Available online at www.sciencedirect.com
ScienceDirect
Phytochemistry 68 (2007) 368–372
PHYTOCHEMISTRY
www.elsevier.com/locate/phytochem

Asperpyrone D and other metabolites of the plant-associated fungal strain *Aspergillus tubingensis* ☆

Jixun Zhan, G.M. Kamal B. Gunaherath, E.M. Kithsiri Wijeratne, A.A. Leslie Gunatilaka *

Southwest Center for Natural Products Research and Commercialization, Office of Arid Lands Studies, College of Agriculture and Life Sciences, The University of Arizona, 250 East Valencia Road, Tucson, AZ 85706-6800, USA

Received 4 May 2006; received in revised form 19 September 2006
Available online 5 December 2006

Abstract

Bioactivity-guided fractionation of a cytotoxic extract of *Aspergillus tubingensis*, a fungal strain occurring in the rhizosphere of the Sonoran desert plant, *Fallugia paradoxa*, afforded a dimeric naphtho-γ-pyrone asperpyrone D, nine known naphtho-γ-pyrones, funalenone, and the cytotoxic cyclic penta-peptide, malformin A_1.

Keywords: *Aspergillus tubingensis*; Rhizosphere fungus; *Fallugia paradoxa*; Secondary metabolites; Asperpyrone D; Naphthopyrones; Malformin A_1; Cytotoxic activity

1. Introduction

Plant-associated microorganisms are known to produce a variety of metabolites with novel structures and interesting biological activities (Tan and Zou, 2001; Schulz et al., 2002; Strobel et al., 2004; Gunatilaka, 2006) and the claimed medicinal properties and biological activities of some plant species have been attributed to the microorganisms living in association with these plants (Kettering et al., 2004; Chomcheon et al., 2005). As part of our ongoing efforts to understand plant-microbial interactions and to discover small molecule natural products with novel structures and/or biological activities from plant-associated microorganisms of the Sonoran desert (Turbyville et al., 2006; Wijeratne et al., 2006), we have investigated the fungal strain *Aspergillus tubingensis* (Trichocomaceae) occurring in the rhizosphere of *Fallugia paradoxa* (Apache plume; Rosaceae). An EtOAc extract of *A. tubingensis* was found to exhibit strong cytotoxic activity against several cancer cell lines. Bioassay-guided fractionation of this extract resulted in the isolation of a new dimeric naphtho-γ-pyrone named asperpyrone D (**1**), a strongly cytotoxic cyclic peptide, malformin A_1 (**2**), funalenone (**3**) and nine known naphtho-γ-pyrones (**4**–**12**). A previous investigation of the sclerotia of *A. tubingensis* (NRRL 4700) has afforded three new aflavinines, one of which has shown insecticidal activity (TePaske et al., 1989). Monomeric and dimeric naphtho-γ-pyrones with a broad range of biological activities have been found to occur in higher plants belonging to the genera *Cassia* (Li et al., 2001), *Paepalanthus* (Coelho et al., 2000), and *Senna* (Barbosa et al., 2004), and in filamentous fungal genera, *Aspergillus* (Galmarini and Stodola, 1965; Wang and Tanaka, 1966; Sakurai et al., 2002; Akiyama et al., 2003) and *Fusarium* (Singh et al., 2003). Malformin A_1 has previously been reported from several *Aspergillus* strains including *A. niger* (Sugawara et al., 1990), *A. ficuum*, *A. awamori*, and *A. phoenicis* (Iriuchijima and Curtis, 1969).

2. Results and discussion

The cytotoxic EtOAc extract of *A. tubingensis*, collected from the rhizosphere of *F. paradoxa*, on fractionation using

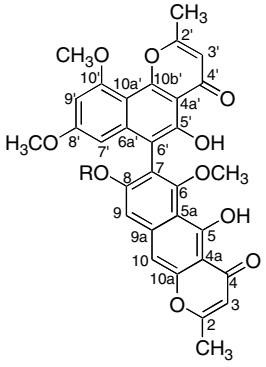
☆ Part 11 in the series, 'Studies on Arid Land Plants and Microorganisms'.

* Corresponding author. Tel.: +1 520 741 1691; fax: +1 520 741 1468.
E-mail address: leslieg@ag.arizona.edu (A.A. Leslie Gunatilaka).

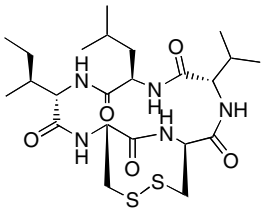
0031-9422/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2006.09.038

a combination of size-exclusion, normal phase, and reversed phase chromatography afforded compounds **1**–**12**. Asperpyrone D (**1**) was determined to have the molecular formula $C_{31}H_{24}O_{10}$ by HR-FAB-MS and ^{13}C NMR spectroscopy and indicated 20° of unsaturation. The bands at 3425 and 1655 cm^{-1} in its IR spectrum suggested the presence of hydroxyl and conjugated carbonyl functionalities. The UV spectrum of **1** showed strong absorption bands at 384, 281, 248 and 225 nm, and was found to be similar to that of asperpyrone C (**13**) (Akiyama et al., 2003), suggesting dimeric naphtho-γ-pyrone chromophore for **1**. This was further supported by the diagnostic signals at δ 14.80 and δ 13.40 for the two phenolic hydroxyl groups in its ^1H NMR spectrum (Gorst-Allman et al., 1980). The ^{13}C NMR spectrum of **1** displayed 30 signals for 31 carbons which consisted of two methyl, three methoxy, six methine, and 20 quaternary carbons. The ^1H NMR spectrum of **1** also showed two methyl singlets (δ_H 2.37 and 2.54), three methoxy singlets (δ_H 3.60, 3.62 and 3.99), six aromatic protons (two *meta*-coupled doublets at δ_H 6.27 and 6.45, and four singlets at δ_H 6.00, 6.33, 7.07 and 7.14), and two phenolic hydroxyls (see above). Both ^1H and ^{13}C NMR data closely resembled those of asperpyrone C (**13**) (Akiyama et al., 2003) except for the presence of an OH group in **1** compared with an OCH_3 in **13**. This OH group in **1** was located at C-8 by the HMBC correlations of H-9 with C-8 (δ_C 155.9). The correlations of H-7′ (δ_H 6.27) with C-6′ (δ_C 106.2), and H-9 (δ_H 7.14) with C-7 (δ_C 116.4) in the HMBC spectrum of **1** confirmed the C-7–C-6′ linkage of the two naphthopyrone moieties (Fig. 1). Thus, the structure of asperpyrone D was established as the dimeric naphtho-γ-pyrone **1** with a linear and angular monomeric moieties linked via C-7 and C-6′.

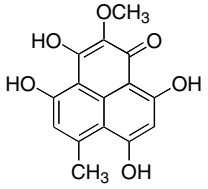
The bioactive compound **2** was identified as malformin A_1 (*cyclo*-Leu-Ile-Cys-Cys-Val) by comparison of NMR spectral data with those reported in the literature (Sugawara et al., 1990). Compounds **3**–**12** were characterized by comparison of their mass and NMR spectral data with those reported in the literature. Compound **3** was identified as funalenone, a rare phenalene with MMP-1 inhibitory activity previously encountered in *A. niger* IFO-5904 (Inokoshi et al., 1999). It is noteworthy that funalenone (**3**) has



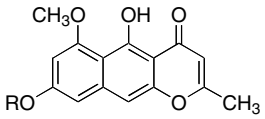
1 R=H
13 R=CH_3



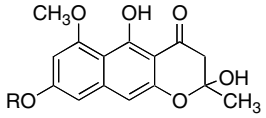
2



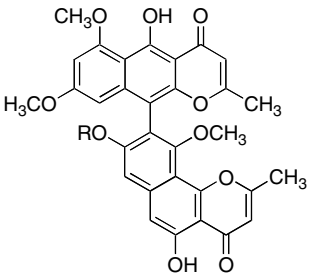
3



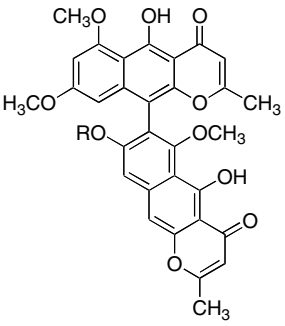
4 R=CH_3
5 R=H



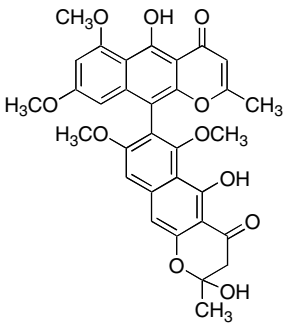
6 R=CH_3
7 R=H



8 R=CH_3
9 R=H



10 R=CH_3
11 R=H



12

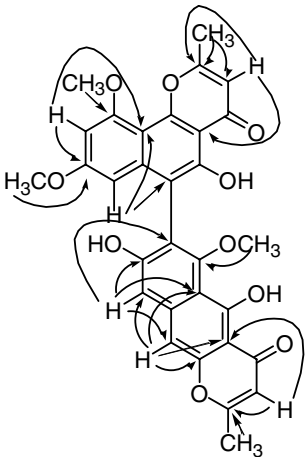


Fig. 1. Selected HMBC correlations of **1**.

recently been reported to inhibit HIV-1 integrase (Shiomi et al., 2005). The remaining metabolites were identified as the monomeric naphtho-γ-pyrones, TMC-256A1 (**4**), rubrofusarin B (**5**), fonsecin B (**6**) and fonsecin (**7**), and the naphtho-γ-pyrone dimers, fonsecinone A (**8**), asperpyrone A (**9**), aurasperone A (**10**), dianhydro-aurasperone C (**11**) and aurasperone E (**12**).

Malformin A_1 (**2**) has been reported to possess a variety of biological activities including plant growth stimulation (John and Curtis, 1974), prevention of interleukin-1 (IL-1) induced endothelial changes by inhibition of protein synthesis (Dawes, 1994), phytochrome-mediated response modulation of *Phaseolus vulgaris* (Curtis and John, 1975), as well as mycotoxic (Franck, 1984), and antibacterial activities (Suda and Curtis, 1966). In the present study malformin A_1 (**2**) was found to be strongly cytotoxic against the human cancer cell lines NCI-H460 (non-small cell lung carcinoma), MIA Pa Ca-2 (pancreatic cancer), MCF-7 (breast cancer), and SF-268 (CNS cancer; glioma) with slight selectivity towards the pancreatic cancer cell line (MIA Pa Ca-2) compared with the normal human primary fibroblast cells WI-38 (Table 1). None of the other metabolites (**1** and **3**–**12**) encountered in this study showed cytotoxicity towards any of the cell lines used when tested at a concentration of 5 μg/ml. However, it is noteworthy that some naphtho-γ-pyrones have been reported to reverse drug resistance in human KB cells (Ikeda et al., 1990).

Table 1
Cytotoxic data for malformin A_1 (**2**) against a panel of cancer cell lines and normal human primary fibroblast cells[a]

Compounds	Cell lines[b]				
	NCI-H460	MIA Pa Ca-2	MCF-7	SF-268	WI-38
2	0.07	0.05	0.10	0.07	0.10
Doxorubicin	0.01	0.07	0.04	0.05	0.30

[a] Results are expressed as IC_{50} values in μM.
[b] NCI-H460, human non-small cell lung cancer; MIA Pa Ca-2, human pancreatic cancer; MCF-7, human breast cancer; SF-268, human CNS cancer (glioma); WI-38, normal human primary fibroblast cells.

3. Experimental

3.1. General

Melting points were determined on an Electrothermal micromelting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer in KBr disks, and UV spectra in MeOH on a Shimadzu UV-1601 spectrometer. 1D and 2D NMR spectra were recorded on a Bruker DRX-500 instrument at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. The Chemical shift values (δ) are given in parts per million (ppm) and the coupling constants in hertz. Low-resolution APCI mass spectra were measured on a Shimadzu LCMS-8000QP α HPLC-MS system. High-resolution FAB-MS were obtained with a JEOL HX110A spectrometer.

3.2. Cytotoxicity assays

The tetrazolium-based colorimetric assay (MTT assay) (Rubinstein et al., 1990) was used for the in vitro assay of cytotoxicity to human non-small cell lung carcinoma (NCI-H460), human breast carcinoma (MCF-7), human glioma (SF-268), human pancreatic cancer (MIA Pa Ca-2) cell lines, and normal human fibroblast (WI-38) cells as previously reported (Wijeratne et al., 2003). All samples for cytotoxicity assays were dissolved in DMSO. During bioassay-guided fractionation, cytotoxicity of fractions was monitored using the NCI-H460 cell line.

3.3. Fermentation of *A. tubingensis*, extraction and isolation of the metabolites

A. tubingensis (Trichocomaceae) was isolated from the rhizosphere of *F. paradoxa* (D. Don) Endl. Ponil. (Apache plume) (Rosaceae) collected in Greasewood Mountains of Tucson, Arizona. The plant identification was made by Dr. Annita Harlan and a voucher specimen was deposited at the University of Arizona Herbarium. The fungal strain was identified by Ms. Donna Bigelow by the analysis of the ITS regions of the ribosomal DNA as previously described (Wijeratne et al., 2003). The fungal strain is deposited in the Division of Plant Pathology, Department of Plant Sciences and the Southwest Center for Natural Products Research and Commercialization of the University of Arizona microbial culture collection under the accession number AH-02-35-F5. The detailed general procedures of isolation, identification and cultivation of rhizosphere fungal strains have been described previously (Wijeratne et al., 2003; Zhan et al., 2004). Methanol (200 ml) was added to each of the 44 T-flasks of a solid culture of *A. tubingensis* in potato dextrose agar (PDA), and the flasks were shaken overnight at room temperature, filtered, and the residue washed with MeOH (50 ml for each flask) yielding a total of 9.9 l of the MeOH extract, which was concentrated to 2.4 l by evaporation under reduced pressure. The concentrated MeOH extract was

extracted with EtOAc (2 l × 3). Evaporation of EtOAc under reduced pressure afforded a dark yellow solid (2.5023 g). A portion (1.9 g) of the EtOAc extract was subjected to size-exclusion chromatography on Sephadex LH-20 (60.0 g) and eluted with CH_2Cl_2–hexane (1:1, 500 ml), CH_2Cl_2–hexane (2:1, 1000 ml), CH_2Cl_2–hexane (4:1, 500 ml), CH_2Cl_2–acetone (1:1, 250 ml), acetone (250 ml), and MeOH (1000 ml). Twenty-two fractions were collected and combined based on their TLC profiles to afford nine combined fractions F_1–F_9 [F_1 (15.3 mg), F_2 (79.8 mg), F_3 (209.4 mg), F_4 (131.0 mg), F_5 (570.5 mg), F_6 (129.4 mg), F_7 (376.2 mg), F_8 (70.5 mg) and F_9 (309.2 mg)]. Of these, only F_3 was found to be cytotoxic and it was separated on a column of silica gel (6.0 g) and by elution with hexane–acetone (4:1, 150 ml), hexane–acetone (3:1, 400 ml), hexane–acetone (2:1, 100 ml), hexane–acetone (1:1, 100 ml), acetone (25 ml) and MeOH (50 ml). Thirty-three fractions were collected and were combined based on their TLC profiles to yield 10 sub-fractions [F_{3A} (11.7 mg), F_{3B} (14.5 mg), F_{3C} (10.5 mg), F_{3D} (10.6 mg), F_{3E} (12.9 mg), F_{3F} (52.7 mg), F_{3G} (39.6 mg), F_{3H} (13.4 mg), F_{3I} (3.3 mg) and F_{3J} (14.3 mg)]. Of these, sub-fractions F_{3H}, F_{3I} and F_{3J} were found to be cytotoxic. These were combined and further separated by silica gel preparative TLC (developer solvent: hexane–acetone, 1:1) followed by size-exclusion chromatography on Sephadex LH-20 by elution with MeOH, yielding malformin A_1 (**2**) (4.0 mg) as a white powder. Sub-fraction F_{3G} was subjected to reversed phase (RP-18) preparative TLC (80% MeOH–H_2O) affording **1** (0.9 mg) and **9** (4.5 mg). Compounds **6** (3.0 mg) and **7** (5.6 mg) were isolated from sub-fraction F_{3C} using reversed phase (RP-18) preparative TLC (75% MeOH–H_2O). Sub-fraction F_{3D} was separated on silica gel preparative TLC (hexane–acetone, 3:2) followed by reversed phase (RP-18) preparative TLC (80% MeOH–H_2O), yielding **8** (0.5 mg) and **10** (2.2 mg). Purification of sub-fraction F_{3F} following a procedure identical with that used for sub-fraction F_{3D} above, afforded **12** (4.5 mg). Compound **3** (57.3 mg) was obtained by silica gel (8.0 g) column chromatography of fraction F_9 and elution with MeOH–CH_2Cl_2 (2:8) followed by purification by silica gel preparative TLC (MeOH–CH_2Cl_2, 3:7). Separation of fraction F_5 on a column of silica gel (15.0 g) and elution with hexane–acetone (2:1) afforded **11** (127.6 mg) and the sub-fractions F_{5A} (31.4 mg), F_{5B} (33.9 mg) and F_{5C} (168.5 mg). TLC analysis of fraction F_4 and the sub-fractions F_{3B} and F_{5C} indicated them to be similar and therefore these were combined and subjected to silica gel preparative TLC (hexane–acetone, 3:2), yielding **4** (101.2 mg) and **5** (101.3 mg).

Asperpyrone D (***1***): Yellow powder, m.p. 200 °C (dec.); UV nm (MeOH) λ_{max} (log ε): 384 (3.86), 281 (4.68), 248 (4.62), 225 (4.52); IR ν_{max} (KBr) cm^{-1}: 3425, 2928, 2858, 2365, 2338, 1655, 1616, 1570, 1427, 1380, 1261, 1204, 1165 and 1065; ^1H NMR (500 MHz, $CDCl_3$): δ 14.80 (1H, *s*, OH-5), 13.40 (1H, *s*, OH-5′), 7.14 (1H, *s*, H-9), 7.07 (1H, *s*, H-10), 6.45 (1H, *d*, $J = 2.2$ Hz, H-9′), 6.33 (1H, *s*, H-3′), 6.27 (1H, *d*, $J = 2.2$ Hz, H-7′), 6.00 (1H, *s*, H-3), 3.99 (3H, *s*, OCH_3-10′), 3.62 (3H, *s*, OCH_3-6), 3.60 (3H, *s*, OCH_3-8′), 2.54 (3H, *s*, CH_3-2′), 2.37 (3H, *s*, CH_3-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.5 (*s*, C-4), 182.7 (*s*, C-4′), 167.6 (*s*, C-2), 166.9 (*s*, C-2′), 162.2 (*s*, C-5 and C-8′), 159.5 (*s*, C-10′), 158.6 (*s*, C-6), 156.6 (*s*, C-5′), 155.9 (*s*, C-8), 155.5 (*s*, C-10b′), 153.1 (*s*, C-10a), 140.7 (*s*, C-6a′), 140.6 (*s*, C-9a), 116.4 (*s*, C-7), 111.5 (*s*, C-5a), 110.4 (*d*, C-3′), 108.0 (*s*, C-4a′), 107.2 (*d*, C-3), 106.2 (*s*, C-6′), 106.0 (*d*, C-9), 105.2 (*s*, C-10a′), 104.4 (*s*, C-4a), 100.9 (*d*, C-10), 97.4 (*d*, C-9′), 96.6 (*d*, C-7′), 62.4 (*q*, OCH_3-6), 56.1 (*q*, OCH_3-10′), 55.3 (*q*, OCH_3-8′), 20.8 (*q*, CH_3-2), 20.6 (*q*, CH_3-2′); HR-FAB-MS: *m*/*z* 557.1431 $[M+1]^+$ ($C_{31}H_{25}O_{10}$ requires 557.1448).

Acknowledgements

The authors thank Arizona Biomedical Research Commission (Grant No. 6015), National Cancer Institute (Grant No. R01CA90265), and College of Agriculture & Life Sciences of The University of Arizona for financial assistance, Dr. Hans D. VanEtten, Dr. Annita Harlan, and Ms. Donna Bigelow (all of Division of Plant Pathology, Department of Plant Sciences, The University of Arizona) respectively, for providing the fungal strain used in this study, identification of the plant species, and assistance in the identification of the fungal strain, and Ms. Manping Liu for the cytotoxicity bioassays.

References

Akiyama, K., Teraguchi, S., Hamasaki, Y., Mori, M., Tatsumi, K., Ohnishi, K., Hayashi, H., 2003. New dimeric naphthopyrones from *Aspergillus niger*. Journal of Natural Products 66, 136–139.

Barbosa, F.G., de Oliveira, M.C.F., Braz-Filho, R., Silveira, E.R., 2004. Anthraquinones and naphthopyrones from *Senna rugosa*. Biochemical Systematics and Ecology 32, 363–365.

Chomcheon, P., Wiyakrutta, S., Sribolmas, N., Ngamrojanavanich, N., Isarangkul, D., Kittakoop, P., 2005. 3-Nitropropionic acid (3-NPA), a potent antimycobacterial agent from endophytic fungi: is 3-NPA in some plants produced by endophytes? Journal of Natural Products 68, 1103–1105.

Coelho, R.G., Vilegas, W., Devienne, K.F., Raddi, M.S.G., 2000. A new cytotoxic naphthopyrone dimer from *Paepalanthus bromelioides*. Fitoterapia 71, 497–500.

Curtis, R.W., John, W.W., 1975. Effect of malformin on phytochrome- and ethrel-mediated responses. Plant and Cell Physiology 16, 719–728.

Dawes, J., 1994. Malformin A prevents IL-1 induced endothelial changes by inhibition of protein synthesis. Thrombosis and Haemostasis 72, 482–483.

Franck, B., 1984. Mycotoxins from mold fungi-weapons of uninvited fellow-boarders of man and animal: structures, biological activity, biosynthesis, and precautions. Angewandte Chemie International Edition 23, 493–505 (in English).

Galmarini, O.L., Stodola, F.H., 1965. Fonsecin, a pigment of an *Aspergillus fonsecaeus* mutant. Journal of Organic Chemistry 30, 112–115.

Gorst-Allman, C.P., Steyn, P.S., Rabie, C.J., 1980. Structural elucidation of the nigerones, four new naphthopyrones from cultures of *Aspergillus niger*. Journal of the Chemical Society Perkin I 11, 2474–2479.

Gunatilaka, A.A.L., 2006. Natural products from plant-associated microorganisms: distribution, structural diversity, bioactivity and implications of their occurrence. Journal of Natural Products 69, 509–526.

Ikeda, S., Sugita, M., Yoshimura, A., Sumizawa, T., Douzono, H., Nagata, Y., Akiyama, S., 1990. *Aspergillus* species strain M39 produces two naphtho-γ-pyrones that reverse drug resistance in human KB cells. International Journal of Cancer 45, 508–513.

Inokoshi, J., Shiomi, K., Masuma, R., Tanaka, H., Yamada, H., Ōmura, S., 1999. Funalenone, a novel collagenase inhibitor produced by *Aspergillus niger*. Journal of Antibiotics 52, 1095–1100.

Iriuchijima, S., Curtis, R.W., 1969. Malformins from *Aspergilllus ficuum*, *A. awamori*, and *A. phoenicis*. Phytochemistry 8, 1397–1399.

John, W.W., Curtis, R.W., 1974. Stimulation of plant growth by malformin A. Experientia 30, 1392–1393.

Kettering, M., Weber, D., Sterner, O., Ankem, T., 2004. Secondary metabolites of fungi – functions and uses. BIOspectrum 10, 147.

Li, X.-C., Dunbar, D.C., ElSohly, H.N., Jacob, M.R., Nimrod, A.C., Walker, L.A., Clark, A.M., 2001. A new naphthopyrone derivative from *Cassia quinquangulata* and structure revision of quinquangulin and its glycosides. Journal of Natural Products 64, 1153–1156.

Rubinstein, L.V., Shoemaker, R.H., Paul, K.D., Simon, R.M., Tosini, S., Skehan, P., Scudiero, D.A., Monks, A., Boyd, M.R., 1990. Comparison of in vitro anticancer drug-screening data generated with a tetrazolium assay versus a protein assay against a diverse panel of human tumor cell lines. Journal of the National Cancer Institute 82, 1113–1118.

Sakurai, M., Kohno, J., Yamamoto, K., Okuda, T., Nishio, M., Kawano, K., Ohnuki, T., 2002. TMC-256A1 and C1, new inhibitors of IL-4 signal transduction produced by *Aspergillus niger* var *niger* TC 1629. Journal of Antibiotics 55, 685–692.

Schulz, B., Boyle, C., Draeger, S., Römmert, A.K., Krohn, K., 2002. Endophytic fungi: a source of novel biologically active secondary metabolites. Mycological Research 106, 996–1004.

Shiomi, K., Matsui, R., Isozaki, M., Chiba, H., Sugai, T., Yamaguchi, Y., Masuma, R., Tomoda, H., Chiba, T., Yan, H., Kitamura, Y., Sugiura, W., Omura, S., Tanaka, H., 2005. Fungal phenalenones inhibit HIV-1 integrase. Journal of Antibiotics 58, 65–68.

Singh, S.B., Zink, D.L., Bills, G.F., Teran, A., Silverman, K.C., Lingham, R.B., Felock, P., Hazuda, D.J., 2003. Four novel bis-(naphtho-γ-pyrones) isolated from *Fusarium* species as inhibitors of HIV-1 integrase. Bioorganic & Medicinal Chemistry Letters 13, 713–717.

Strobel, G., Daisy, B., Castillo, U., Harper, J., 2004. Natural products from endophytic microorganisms. Journal of Natural Products 67, 257–268.

Suda, S., Curtis, R.W., 1966. Antibiotic properties of malformin. Applied Microbiology 14, 475–476.

Sugawara, F., Kim, K.W., Uzawa, J., Yoshida, S., Takahashi, N., Curtis, R.W., 1990. Structure of malformin A_2, reinvestigation of phytotoxic metabolites produced by *Aspergillus niger*. Tetrahedron Letters 31, 4337–4340.

Tan, R.X., Zou, W.X., 2001. Endophytes: a rich source of functional metabolites. Natural Product Reports 18, 448–459.

TePaske, M.R., Gloer, J.B., Wicklow, D.T., Dowd, P.F., 1989. Three new aflavinines from the sclerotia of *Aspergillus tubingensis*. Tetrahedron 45, 4961–4968.

Turbyville, T.J., Wijeratne, E.M.K., Liu, M.X., Burns, A.M., Seliga, C.J., Luevano, L.A., David, C.L., Faeth, S.H., Whitesell, L., Gunatilaka, A.A.L., 2006. Studies on arid lands plants and microorganisms, Part 7. Search for hsp90 inhibitors with potential anticancer activity: isolation and SAR studies of radicicol and monocillin I from two plant-associated fungi of the Sonoran desert. Journal of Natural Products 69, 178–184.

Wang, P.-L., Tanaka, H.A., 1966. Yellow pigments of *Aspergillus niger* and *Aspergillus awamori*. II Chemical structure of aurasperone A. Agricultural and Biological Chemistry 30, 683–687.

Wijeratne, E.M.K., Turbyville, T.J., Zhang, Z., Bigelow, D., Pierson Jr., L.S., VanEtten, H.D., Whitesell, L., Canfield, L.M., Gunatilaka, A.A.L., 2003. Cytotoxic constituents of *Aspergillus terreus* from the rhizosphere of *Opuntia versicolor* of the Sonoran Desert. Journal of Natural Products 66, 1567–1573.

Wijeratne, E.M.K., Paranagama, P.A., Gunatilaka, A.A.L., 2006. Five new isocoumarins from Sonoran desert plant-associated fungal strains *Paraphaeosphaeria quadriseptata* and *Chaetomium chiversii*. Tetrahedron 62, 8439–8446.

Zhan, J., Wijeratne, E.M.K., Seliga, C.J., Zhang, J., Pierson, E.E., Pierson Jr., L.S., VanEtten, H.D., Gunatilaka, A.A.L., 2004. A new anthraquinone and cytotoxic curvularins of a *Penicillium* sp. from the rhizosphere of *Fallugia paradoxa* of the Sonoran desert. Journal of Antibiotics 57, 341–344.