± 6.2	–
4	82.5 ± 5.1	281.5 ± 6.7	268.7 ± 7.1	–	228.5 ± 4.7	> 391.0
5	35.6 ± 3.3	234.5 ± 6.3	119.4 ± 8.4	–	42.7 ± 2.6	> 357.0
6	125.2 ± 4.1	–	196.8 ± 4.1	–	111.0 ± 4.1	–
7	76.2 ± 3.6	–	–	–	82.2 ± 3.3	–
1a	8.9 ± 0.8	33.4 ± 1.5	18.4 ± 1.2	–	7.8 ± 0.5	35.0 ± 1.1
Cisplatin	7.3 ± 0.8	5.5 ± 0.2	9.3 ± 0.4	13.6 ± 2.0	30.0 ± 4.1	–

"–" Means no test; purity of **1**–**7** and **1a** is ≥ 98%; cisplatin was bought from J&K Scientific Ltd., and its purity is 99%

lute configuration in **1** was determined by a modified Mosher ester NMR method, the 11*S* absolute configuration was further confirmed. Thus, the 6*S*,11*S*,13*R* absolute configuration was deduced for **1**; its structure was determined to be as shown, and the compound was named oxalicumone A.

Compound **2** had the same molecular formula of $C_{19}H_{20}O_9S$ as oxalicumone A (**1**), which was determined by its (+)-ESIMS (*m/z* 447.08 $[M + Na]^+$) and NMR spectra. The ^1H and ^{13}C NMR spectral data of **2** showed great similarities to those of **1** with the only obvious difference of the downfield shift of C-11 (from δ_C 79.6 in **1** to δ_C 86.2 in **2**). Detailed analysis of the HMBC spectrum of **2** proved that **2** had the same plane structure as **1**. The absolute stereochemistry of **2** was further determined by using the modified Mosher ester method and circular dichroism data of *in situ* formed $[Rh_2(OCOCF_3)_4]$ and $[Mo_2(OAc)_4]$ complexes.

Compound **2** was treated separately with (*S*)-(+)- and (*R*)-(−)-MTPA-Cl in dry pyridine to yield the (*R*)- and (*S*)-MTPA ester derivatives **2a** and **2b**, respectively. The shifted signals (H-6, H-7, OH-11, H-12, Me-16, and Me-17) of the diastereomeric MTPA esters (**2a** and **2b**) were clearly different, and the observed chemical shift differences ($\Delta\delta_{S-R}$, see Supporting Information **Fig. 34S**) clearly indicated the absolute configuration of C-13 in **2** to be *R*.

The 6*R* absolute configuration was proved by the CD data of **2** (see Supporting Information **Fig. 35S**) that showed opposite Cotton effects at around 300 to 350 nm compared with that of oxalicumone A (**1**) (**Fig. 4**). In addition, we also obtained a known chromone coniochaetone B [21]. The CD spectra of **2** and coniochaetone B (see Supporting Information **Fig. 36S**) had similar positive Cotton effects at around 310 to 350 nm, which further supported the *R* absolute configuration of C-6 in **2**, because the absolute configuration of the asymmetric carbon atom in coniochaetone B had been deduced to be *R* by application of Horeau's method [21].

The absolute configuration of the C-11 tertiary alcohol in **2** was assigned via the CD data of the *in situ* formed $[Rh_2(OCOCF_3)_4]$ complex of **2b** (MTPA ester of **2**), with the inherent contribution subtracted. According to the bulkiness rule [22,23], the Rh-complex of **2b** showed a positive E band at ca. 350 nm (see Supporting Information **Fig. 37S**), revealing the 11*S* absolute configurations in **2b** and **2**. In order to further verify the result, the absolute configuration of the tert/sec 11,13-diol moiety in **2** was assigned using the *in situ* dimolybdenum CD method [24,25]. Upon addition of dimolybdenum tetraacteate $[Mo_2(OAc)_4]$ to **2** in DMSO solution, a metal complex was generated as an auxiliary chromophore. The observed sign of the Cotton effect in the induced spectrum originated solely from the chirality of the 1,3-diol moiety expressed by the sign of the O–C–C–C–O torsion angle. In the experiment (see Supporting Information **Fig. S38**), the negative Cotton effect was observed at around 400 nm. Based on the empirical rule proposed by Frelek [24,25], two absolute configurations of (11*S*,13*R*) and (11*R*,13*S*) were permitted deduction. Because the 11*S* absolute configuration in **2** was determined, the 13*R* absolute configuration in **2** was further confirmed. Thus, the 6*R*,11*S*,13*R* absolute configuration was deduced for **2**; the structure of **2** was determined to be as shown, and the compound was named oxalicumone B.

Compound **3** exhibited the molecular formula $C_{17}H_{18}O_8$ as deduced from NMR data and ESIMS. Comparison of the ^1H and ^{13}C NMR spectral data between **1** and **3** suggested that **3** also had a 1-hydroxy-3-methylchromone core. Furthermore, in the HMBC spectrum of **3**, correlations from H-15 to C-7 (δ_C 167.0)/C-8 (δ_C 118.2)/C-9 (δ_C 181.6)/C-16 (δ_C 173.1), and from Me-17 to C-16, suggested a 2-hydroxyl methyl acetate unit attached to C-8; HMBC correlations from H-11 to C-7/C-8/C-12 (δ_C 31.2)/C-13 (δ_C 172.0), and from Me-14 to C-13, suggested that a methyl propionate unit joined with C-7. By detailed analysis of its NMR data and comparison of its physical and spectral data with those reported in the literature [15], the structure of **3** was determined to be as shown, and the compound was named oxalicumone C. This is the first published assignment of the NMR data of **3**.

Compounds **4**–**7** were the acetylated analogues of **1** that were gained from **1** treated with acetic anhydride and 4-dimethylaminopyridine in dry pyridine at room temperature. Their structures were determined based on analysis of their HRESIMS, ^1H and ^{13}C NMR data (**Tables 1** and **2**), and comparison with those of **1**.

Compounds **1**–**7** and **1a** were tested for cytotoxicity against human melanoma A375, lung carcinoma A549, cervical carcinoma HeLa, liver hepatocellular carcinoma HepG2, colonic adenocarcinoma SW-620, and normal liver L-02 cell-lines (**Table 3**). Towards A375 and SW-620 cell lines, **1a** showed significant cytotoxicity with IC_{50}s of 8.9 and 7.8 μM, **1** had moderate cytotoxicity with IC_{50}s of 11.7 and 22.6 μM, **2** and **5** showed mild cytotoxicities, while the positive control cisplatin showed IC_{50} values of 7.3 and 30.0 μM, respectively. Compound **3** had no cytotoxicity towards all test cells. The results indicated that the 2,3-dihydrothiophene unit was important for the cytotoxicities of these chromones, and the substituent at OH-13, with large steric hindrance, might improve their cytotoxicities, whereas acetylation at C-1, C-11, and/or C-13 reduced them.

Materials and Methods

Strain and host gorgonian

The fungus *Penicillium oxalicum* SCSGAF 0023 was isolated from the South China Sea gorgonian *Muricella flexuosa*. Detailed information of fungal ITS gene sequencing and identification was given by Zhang et al. [10]. The gorgonian was collected from the South China Sea, Sanya (18°11′ N, 109°25′ E), in August 2010, and identified by Dr. Hui Huang and Xiu-bao Li (South China Sea Institute of Oceanology, Chinese Academy of Sciences). The strain of *P. oxalicum* (No. SCSGAF 0023) and a gorgonian voucher specimen (*M. flexuosa*) were deposited in South China Sea Institute of Oceanology, Chinese Academy of Sciences.

Isolates

Oxalicumone A (**1**): yellow oil; $[\alpha]_D^{20}$ +31.43 (*c* 0.42, $CHCl_3$), UV (MeOH) λ_{max} (log ε) 228 (3.88), 239 (3.90), 326 (3.18) nm; IR (KBr): 3437, 1742, 1658, 1625, 1490, 1456, 1384, 1263, 1209, 1147, 1125, 1072, 1034, 996 cm^{-1}; ^1H and ^{13} C NMR data, see ◉ **Tables 1** and **2**; (+)-ESIMS *m/z* 447 $[M + Na]^+$; (+)-HRESIMS *m/z*: $[M + Na]^+$ 447.0693 (calcd. for $C_{19}H_{20}O_9SNa$, 447.0726).

Oxalicumone B (**2**): yellow oil; $[\alpha]_D^{20}$ +31.76 (*c* 0.17, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 226 (3.58), 241 (3.89), 326 (3.18) nm; IR (KBr): 3437, 1746, 1658, 1491 cm^{-1}; ^1H and ^{13} C NMR data, see ◉ **Tables 1** and **2**; (+)-ESIMS *m/z* 447 $[M + Na]^+$; (+)-HRESIMS *m/z*: $[M + Na]^+$ 447.0726 (calcd. for $C_{19}H_{20}O_9SNa$, 447.0726).

Oxalicumone C (**3**): yellow oil; $[\alpha]_D^{20}$ +11.25 (*c* 0.12, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) δ 11.95 (1H, s, 1-OH), 4.03 (1H, d, *J* = 6.9 Hz, 15-OH), 6.67 (1H, s, H-2), 6.62 (1H, s, H-4), 5.23 (1H, d, *J* = 6.9 Hz, H-15), 3.80 (3H, s, H-17), 3.73 (3H, s, H-14), 3.13 (2H, td, *J* = 7.4, 3.6 Hz, H-11), 2.83 (2H, t, *J* = 7.4 Hz, H-12), 2.40 (3H, s, H-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.3 (s, C-1), 107.2 (d, C-2), 147.9 (s, C-3), 112.4 (d, C-4), 156.0 (s, C-5), 167.0 (s, C-7), 118.2 (s,C-8), 181.6 (s, C-9), 108.0 (s, C-10), 26.9 (t, C-11), 31.0 (t, C-12), 172.0 (s, C-13), 52.2 (-OCH_3, C-14), 66.3 (d, C-15), 173.1 (s, C-16), 53.1 (-OCH_3, C-17), 22.5 (CH_3, C-18).

Supporting information

General experimental methods, details on the fermentation, extraction, isolation, and MS, 1D-, and 2D- NMR spectra for compounds **1**–**7**, $\Delta\delta$ ($\delta_S - \delta_R$) values in ppm for MTPA esters of **2**, CD spectra of **2**, coniochaetone B, Rh-complex of **2b** and **2** in DMSO containing $Mo_2(OAc)_4$ with the inherent CD spectrum subtracted can be found as Supporting Information.

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Conflict of Interest

All the authors have no conflicts of interest.

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