# Fusapyridons A and B, Novel Pyridone Alkaloids from an Endophytic Fungus, *Fusarium* sp. YG-45

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Through our screening for new natural compounds, two 3,4,5-trisubstituted *N*-methyl-2-pyridone alkaloids, fusapyridons A (**1**) and B (**2**), along with the known compounds sambutoxin (**3**), *N*-demethylsambutoxin (**4**), (–)-oxysporidinone (**5**), and the dimethyl ketal of oxysporidinone (**6**) were isolated from the fermentation extract of *Fusarium* sp. YG-45. Their structures were determined by spectroscopic analyses including NMR, MS, UV and IR. Compound **1** showed antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

*Key words: Fusarium* sp., Endophyte, Pyridone, Sambutoxin, Fusapyridons A and B

## Introduction

Endophytic fungi are microorganisms living within the tissues of the host plants. Recently these microorganisms were recognized as rich and untapped resources of structurally diverse natural products, some of them with interesting biological activities [1]. Our previous investigation of endophytic fungi isolated from plants in Japan resulted in some bioactive and structurally unique metabolites [2 – 4]. In our continuing search for novel bioactive compounds from endophytic fungi from Germany, healthy stems and bark of trees were submitted to the isolation of endophytes, and 58 strains were isolated. Among them, *Fusarium* sp. YG-45, isolated from the stem of *Maackia chinensis* (common name: Chinese maackia, Family: *Leguminosae*), was selected for chemical screening. From the solid-state fermentation of *Fusarium* sp. YG-45 two novel compounds, fusapyridons A (**1**) and B (**2**), and four known compounds, sambutoxin (**3**) [5], *N*-demethylsambutoxin (**4**) [6], (–)-oxysporidinone (**5**) [6], and the dimethyl ketal of oxysporidinone (**6**) [6] have been isolated (Fig. 1). The present report describes the isolation and structure determination of these metabolites, and their biological activities are also discussed.

## Result and Discussion

The producing fungus, *Fusarium* sp. YG-45, was isolated from *Maackia chinensis*. The fungus YG-45 was stationarily cultured at 25 °C for 3 weeks on unpolished rice. After fermentation, the MeOH extract of a brown rice culture of this fungus was concentrated *in vacuo* to a small volume and then partitioned between EtOAc and water. The chromatographic separation of the organic layer resulted in the isolation of two new compounds **1** and **2**, and four known compounds, sambutoxin (**3**), *N*-demethylsambutoxin (**4**), (–)-oxysporidinone (**5**), and the dimethyl ketal of oxysporidinone (**6**).

The structures of **3**, **4**, **5**, and **6** were established on the basis of FABMS, $^1$H, $^{13}$C NMR, $^1$H-$^1$H COSY, $^{13}$C-$^1$H COSY, and HMBC data. The $^1$H and $^{13}$C NMR data were identical to those previously reported in the literature [5, 6].

Fusapyridon A (**1**) has the molecular formula $C_{29}H_{43}NO_5$ as revealed by HRFABMS, requiring nine degrees of unsaturation. The IR spectrum suggested the presence of a hydroxy group (3500 cm$^{-1}$), a ketone (1725 cm$^{-1}$), and an amide carbonyl function (1664 cm$^{-1}$). The analysis of $^{13}$C NMR and DEPT spectra indicated the presence of seven methyls, seven methylenes, eight methines, and seven quaternary carbons. Since five out of the nine unsaturation equivalents were accounted for by the $^{13}$C NMR data, **1** was inferred to have four rings. The $^1$H NMR also showed signals due to two olefinic protons ($\delta_H$ = 5.07, 7.20), three oxymethine protons ($\delta_H$ = 3.36, 4.77, 4.98), and seven methyls ($\delta_H$ = 0.69, 0.82, 0.83, 0.87, 1.58,

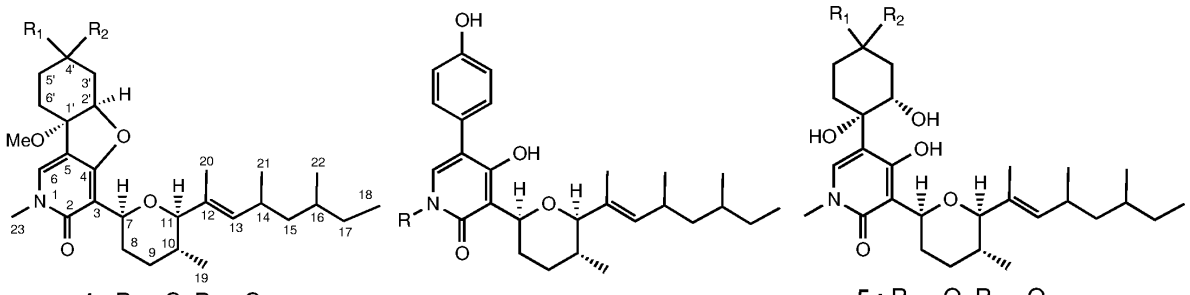


Fig. 1. Structures of fusapyridons A (**1**), B (**2**), sambutoxin (**3**), *N*-demethylsambutoxin (**4**), (–)-oxysporidinone (**5**), and the dimethyl ketal of oxysporidinone (**6**).

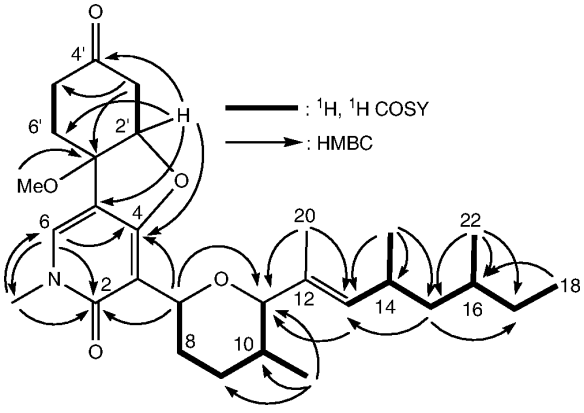


Fig. 2. $^{1}$H-$^{1}$H COSY (bold lines), and HMBC (arrows) correlations observed for **1**.

3.19, 3.48). The $^{1}$H-$^{1}$H COSY spectrum of **1** showed the connectivities for four proton-networks: from 2′-H to 3′-$H_2$, from 5′-$H_2$ to 6′-$H_2$, from 13-H to 18-H, from 21-$H_3$ to 14-H, 22-$H_3$ to 16-H, from 7-H to 11-H, and from 19-$H_3$ to 10-H. Evidence for the connections of these partial structures was provided by the HMBC $^{1}$H-$^{13}$C long-range connectivity data (Fig. 2).

The presence of the 4-*O*-methoxy-cyclohexenone moiety was established by HMBC correlations (Table 1) from 2′-H to C-4′ and C-6′, 3′-$H_2$ to C-1′ and C-5′, and 1′-$OCH_3$ to C-1′. The presence of a 3,4,5-trisubstituted *N*-methyl-2-pyridone ring moiety was indicated by the characteristic $^{13}$C and $^{1}$H NMR signals [5 – 7], and HMBC correlations from 23-$H_3$ to C-2 and C-6, and from 6-H to C-2 and C-4. The structure of the tetrahydro-3-methyl-2*H*-pyranyl moiety was deduced from HMBC correlations from 19-$H_3$ to C-9, C-10 and C-11, and 7-H to C-11. HMBC correlations from 20-$H_3$ and 21-$H_3$ to C-13 indicated the presence of the 4,6-dimethyl-oct-2-ene moiety. Furthermore, the 20-$H_3$ signal correlated with C-11, suggesting that the

Table 1. $^{1}$H and $^{13}$C-NMR data of compound **1**[a].

| No. | $\delta_H$ | $\delta_C$ | HMBC |
|---|---|---|---|
| 2 | 163.2 s | | |
| 3 | 109.9 s | | |
| 4 | 166.3 s | | |
| 5 | 111.3 s | | |
| 6 | 133.1 d | 7.20 (1H, s) | 2, 4, 5, 23, 1′ |
| 7 | 71.7 d | 4.77 (1H, dd, 11.5, 2.2) | 2, 3, 4, 11 |
| 8 | 29.2 t | 1.55 – 1.60[b] | |
| | | 2.03 – 2.09 (1H, m) | |
| 9 | 32.8 t | 1.27 – 1.34[b] | |
| | | 1.83 – 1.87 (1H, m) | |
| 10 | 31.7 t | 1.55 – 1.60[b] | |
| 11 | 91.1 d | 3.36 (1H, d, 9.8) | 12, 13, 20 |
| 12 | 132.4 s | | |
| 13 | 135.8 d | 5.07 (1H, d, 9.5) | 11, 14, 20 |
| 14 | 29.4 d | 2.41 – 2.46 (1H, m) | |
| 15 | 44.9 t | 0.97 – 1.08 (1H, m) | 13, 17 |
| | | 1.12 – 1.19 (1H, m) | 13, 17 |
| 16 | 31.8 d | 1.27 – 1.34[b] | |
| 17 | 29.7 t | 1.27 – 1.34[b] | |
| 18 | 11.2 q | 0.83 (3H, d, 7.1) | 16 |
| 19 | 17.9 q | 0.69 (3H, d, 6.7) | 9, 10, 11 |
| 20 | 11.0 q | 1.58 (3H, s) | 11, 12, 13 |
| 21 | 20.6 q | 0.87 (3H, d, 6.6) | 13, 14, 15 |
| 22 | 19.5 q | 0.82 (3H, d, 7.1) | 15, 16, 17 |
| 23 | 38.2 q | 3.48 (3H, s) | 2, 6 |
| 1′ | 82.1 s | | |
| 2′ | 84.3 d | 4.98 (1H, t, 5.3) | 4, 5, 4′, 6′ |
| 3′ | 42.4 t | 2.77 (1H, dd, 16.6, 5.3) | 1′, 5′ |
| | | 2.86 (1H, dd, 16.6, 5.3) | 1′, 5′ |
| 4′ | 207.1 s | | |
| 5′ | 35.0 t | 2.32 – 2.39[b] | |
| | | 2.10 – 2.18[b] | |
| 6′ | 31.9 t | 2.32 – 2.39[b] | |
| | | 2.10 – 2.18[b] | |
| 1′-OMe | 50.8 q | 3.19 (3H, s) | 1′ |

[a] Measured in $CDCl_3$, values in parentheses are coupling constants in Hz; [b] overlapping signals.

Table 2. $^{1}H$ and $^{13}C$-NMR data of compound **2**[a].

| No. | $\delta_H$ | $\delta_C$ | HMBC |
|---|---|---|---|
| 2 | 163.7 s | | |
| 3 | 111.2 s | | |
| 4 | 166.6 s | | |
| 5 | 111.5 s | | |
| 6 | 132.1 d | 7.16 (1H, s) | 2, 5, 23, 1′ |
| 7 | 71.8 d | 4.80 (1H, dd, 11.7, 2.3) | 2, 4, 11 |
| 8 | 29.2 t | 1.56 – 1.62[b] | |
| | | 2.06 – 2.15[b] | |
| 9 | 32.9 t | 1.28 – 1.38[b] | |
| | | 1.82 – 1.86 (1H, m) | |
| 10 | 31.8 d | 1.56 – 1.62[b] | |
| 11 | 91.1 d | 3.37 (1H, d, 9.8) | 12, 13, 20 |
| 12 | 132.3 s | | |
| 13 | 135.7 d | 5.08 (1H, d, 9.3) | 11, 14, 20 |
| 14 | 29.4 d | 2.38 – 2.45 (1H, m) | |
| 15 | 44.9 t | 0.96 – 1.06[b] | |
| | | 1.11 – 1.18 (1H, m) | 13, 17 |
| 16 | 31.7 d | 1.28 – 1.38[b] | |
| 17 | 29.5 t | 0.96 – 1.06[b] | |
| | | 1.28 – 1.38[b] | |
| 18 | 11.0 q | 0.81 (3H, t, 6.9) | 16 |
| 19 | 17.9 q | 0.68 (3H, d, 6.7) | 9, 10, 11 |
| 20 | 11.2 q | 1.59 (3H, s) | 11, 12, 13 |
| 21 | 20.5 q | 0.86 (3H, d, 6.7) | 13, 14, 15 |
| 22 | 19.5 q | 0.80 (3H, d, 6.9) | 15, 16, 17 |
| 23 | 38.1 q | 3.45 (3H, s) | 2, 6 |
| 1′ | 81.0 s | | |
| 2′ | 87.9 d | 4.75 (1H, dd, 10.3, 7.1) | 4, 5, 4′ |
| 3′ | 36.4 t | 1.28 – 1.38[b] | |
| | | 2.51 (1H, ddd, 13.6, 7.1, 2.4) | 1′, 5′ |
| 4′ | 99.2 s | | |
| 5′ | 28.2 t | 1.28 – 1.38[b] | |
| | | 1.91 – 1.99[b] | |
| 6′ | 26.2 t | 1.91 – 1.99[b] | |
| | | 2.06 – 2.15[b] | |
| 1′-OMe | 50.0 q | 3.06 (3H, s) | 1′ |
| 4′-OMe | 47.8 q | 3.17 (3H, s) | 4′ |
| 4′-OMe | 48.0 q | 3.14 (3H, s) | 4′ |

[a] Measured in $CDCl_3$, values in parentheses are coupling constants in Hz; [b] overlapping signals.

oct-ene moiety was connected to the pyranyl moiety at C-11. The methine proton at C-6 of the 2-pyridone ring correlated with C-1′ and the methine proton at C-2′ with C-4 in the HMBC spectrum. These results lead to the conclusion that the 2-pyridone and cyclohexenone rings give rise to be a 6/5/6 skeleton formed by cyclization of C-4 and C-2′ through an ether bridge. Thus, the planar structure of fusapyridon A was elucidated to be **1** (Fig. 1).

The relative stereochemistry of **1** was partially determined by analysis of $^{1}H$-$^{1}H$ coupling constants and NOE experiments. The relative stereochemistry at C-7 and C-11 was determined to be *cis* on the basis of an NOE correlation from 7-H to 11-H. The coupling constant between 10-H and 11-H ($J$ = 9.8 Hz) indicated that the methyl group at C-10 was $\alpha$-oriented. The configuration of the double bond between C-12 and C-13 was determined to be *E*, based on NOE correlations from 11-H to 13-H. Furthermore, the NOE correlation from 1′-OMe to 2′-H showed that the relative configuration at C-1′ and C-2′ give a *cis* ring fusion. The partial relative stereochemistry is shown in Fig. 1.

The molecular formula of fusapyridon B (**2**) was established by HRFABMS as $C_{31}H_{49}NO_6$ that accounted for eight degrees of unsaturation. The IR spectrum of **2** revealed the presence of an amide carbonyl group (1668 $cm^{-1}$) and the absence of the ketone carbonyl function observed in **1**. Compound **2** exhibits spectral data similar to those of **1** (Table 2). No signal due to the carbonyl carbon at C-4′ as in **1** was detected for **2**, however, new signals of two methoxy groups [$\delta_C$ = 47.8, 48.0; $\delta_H$ = 3.17 (s, 3H), 3.14 (s, 3H)] and one quaternary carbon ($\delta_C$ = 99.2) were detected in the $^{1}H$ and $^{13}C$ NMR spectra, indicating the lack of carbonyl functions. HMBC correlations (Table 2) between the methoxy group and the quaternary carbon ($\delta_C$ = 99.2) confirmed their geminal position on carbon C-4′. The structure of **2** was also deduced from the 2D NMR spectra including $^{13}C$-$^{1}H$ COSY and HMBC. In the NOE experiments, correlations between 2′-H and 1′-OMe, between 7-H and 11-H, and between 11-H and 13-H were observed. Thus, the structure of **2** was determined as the dimethyl ketal derivative of **1**. The possibility of **2** being an artifact produced during the separation could be excluded because **1** was shown to be stable for one week in MeOH.

The structures of **1** – **6** were determined as shown in Fig. 1. These compounds were structurally related to farinosones A, B and C from the entomogenous deuteromycete *Paecilomyces farinosus* [7], militarinone A from *Paecilomyces militaris* [8], TMC-69 from *Chrysosporium* sp. TC 1068 [9], YM-215343 from *Phoma* sp. QN04621 [10], and apiosporamide from *Apiospora montagnei* [11], all of which possess a 2-pyridone ring moiety. Among these compounds, apiosporamide, YM-215343, and (–)-oxysporidinone (**5**) were reported to show antifungal activity against phytopathogenic fungi, while sambutoxin (**3**), *N*-demethylsambutoxin (**4**), dimethyl ketal of oxysporidinone (**6**), 6′-*epi*-oxysporidinone [6] exhibited no antifungal activity against *Aspergillus flavus* and *Fusarium verticillioides*. The antimicrobial activity of **1** – **6** was tested by the agar dilution method. The antimicrobial activities of compounds **1** – **6** are expressed by the

Table 3. MIC ($\mu g\,mL^{-1}$) of fusapyridons A (**1**), B (**2**), sambutoxin (**3**), *N*-demethylsambutoxin (**4**), (–)-oxysporidinone (**5**), and the dimethyl ketal of oxysporidinone (**6**).

| Microorganisms | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| *Pseudomonas aeruginosa* ATCC 15442 | 6.25 | > 100 | > 100 | > 100 | > 100 | > 100 |
| *Staphylococcus aureus* NBRC 13276 | 50 | > 100 | > 100 | > 100 | > 100 | > 100 |
| *Aspergillus clavatus* F318a | > 100 | > 100 | > 100 | > 100 | > 100 | > 100 |
| *Candida albicans* ATCC 2019 | > 100 | > 100 | > 100 | > 100 | > 100 | > 100 |

minimum inhibitory concentration (MIC) in Table 3. The assay results indicate that **1** has activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, with MIC values of 6.25 and 50 $\mu g\,mL^{-1}$, respectively. None of the tested compounds showed activity against *Aspergillus clavatus* and *Candida albicans* ($> 100\ \mu g\,mL^{-1}$).

Pyridone alkaloids of 3-acyl-5-(4-hydroxyphenyl)-pyridin-2-one are conceived to be biogenetically produced by condensation of tyrosine (tyrosine derivative) and polyketide precursors, followed by cyclization to form the 2-pyridone ring *via* a tetramic acid derivative [12, 13]. It is likely that **1** and **2** also are formed by a similar biosynthetic pathway. The formation of **1** and **2** is thought to occur *via* oxysporidinone (**5**) and the dimethyl ketal of oxysporidinone (**6**), followed by intramolecular cyclization.

## Experimental Section

*General experimental procedures*

Optical rotation was measured with a Horiba model SEPA-300 polarimeter, IR spectra were recorded with a JASCO J-20A spectrophotometer, and UV spectra were recorded with a Shimadzu UV mini-1240 instrument. Mass spectra were obtained with a JEOL JMS-700 instrument, and $^1H$ and $^{13}C$ NMR spectra with a JEOL EX-400 spectrometer. Chemical shifts are given on a $\delta$ (ppm) scale with TMS as an internal standard. Column chromatography was conducted on silica gel 60 (Kanto Chemical Co., Inc.) and ODS (Fuji Silysia). TLC was performed on a precoated silica gel plate (Merck), and spots were detected by spraying with vanillin-sulphuric acid reagent followed by heating or by UV irradiation.

*Isolation of the endophytic fungus*

The endophytic fungus *Fusarium* sp. YG-45 was isolated from the healthy stem of *Maackia chinensis* (Common name: Chinese maackia, Family: *Leguminosae*) collected in October 2005 in Göttingen (Germany). A twig segment from *Maackia chinensis* was surface sterilized by successively submersion in 70 % EtOH for 1 min, 5 % sodium hypochlorite for 5 min and 70 % EtOH for 1 min, and then rinsed twice with sterile water. The sterilized samples were dried on sterilized paper and cut into 1-cm pieces. The pieces were placed on plates of potato dextrose agar (PDA) containing chloramphenicol (100 $mg\,L^{-1}$). Successive subculturing of the outgrowing fungi resulted in a pure culture initially coded YG-45. Identification of this fungus was carried out by Centraalbureau voor Schimmelcultures (The Netherlands). The strain *Fusarium* sp. YG-45 has been deposited at the laboratory of the Faculty of Agriculture, Yamagata University, Yamagata, (Japan).

*Cultivation of the endophytic fungus, extraction and isolation of compounds **1** and **2***

*Fusarium* sp. YG-45 was cultivated on sterilized unpolished rice (20 g/Petri dish ×100) at 25 °C for 3 weeks. The moldy unpolished rice was extracted with MeOH, and the MeOH extract was concentrated. The resulting aqueous concentrate was partitioned into *n*-hexane and EtOAc layers. The purification of the EtOAc layer was guided by the characteristic intense blue color with vanillin-sulfuric acid solution on TLC plates. The EtOAc layer was chromatographed on a silica gel column using a gradient of *n*-hexane-EtOAc (100 : 0 – 0 : 100) to give fractions 1 – 10 (Fr. 1-1 – 1-10). Fr. 9 (*n*-hexane-EtOAc, 20 : 80) and 10 (*n*-hexane-EtOAc, 10 : 90) were combined (15.2 g) and subjected to silica gel column chromatography by eluting with $CHCl_3$ and an increasing ratio of MeOH. Thirteen fractions (Fr. 2-1 – 2-13) were obtained. Fr. 2-4 (0.25 g) was subjected to silica gel flash column chromatography with a mixture of $CHCl_3$-MeOH (90 : 10) to afford sambutoxin (**3**, 12.5 mg). Fr. 2-5 (0.58 g) was purified by prep. TLC ($CHCl_3$-MeOH, 80 : 20) to afford *N*-demethylsambutoxin (**4**, 11.5 mg). Fr. 2-13 (3.3 g) was further chromatographed on ODS by eluting with mixtures of $H_2O$ and MeOH to afford eleven fractions (Fr. 3-1 – 3-11). Fr. 3-10 (0.24 g, $H_2O$-MeOH, 10 : 90) was subjected to silica gel flash column chromatography with a mixture of $CHCl_3$-MeOH (90 : 10) to yield (–)-oxysporidinone (**5**, 30.0 mg, $[\alpha]_D^{26} = -80$ ($c$ = 0.03, EtOH), [lit: [6]: $[\alpha]_D^{26} = -68.8$ ($c$ = 0.15, EtOH)] and the dimetyl ketal of oxysporidinone (**6**, 50.0 mg). Fr. 3-11 (1.0 g, $H_2O$-MeOH, 0 : 100) was further applied to silica gel flash column chromatography with a mixture of $CHCl_3$-MeOH (90 : 10) to yield fusapyridons A (**1**, 41.3 mg) and B (**2**, 13.7 mg).

*Fusapyridon A (**1**)*

Oil. – $[\alpha]_D^{20} = -59.9$ ($c$ = 0.67, MeOH). – UV (MeOH): $\lambda_{max}$ ($\lg \varepsilon_{max}$) = 291 nm (3.6). – IR (KBr): $\nu$ = 3500 (OH), 2954, 1725 (C=O), 1664 (CONH), 1590, 1093 $cm^{-1}$. – $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C, TMS) and $^{13}C$ NMR (100 MHz, $CDCl_3$): see Table 1. – HRMS (positive mode, FAB): $m/z$ = 486.3215 (calcd. 486.3219 for $C_{29}H_{44}NO_5$, $[M+H]^+$). – MS (positive mode, FAB): $m/z$ = 486 $[M+H^+]$.

*Fusapyridon B (**2**)*

Oil. – $[\alpha]_D^{20} = -49.8$ ($c$ = 1.3, MeOH). – UV (MeOH): $\lambda_{max}$ ($\lg \varepsilon_{max}$) = 292 nm (3.7). – IR (KBr): $\nu$ = 3565 (OH), 2956, 1668 (CONH), 1594, 1054 $cm^{-1}$. – $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C, TMS) and $^{13}C$ NMR (100 MHz, $CDCl_3$): see Table 2. – HRMS (positive mode, FAB): $m/z$ = 532.3637 (calcd. 532.3638 for $C_{31}H_{50}NO_6$, $[M+H^+]$). – MS (positive mode, FAB): $m/z$ = 532 $[M+H^+]$.

*Assay for antimicrobial activity*

This assay was performed as reported [3].

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