



## Determination of the absolute configuration of chaetoviridins and other bioactive azaphilones from the endophytic fungus *Chaetomium globosum*



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### ABSTRACT

Chemical investigation of an endophytic fungus *Chaetomium globosum* isolated from leaves of *Wikstroemia uva-ursi* led to the isolation of two new azaphilones, chaetoviridins J and K (**1** and **3**), along with five known derivatives (**2** and **4–7**). The structures of azaphilones were determined by NMR, X-ray diffraction, Mosher's method, and CD analysis. The isolated compounds were evaluated for their cancer chemopreventive-potential based on their abilities to inhibit tumor necrosis factor alpha (TNF- $\alpha$ )-induced nuclear factor-kappa B (NF- $\kappa$ B). Compounds **4**, **5**, **7**, and synthetic **8** and **9** inhibit nitric oxide (NO) production with IC<sub>50</sub> values in the range of 0.3–5.8  $\mu$ M. Compounds **4**, **5**, and **9** also displayed (TNF- $\alpha$ )-induced NF- $\kappa$ B activity with IC<sub>50</sub> values in the range of 0.9–5.1  $\mu$ M.

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Endophytes have been recognized as important sources of a variety of structurally novel active secondary metabolites with anticancer, antimicrobial, and other biological activities.<sup>1,2</sup> *Chaetomium* is the largest genera of saprophytic ascomycetes. It belongs to the Chaetomiaceae family and comprises approximately 92 species.<sup>3</sup> Previous investigation on secondary metabolites from the *Chaetomium* species resulted in the isolation of numerous types of compounds such as benzoquinone derivatives,<sup>4</sup> tetra-*s*-methyl derivatives,<sup>5</sup> azaphilones,<sup>6,7</sup> indol-3-yl-[13]cytochalasans,<sup>8</sup> and chaetoglobosin<sup>9</sup> analogs. In recent studies, the endophytic strain *Chaetomium globosum* isolated from the leaves of *Viguiera robusta*, was found to produce cytotoxic chaetoglobosins in Czapek medium,<sup>9</sup> while cytotoxic azaphilones and cytochalasan alkaloids were reported from the endophytic *C. globosum* isolated from the leaves of *Ginkgo biloba*.<sup>10</sup>

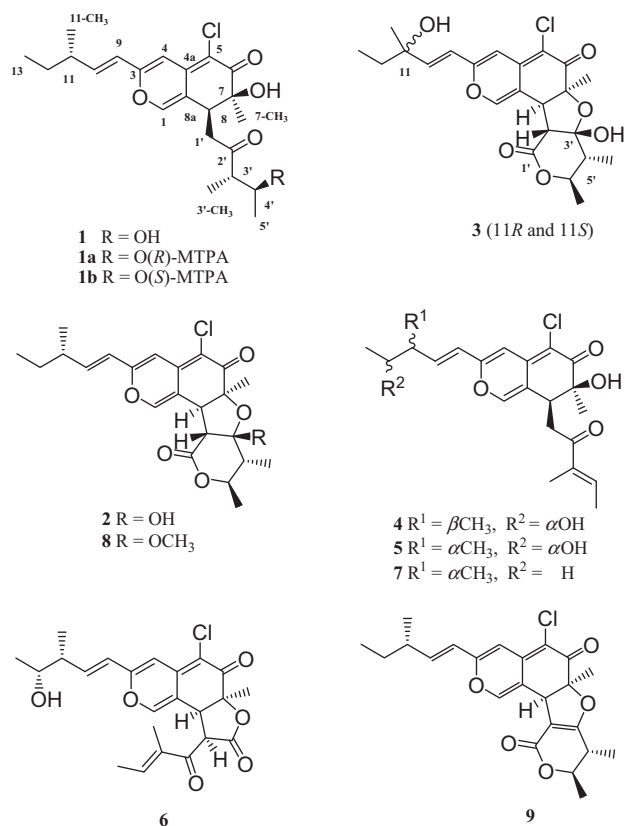
A crude ethyl acetate extract from the fermentation cultures of *C. globosum* found in Hawai'ian native plant, *Wikstroemia uva-ursi*, demonstrated in vitro inhibitory effects at a concentration of 20  $\mu$ g/mL on the tumor necrosis factor-alpha (TNF- $\alpha$ )-induced NF- $\kappa$ B activity in transfected human embryonic kidney cells 293

cells, and lipopolysaccharide (LPS)-induced nitric oxide production using murine macrophage RAW 264.7 cells. Bioassay-guided fractionation of this extract resulted in the isolation of two new chaetoviridins J and K (**1** and **3**), together with five known compounds **2** and **4–7**. Two chaetomugilins E and F (**8** and **9**) were obtained from **2** (Fig. 1). This paper reports the isolation and structure elucidation of the new chaetoviridins and the biological activity.

Compound **1**<sup>11</sup> was obtained as a yellow amorphous powder and gave a molecular ion at *m/z* 431.1499 [M+Na]<sup>+</sup> (Calcd for C<sub>22</sub>H<sub>29</sub>ClO<sub>5</sub>Na, 431.1435) in the positive-ion HRESIMS, corresponding to a molecular formula of C<sub>22</sub>H<sub>29</sub>ClO<sub>5</sub>. The ratio of isotope peak intensities (MH<sup>+</sup>/[MH+2]<sup>+</sup>) supports one chlorine atom. The UV spectrum showed absorption bands at 255, 297, 388 nm indicating a highly conjugated system. The IR spectrum exhibited bands at 3350, 1700 cm<sup>-1</sup>, characteristic of a hydroxyl and an  $\alpha,\beta$ -unsaturated carbonyl functionalities, respectively. The NMR (Table 1), HSQC, and HMBC spectra revealed the presence of a number of olefinic groups; trisubstituted two olefinic groups at [ $\delta_{\text{H}}$  7.44/ $\delta_{\text{C}}$  145.3 (C-1) and 119.5 (C-8a) and  $\delta_{\text{H}}$  6.46/ $\delta_{\text{C}}$  104.4 (C-4) and 157.3 (C-3)], a *trans*-olefinic group at [ $\delta_{\text{H}}$  6.51 (dd, *J* = 15.6, 8.0 Hz)/ $\delta_{\text{C}}$  146.3 (C-10) and  $\delta_{\text{H}}$  6.03 (d, *J* = 15.6 Hz)/ $\delta_{\text{C}}$  120.2 (C-9)] due to large coupling constants, one quaternary olefinic carbon at  $\delta_{\text{C}}$  141.7 (C-4a), and an upfield shifted olefinic quaternary carbon ( $\delta_{\text{C}}$  106.6) indicating the

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**Figure 1.** Chemical structures of compounds **1–9**.

attachment of a chlorine atom at C-5.<sup>12</sup> All of the olefinic groups were confirmed to be closely connected to each other through the HMBC analysis (Fig. 2), which indicated a typical conjugation system of the azaphilones.<sup>6,12,13</sup>

The <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 1) revealed additional signals for three aliphatic secondary methyls (11-CH<sub>3</sub>, 3'-CH<sub>3</sub>, and CH<sub>3</sub>-5'), a tertiary methyl (7'-CH<sub>3</sub>), a terminal ethyl (C-12–C-13), a methylene (C-1'), three methines (C-11, C-8, and C-3'), an oxygen-bearing methine (C-4'), an oxygenated quaternary carbon (C-7), and two carbonyl carbons (C-6 and C-2'), which were almost identical with chaetomugilin J (**7**) (Fig. S32, Supplementary data),<sup>14</sup> except for the oxygenated methine group (C-4') replacing the olefinic double bond (C-3'–C-4') in **7**. The HMBC correlations between H-4' and C-2'/3'-CH<sub>3</sub>/CH<sub>3</sub>-5' supported the position of the oxymethine group (Fig. 2). The absolute stereochemistry at C-7 of azaphilones has been established as *S* by circular dichroism (CD) and X-ray analyses.<sup>6,13,15</sup> The absolute configuration at C-7 of **1** was also determined as *S* by comparison of the CD spectrum (Fig. 6).<sup>12</sup> The NOESY spectrum of **1** showed a correlation between H-8 and 7-CH<sub>3</sub>, implying that H-8 is oriented as *cis* to the 7-CH<sub>3</sub> group (Fig. S5, Supplementary data). The modified Mosher's method was applied to determine the absolute stereochemistry of the secondary hydroxy group at C-4'. Esterification of **1** with (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPA-Cl) gave bis (*R*)- and (*S*)-MTPA esters, **1a** and **1b**, respectively, (Fig. 3).

A negative Δδ<sup>SR</sup> value for proton CH<sub>3</sub>-5' and positive values for H-1', H-3', and 3'-CH<sub>3</sub> were observed in the <sup>1</sup>H NMR spectra of **1a** and **1b**, which established the absolute configuration at C-4' as *S*. The stereochemistry at C-11 and C-3' was determined as *S* by comparison of NMR data with previously published value.<sup>6,12–14</sup> These evidences allowed assignment of the configuration of the

**Table 1**  
<sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data of compounds **1–3**

Position	<b>1</b> <sup>a</sup>		<b>2</b> <sup>a</sup>		<b>3</b> <sup>a</sup>		<b>2</b> (in DMSO- <i>d</i> <sub>6</sub> )
	δ <sub>H</sub> , mult. ( <i>J</i> in Hz)	δ <sub>C</sub>	δ <sub>H</sub> , mult. ( <i>J</i> in Hz)	δ <sub>C</sub>	δ <sub>H</sub> , mult. ( <i>J</i> in Hz)	δ <sub>C</sub>	δ <sub>H</sub> , mult. ( <i>J</i> in Hz)
1	7.44 s	145.3	7.29 s	146.8	7.30 s	145.7	7.49 s
2							
3		157.3		157.7		157.2	
4	6.46 s	104.4	6.56 s	104.9	6.64 s	106.1	6.67 s
4a		141.7		140.3		140.1	
5		106.6		110.1		110.5	
6		191.6		189.2		189.3	
7		74.1		83.9		83.9	
8	3.47 dd (9.6, 3.2)	39.9	3.00 d (10.0)	50.5	3.00 d (10.0)	50.0	3.39 <sup>b</sup>
8a		119.5		114.3		114.3	
9	6.03 d (15.6)	120.2	6.07 d (15.6)	120.1	6.39 d (15.6)	119.2	6.39 d (16.0)
10	6.51 dd (15.6, 8.0)	146.3	6.51 dd (15.6, 8.4)	145.5	6.63 d (15.6)	145.5	6.50 dd (16.0, 7.6)
11	2.26 m	38.7	2.27 m	38.8		73.5	2.26 m
12	1.44 m	29.2	1.44 m	29.1	1.66 q (7.6)	35.0	1.40 m
13	0.91 t (7.4)	11.6	0.91 t (7.6)	11.6	0.94 t (7.6)	8.1	0.86 t (7.6)
7-CH <sub>3</sub>	1.32 s	26.6	1.41 s	23.4	1.42 s	23.2	1.23 s
11-CH <sub>3</sub>	1.09 d (6.8)	19.3	1.09 d (6.4)	19.4	1.38 s	27.7	1.04 d (6.8)
1'a	3.22 dd (18.4, 3.2)	40.6		170.6		170.5	
1'b	2.40 dd (18.4, 9.6)						
2'		213.7	3.08 d (10.0)	58.2	3.08 d (10.0)	58.2	2.72 d (10.8)
3'	2.43 dq (7.6, 7.2)	54.0		104.1		104.1	
4'	3.87 dq (7.6, 6.4)	69.7	1.90 dq (10.0, 6.6)	44.9	1.90 m	44.9	1.69 dq (10.2, 6.8)
5'	1.14 d (6.4)	20.9	4.31 dq (10.0, 6.6)	77.2	4.32 m	77.2	4.31 dq (10.2, 6.4)
6'			1.43 d (6.6)	18.8	1.43 d (6.8)	18.9	1.28 d (6.4)
3'-CH <sub>3</sub>	1.05 d (7.2)	13.7					
4'-CH <sub>3</sub>			1.15 d (6.6)	8.7	1.15 d (6.8)	8.7	1.01 d (6.8)
3'-OH							6.31 s

<sup>a</sup> Spectra recorded at <sup>1</sup>H (400 MHz) and <sup>13</sup>C NMR (100 MHz) in CDCl<sub>3</sub>. Chemical shift (δ) are in ppm, and coupling constants (*J* in Hz) are given in parentheses. The assignments were based on DEPT, COSY, NOESY, HSQC, and HMBC experiments.

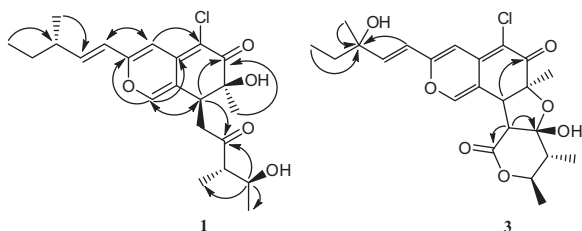


Figure 2. Important HMBC correlations for compounds **1** and **3**.

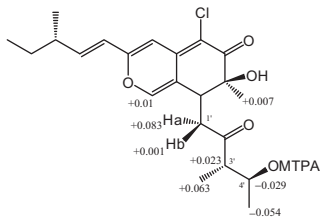


Figure 3.  $^1\text{H}$  chemical-shift difference ( $\Delta\delta = \delta_S - \delta_R$ ) between the (*R*)- and (*S*)-MTPA esters (**1a** and **1b**).

asymmetric carbons (7*S*, 8*S*, 11*S*, 3'*S*, and 4'*S*), and has been named chaetoviridin J.

Compound **2**<sup>16</sup> was obtained as a yellow amorphous powder and its MS and NMR spectra were in good agreement with those of the known compound, chaetomugilin D (Fig. 1);<sup>6,12</sup> the structure

was further confirmed by HSQC and HMBC analyses. The stereochemistry of **2** was established from its CD and NOESY correlations of H-2' with H-4'/4'-CH<sub>3</sub> and of H-5' with H-8/7-CH<sub>3</sub> (Fig. 4), along with the comparison of those of synthetic, chaetomugilin E (**8**) and chaetomugilin F (**9**) (Scheme S1).<sup>12,17,18</sup>

In addition, the absolute configuration of **2** was supported by means of X-ray crystallographic analysis through its chemical derivatization. The treatment of **2** with *p*-bromobenzoic acid in the presence of *N,N*-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) gave the *p*-bromobenzoate ester **2a**, where attached to C-7 and C-3' positions derived from **2**,<sup>19</sup> as shown in Scheme S2 (Supplementary data), revealing the chemical conversion and its stereochemistry.<sup>12,14</sup>

This chemical transformation facilitated the determination of the absolute stereochemistry of the asymmetric positions through X-ray crystallographic analysis (Fig. 5).

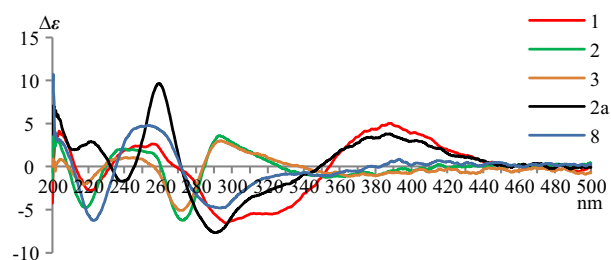


Figure 6. CD spectra of **1–3**, **2a**, and **8**.

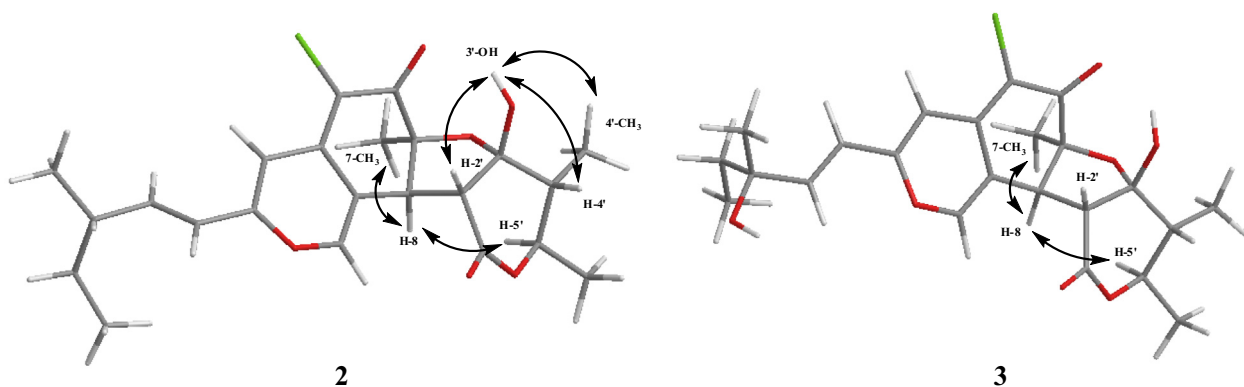


Figure 4. Key NOESY correlations for compounds **2** and **3**.

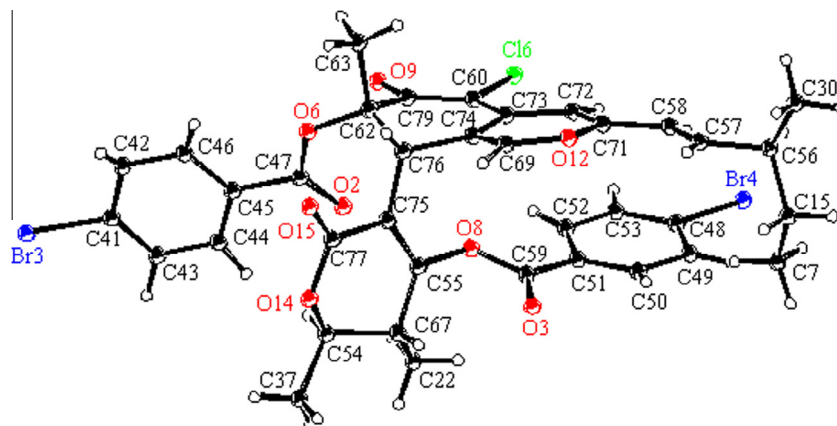


Figure 5. ORTEP drawing of one of the two crystallographically independent molecules in the unit cell of compound **2a**; displacement ellipsoids are drawn at the 50% probability level at 90K.

**Table 2**  
Inhibition effect of compounds **1–5** and **7–9** against the TNF- $\alpha$ -induced NF- $\kappa$ B activity and NO production in LPS-stimulated RAW 264.7 cells

Compounds	NF- $\kappa$ B			Nitrite assay (NO)			
	% Inhib. <sup>a</sup>	% Surv. <sup>b</sup>	IC <sub>50</sub> ( $\mu$ M)	% Inhib. <sup>c</sup>	% Surv. <sup>d</sup>	IC <sub>50</sub> ( $\mu$ M)	Cytotoxicity (IC <sub>50</sub> $\mu$ M)
<b>1</b>	32.6 $\pm$ 5.0	100 $\pm$ 12.3	nd <sup>e</sup>	95.4 $\pm$ 2.0	71.1 $\pm$ 4.0	nd	
<b>2</b>	28.2 $\pm$ 0.9	100 $\pm$ 15.8	nd	68.2 $\pm$ 1.9	85.3 $\pm$ 2.3	28.1 $\pm$ 4.1	
<b>3</b>	33.4 $\pm$ 2.5	100 $\pm$ 8.9	nd	39.4 $\pm$ 2.9	95.7 $\pm$ 2.1	nd	
<b>4</b>	99.9 $\pm$ 0.1	100 $\pm$ 11.0	0.9 $\pm$ 0.2	99.6 $\pm$ 0.4	32.9 $\pm$ 1.3	0.8 $\pm$ 0.7	6.8 $\pm$ 1.4
<b>5</b>	99.9 $\pm$ 0.2	59.2 $\pm$ 12.0	0.9 $\pm$ 0.2	99.9 $\pm$ 0.2	37.1 $\pm$ 1.5	0.3 $\pm$ 0.1	1.5 $\pm$ 0.1
<b>7</b>	74.2 $\pm$ 1.9	83.4 $\pm$ 6.2	7.6 $\pm$ 1.4	99.9 $\pm$ 2.1	36.2 $\pm$ 5.6	4.2 $\pm$ 0.9	4.2 $\pm$ 0.9
<b>8</b>	88.5 $\pm$ 3.8	100 $\pm$ 16.4	11.6 $\pm$ 2.1	97.9 $\pm$ 0.7	28.0 $\pm$ 6.1	5.8 $\pm$ 0.6	39.8 $\pm$ 5.8
<b>9</b>	97.7 $\pm$ 3.1	82.8 $\pm$ 3.3	5.1 $\pm$ 1.9	99.3 $\pm$ 0.2	28.5 $\pm$ 1.0	1.9 $\pm$ 0.1	20.7 $\pm$ 1.0
L-NMMA <sup>f</sup>						25.1 $\pm$ 2.3	
TPCK <sup>g</sup>			3.8 $\pm$ 0.6				
BAY-11 <sup>g</sup>			2.0 $\pm$ 0.3				

Assays were conducted in triplicate, and the each result is expressed as the average  $\pm$  standard deviation.

<sup>a</sup> % Inhibition of NO production at 50  $\mu$ M.

<sup>b</sup> % cell survival at concentration of 50  $\mu$ M.

<sup>c</sup> % Inhibition of NF- $\kappa$ B at 50  $\mu$ M.

<sup>d</sup> % Survival at concentration of 50  $\mu$ M.

<sup>e</sup> nd, not determined.

<sup>f</sup> Positive control for NO.

<sup>g</sup> Positive control for NF- $\kappa$ B.

Compound **3**<sup>20</sup> was obtained as a white amorphous powder and its molecular formula was established as C<sub>23</sub>H<sub>27</sub>ClO<sub>7</sub> by HRESIMS (observed, 473.1350; Calcd for [M+Na]<sup>+</sup> 473.1338), corresponding to a molecular formula of C<sub>23</sub>H<sub>27</sub>ClO<sub>7</sub>Na. The ratio of isotope peak intensities (MH<sup>+</sup>/[MH+2]<sup>+</sup>) indicated one chlorine atom was present. The <sup>1</sup>H and <sup>13</sup>C NMR spectra displayed highly conjugated olefinic system, four methyls, and three methines, including an oxygenated methine, a methylene, an ester carbonyl carbon, a conjugated carbonyl carbon, an oxygenated quaternary carbon, and a hemiacetal carbon, closely resembled to those of **2**. However, the NMR spectra of **3** showed additional signals for a quaternary methyl group at  $\delta$ <sub>H</sub> 1.38 (3H, s)/ $\delta$ <sub>C</sub> 27.7 (11-CH<sub>3</sub>), an oxygenated quaternary carbon at  $\delta$ <sub>C</sub> 73.5 (C-11), and a *trans*-doublet olefinic proton at  $\delta$ <sub>H</sub> 6.63 (d, *J* = 15.6 Hz, H-10), instead of the doublet methyl (11-CH<sub>3</sub>), the methine group (H-11), and the *trans*-doublet olefinic proton (H-10) in the 3-(3-methyl-1-pentenyl) moiety of **2**. The HMBC correlations between 11-CH<sub>3</sub>/CH<sub>3</sub>-13/H-10 and the oxygenated quaternary carbon (C-11), along with the HRESIMS analysis suggested that a hydroxyl group was attached at C-11 position (Fig. 2). Two sets of the NMR signals corresponding to the side chain, 3-(3-methylpent-1-en-3-ol) group indicated that **3** was, in fact, a mixture of unresolvable diastereoisomer. The attempts at purification of this mixture by chiral columns were unsuccessful. The configuration of asymmetric centers except for C-11 in **3** was determined to be the same with those of chaetomugilin D (**2**) and its derivative **2a**, as shown in Scheme S2, by comparison of their NMR and NOESY spectra (Table 1 and Figs. 4 and S17), along with physicochemical analyses,<sup>6,13,15</sup> and has been named chaetoviridin K.

The other four isolates were identified as the known compounds, 11-*epi*-chaetomugilin I (**4**),<sup>12</sup> chaetomugilin I (**5**),<sup>12</sup> chaetomugilin N (**6**),<sup>14</sup> and chaetomugilin J (**7**),<sup>14</sup> along with the derivatives of **2**, namely, chaetomugilins E (**8**) and F (**9**),<sup>17,18</sup> by comparison of their physical and spectral data with published values.

Compounds **1–5**, **7**, and the chaetomugilins E and F (**8** and **9**) were subsequently evaluated for their cancer chemopreventive potential based on their ability to inhibit tumor necrosis factor alpha (TNF- $\alpha$ )-induced NF- $\kappa$ B activity and nitric oxide (NO) production (Table 2). Among tested compounds, **4** and **5** inhibited TNF- $\alpha$ -induced NF- $\kappa$ B activity with the same IC<sub>50</sub> value of 0.9  $\mu$ M, but **4** showed no cytotoxicity at a concentration at 50  $\mu$ M. Compounds **7–9** showed moderate inhibitory activity with

IC<sub>50</sub> values ranging from 5.1 to 11.6  $\mu$ M. The NO inhibitory activity of these compounds was initially evaluated at a fixed concentration at 50  $\mu$ M. Compounds **1**, **4**, **5**, and **7–9** exhibited strong inhibitory activity against NO production (95.4–99.9%). Among them, compounds **4** and **5** inhibited NO release, with IC<sub>50</sub> values of 0.8  $\pm$  0.7 and 0.3  $\pm$  0.1  $\mu$ M, respectively, which demonstrated more potency than the positive control, *N*-monomethyl-L-arginine (25.1  $\mu$ M). However, cytotoxicity of both compounds was observed at 50  $\mu$ M. Compounds **7–9** also showed considerable inhibitory activity with IC<sub>50</sub> values ranging from 1.9 to 5.8  $\mu$ M, while compound **3** exhibited a weak response.

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## Supplementary data

The X-ray crystallography data of compound **2a** in this Letter has been deposited with the Cambridge Crystallography Data Center as supplementary publications No. CCDC1025151-102515. The data can be obtained free of charge from the Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmcl.2015.08.063>.

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11. Chaetoviridin J (**1**): yellow amorphous powder;  $[\alpha]_D^{20} = +130^\circ$  (c 0.2, MeOH); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 292 (2.6), 386 (4.5), 407 (4.0) nm; CD (c 0.1, MeOH) 255 (+2.6), 297 (−6.5), 388 (+2.6); IR  $\nu_{\max}$  (KBr) 3350, 1700  $\text{cm}^{-1}$ ;  $^1\text{H}$  (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) data, see Table 1; HRESIMS  $m/z$  431.1499  $[\text{M}+\text{Na}]^+$  (Calcd for  $\text{C}_{22}\text{H}_{29}\text{ClO}_5\text{Na}$ , 431.1435).
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16. Chaetomugilin D (**2**): yellow amorphous powder;  $[\alpha]_D^{10} = +140^\circ$  (c 0.05, MeOH); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 284 (3.5), 385 (4.2), 405 (4.5) nm; CD (c 0.1, MeOH) 240 (+2.0), 272 (−6.2), 293 (+3.5); IR  $\nu_{\max}$  (KBr) 3340, 1765  $\text{cm}^{-1}$ ;  $^1\text{H}$  (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) data, see Table 1; HRESIMS  $m/z$  435.1577  $[\text{M}+\text{H}]^+$  (Calcd for  $\text{C}_{23}\text{H}_{28}\text{ClO}_6$ , 435.1569).
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19. Compound (**2a**): yellow crystal;  $[\alpha]_D^{20} = +220^\circ$  (c 0.1, MeOH); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 252 (4.0), 387 (3.2), 403 (3.0) nm; CD (c 0.1, MeOH) 255 (+2.6), 297 (−6.5), 388 (+2.6);  $^1\text{H}$  (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) data, see Figures S17 and S18.
20. Chaetoviridin K (**3**): yellow amorphous powder;  $[\alpha]_D^{20} = +360^\circ$  (c 0.025, MeOH); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 254 (4.0), 388 (3.0), 405 (3.2) nm; CD (c 0.1, MeOH) 244 (+1.0), 271 (−5.0), 293 (+2.99);  $^1\text{H}$  (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) data, see Table 1; HRESIMS  $m/z$  473.1350  $[\text{M}+\text{Na}]^+$  (Calcd for  $\text{C}_{23}\text{H}_{27}\text{ClO}_7\text{Na}$ , 473.1338).