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Aspernolides L and M, new butyrolactones from the endophytic fungus *Aspergillus versicolor*

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Abstract: During the systematic search of active compounds from endophytic fungi, two new butyrolactones, namely aspernolides L (**2**) and M (**4**), together with four known compounds: 1-*O*-acetylglycerol (**1**), butyrolactone I (**3**), butyrolactone VI (**5**), and (+) alantrypinone (**6**) were characterized from the EtOAc extract of the endophytic fungus *Aspergillus versicolor* isolated from the roots of *Pulicaria crispa* (Asteraceae). Extensive spectroscopic analysis, including 1D, 2D NMR, and HRESIMS, was used to elucidate their structures. Compounds **1**, **5**, and **6** are reported for the first time from this fungus.

Keywords: *Aspergillus versicolor*; Aspernolide; butyrolactones; endophytic fungi; *Pulicaria crispa*.

1 Introduction

Bioactive secondary metabolites from endophytic fungi, isolated from higher plants, are a major focus of natural product research [1–4]. They have been utilized as drugs and/or lead compounds in the pharmaceutical industry [1–5]. The specific habitats, metabolic pathways, and bioactivities of the endophytic fungi make them a good source of structurally novel and/or biologically active secondary metabolites [5, 6]. Fungi of the genus *Aspergillus* (Moniliaceae) have been reported as prolific producers of bioactive compounds as xanthones, butyrolactones, anthraquinones, polyketides, and alkaloids [1, 2, 5–10], some of them possess various biological activities [11–14]. In the course of our search for secondary metabolites from endophytic fungi, we investigated the fungal strain *Aspergillus versicolor* isolated from the roots of *Pulicaria crispa* (Asteraceae), which was collected from Gabal Al-aquiq, Al Madinah Al Munawwarah, Saudi Arabia. As a result, two new butyrolactones, namely aspernolides L (**2**) and M (**4**), and four known compounds (**1**, **3**, **5**, and **6**) were isolated from this strain (Figure 1). The structures of these compounds were elucidated on the basis of a comprehensive analysis of 1D and 2D NMR spectra.

2 Materials and methods

2.1 General

Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter (Perkin-Elmer Inc., Waltham, MA, USA). UV spectra were recorded in MeOH on a Shimadzu 1601 UV/VIS spectrophotometer (Shimadzu, Kyoto, Japan). The IR spectra were measured on a Shimadzu Infrared-400 spectrophotometer (Shimadzu, Kyoto, Japan). ESIMS spectra were obtained with an LCQ DECA mass spectrometer (ThermoFinnigan, Bremen, Germany) coupled to an Agilent 1100 HPLC system equipped with a photodiode array detector. HRESIMS was recorded on LTQ Orbitrap mass spectrometer (ThermoFinnigan, Bremen, Germany). 1D and 2D NMR spectra (chemical shifts in ppm, coupling constants in Hz) were recorded on Bruker Avance DRX 500 MHz spectrometers (Bruker BioSpin, Billerica, MA, USA) using DMSO-d_6 as solvent. For column chromatography, silica gel (0.063–0.200 mm, Merck, Darmstadt, Germany), RP_{18} (0.04–0.063 mm, Merck, Darmstadt, Germany), and Sephadex LH-20 (0.25–0.1 mm, Sigma-Aldrich) were used. Pre-coated silica gel 60 F_{254} plates (0.2 mm, Merck, Darmstadt, Germany) were used for thin-layer chromatography (TLC).

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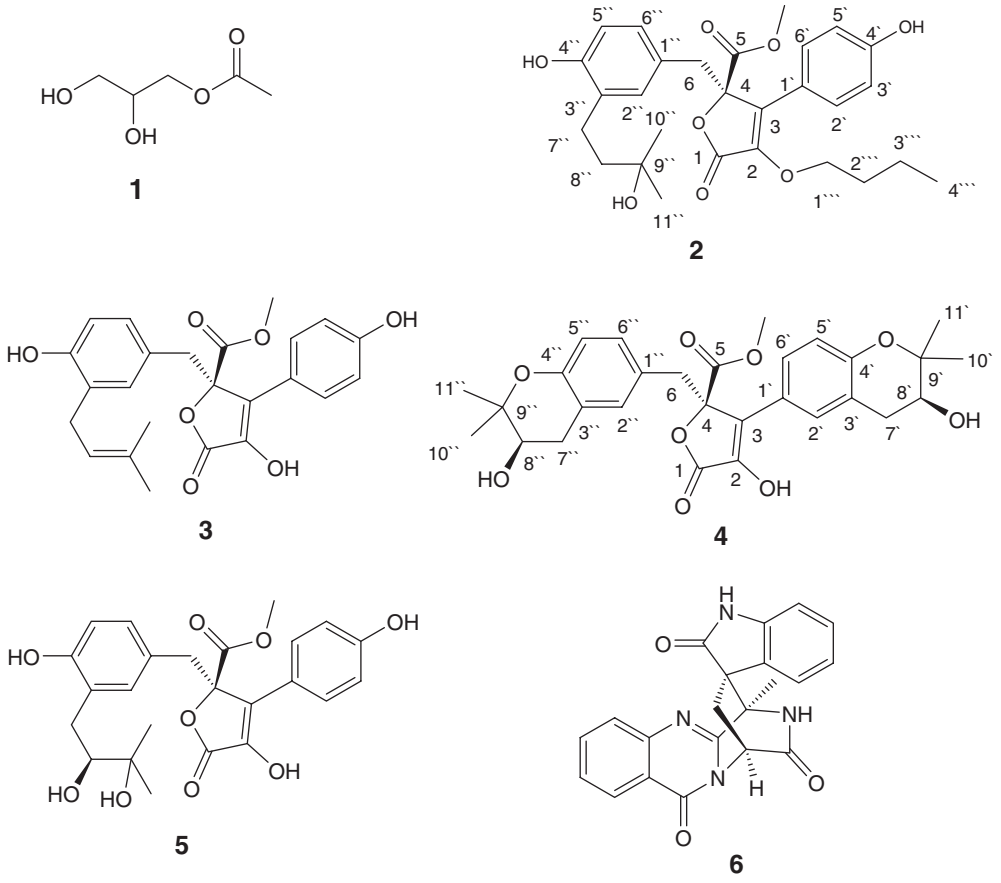


Figure 1: Structures of isolated compounds **1–6**.

2.2 Isolation and cultivation of the fungal material

Pulicaria crispa was collected from Gabal Al-aquiq, Al Madinah Al Munawwarah, Saudi Arabia in March 2014. The plant was authenticated by Dr. Emad Alsherif, Associate Professor of Plant Ecology, Department of Biology, Faculty of Science and Arts, Khulais, King Abdulaziz University, Saudi Arabia. A specimen (PC-3-2014) was preserved at the herbarium of the Department of Natural Products and Alternative Medicine, Faculty of Pharmacy, King Abdulaziz University. *Aspergillus versicolor* was isolated from the internal roots tissue of *P. crispa*. The inner root tissues were carefully dissected under sterile conditions and placed on potato dextrose agar plates (PDA, Difco), containing chloramphenicol and gentamicin as antibacterial agents to prevent bacterial growth. The dishes were incubated at 27 °C for 4–6 weeks. Then, hyphal tips of the fungi were periodically removed and transferred to fresh PDA plates. The fungi were identified on the basis of their colonial morphological trait and microscopic observation, using light microscopy (CX31RBSF, Olympus) [15], which was genetically reinforced by the analysis of ITS sequence (Genbank Accession number AV191832.1). The fungus was deposited at the Department of Microbiology, Faculty of Pharmacy, Taibah University, Al Madinah Al Munawwarah, Saudi Arabia (PC No. MAR32014). The fresh fungal culture was transferred into 10 Erlenmeyer flasks (1 L each) for isolation and identification of secondary metabolites, containing rice solid cultures (100 mL of distilled water were added to 100 g commercially available rice and kept overnight prior to autoclaving). The cultures were then incubated at room temperature for 30 days under septic conditions.

2.3 Extraction and isolation

The rice cultures were extracted with EtOAc and concentrated under vacuum. The concentrated extract was mixed with 100 mL distilled H_2O and partitioned between *n*-hexane and 90% MeOH. The total 90% MeOH extract (5.9 g) was subjected to SiO_2 vacuum liquid chromatography (VLC) using *n*-hexane, EtOAc, and MeOH, which were separately concentrated to give FV1 (1.4 g), FV2 (1.9 g), and FV3 (2.3 g),

respectively. Fraction FV-2 (1.9 g) was subjected to normal phase VLC using $CHCl_3$:MeOH gradients (100% $CHCl_3$ to 50:50 $CHCl_3$:MeOH), 100 mL fractions were collected and monitored by TLC to obtain nine sub-fractions: FVE2-1 to FVE2-9. Sub-fraction FVE2-2 (95 mg) was chromatographed over SiO_2 CC (20 g, 50×2 cm) using $CHCl_3$:MeOH (99.5:0.5 to 97:3) as an eluent to give impure **1**, which was further purified by repeated chromatography on a SiO_2 CC using *n*-hexane:EtOAc gradient to afford **1** (12.7 mg, white amorphous powder). SiO_2 CC (40 g, 50×2 cm) of sub-fraction FVE2-3 (153 mg) using $CHCl_3$:MeOH in order of increasing polarity afforded impure **2**, which was purified on RP_{18} column (0.04–0.063 mm; 40 g, 50×2 cm) using H_2O:MeOH gradient to give **2** (4.7 mg, yellow gum). Sub-fraction FVE2-4 (391 mg) was chromatographed over sephadex LH-20 (30 g, 50×2 cm) using MeOH as an eluent to yield impure **3** and **4**. Separately, each one was purified on RP-18 column (0.04–0.063 mm; 40 g, 50×2 cm) using H_2O:MeOH gradient to obtain **3** (9.9 mg, yellow gum) and **4** (3.8 mg, yellow gum). Separately, sub-fractions FVE2-5 (186 mg) and FVE2-6 (142 mg), each one was subjected to repeated SiO_2 CC (50 g, 50×2 cm) using $CHCl_3$: MeOH (95 to 85:15) as an eluent to give **5** (15.1 mg, yellow gum, sub-fraction FVE2-5) and **6** (21.0 mg, white powder, sub-fraction FVE2-6).

Aspernolide L (**2**): Yellow gum. - $[\alpha]_D^{25}$ +48 (*c* 0.05, MeOH). - UV (MeOH): λ_{max} (log ε) = 209 (4.31), 226 (4.03), 316 (3.86) nm. - IR (KBr): 3436, 2978, 1729, 1667, 1056 cm^{-1}. - NMR data (DMSO-d_6, 500 and 125 MHz) see Table 1. - HRESIMS *m/z* 499.2329 (calcd for 499.2332 $[M+H]^+$, $C_{28}H_{35}O_8$).

Aspernolide M (**4**): Yellow. - $[\alpha]_D^{25}$ +85 (*c* 0.03, MeOH). - UV (MeOH): λ_{max} (log ε) = 216 (4.12), 236 (3.97), 331 (3.41) nm. - IR (KBr): 3423, 2945, 1733, 1669, 1440, 1117, 1025 cm^{-1}. - NMR data (DMSO-d_6, 500 and 125 MHz) see Table 1. - HRESIMS *m/z* 525.2121 $[M+H]^+$ (calcd $C_{29}H_{33}O_9$, 525.2125).

Table 1: NMR spectroscopic data of compounds **2** and **4** (DMSO-d_6, 500 and 125 MHz).

Position	2		Position	4	
	δ_H (mult., J [Hz])	δ_C (mult.)		δ_H (mult., J [Hz])	δ_C (mult.)
1	–	168.1 C	**1**	–	168.5 C
2	–	138.2 C	**2**	–	138.2 C
3	–	128.1 C	**3**	–	128.7 C
4	–	84.7 C	**4**	–	84.7 C
5	–	169.8 C	**5**	–	169.9 C
6	3.42 d (14.9) 3.38 d (14.9)	38.1 CH_2	**6**	3.41 d (16.0) 3.36 d (16.0)	38.1 CH_2
1′	–	119.9 C	**1′**	–	121.4 C
2′	7.50 d (8.2)	128.8 CH	**2′**	6.87 d (2.5)	128.8 CH
3′	6.87 d (8.2)	115.7 CH	**3′**	–	119.6 C
4′	–	157.9 C	**4′**	–	157.5 C
5′	6.87 d (8.2)	115.7 CH	**5′**	6.51 d (7.5)	115.8 CH
6′	7.50 d (8.2)	128.8 CH	**6′**	7.49 dd (7.5, 2.5)	131.6 CH
1″	–	123.9 C	**7′**	2.64 dd (16.1, 4.8) 2.40 dd (16.1, 7.3)	31.0 CH_2
2″	6.43 d (2.2)	131.4 CH	**8′**	3.71 dd (7.3, 4.8)	68.5 CH
3″	–	121.1 C	**9′**	–	77.2 C
4″	–	152.5 C	**10′**	1.18 s	25.7 CH_3
5″	6.49 d (8.0)	116.0 CH	**11′**	1.18 s	25.7 CH_3
6″	6.47 dd (8.0, 2.2)	128.7 CH	**1″**	–	124.4 C
7″	2.31 t (6.8)	28.1 CH_2	**2″**	6.42 d (2.0)	131.7 CH
8″	1.59 t (6.8)	39.6 CH_2	**3″**	–	119.6 C
9″	–	73.9 C	**4″**	–	151.7 C
10″	1.23 s	26.6 CH_3	**5″**	6.52 d (8.0)	115.6 CH
11″	1.24 s	26.4 CH_3	**6″**	6.47 dd (8.0, 2.0)	129.0 CH
1‴	4.14 dd (14.5, 6.8) 3.90 dd (14.5, 5.3)	65.5 CH_2	**7″**	2.64 dd (16.1, 5.5) 2.40 dd (16.1, 8.0)	31.0 CH_2
2‴	1.62 m	31.9 CH_2	**8″**	3.74 dd (8.0, 5.5)	68.0 CH
3‴	1.25 m	21.7 CH_2	**9″**	–	77.0 C
4‴	0.84 t (6.6)	14.0 CH_3	**10″**	1.21 s	25.8 CH_3
-OCH_3	3.76 s	53.5 CH_3	**11″**	1.21 s	25.8 CH_3
4′-OH	10.71 s	–	**-OCH_3**	3.73 s	53.5 CH_3
4″-OH	9.85 s	–	**OH**	5.13 brs	–

The bold values are the atoms positions.

3 Results and discussion

The culture of *A. versicolor* was extracted with EtOAc. The extract was subjected repeatedly to SiO_2, sephadex, and RP_{18} CC to afford two new and four known compounds. Compounds **1**, **3**, **5**, and **6** were identified by combined spectroscopic analyses as 1-*O*-acetylglycerol [16], butyrolactone I [17], butyrolactone VI [1, 2], and (+) alantrypinone [18, 19], respectively. The spectroscopic data for these compounds were in good agreement with those reported in the literature.

Compound **2** was obtained as a yellow gum. Its molecular formula $C_{28}H_{34}O_8$ was determined by HRESIMS pseudo-molecular ion peak at *m/z* 499.2329 (calculated for 499.2332 $[M+H]^+$, $C_{28}H_{35}O_8$), indicating 12 degrees of unsaturation. The ^1H and ^{13}C NMR spectral data of **2** revealed that 8 of the 12 units of unsaturation were attributed to two phenyl moieties (Figures S3 and S4). In addition, two carbonyls and two olefinic carbons account for three degrees of unsaturation. The IR spectrum showed absorption bands of hydroxyl, carbonyl group, and C–H aromatic at 3436, 1729, and 1667 cm^{-1}, respectively. The ^{13}C, DEPT, and HSQC spectra of **2** revealed the presence of 28 carbon resonances: three methyls, one methoxy (δ_C 53.5, 5-OCH_3), five methylenes, an oxymethylene δ_C 65.5 (C-1‴), seven methines, and 11 quaternary carbons, including two carbonyls at δ_C 169.8 (C-5) and 168.1 (C-1), two oxygen-bonded aromatic carbons at δ_C 157.9 (C-4′) and 152.5 (C-4″), and an oxygenated aliphatic carbon (δ_C 84.7, C-4), which suggested that **2** had a butyrolactone skeleton. The ^1H NMR and ^1H-^1H COSY spectra displayed four *ortho*-coupled aromatic protons of a 1,4-disubstituted benzene moiety at δ_H 7.50 (d, 2H, *J* = 8.2 Hz, H-2′,6′) and 6.87 (d, 2H, *J* = 8.2 Hz, H-3′,5′) (Figure 2). They correlated to the carbons at δ_C 128.8 and 115.7, respectively, in the HSQC spectrum (Figure S5, Table 1). Three aromatic signals at δ_H 6.43 (d, *J* = 2.2 Hz, H-2″)/δ_C 131.4, 6.49 (d, *J* = 8.0 Hz, H-5″)/116.0, and 6.47 (dd, *J* = 8.0, 2.2 Hz, H-6″)/128.7 characteristic for a 1,3,4-*tri*-substituted benzene ring were observed. The observed HMBC cross peaks of H-2′ and H-6′/C-1′ and C-4′, H-3′ and H-5′/C-1′, C-4′, and C-6′, H-2″/C-1″, C-3″, C-4″, and C-6″, H-5″/C-1″ and C-3″, and H-6″/C-1″ and C-2″ confirmed these moieties (Figure 3). Furthermore, a side chain consisting of an oxygenated quaternary carbon (δ_C 73.9 C-9″), two methylenes at δ_H 1.59 (t, *J* = 6.8 Hz, H-8″)/δ_C 39.6 (C-8″) and 2.31 (t, *J* = 6.8 Hz, H-7″)/δ_C 28.1 (C-7″), and two singlet methyls at δ_H 1.23 (H-10″)/26.6 (C-10″), and 1.24 (H-11″)/26.4 (C-11″) was observed characteristic for 3-hydroxy-3-methylbutyl moiety. This was confirmed by the observed ^1H-^1H COSY and HMBC correlations (Figure 3). The HMBC correlations of H-7″/C-2″ and C-4″, H-8″/C-3″, and H-2″/C-7″ indicated its attachment at C-3″ (Figure S6). A methylene group at δ_H 3.42 and 3.38 (2H, each d, *J* = 14.9 Hz, H-6)/δ_C 38.1 (C-6) was observed. The HMBC cross peaks of H-6/C-4, C-1″, C-2″, and C-6″ indicated that this methylene was connected to C-4 and C-1″ of the *tri*-substituted phenyl residue. The singlet signal at δ_H 3.76 showed HSQC cross peak to the carbon at δ_C 53.5, attributable to a methoxy group. It had HMBC cross peak to C-5 (δ_C 169.8). Furthermore, the oxygen-bearing methylene group at δ_H 4.14 (dd, *J* = 14.5, 6.8 Hz, H-1‴A) and 3.90 (dd, *J* = 14.5, 5.3 Hz, H-1‴B)/δ_C 65.5 (C-1‴), two multiplet methylenes at δ_H 1.62 (H-2‴)/31.9 (C-2‴) and 1.25 (H-3‴)/21.7 (C-3‴), and a triplet methyl at δ_H 0.84 (*J* = 6.6 Hz, H-4‴)/14.0 (C-4‴), indicated the presence of a butyloxy group in **2**. The HMBC cross peaks of H-1‴ to C-2 confirmed the connectivity of this group at C-2. The configuration at C-4 of **2** was deduced to be 4*R* based on biosynthetic considerations and its specific rotation ($[\alpha]_D$ +48 (*c* 0.05, MeOH)). It was reported that the configuration at C-4 could be assigned on the basis of the optical rotation's sign. Butyrolactones with *R*-configured C-4 had positive optical rotation values such as butyrolactones I-VIII [20, 21]; however; those with negative optical rotation values possessed *S*-configured C-4 as in isobutyrolactone II and V [22]. Thus, the structure of **2** was assigned as methyl (*R*)-4-butoxy-2-(4-hydroxy-3-(3-hydroxy-3-methylbutyl)benzyl)-3-(4-hydroxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylate and named aspernolide L.

Compound **4** was also obtained as a yellow gum with a molecular formula $C_{29}H_{32}O_9$ determined by its HRESIMS pseudo-molecular ion peak at *m/z* 525.2121 $[M+H]^+$ (calculated $C_{29}H_{33}O_9$, 525.2125), requiring 14 degrees of unsaturation. Compound **4** was 26 mass units and 2 degrees of unsaturation more than **2**. The 1D and 2D NMR spectral data (Table 1) revealed that the structure of **4** was very similar to those of **2** except the absence of the signals associated with the 3-hydroxy-3-methylbutyl, butyloxy, and 1,4-disubstituted benzene moieties. It had a 1,3,4-*tri*-substituted phenyl moiety at δ_H 6.87 (d, *J* = 2.5 Hz, H-2′)/δ_C 128.8, 6.51 (d, *J* = 7.5 Hz, H-5′)/115.8, and 7.49 (dd, *J* = 7.5, 2.5 Hz, H-6′)/131.6 instead of the 1,4-disubstituted phenyl moiety in **2** (Figures S9 and S10). It was confirmed by the HMBC cross peaks of H-2′ to C-4′ and C-6′, H-5′ to C-1′, C-3′, and C-4′, and H-6′ to C-1′, C-4′, and C-5′. Its connectivity at C-3 was established by the HMBC cross peaks of H-2′ and H-6′ to C-3. Compared with **2**, the two additional degrees of unsaturation, along with the observed ^1H and ^{13}C NMR signals, indicating the presence of two 2,2-dimethyltetrahydro-2*H*-pyran-3-ol rings fused to the two *tri*-substituted phenyl rings in **4**, which was further confirmed by the HMBC correlations of H-7′ to C-2′, C-4′, and C-9′, H-8′ to C-3′, C-10′, and C-11′, H-10′ and H-11′ to C-8′ and C-9′, H-7″ to C-2″, C-4″, and C-9″, H-8″ to C-3″, C-10″,

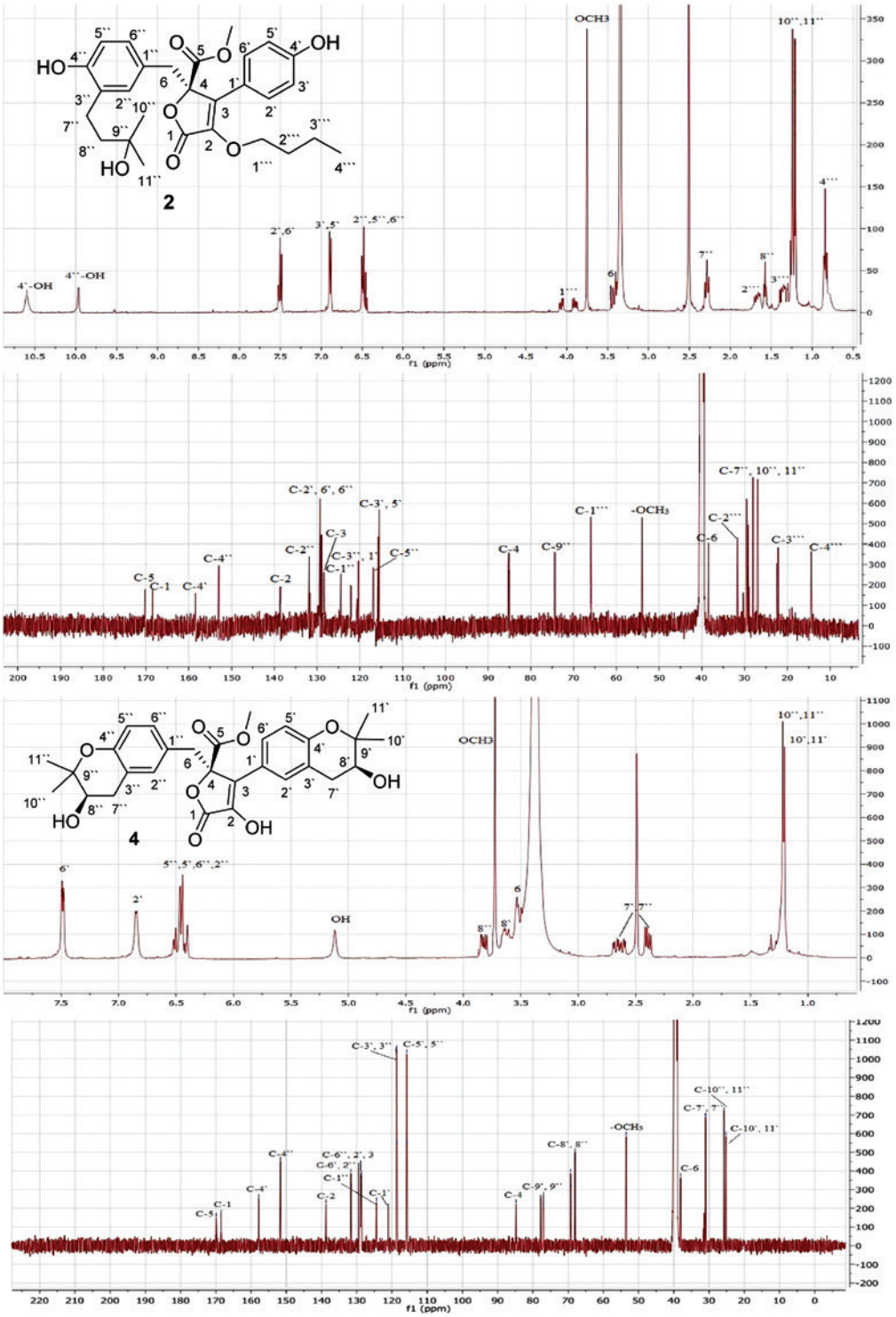
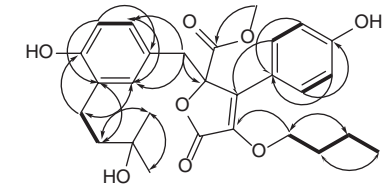


Figure 2: ^{1}H and ^{13}C NMR spectra of compounds **2** and **4** (DMSO-d_6, 500 and 125MHz).

and C-11″, and H-10″ and H-11″ to C-8″ and C-9″, establishing their attachment at $C_{3'}$-$C_{4'}$ and $C_{3''}$-$C_{4''}$, respectively (Figure S12). The configuration of the secondary alcohols at C-8′ and C-8″ was assigned as *S*-configured based on the comparison of the ^{1}H and ^{13}C NMR chemical shifts as well as optical rotation value ($[\alpha]_D$ +85 (*c* 0.03, MeOH)) with those of previously reported butyrolactones [1, 2, 23, 24]. This unambiguously led to the elucidation of **4** as methyl (*R*)-4-hydroxy-3-((*S*)-3-hydroxy-2,2-dimethylchroman-6-yl)-2-(((*R*)-3-hydroxy-2,2-dimethylchroman-6-yl) methyl)-5-oxo-2,5-dihydrofuran-2-carboxylate and named aspernolide M.



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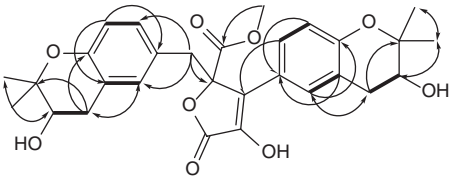

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Figure 3: Some key ^{1}H-^{1}H COSY (—) and HMBC (H → C) correlations of **2** and **4**.

4 Conclusions

Six compounds (**1–6**) were isolated and characterized from the EtOAc extract of the *Aspergillus versicolor* isolated from the roots of *Pulicaria crispa* (Asteraceae), two of them are new natural products (**2** and **4**). Compounds **1**, **5**, and **6** are reported for the first time from this fungus.

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