Thiazolo[5,4-b]pyridine Alkaloid and Seven *ar*-Bisabol Sesquiterpenes Produced by the Endophytic Fungus *Penicillium janthinellum*

Wen-Jing Wang,[†] Liang-Xiu Liao,[†] Ze-Diao Huang, Fu-Ting Wei, and Xiao-Long Yang*

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Taxus wallichiana var. *chinensis* (Pilger) Florin

Penicillium janthinellum
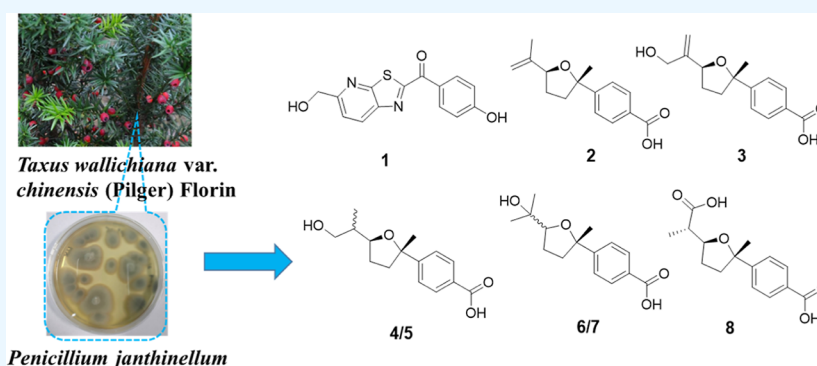
ABSTRACT: We investigated the secondary metabolites present in *Penicillium janthinellum* MPT-25, an endophytic fungus isolated from *Taxus wallichiana* var. *chinensis* (Pilger) Florin. Chemical characterization of the solid cultured extract resulted in the isolation of 11 compounds, including eight previously undescribed metabolites: a thiazolo[5,4-b]pyridine alkaloid, janthinedine A (**1**), and seven *ar*-bisabol sesquiterpenes, janthinepenes A–G (**2−8**). Their structures were elucidated by a combination of extensive spectroscopic methods, including single-crystal X-ray diffraction and ECD spectra. The antimicrobial activities of these compounds were evaluated against seven agricultural pathogenic fungi and eight clinically drug-resistant bacteria.

■ INTRODUCTION

Plant endophytic fungi can inhabit various types of healthy tissues in host plants without causing disease symptoms.[1] The mutually beneficial symbiotic relationship between host plants and their endophytic fungi has been established due to a long period of co-evolution and, consequently, endowed with the ability of fungi to encode biologically active metabolites with distinctive scaffolds.[2−6] Since Strobel discovered the "gold" bioactive compound taxol from an endophytic fungus acquired from the phloem of *Taxus brevifolia*, endophytic fungi have received increasing attention as potential producers of peculiar and bioactive metabolites.[7] Furthermore, the endophytic fungus *Fusarium proliferatum* (MTCC 9690), isolated from *Dysoxylum binectariferum*, can produce the same chromane alkaloid, rohitukine, as the host plant, which suggests that the metabolites generated by endophytic fungi are potential candidates for natural medicines that can be directly isolated from plant tissues.[8] Additionally, chemical investigations on endophytic fungi have provided new methods to solve the problem of shortage of some natural plants.[9]

Owing to our interest in antimicrobial compounds extracted from endophytic fungi, the strain MPT-25, which was obtained from the stems of *Taxus wallichiana* var. *chinensis* (Pilger)

Florin and identified as *Penicillium janthinellum*, has attracted our attention. *P. janthinellum* produces diverse metabolites, including brefeldin A (BFA) derivatives,[10−12] alkaloids,[13−20] azaphilones,[21,22] terpenoids,[23,24] meroterpenoids,[25] restricticin derivatives,[26] and heterocyclic dipeptides,[27,28] and exhibits extensive antitumoral,[10,12,19] antibacterial,[15,16,18,21] and cyto-protective activities.[27,28] A phytochemical investigation on the EtOAc extract of this fungus led to the isolation of 11 metabolites: janthinedine A (**1**), janthinepenes A–G (**2−8**), and three known compounds (**9−11**). Janthinedine A possesses a thiazolo[5,4-b]pyridine skeleton[29] and janthine-penes A–G belong to a medicinally interesting class of sesquiterpenes—*ar*-bisabol sesquiterpenes.[30,31] Herein, the detailed isolation and structural elucidation, in addition to the antimicrobial activities, are described.
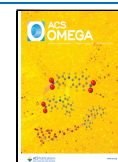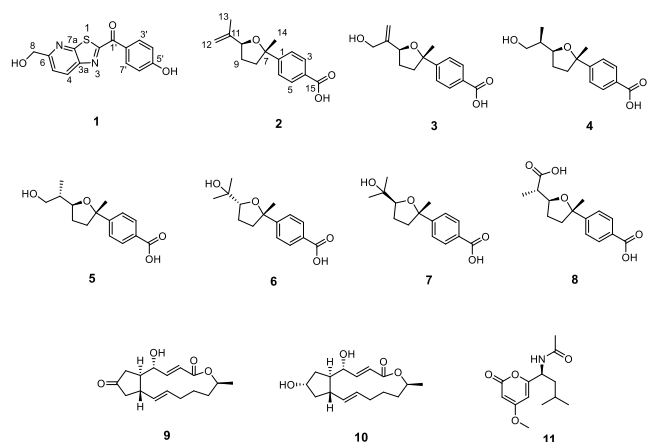
RESULTS AND DISCUSSION

Janthinedine A (**1**) was isolated as yellow crystals. The molecular formula of $C_{14}H_{10}N_2O_3S$ with 11 degrees of unsaturation was deduced by positive high-resolution electrospray ionization mass spectrometry (HRESIMS), with an ion peak at m/z 287.04841. Data analysis of ^1H, ^{13}C, and heteronuclear single-quantum correlation (HSQC) NMR spectra (Table 1) revealed the presence of a para-substituted benzene moiety, with significant signals at δ_H 8.53 (2H, d, J = 8.9 Hz) and 6.93 (2H, d, J = 8.9 Hz); δ_C 165.4 (C-5′), 135.3 (C-3′), 135.3 (C-7′), 127.1 (C-2′), 116.5 (C-4′), and 116.5 (C-6′). The other signals displayed one ketone carbonyl carbon at δ_C 183.8 (C-1′); four sp² quaternary carbons at δ_C

Table 1. ^1H (500 MHz) and ^{13}C (125 MHz) NMR Data of Compound 1 in CD₃OD

no.	δ_H (J in Hz)	δ_C	no.	δ_H (J in Hz)	δ_C
2		169.4	1′		183.8
3a		147.5	2′		127.1
4	8.57 d (8.5)	134.6	3′	8.53 d (8.9)	135.3
5	7.80 d (8.5)	120.9	4′	6.93 d (8.9)	116.5
6		163.7	5′		165.4
7a		159.2	6′	6.93 d (8.9)	116.5
8	4.85 s	65.8	7′	8.53 d (8.9)	135.3

169.4 (C-2), 163.7 (C-6), 159.2 (C-7a), and 147.5 (C-3a); two sp² methines [δ_H 8.57 (1H, d, J = 8.5 Hz), δ_C 134.6 (C-4); 7.80 (1H, d, J = 8.5 Hz), δ_C 120.9 (C-5)]; and one oxygenated methylene at δ_H 4.85 (2H, s) and δ_C 65.8 (C-8). The heteronuclear multiple-bond correlations (HMBC) from H-3′ (H-7′) to C-1′ and C-5′ and from H-4′ (H-6′) to C-2′, demonstrated the presence of the 4-substituted benzoyl group. Furthermore, the thiazolopyridine moiety, similar with phenyl-(thiazolo[5,4-b]pyridin-2-yl)methanone,[32] was supported by the correlation spectroscopy (COSY) cross-signal of H-4/H-5; HMBC correlations of H-4 with C-6 and C-7a and H-5 with C-3a, C-6, and C-7a (Figure 1); and the molecular formula. Correlations of H-8 with C-5 and C-6 in the HMBC spectrum indicated that the oxygenated methyl unit was located at C-6. Therefore, the skeleton structure of compound **1** was composed of a 4-substituted benzoyl group and a 2-substituted thiazolo[5,4-b]pyridin-5-ylmethanol. According to the similar chemical shifts of **1** [δ_C 183.8 (C-1′), 169.4 (C-2)] and phenyl(thiazolo[5,4-b]pyridin-2-yl)methanone [δ_C 185.3 (C-1′), 167.8 (C-2)], the benzoyl group was assigned to C-2. Then, a hydroxyl group was attached to the benzoyl group based on the molecular formula. Successful crystallization and subsequent X-ray diffraction (Figure 2) allowed for unambiguous determination of the entire structure of **1**.
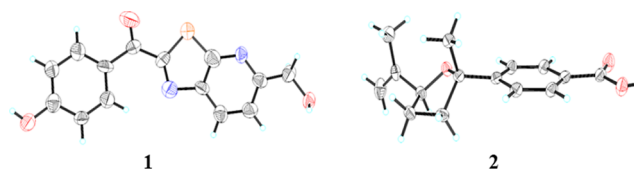

Figure 2. X-ray ORTEP drawing of compounds **1** and **2**.

Janthinepene A (**2**) was obtained as colorless crystals. The negative-mode HRESIMS spectrum of **2** displayed an [M − H]⁻ ion peak at m/z 245.11912, corresponding to a molecular formula of $C_{15}H_{18}O_3$ with 13 indices of hydrogen deficiency. The ^1H NMR resonance signals (Table 2) indicated one 1,4-disubstituted benzene ring with a coupling pattern of [δ_H 7.98 (2H, d, J = 8.4 Hz) and 7.51 (2H, d, J = 8.4 Hz)] and one terminal double bond [δ_H 5.07 (1H, s) and 4.85 (1H, s)]. In
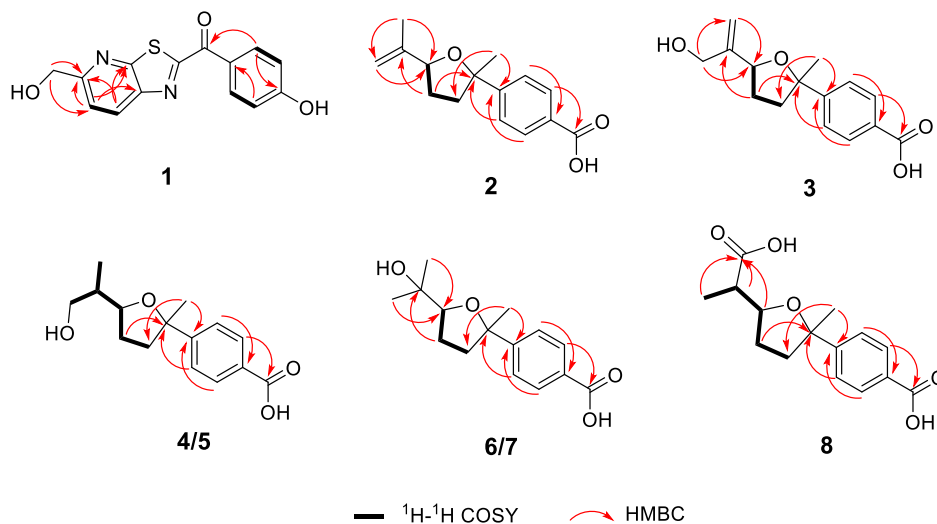

Figure 1. Key ^1H–^1H COSY and HMBC correlations of compounds **1**−**8**.

Table 2. ^{1}H NMR Data for Compounds 2−8 (500 MHz, CD$_3$OD)

no.	2	3	4	5	6	7	8
2	7.51 d (8.4)	7.52 d (8.5)	7.49 d (8.4)	7.48 d (8.4)	7.56 d (8.4)	7.50 d (8.4)	7.49 d (8.5)
3	7.98 d (8.4)	7.98 d (8.5)	7.96 d (8.4)	7.96 d (8.4)	7.95 d (8.4)	7.96 d (8.4)	7.95 d (8.5)
4							
5	7.98 d (8.4)	7.98 d (8.5)	7.96 d (8.4)	7.96 d (8.4)	7.95 d (8.4)	7.96 d (8.4)	7.95 d (8.4)
6	7.51 d (8.4)	7.52 d (8.5)	7.49 d (8.4)	7.48 d (8.4)	7.56 d (8.4)	7.50 d (8.4)	7.49 d (8.5)
8α	2.23 m	2.24 dt (12.3, 7.1)	2.21 dt (12.4, 7.5)	2.19 dt (12.4, 7.7)	2.19 m	2.23 m	2.22 dt (12.4, 7.4)
8β	2.14 m	2.16 m	2.11 ddd (12.4, 8.2, 6.2)	2.14 m	2.07 m	2.09 m	2.15 m
9α	1.94 m	1.92 m	1.85 m	1.88 m	2.04 m	1.93 m	1.91 m
9β	1.85 m	2.00 m	1.82 m	1.80 m	1.87 m	1.73 m	1.80 m
10	4.46 t (7.1)	4.58 t (7.1)	3.98 dd (13.7, 6.3)	3.87 dd (14.9, 7.4)	4.00 t (7.1)	3.82 t (7.2)	4.17 dd (15.0, 7.2)
11			1.79 m	1.84 m			2.57 m
12	5.07 s	4.16 s	3.65 dd (10.7, 5.8)	3.77 dd (10.7, 5.2)	1.19 s	1.22 s	1.16 d (7.0)
	4.85 s		3.48 dd (10.7, 6.7)	3.54 dd (10.7, 6.4)			
13	1.78 s	5.25 s	1.06 d (6.8)	0.95 d (6.9)	1.21 s	1.25 s	
		5.17 s					
14	1.56 s	1.56 s	1.49 s	1.50 s	1.49 s	1.52 s	1.50 s

combination with the HSQC data, signals were observed corresponding to one carbonyl carbon [δ_C 170.1 (C-15)], two olefinic carbons [δ_C 147.2 (C-11) and 110.0 (C-12)], one oxygenated methine [δ_H 4.46 (1H, t, J = 7.1 Hz); δ_C 83.7 (C-10)], one oxygenated tetrasubstituted carbon [δ_C 86.3 (C-7)], two sp^3 methylenes [δ_H 2.23 (1H, m), 2.14 (1H, m), 1.94 (1H, m), and 1.85 (1H, m); δ_C 40.2 (C-8), 31.8 (C-9)], and two methyl groups [δ_H 1.78 (3H, s) and 1.56 (3H, s); δ_C 30.3 (C-14), 18.3 (C-13)] in ^{13}C NMR (Table 3) and DEPT spectra.

Table 3. ^{13}C (125 MHz) NMR Data of Compounds 2−8 in CD$_3$OD

no.	2	3	4	5	6	7	8
1	154.9	155.0	154.8	155.0	154.3	154.5	154.7
2	125.8	125.8	125.6	125.7	125.7	125.7	125.7
3	130.8	130.8	130.7	130.7	130.4	130.7	130.7
4	125.8	125.8	125.6	125.7	125.7	125.7	125.7
5	130.8	130.8	130.7	130.7	130.4	130.7	130.7
6	125.8	125.8	125.6	125.7	125.7	125.7	125.7
7	86.3	86.1	85.6	85.3	85.8	86.0	86.0
8	40.2	40.1	40.4	40.6	40.3	40.4	40.3
9	31.8	32.4	30.3	30.2	27.4	27.5	29.9
10	83.7	81.1	82.8	81.8	86.5	86.9	82.0
11	147.2	151.2	42.5	41.9	72.8	72.5	47.2
12	110.0	63.3	66.2	65.9	25.6	25.8	14.0
13	18.3	110.0	13.4	12.9	26.3	25.9	179.7
14	30.3	30.3	30.8	30.6	28.9	30.4	30.7
15	170.0	169.8	171.0	170.4	172.8	171.4	171.1

The aforementioned data suggested that **2** was an *ar*-bisabol sesquiterpene similar to (+)-sielboldianin B.[30,31] Further analysis of the 2D NMR spectra indicated the planar structure. ^{1}H−^{1}H COSY correlations between H-8/H-9/H-10 of the spin system and HMBC correlations of H-12 with C-10/C-13, H-13 with C-10/C-12, H-10 with C-12/C-13, and H-9 with C-11 demonstrated the location of the isopropenyl fragment at C-10 (Figure 1). Moreover, a carboxyl unit was connected to the benzene ring based on the key HMBC correlation of H-3 (H-5) with C-15. Thus, the planar structure of **2** was determined, as shown. To understand the relative configuration, we acquired the nuclear Overhauser effect spectroscopy (NOESY) spectrum of **1**. The observed NOESY correlations between H-10 and H-8α/H-12/H-2 and between H$_3$-14 and H-9β indicated that H-10, H-8α, and the benzene ring were found in a co-facial orientation on the tetrahydrofuran ring, while H$_3$-14 and H-9β were on the opposite side (Figure 3). The X-ray diffraction experiment using Ga Kα radiation with a Flack parameter of 0.01(4) confirmed the 7S,10S absolute configuration of compound **2** (Figure 2).

Janthinepene B (**3**) was a colorless oil with a molecular formula of C$_{15}$H$_{18}$O$_4$, which was confirmed by the (−)-HRESIMS ion peak at m/z 261.11433 [M − H]$^-$ [calcd for C$_{15}$H$_{17}$O$_4$ (261.11268)], indicating seven degrees of unsaturation. The ^{1}H and ^{13}C NMR data (Tables 2 and 3) of **3** closely resemble those of **2**, indicating their structural similarity. However, these 1D NMR data, in conjunction with the HSQC spectrum, revealed that compound **3** has one less methyl group but one additional oxygenated methylene signal
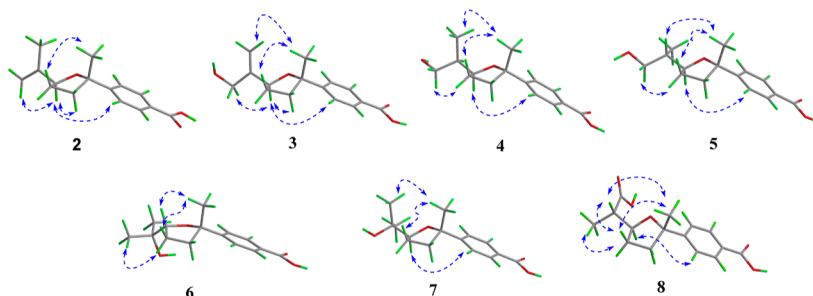

Figure 3. Key NOESY correlations of compounds 2−8.

[δ_H 4.16 (2H, s); δ_C 63.3 (C-12)] compared with **2**. We further constructed the planar structure of **3** by 2D NMR spectroscopic analysis (Figure 1). Key HMBC correlations of H-12 (δ_H 4.16) with C-10/C-13 and of H-13 (δ_H 5.25, 5.17) with C-10/C-12, indicated that the C-12 position was oxygenated and the terminal double bond was between C-11 and C-13. Thereby, we established the planar structure of **3**, as depicted. In addition, the obvious NOESY correlations between H-10 and H-8α/H-13/H-2 and between H$_3$-14 and H-12/H-9β revealed that **3** and **2** share the same relative configurations (Figure 3). Finally, the absolute stereochemistry was deduced based on the similar ECD (electronic circular dichroism) curves of **2** and **3** (Figure 4).
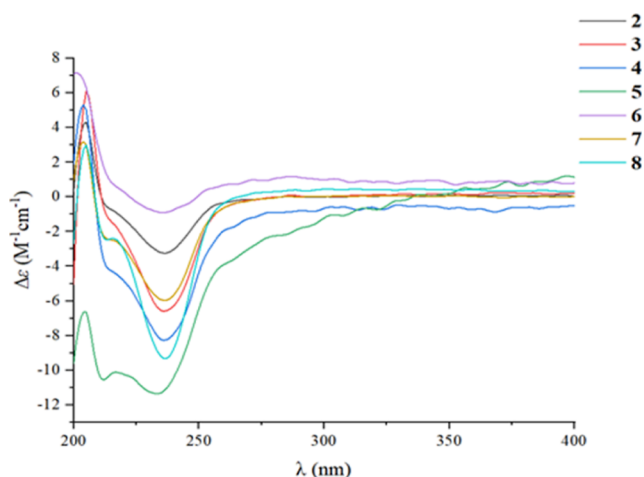

Figure 4. Experimental ECD spectra of janthinepenes A−G (**2−8**) in MeOH.

Janthinepenes C (**4**) and D (**5**) shared the same molecular formula of $C_{15}H_{20}O_4$, shown by the (+)-HRESIMS ion peaks at m/z 265.14340 [M + H]$^+$ [calcd for $C_{15}H_{21}O_4$ (265.14398)]. The ^{1}H and ^{13}C NMR data (Tables 2 and 3) of **4** and **5** closely resembled those of **2**, evidencing their structural similarity. ^{1}H−^{1}H COSY spectra displayed the spin systems of H-12/H-11/H-10/H-9/H-8 and H$_3$-13/H-11 in combination with the molecular formula, and the location of the isopropanol group was determined as C-10 in compounds **4** and **5** (Figure 1). Further interpretation of the 2D NMR spectra indicated they possessed the same planar structure. The relative stereochemistry of the tetrahydrofuran ring was determined to be the same as in the aforementioned ar-bisabol sesquiterpenes based on key NOESY correlations between H-10 and H-2 and between H-9β and H$_3$-14 in **4** and **5**. The NOESY correlations between H-12 and H-9 and between H$_3$-13 and H$_3$-14 in **4**, while NOESY correlations of H-12/H-9 and H-11/H$_3$-14 in **5**, suggested that the relative configurations of C-11 was as shown. Additionally, we ultimately determined the absolute stereochemistry of **4** and **5** based on the similarities in their ECD curves with those of **2** (Figure 4).

The molecular formula of janthinepenes E (**6**) and F (**7**) was determined to be $C_{15}H_{20}O_4$ based on their HRESIMS data—the same as for **4** and **5**. Subsequent comparison of the 1D NMR data (Tables 2 and 3) confirmed that **6** and **7** contain an additional methyl and an oxygenated tetrasubstituted carbon (**6**: δ_C 72.8; **7**: δ_C 72.5), replaying the methine and oxygenated methylene groups in **4** and **5**. In HMBC spectra, cross-peaks from H$_3$-12/H$_3$-13 to C-10 and H-9 to C-

11 indicated that a propane-2,2-diyl-2-ol unit was located at C-10. Thus, we determined the planar structures of **6** and **7**. As shown in Figure 4, the NOESY cross-peaks from H$_3$-14 to H-10/H-9β and H$_3$-12 to H-9α/H-9β in **6** and from H-10 to H-2 and H$_3$-14 to H$_3$-12/H-9β in **7** indicated the relative configurations. Finally, the similar ECD curves of these ar-bisabol sesquiterpenes allowed us to determine the absolute configurations as 7*S*,10*R* in **6** and 7*S*,10*S* in **7**.

Janthinepene G (**8**) has a molecular formula of $C_{15}H_{18}O_5$, with seven degrees of unsaturation. The 1D NMR data revealed that **8** was an ar-bisabol sesquiterpene equipped with the same 4-(tetrahydrofuran-2-yl)benzoic acid unit. Meanwhile, extensive analysis of the 2D spectra indicated isopropionic acid connected to C-10 based on ^{1}H−^{1}H COSY correlations of H-8/H-9/H-10/H-11/H$_3$-12 and HMBC cross-peaks from H-10/H-11/H$_3$-12 to C-13. Hence, the planar structure of **8** was established. The relative configuration of the *p*-furanbenzoic acid skeleton was similar to that of **2−5** based on the NOESY cross-peaks of H-10 to H-2 and H-9β to H$_3$-14. Furthermore, the NOESY correlations between H$_3$-12 and H-9 and between H-11 and H-9β/H$_3$-14 indicated the relative stereochemistry of C-11. As these ar-bisabol sesquiterpenes should share the same biosynthetic pathway in these fungi and the similar optical rotations and ECD curves, we presumed that the absolute configuration of the tetrahydrofuran ring was 7*S*,10*S*.

In addition to the new structures described above, we confirmed the presence of three known compounds (**9−11**) as 7-dehydrobrefeldin A (**9**),[11] BFA (**10**),[33] and campyrone B (**11**)[34] through a comparison of their spectroscopic data with values in the literature.

The antimicrobial activities of compounds **1−11** were evaluated against eight clinically drug-resistant bacteria and seven agricultural pathogenic fungi. Compound **9** showed weak antifungal activity against *Alternaria fragriae*, with an MIC value of 25 μg/mL, and compound **10** exhibited moderate antifungal activity against *A. fragriae*, with an MIC value of 12.5 μg/mL (Table S1). None of the evaluated compounds were active against the selected drug-resistance bacteria (Table S2).

To summarize, we isolated 11 metabolites including eight previously uncharacterized structures, janthinedine A (**1**) and janthinepenes A−G (**2−8**), from the endophytic fungus *P. janthinellum*. Janthinedine A represents the first example of a natural product featuring the novel thiazolo[5,4-*b*]pyridine skeleton, and the ar-bisabol sesquiterpenes were first obtained from *P. janthinellum*.[35−40] The evaluation of the antimicrobial activities revealed that compounds **9** and **10** possess weak antifungal capabilities. Our findings indicate that plant endophytic fungi are an important source of new natural products with potential antimicrobrial applications.

■ EXPERIMENTAL SECTION

General Experimental Procedures. A WRX-4 micromelting point apparatus was used to record the melting points (Changzhou Dedu Inc., Changzhou, China). An Autopol IV automatic polarimeter equipped with a 1.0 mL cell was arranged to measure optical rotations (Rudolph Research Analytical, Hackettstown, NJ, U.S.A.). An IRTracer-100 spectrophotometer was used to record IR spectra (Shimadzu, Kyoto, Japan). UV spectra were acquired using a UH5300 spectrophotometer (Hitachi Limited, Tokyo, Japan). A Chirascan plus circular dichroism spectrophotometer was applied to obtain the ECD data (Applied Photophysics Ltd,

Leatherhead, Surrey, U.K.). An APEX-II CCD/BRUKER D8 QUEST diffractometer equipped with graphite-monochromatized Ga Kα radiation was arranged to measure the X-ray crystallography data (Bruker, Karlsruhe, Germany). HRESIMS data were obtained using a SolariX spectrometer (Bruker, Karlsruhe, Germany). 1D and 2D NMR spectra were recorded using a DRX-500 MHz spectrometer (Bruker, Karlsruhe, Germany). Chemical shifts are expressed in parts per million, with reference to the CD_3OD (δ_H 3.31/δ_C 49.0) signals. Compounds were purified on a Hanbon newstyle semi-preparative HPLC system equipped with a UV detector (Hanbon Sci. and Tech., Jiangsu, China). Silica gel (80−100, 100−200, and 200−300 mesh; Anhui Liangchen Inc., Anhui, China), ODS (50 μm; YMC, Kyoto, Japan), and Sephadex LH-20 (Pharmacia Biotech, Uppsala, Sweden) were used as the packing materials for column chromatography (CC). Medium-pressure liquid chromatography (MPLC) was applied using a Sanotac MP0502C system (Shanghai Sanwei Scientific Instrument Co., Ltd., Shanghai, China).

Fungal Material. The strain MPT-25 was isolated from the stems of *T. wallichiana* var. *chinensis* (Pilger) Florin, collected in Shijiazhuang, Hebei province, PR China, in September 2015, and then identified as *P. janthinellum* based on analysis and comparison of the ITS region of the rDNA sequence (GenBank accession no. MZ048774). The voucher strain is maintained at the School of Pharmaceutical Sciences, South-Central Minzu University.

Fermentation and Isolation. To prepare the seed culture, the strain *P. janthinellum* MPT-25 was cultivated on potato dextrose agar (PDA) for 7 days under 28 °C. We first filled each tissue culture flasks (500 mL) with 80 mL of distilled water and 100 g of rice and then sterilized by autoclaving. The PDA plates were cut into small pieces (approximately 0.5 × 0.5 × 0.5 cm^3) and inoculated into tissue culture flasks. A total of 400 flasks for fungal fermentation were used. After inoculation, all tissue cultures were statically incubated at 28 °C. After 38 days of fermentation, cultures were harvested from the flasks for chemical characterization. Rice medium was ultrasonically extracted with the same volume of CH_3CH_2OH five times to give a brown syrup, followed by suspending in H_2O and extracting with EtOAc to yield an crude extract (200 g).

The EtOAc extract (200 g) was separated by silica gel CC (100−200 mesh) and eluted with CH_2Cl_2−MeOH (100:1− 0:1, v/v) to give six fractions (Fr. A−F).

Fr. C (20.6 g) was chromatographed on reversed-phase ODS MPLC (MeOH−H_2O, 20:80−100:0) to afford six fractions (C1−C6). Fr. C3 was chromatographed on Sephadex LH-20 (CH_2Cl_2−MeOH 1:1) and followed by semi-preparative HPLC (MeOH−H_2O−HCOOH, 72:28:0.05, v/v) to yield **2** (12.7 mg, t_R = 19.0 min, 3.0 mL/min).

Fr. D (48.4 g) was chromatographed on reversed-phase ODS MPLC (MeOH−H_2O, 20:80−100:0) to obtain seven fractions (D1−D7). Fr. D2 was chromatographed on Sephadex LH-20 (MeOH) to obtain five subfractions (Fr. D2.1−Fr. D2.5). Fr. D2.1 was further purified by semi-preparative HPLC (MeCN−H_2O, 30:70, v/v) to yield **11** (20.5 mg, t_R = 21.0 min, 2.0 mL/min). Chromatography of Fr. D2.2 on a silica gel column was carried out, eluting with a gradient system of CH_2Cl_2−MeOH (100:1−70:1, v/v), followed by semi-preparative HPLC (MeOH−H_2O, 65:35, v/v) to yield **9** (2 mg, t_R = 17.0 min, 2.0 mL/min). Chromatography of Fr. D2.3 on a silica gel column was carried out, eluting with CH_2Cl_2− MeOH (70:1, v/v) to yield **3** (25.7 mg). Fr. D2.4 was further

purified on semi-preparative HPLC (MeCN−H_2O, 32:68, v/v) to yield **1** (11.8 mg, t_R = 26.0 min, 2.0 mL/min).

Fr. E (39.2 g) was separated by MPLC (MeOH−H_2O, 20:80−100:0) to obtain eight fractions (E1−E8). Fr. E4 was chromatographed on Sephadex LH-20 (MeOH) to give three subfractions (Fr. E4.1−Fr. E4.3). Chromatography of Fr. E4.2 on a silica gel column was carried out, eluting with a gradient of PE−EA (4:1−1:1, v/v) to give two subfractions (Fr. E4.2.1−Fr. E4.2.2). Fr. E4.2.1 was further purified by semi-preparative HPLC (MeCN−H_2O−HCOOH, 33:67:0.05, v/v) to yield **6** (1.1 mg, t_R = 18.0 min, 3.0 mL/min) and **7** (1.4 mg, t_R = 19.0 min, 3.0 mL/min). Chromatography of Fr. E4.3 on a silica gel column was carried out, eluting with a gradient of PE−EA−HAc (5:1:0.006, v/v) to offer four subfractions. Fr. E4.3.2 was further purified by semi-preparative HPLC (MeCN−H_2O−HCOOH, 35:65:0.05, v/v) to yield **4** (3.9 mg, t_R = 20.0 min, 2.0 mL/min) and **5** (3.0 mg, t_R = 23.0 min, 2.0 mL/min). Fr. E4.3.3 was further purified by semi-preparative HPLC (MeCN−H_2O−HCOOH, 30:70:0.05, v/v) to yield **8** (2.6 mg, t_R = 28.0 min, 3.0 mL/min). Fr. E4.3.4 was further purified using semi-preparative HPLC (MeCN− H_2O−HCOOH, 27:73:0.05, v/v) to yield **10** (3.4 mg, t_R = 37.0 min, 4.0 mL/min).

Janthinedine A (1). Yellow crystals, mp 189.4−226.4 °C, UV (MeOH) λ_{max} (log ε): 215 (4.11), 335 (4.04) nm; IR (KBr) ν_{max}: 1080, 1126, 1174, 1282, 1319, 1577, 1600, 2850, 2920 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESIMS m/z: 287.04841 [M + H]$^+$ (calcd for $C_{14}H_{11}N_2O_3S^+$, 287.04904).

Janthinepene A (2). White crystals, mp 121.4−122.6 °C, $[\alpha]_D^{20}$ −46.6 (c 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 235 (4.03) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 205 (4.31), 236 (−3.24) nm; IR (KBr) ν_{max}: 1541, 1558, 2360, 2924 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; HRESIMS m/z: 245.11912 [M − H]$^-$ (calcd for $C_{15}H_{17}O_3^-$, 245.11777).

Janthinepene B (3). Colorless oil, $[\alpha]_D^{20}$ −24.4 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 235 (4.60) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 205 (6.09), 236 (−6.60) nm; IR (KBr) ν_{max}: 1016, 1080, 1267, 1701, 2972 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; HRESIMS m/z: 261.11433 [M − H]$^-$ (calcd for $C_{15}H_{17}O_4^-$, 261.11268).

Janthinepene C (4). Colorless oil, $[\alpha]_D^{20}$ −17.1 (c 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 235 (4.83) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 204 (5.31), 236 (−8.27) nm; IR (KBr) ν_{max}: 1016, 1261, 1406, 1701, 2970 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; HRESIMS m/z: 265.14340 [M + H]$^+$ (calcd for $C_{15}H_{21}O_4^+$, 265.14398).

Janthinepene D (5). Colorless oil, $[\alpha]_D^{20}$ −21.3 (c 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 235 (4.89) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 205 (−6.63), 233 (−11.36) nm; IR (KBr) ν_{max}: 1016, 1261, 1406, 1701, 2970 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; HRESIMS m/z: 265.14340 [M + H]$^+$ (calcd for $C_{15}H_{21}O_4^+$, 265.14398).

Janthinepene E (6). Colorless oil, $[\alpha]_D^{20}$ −20.0 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 235 (4.12) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 201 (7.17), 236 (−0.90) nm; IR (KBr) ν_{max}: 1083, 1409, 1610, 1697, 2920 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; HRESIMS m/z: 265.14378 [M + H]$^+$ (calcd for $C_{15}H_{21}O_4^+$, 265.14398).

Janthinepene F (7). Colorless oil, $[\alpha]_D^{20}$ −22.0 (c 0.5, MeOH); UV (MeOH) λ_{max} (log ε): 235 (4.73) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 204 (3.18), 236 (−5.97) nm; IR (KBr) ν_{max}: 1261, 1406, 1610, 1697, 2974 cm^{-1}; ^1H and ^{13}C NMR

data, see Tables 2 and 3; HRESIMS m/z: 263.12998 [M − H]$^-$ (calcd for $C_{15}H_{19}O_4{}^-$, 263.12833).

Janthinepene G (8). Colorless oil, $[\alpha]_D^{20}$ −27.6 (c 1.0, MeOH); UV (MeOH) λ_{max} (log ε): 235 (4.38) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 205 (3.00), 237 (−9.33) nm; IR (KBr) ν_{max}: 1078, 1290, 1417, 1691, 2980 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; HRESIMS m/z: 277.10941 [M − H]$^-$ (calcd for $C_{15}H_{17}O_5{}^-$, 277.10760).

X-ray Crystal Structure Analysis. Crystals of **1** and **2** were obtained from MeOH−H$_2$O. Intensity data were collected on a Bruker D8 QUEST diffractometer equipped with an APEX II CCD using Ga Kα radiation. Cell refinement and data reduction were conducted using a Bruker SAINT, and data were corrected for absorption effects using the multi-scan method (SADABS). The structures were solved using the Bruker SHELXTL software package.[41] Crystallographic data (excluding structure factor tables) for compounds **1** and **2** were deposited at the Cambridge Crystallographic Data Center (CCDC) as supplementary publications no. CCDC 2156926 for **1** and CCDC 2156925 for **2**.

Crystal Data for 1. $C_{14}H_{10}N_2O_4S$, $M = 302.30$, $a = 11.883(8)$ Å, $b = 53.61(4)$ Å, $c = 4.243(4)$ Å, $\alpha = 90°$, $\beta = 90.06(4)°$, $\gamma = 90°$, $V = 2703(4)$ Å^3, $T = 200.15$ K, space group Cc, $Z = 8$, $D_{calc} = 1.486$ g/cm^3, $F(000) = 1248.0$, μ (Ga Kα) = 1.507 mm^{-1}, 12 612 reflections measured, 5454 independent reflections ($R_{int} = 0.1066$, $R_\sigma = 0.1064$). The final R_1 value was 0.2390 [$I > 2\sigma(I)$]. The final wR_2 value was 0.5007 [$I > 2\sigma(I)$]. The final R_1 value was 0.2429 (all data). The final wR_2 value was 0.5170 (all data). The goodness of fit on F^2 was 2.345.

Crystal Data for 2. $C_{30}H_{36}O_6$, $M = 492.59$, $a = 5.8678(9)$ Å, $b = 11.0202(16)$ Å, $c = 41.904(6)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2709.7(7)$ Å^3, $T = 200(2)$ K, space group $P2_12_12_1$, $Z = 4$, $D_{calc} = 1.207$ g/cm^3, $F(000) = 1056.0$, μ (Ga Kα) = 0.427 mm^{-1}, 47 437 reflections measured, 6366 independent reflections ($R_{int} = 0.0477$, $R_\sigma = 0.0278$). The final R_1 value was 0.0423 [$I > 2\sigma(I)$]. The final wR_2 value was 0.1167 [$I > 2\sigma(I)$]. The final R_1 value was 0.0437 (all data). The final wR_2 value was 0.1179 (all data). The goodness of fit on F^2 was 1.048. Flack parameter = 0.01(4).

■ BIOLOGICAL ASSAYS

Antibacterial Assay. Methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Klebsiella neumonia*, carbapenems-resistant *Acinetobacter baumannii*, carbapenems-resistant *Escherichia coli*, carbapenems-resistant *Pseudomonas aeruginosa*, multidrug-resistant *Enterococcus faecium*, multidrug-resistant *Staphylococcus epidermidis*, and multidrug-resistant *Enterococcus faecalis* were cultivated to evaluate the antibacterial activities of compounds **1−11** *in vitro*. According to the previous report,[42] samples were assayed in sterile 96-well plates based on the modified broth dilution test method with DMSO and ciprofloxacin as the negative and positive control, respectively.

Antifungal Assay. The isolated compounds were also evaluated for their antifungal activity against agricultural pathogenic fungi (*Verticillium dahliae* Kleb, *Sclerotinia sclerotiorum*, *Rhizoctonia solani*, *A. fragriae*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Botryospuaeria berengeriana*, and *Helminthosporium maydis*) previously described with DMSO and ketoconazole as the negative and positive control, respectively.[42]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04434.

> HRESIMS, IR, UV, 1D and 2D NMR spectra of **1−8**, and bioassay data for **1−11** (PDF)
>
> X-ray crystallographic data of **1** (PDF)
>
> X-ray crystallographic data of **2** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Xiao-Long Yang − *The Modernization Engineering Technology Research Center of Ethnic Minority Medicine of Hubei Province, School of Pharmaceutical Sciences, South-Central Minzu University, Wuhan 430074, P. R. China;* ⓘ orcid.org/0000-0002-3838-4084; Email: yxl19830915@163.com

Authors

Wen-Jing Wang − *The Modernization Engineering Technology Research Center of Ethnic Minority Medicine of Hubei Province, School of Pharmaceutical Sciences, South-Central Minzu University, Wuhan 430074, P. R. China*

Liang-Xiu Liao − *The Modernization Engineering Technology Research Center of Ethnic Minority Medicine of Hubei Province, School of Pharmaceutical Sciences, South-Central Minzu University, Wuhan 430074, P. R. China*

Ze-Diao Huang − *The Modernization Engineering Technology Research Center of Ethnic Minority Medicine of Hubei Province, School of Pharmaceutical Sciences, South-Central Minzu University, Wuhan 430074, P. R. China*

Fu-Ting Wei − *The Modernization Engineering Technology Research Center of Ethnic Minority Medicine of Hubei Province, School of Pharmaceutical Sciences, South-Central Minzu University, Wuhan 430074, P. R. China*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.2c04434

Author Contributions

[†]W.-J.W. and L.-X.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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