Natural Product Research

Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: https://www.tandfonline.com/loi/gnpl20

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To cite this article: Ju-Tao Wang, Zong-Hui Ma, Guo-Kai Wang, Feng-Qing Xu, Yang Yu, Gang Wang, Dai-Yin Peng & Jin-Song Liu (2019): Chemical constituents from plant endophytic fungus *Alternaria alternata*, Natural Product Research, DOI: 10.1080/14786419.2019.1639699

To link to this article: https://doi.org/10.1080/14786419.2019.1639699

NATURAL PRODUCT RESEARCH
https://doi.org/10.1080/14786419.2019.1639699

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SHORT COMMUNICATION

Chemical constituents from plant endophytic fungus *Alternaria alternata*

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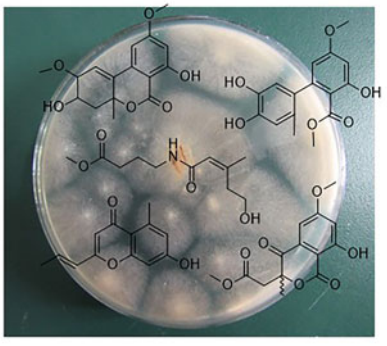
ABSTRACT

Five new natural compounds (**1**–**5**) along with four known ones, involving dibenzo-α-pyrone derivatives, a benzo-γ-pyrone derivative and an amide-type compound were obtained from *Alternaria alternata*, an endophyte isolated from *Paeonia lactiflora*. The structures of these isolates were elucidated by intensive analysis of spectroscopic data including NMR, HRMS (ESI and EI), UV and IR spectra. Compounds (**1**–**4**) were evaluated for their cytotoxicities against five selected human tumourtumour cell lines (A-549, MDA-MB-231, MCF-7, KB and KB-VIN), and compound **3** exhibited activities against MDA-MB-231and MCF-7 with IC_{50} values of 20.1 μM and 32.2 μM.



ARTICLE HISTORY
Received 23 January 2019
Accepted 29 June 2019

KEYWORDS
Alternaria alternata; *Paeonia lactiflora*; benzo-α-pyrone derivatives; cytotoxic activity

1. Introduction

The root of *Paeonia lactiflora*, known as "Chishao" mainly distributed in China, has been widely utilised as one of the crude drugs among multiple traditional Chinese

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Supplemental data for this article can be accessed at https://doi.org/10.1080/14786419.2019.1639699.

medicines for long time, owing to its vital pharmacological values of anti-inflammatory, anti-coagulative and analgesic activities. As to chemical investigation of "Chishao", diverse bioactive components have been reported continuously, especially the characteristic chemotaxonomic markers – monoterpene glycosides (Fu et al. 2016; Shi et al. 2016). Omnipresent fungi, among which many resides in plants, are a paradigm of harbouring various natural occurrences with unique structures and biological activities (Yao et al. 2017). Also, endophyte infections could alter patterns of gene expression in plant host (Jalgaonwala et al. 2011). On the ground of these factors, endophytes have been among high-profile subjects investigated, especially in the aspect of their chemical investigation.

In our continuous search on chemical constituents from endophytes derived from plants with significant medicinal values (Wang et al. 2018; Zhang et al. 2018; Wang et al. 2019), *Alternaria alternata* (Lou et al. 2013), a fungus reported to deliver diverse bioactive secondary metabolites, was isolated from *Paeonia lactiflora*. Furthermore, compounds **1**–**5**, along with four known chemical components (**6**–**9**) were isolated from the promising endophyte. In our aim of uncovering natural lead compounds with biological functions, compounds **1**–**4** were screened for cytotoxicities against five selected tumour cell lines. Compound **3** displayed activities against MDA-MB-231 and MCF-7 with IC_{50} values of 20.1 μM and 32.2 μM, respectively. Herein, structural elucidation and biological evaluation of these novel natural components yielded from the endophyte were discussed.

2. Results and discussion

Compound **1**, white powder, had a molecular formula of $C_{16}H_{18}O_6$ deduced by its quasi-molecule ion peak at *m/z* 329.0997 $[M+Na]^+$ (calcd. for $C_{16}H_{18}O_6Na$, 329.0996) in the positive HR-ESI-MS, requiring eight degrees of unsaturation. The IR spectrum indicated the presence of hydroxyl (3440 cm^{-1}), conjugated ester carbonyl (1654 cm^{-1}) and moiety of benzene ring (1621, 583 cm^{-1}). The ^{13}C NMR data of compound **1** suggested sixteen carbon signals, assigned as seven quaternary carbons including one carbonyl (δ_C169.7), two oxygenated sp^2 carbons (δ_C 165.4 and 167.9), three sp^2 carbons (δ_C 136.8, 139.6 and 115.5), and one oxygenated carbon (δ_C 82.9); one methylene (δ_C 40.3); five methines including three sp^2 carbons (δ_C 102.3, 104.0 and 126.3) and two oxygenated sp^3 carbons (δ_C 67.5 and 76.6); and three methyls including two methoxyls (δ_C 56.3 and 58.9). According to the ^1H NMR data, two olefinic protons both showed two doublets with coupling constants 2.3 Hz, indicating the 1, 2, 3 and 5 positions in the benzene ring (A ring) were substituted. Two singlets of methoxyls can be found at δ_H 3.54 and 3.87 respectively. The HSQC spectrum and the above data rendered as the linchpin to assign the data of proton signals corresponding to carbon signals in compound **1** as shown in the Supplementary material Table S1. The methoxyls (δ_C 56.3; δ_H 3.87, s), (δ_C 58.9; δ_H 3.54, s) were confirmed to be linked to C-9, C-2 respectively, via HMBC correlations (see Supplementary material Figure S1). And the HMBC correlations from H-1 to C-3 and C-4a, from H_2-4 to C-3, C-4a and C-10b confirmed the presence of B ring. Also, the HMBC correlations from methyl proton at C-4a to C-4a, C-4 and C-10b corroborated the linkage of methyl to C-4a. The linkage

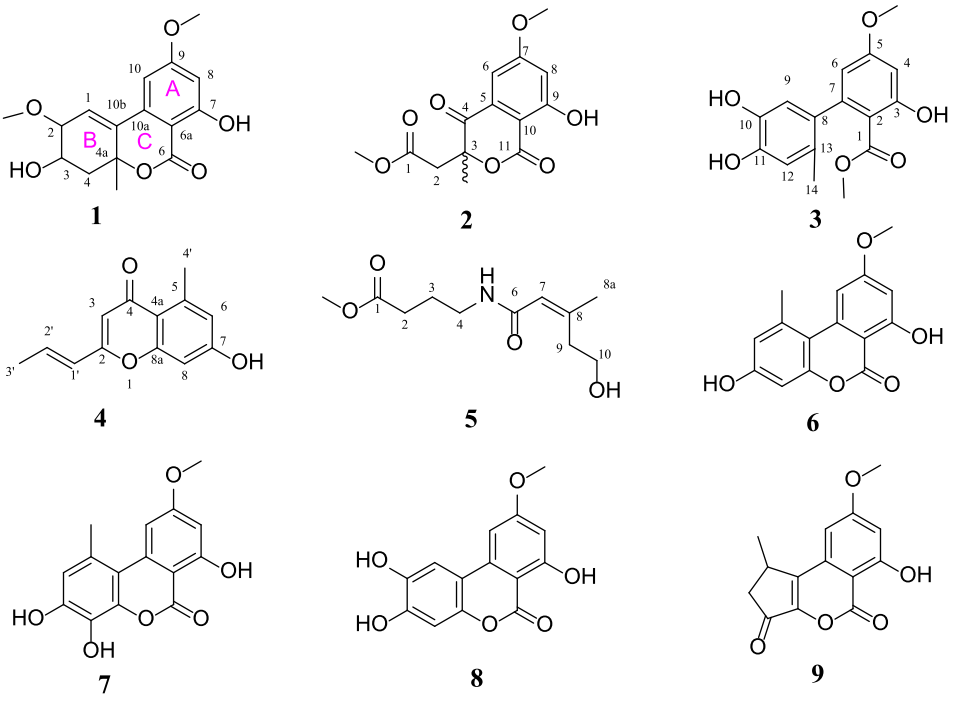

Figure 1. Structures of compounds **1**–**9**.

between A ring to B ring was also established via the linkage of C-10a/C-10b due to the HMBC correlations from H-1 to C-10a and from H-10 to C-10b. Given the fact that compound **1** required eight degrees of unsaturation and the downfield region of C-4a, it was highly plausible that compound **1** bore the C ring as depicted in Figure 1. Taken together, compound **1** was elucidated to have high similarity with 2-acetoxy-2-*epi*-altenuene (Tian et al. 2017), the only difference found between two compounds was the substituents at C-2. Since the chemical shifts of H-2 and H-3 were nearly identical, it was indistinguishable to analysethe ROESY correlations of Me-4a/H-2/H-3 and the coupling constants between H-2 and H-3. The relative configuration of Me-4a remained to be resolved. Hence, the structure of compound **1** was established as alternate A.

Compound **2** was obtained as yellow oil, and its molecular formula was determined as $C_{14}H_{14}O_7$ by the HR-ESI-MS (*m/z* 317.0629 $[M+Na]^+$) and NMR data, corresponding to eight degrees of unsaturation. The IR spectrum also showed that compound **2** possessed the moieties of aromatic ring A (1617, 585 cm^{-1}), conjugated ester carbonyl (1674 cm^{-1}), and hydroxyl (3439 cm^{-1}). Compound **2** was determined to be the 1,2,3,5-tetrasubstituted benzene derivatives similar to compound **1**, as supported by the 2 D NMR analysis. HMBC correlations from H-6 to C-4 (δ_C, 194.5), C-5 (δ_C, 133.4), C-7, C-8 and C-10, from proton-methoxyl (δ_H 3.93, s) to C-7, from H-8 to C-7, C-9 and C-10, from H_2-2 (3.45, d, $J = 17.5$ Hz; 3.04, d, $J = 17.6$ Hz) to C-3 and C-4, from proton-methyl (H_3-3a, δ_H 1.59, s) to C-3 and C-4 (Supplementary material Figure S1) suggested that compound **2** bore rings A and C similar with those of compound **1**. The HMBC correlations from methoxyl proton (δ_H 3.58, s) to C-1 (δ_C, 171.6) and from H_2-2 to C-1,

C-3 and C-4 offered solid evidence that the side chain containing three carbons as depicted in Figure 1 was attached to C-3 of C ring. Therefore, compound **2** was elucidated as alternate B.

Compound **3** was isolated as white powder, and had the molecular formula $C_{16}H_{16}O_6$ determined by HR-EI-MS with nine degrees of unsaturation. Due to nine degrees of unsaturation, the ^{1}H NMR data (δ_H 6.21–6.70, 4H) and the ^{13}C NMR data (δ_C 100.0–165.0, 12 C) in **3** suggested compound **3** possessed two benzene moieties. This deduction was supported by further analysis of the HMBC spectrum. HMBC correlations from H-6 (δ_H 6.21, d, $J = 2.6$ Hz) to C-2 (δ_C 105.3), C-5 (δ_C 163.8) and C-8 (δ_C 135.2), from H-4 (δ_H 6.47, d, $J = 2.6$ Hz) to C-2, C-3 (δ_C 164.4) and C-6 (δ_C 110.9), from H-9 (δ_H 6.56, s) to C-7 (δ_C 140.5), C-11 (δ_C 145.6) and C-13 (δ_C 127.8), from H-12 (δ_H 6.70, s) to C-11 and C-13, indicated that the two benzene rings were linked to each other via C-7 and C-8. The HMBC correlation from methoxyl proton (δ_H 3.48, s) to C-1 (δ_C 171.4) along with the ^{13}C NMR signals C-2 (δ_C 105.3) and C-7 (δ_C 140.5) suggested the linkage of methoxycarbonyl to C-2. The HMBC correlations from methoxyl proton (δ_H 3.81, s) to C-5 and from H_3-14 to C-8, C-12 (δ_C 116.1) and C-13 suggested the methoxyl was linked to C-5 and the methyl was linked to C-13, respectively. In view of planar structures, compound **3** was eventually elucidated to be the esterified product of alutenusin (Uchida et al. 1999) and altenusin (Singh et al. 2003). Compound **3** was eventually named as alternate C.

Compound **4**, yellow oil, had the molecular formula $C_{13}H_{12}O_3$ based on HR-ESI-MS spectrum. Analysis of ^{1}H and ^{13}C NMR data revealed the presence of two methyls (at $\delta_{C\text{-}3'}$ 18.6, δ_H 1.96, s; $\delta_{C\text{-}4'}$ 23.1, δ_H 2.70, s), five olefinic methines (at $\delta_{C\text{-}3}$, 110.0, δ_H 5.89, s; $\delta_{C\text{-}6}$, 118.0, δ_H 6.62, br d, $J = 2.3$ Hz; $\delta_{C\text{-}8}$, 101.7, δ_H 6.68, br d, $J = 2.3$ Hz; $\delta_{C\text{-}1'}$, 124.7, δ_H 6.25, ddd, $J = 15.6$, 3.2, 1.6 Hz; $\delta_{C\text{-}2'}$, 137.3, δ_H 6.83, m), six olefinic quaternary carbons (at $\delta_{C\text{-}2}$ 162.0, $\delta_{C\text{-}4a}$ 116.0, $\delta_{C\text{-}5}$ 143.6, $\delta_{C\text{-}7}$ 163.4, $\delta_{C\text{-}8a}$ 160.9, one carbonyl at $\delta_{C\text{-}4}$ 182.3). Further analysis of 2 D NMR spectra suggested that compound **4** possessed the chromatic skeleton and to be the analogue of 7-hydroxy-2-hydroxymethyl-5-methyl-4*H*-chromen-4-one (Kimura et al. 1992). The only difference between compound **4** and 7-hydroxy-2-hydroxymethyl-5-methyl-4*H*-chromen-4-one was that the hydroxymethyl in the latter was replaced with propenyl group in **4**. HMBC correlations from H_3-3′ to C-2′ and C-1′, from H-1′ to C-2, and from H-3 to C-1′ verified the linkage of propenyl to C-2, as drawn in Supplementary material Figure S1. The coupling constant (15.6 Hz) between H-1′ and H-2′ indicated the *E* configuration for the $\Delta^{1',2'}$ double bond. Ultimately, compound **4** was assigned as alternate D.

Compound **5** was obtained as white cubic crystal. Its molecular formula $C_{11}H_{19}NO_4$, with three indices of hydrogen deficiency, was established from HR-ESI-MS. Its ^{13}C NMR data showed eleven carbon signals in compound **5**, involving three quaternary carbons (two carbonyls at $\delta_{C\text{-}1}$ 175.3, $\delta_{C\text{-}6}$ 169.7 and one olefinic carbon at $\delta_{C\text{-}8}$ 151.6), one methine (olefinic carbon at $\delta_{C\text{-}7}$ 120.8), five methylenes (at $\delta_{C\text{-}2}$ 32.1, $\delta_{C\text{-}3}$ 25.8, $\delta_{C\text{-}4}$ 39.2, $\delta_{C\text{-}9}$ 44.5 and $\delta_{C\text{-}10}$ 60.8) and two methyls (at $\delta_{C\text{-}8a}$ 18.4, one methoxyl at δ_C 52.0). The COSY correlations of H_2-2 (δ_H 2.35, m)/H_2-3 (δ_H 1.79, m)/H_2-4 (δ_H 3.21, t, $J = 6.9$ Hz) and H_2-9 (δ_H 2.31, t, $J = 6.6$ Hz)/H_2-10 (δ_H 3.68, t, $J = 6.6$ Hz) showed two isolated spin systems. And the HMBC correlations from H_3-8a to C-8, C-7 and C-9 confirmed the existence of oxygenated prenyl group. The key HMBC correlations from H_2-4 to C-6

confirmed the linkage of amide group. Also, HMBC correlations from the methoxyl proton to C-1, from H_2-2 to C-1, along with the above deductions constituted the compound **5** depicted in Figure 1. Compound **5** was thus elucidated as alteamide.

Herein, four known natural products (**6**–**9**) were also isolated from *Alternaria alternata*, elucidated as djalonensone (Sun et al. 2013), 3-Hydroxyalternariol 5-O-methyl ether (Aly et al. 2008), altenuisol (Tian et al. 2017) and 1-deoxyrubralactone (Naganuma et al. 2008) referring to corresponding literature.

Given the fact that compounds **1–4** are structurally related to Porritoxins, proved to be anti-tumour-promoting active compounds (Tokuda et al. 2006), compounds **1–4** were tested for cytotoxic activities against five selected tumour cell lines (human lung adenocarcinoma A-549 cell, breast cancer MDA-MB-231 and MCF-7 cells, nasopharyngeal carcinoma KB and KB-VIN cells). Compound **3** showed activities against MDA-MB-231 and MCF-7 with IC_{50} values of 20.1 μM and 32.2 μM, respectively, while other novel compounds were inactive ($IC_{50} > 40$ μM).

3. Experimental

3.1. General experimental procedures

Optical rotations were recorded on a JASCO P-1020 digital polarimeter (Horiba, Kyoto, Japan). UV/Vis spectra were obtained using a Shimadzu UV2401PC spectrometer (Shimadzu, Kyoto, Japan). IR spectra were obtained using a Bruker Tensor 27 FT-IR spectrometer (Bruker Optics, Inc., Billerica, MA) with KBr pellets. 1 D and 2 D NMR spectra were measured on a Bruker Avance III 500 MHz spectrometers (Bruker Biospin GmbH, Karlsruhe, Germany). HRESIMS were recorded on an Agilent 6200 Q-TOF MS system (Agilent Technologies, Santa Clara, CA, USA). HREIMS were recorded on a Waters AutoSpec Premier P776 MS system. Silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd, P. R. China) and Sephadex LH-20 (Amersham Biosciences, Sweden) were used for column chromatography. (Medium Pressure Liquid Chromatography) MPLC was performed on a Büchi Sepacore System equipped with pump manager C-615, pump modules C-605 and fraction collector C-660 (Büchi Labortechnik AG, Switzerland), and columns packed with Chromatorex C18 (40–75 mm, Fuji Silysia Chemical Ltd., Japan). Preparative HPLC was performed on an Agilent 1260 liquid chromatography system equipped with two types of Zorbax SB-C18 columns (9.4 mm $\times$ 150 mm and 21.2 mm $\times$ 150 mm, particle size 5 μm).

3.2. Fungal material, fermentation, extraction and isolation

The isolation, identification and fermentation of *A. alternata* along with the extraction and preliminary purification towards its culture were described previously (Wang et al. 2019).

Fr. A was subjected to normal-phase silica gel column with an isocratic elution of petroleum/acetone (20:1, v/v) to obtain eleven subfractions (A1–A11) based on TLC analysis. Fr. A11 was then eluted isocratically with petroleum/acetone (10:1, v/v) through silica gel column and then subjected to prep-HPLC using a gradient elution (MeCN-H_2O 20%–70%, 7 mL·min^{-1}, 20 min) to obtain compound **5** (3.3 mg). Fractions

D, F, G and J were subjected by silica gel column with an isocratic elution of petroleum/acetone (10:1, v/v) to obtain ten subfractions Fr. D1–10, Fr. F1–6, Fr. G1–8 and Fr. J1–13. Fr. D7 was subjected to Sephadex LH-20 ($CHCl_3$/MeOH 1:1, v/v) to yield compound **3** (3.3 mg). Fr. D8 was eluted via silica gel column with petroleum/acetone (10:1, v/v), and purified by Sephadex LH-20 (MeOH), then subjected to HPLC with a gradient elution (MeCN/H_2O 20%–45%, 7 mL·min^{-1}, 40 min) to eventually obtain compound **8** (1.1 mg). Compound **1** (4.2 mg) was obtained from Fr. F1 sequentially subjected to silica gel column with an isocratic elution of petroleum/acetone (20:1, v/v), HPLC using a gradient elution (MeCN-H_2O 20%–70%, 7 mL·min^{-1}, 20 min) and purified by Sephadex LH-20 (acetone). Compound **2** (2.1 mg) was yielded from Fr. G3 by HPLC using a gradient elution (MeCN-H_2O 27%–38%, 7 mL·min^{-1}, 30 min). Compound **4** (2.8 mg) was obtained from Fr. G4 by HPLC with a gradient elution (MeCN-H_2O 21%–24%, 7 mL·min^{-1}, 35 min). Compound **9** (1.6 mg) was obtained from Fr. G6 subjected to HPLC with a gradient elution (MeCN-H_2O 30%–45%, 7 mL·min^{-1}, 35 min) and then purified by Sephadex LH-20 (acetone). Fr. I was eluted by silica gel column with an elution of petroleum/acetone (10:1, v/v) to obtain the sediment, which was recrystallized and purified by Sephadex LH-20 (MeOH) to obtain compound **6** (5.2 mg). Compound **7** (4.1 mg) was obtained from Fr. J9 by HPLC with a gradient elution (MeCN-H_2O 33%–55%, 7 mL·min^{-1}, 30 min).

Alternate A (**1**): White powder; $[\alpha]_D^{23.4}$ −1.8° (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 322 (3.69), 280 (3.94), 242 (4.44), 198 (4.08) nm; IR (KBr) υ_{max} 3440, 2929, 1654, 1621, 583 cm^{-1}; ^{1}H and ^{13}C NMR data see Supplementary material Table S1; HRESIMS: *m/z* 329.0997 $[M + Na]^+$ (calcd for $C_{16}H_{18}O_6Na$, 329.0996).

Alternate B (**2**):Yellow oil; $[\alpha]_D^{23.8}$ −17.9° (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) 199 (4.06), 235 (4.39), 248 (4.26), 283 (3.66), 340 (3.66) nm; IR (KBr) υ_{max} 3439, 2955, 1674, 1617, 1383, 585 cm^{-1}; ^{1}H and ^{13}C NMR data see Supplementary material Table S2; HRESIMS: *m/z* 317.0629 $[M + Na]^+$ (calcd for ($C_{14}H_{14}O_7Na$, 317.0632).

Alternate C (**3**): White powder; $[\alpha]_D^{23.1}$ −20.3° (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ε) 296 (3.78), 256 (4.00), 208 (4.46) nm; IR (KBr) υ_{max} 3421, 2951, 1611, 786 cm^{-1}; ^{1}H and ^{13}C NMR data see Supplementary material Table S3; HREIMS: m/z 304.0936 $[M]^+$ (calcd for $C_{16}H_{16}O_6$, 304.0947).

Alternate D (**4**): Yellow oil; UV (MeOH) λ_{max} (log ε) 306 (4.10), 256 (4.16), 237 (4.13), 208 (4.35) nm; IR (KBr) υ_{max} 3430, 2926, 1626, 1390, 1117, 589 cm^{-1}; ^{1}H and ^{13}C NMR data, see Supplementary material Table S4; HRESIMS: *m/z* 215.0717 $[M–H]^-$ (calcd for $C_{13}H_{11}O_3$, 215.0714).

Alteamide (**5**): White cubic crystal; UV (MeOH) λ_{max} (log ε) 219 (3.96), 195 (3.66) nm; IR (KBr) υ_{max} 3382, 3310, 2949, 1736, 1631, 1172 cm^{-1}; ^{1}H and ^{13}C NMR data, see Supplementary material Table S5; HRESIMS: *m/z* 252.1201 $[M + Na]^+$ (calcd for $C_{11}H_{19}NO_4Na$, 252.1206).

3.3. Cytotoxicity assay in vitro

The bioactivities against five human tumour cells (human lung adenocarcinoma A549 cell, breast cancer MDAMB-231 and MCF-7 cells, nasopharyngeal carcinoma KB and KB-VIN cell lines) provided by the Natural Products Research Center in the University

of North Carolina at Chapel Hill were performed as previously described (Wang et al. 2018; Zhang et al. 2018).

4. Conclusion

Aimed at exploring the diversity of molecules in fungus *Aternaria alternata*, chemical investigation on the species led to the isolation and identification of five new natural compounds along with four known ones, featuring dibenzo-α-pyrone derivatives, a benzo-γ-pyrone derivative and an amide-type compound. The structures of these compounds were assigned on the basis of in-depth analysis of the spectroscopic data. Still, it was a pity that the absolute structures of the dibenzo-α-pyrone derivatives remained to be identified. Compounds **1–4** were evaluated for cytotoxic activities against five selected human tumour cell lines, and compound **3** exhibited moderate cytotoxic activities against tumour cell lines.

Considering the fact that only compound **3** showed certain cytotoxicities against tumour cell lines among compounds **1–4** and comparing the structures of compounds **1** and **3** with structures of compounds in literatures (Aly et al. 2008; Wang et al. 2014), B ring of benzene seemed to be a necessity for the cytotoxic activities; the presence of C ring, the lactone ring may increase the activities, but not the demanding part.

Disclosure statement

The authors declare no competing financial interest.

Funding

This work was financially supported by the special project to guide the Development of Local Science and Technology in Anhui Province (grant number 18030801128), Key Project in Natural Science Research among Colleges in Anhui Province (grant number KJ2019A0462) and Key Project in Natural Science Research among Colleges in Anhui Province (grant number KJ2019A0477).

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