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Polyketide butenolide, diphenyl ether, and benzophenone derivatives from the fungus *Aspergillus flavipes* PJ03-11

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ABSTRACT

Five new polyketides including three new butenolides (**1**–**3**), one new diphenyl ether (**4**), and one new benzophenone (**5**), together with eleven known compounds (**6**–**16**) were isolated from a wetland fungus *Aspergillus flavipes* PJ03-11. Their structures were elucidated on the basis of detailed spectroscopic analysis. All the isolated compounds were tested for their α-glucosidase inhibitory activities. The results showed that compounds **1**–**3**, **6**, **7**, **11**, **15** and **16** exhibited stronger inhibitory activities than acarbose. And the preliminary structure–activity relationships of aspulvinone and diphenyl ether compounds on the α-glucosidase inhibitory activity were reported.

Diabetes mellitus is a chronic metabolic disease caused by insulin insufficiency or insulin dysfunction, characterized by sustained high blood sugar and could cause numerous serious complications, especially the blood vessels and nerves.[1,2] The World Health Organization reported that worldwide in 2015 around 347 million people live with diabetes and annually there are 1.5 million deaths directly attributed to diabetes.[3] Being an increasingly global public health crisis, it is an urgent need to find new chemotherapy drugs. α-Glucosidase, a key enzyme in carbohydrate metabolism, can catalyze the hydrolysis of the terminal glycosidic bonds at the nonreducing end of saccharide polymers to release α-glucose.[4] Inhibition of α-glucosidase can especially control the postprandial blood level of diabetic patients due to their ability of slowing the uptake of dietary carbohydrates.[5] α-Glucosidase inhibitors have been postulated to be the powerful therapeutic agents in carbohydrate metabolic disorders, especially in diabetes.[6] So, α-glucosidase inhibitors could be considered as an effective therapeutic for the treatment of diabetes.

The genus *Aspergillus* contains a large number of species that are capable of producing numerous metabolites with diverse structural features and significant biological activities.[7] Although *Aspergillus* species are very common in their distributions, the bioactive components of this genus have remained largely un-explored. There are reports that acarbose and voglibose, two clinically useful α-glucosidase inhibitors, were isolated from microorganisms.[8] In recent years, isolations of α-glucosidase inhibitors from *Aspergillus* sp. have gained increasing interest. Such as, 6-*O*-demethylmonocerin (isocoumarine),[9] aspergones A, B, E, J, K and N–Q (polyketides),[9] aspergifuranone (polyketide),[10] pestaphthalides A (phthalide),[10] isoaspulvinone E (butenolide),[11] aspulvinone E (butenolide),[11] butyrolactone I and II (butenolide),[11–13] oleic acid (olefin acid),[12] rubasperone C (dimeric naphtho-γ-pyrone),[14] Aspergillusol A (tyrosine derivative)[15] and piperumbellactams A–C (alkaloids).[16] Thus, the genus *Aspergillus* has been shown to be capable of producing α-glucosidase inhibitors.

Motivated by the search for new α-glucosidase inhibitors from the genus *Aspergillus*, a wetland fungus identified as *Aspergillus flavipes* PJ03-11 (Genbank Accession number KT809365) was isolated from the wetland mud collected from Panjin Red Beach National Nature Reserve in Liaoning Province, China. Panjin Red Beach National Nature Reserve is located in the northeast of the Bohai Bay and in the Liaohe River Delta wetland. It is one of the best preserved and the largest wetland reserve in the global. *Aspergillus flavipes* PJ03-11 has the remarkable color feature with the bright

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yellow pigment on the early stage of growth and the fluorescent yellow metabolic extract. The crude extract of solid culture of this fungus exhibited significant α-glucosidase inhibitory activity with an IC_{50} value of 4.25 ± 0.11 μg/mL. Then, the chemical investigation of the fungus was carried out, which led to the isolation of five new polyketides including three new butenolides, aspulvinone P (**1**), aspulvinone Q (**2**), and methybutyrolactoneIII (**3**), one new diphenyl ether, 5-hydroxymethylasterric acid (**4**), and one new benzophenone, 3,5-dichlorosulochrin (**5**), along with eleven known compounds (**6**–**16**) (Fig. 1). Herein, the isolation and structure elucidation as well as the biological activities of all compounds are described.

Aspulvinone P (**1**) was obtained as a yellow amorphous powder. The molecular formula was determined to be $C_{19}H_{16}O_7$ by HR ESI-TOF MS at *m*/*z* 379.0783 $[M+Na]^+$, indicating 12 degrees of unsaturation. The ^1H NMR spectrum (Table 1) showed a 4H A_2B_2 system at δ_H 7.75 (2H, d, *J* = 8.4 Hz, H-13/H-17) and 6.82 (2H, d, *J* = 8.4 Hz, H-14/H-16), indicating the presence of a *para*-disubstituted phenyl group. Two aromatic signals at δ_H 7.02 (2H, s) were indicative of the presence of symmetrical tetrasubstituted phenyl unit in the molecule, and two methoxy signals at δ_H 3.81 (6H, s) were magnetic equivalent. The ^{13}C NMR spectrum (Table 1) only showed fourteen resonances, five of them at δ_C 148.1, 128.7, 115.2, 108.1 and 56.1 showed very high intensities, indicating the occurrence of ten overlapping carbon signals. Furthermore, a lactone group at δ_C 168.2 and eight sp^2 carbons at δ_C 161.9, 156.6, 140.6, 137.3, 123.2, 120.7, 107.9 and 100.1 were observed. Detailed comparison of the NMR data of compound **1** with those of aspulvinone E (**17**)[17] suggested that they shared the same core frame unit except that the right-hand benzene ring is tetrasubstituted. The structure was further determined by HMBC spectra (Fig. 2), the correlations from H-5 to C-3, C-4 and C-11, from H-7 to C-5, C-8 and C-9, as well as from 8-MeO/10-MeO to C-8/C-10 confirmed the assignment of the methoxy unit. On the basis of these data, the planar structure of compound **1** was established.

Aspulvinone Q (**2**) was also obtained as a yellow amorphous powder, the HR ESI-TOF MS of **2** ($[M+Na]^+$ *m*/*z* 349.0677) combined with the ^{13}C NMR and ^1H NMR data indicated a molecular formula of $C_{18}H_{14}O_6$ with the same degree of unsaturation as compound **1**. Comparing the 1D NMR data of compound **2** with those of compound **1**, the significant difference was due to the disappearance of a phenolic methoxy unit, suggesting that the right-hand benzene right is a 3H ABX system [δ_H 6.85 (1H, d, *J* = 8.2 Hz, H-10), 7.18 (1H, dd, *J* = 8.2, 1.8 Hz, H-11) and 7.30 (1H, d, *J* = 1.8 Hz, H-7)]. The HMBC correlations as shown in Figure 2 supported this deduction.

As the configuration for the exocyclic double bond of compounds **1** and **2**, there was reported that, in the case of *E*-isomer of synthetically analogous pulvinones, the $\triangle\delta$ in

Table 1
^1H NMR and ^{13}C NMR spectroscopic data for compound **1** and **2**

Position	1		2	
	δ_H (*J* in Hz)[a]	δ_C[c]	δ_H (*J* in Hz)[b]	δ_C[c]
1		168.2		168.7
2		100.1		99.5
3		161.9		163.5
4		140.6		141.2
5	6.54, s	107.9	6.51, s	106.5
6		137.3		128.6
7	7.02, s	108.1	7.30, d (1.8)	113.6
8		148.1		147.7
9		123.2		147.6
10		148.1	6.85, d (8.2)	115.9
11	7.02, s	108.1	7.18, dd (8.2, 1.8)	124.0
12		120.7		124.6
13, 17	7.75, d (8.4)	128.7	7.79, d (8.4)	128.0
14, 16	6.82, d (8.4)	115.2	6.79, d (8.4)	115.0
15		156.6		155.9
8-OMe	3.81, s	56.1	3.81, s	55.6
10-OMe	3.81, s	56.1		
9-OH			9.51, s	
10-OH			9.48, s	

[a] ^1H NMR spectroscopic data recorded at 400 MHz in DMSO-d_6.
[b] ^1H NMR spectroscopic data recorded at 600 MHz in DMSO-d_6.
[c] ^{13}CNMR spectroscopic data recorded at 100 MHz in DMSO-d_6.

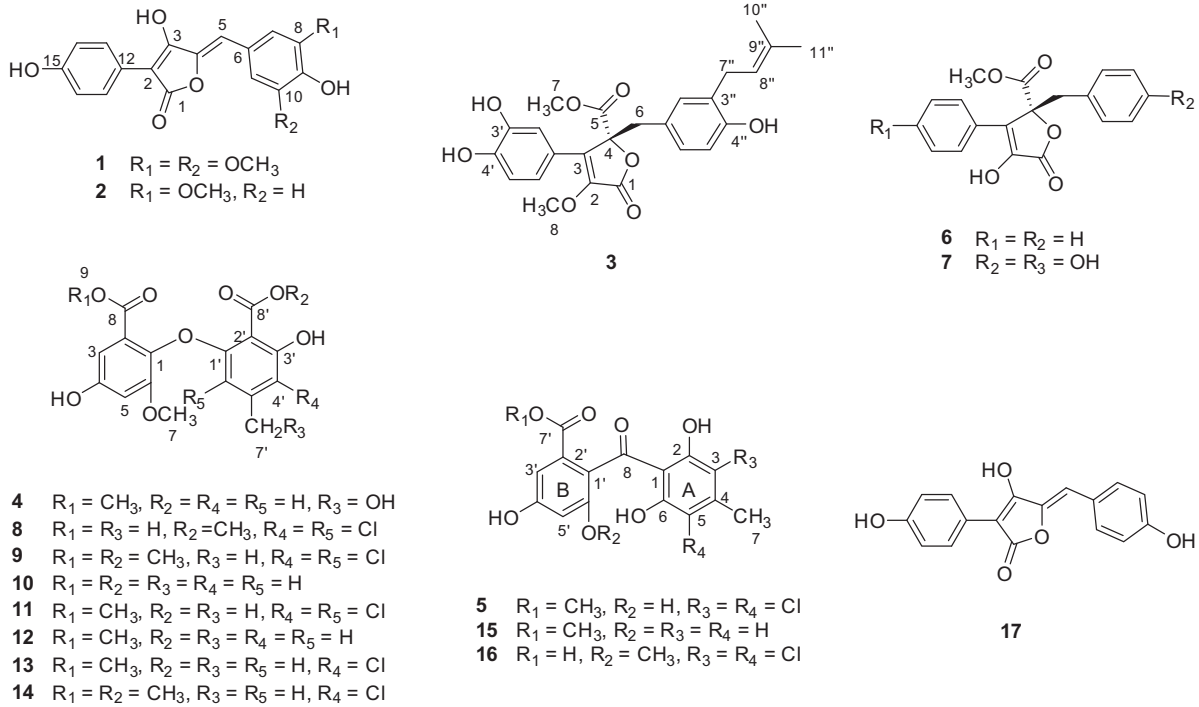

Figure 1. Structures of compounds **1**–**16**.