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Quinofuracins A−E, Produced by the Fungus *Staphylotrichum boninense* PF1444, Show p53-Dependent Growth Suppression

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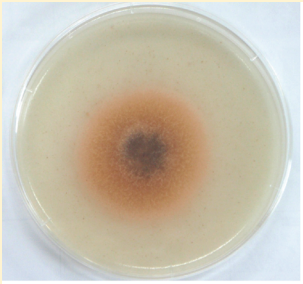
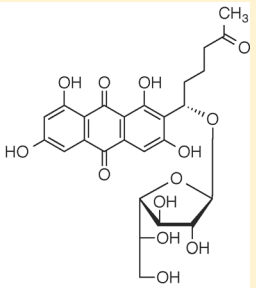
Supporting Information

ABSTRACT: Quinofuracins A−E, novel anthraquinone derivatives containing β-D-galactofuranose that were isolated from the fungus *Staphylotrichum boninense* PF1444, induced p53-dependent cell death in human tumor cells. The structures of quinofuracins A−E, including absolute configurations, were elucidated by extensive spectroscopic analysis and chemical transformation studies. Quinofuracins were classified into three groups according to the aglycone moieties. 5′-Oxoaverantin was present in quinofuracins A−C, whereas averantin and versicolorin B were identified in quinofuracins D and E, respectively. These quinofuracins induced p53-dependent growth suppression in human glioblastoma LNZTA3 cells.



Staphylotrichum boninense PF1444



Quinofuracin D

In eukaryote cells, cell cycle signaling pathways are required for cell cycle arrest and induction of apoptosis after exposure to DNA-damaging agents (UV, IR, and chemical agents). The transcription factor p53, a member of the cell cycle signaling pathway, is known as a tumor suppressor. In human cancers, inactivation of p53 is common.[1] In ∼50% of human cancers, p53 is inactivated by deletion or mutation of its gene. In the remaining cancers, p53 retains wild-type status, but its tumor suppressor function is inhibited by multiple mechanisms. One major inhibitory mechanism is mediated by its primary cellular inhibitor Mdm2, which binds directly to p53 and inhibits p53 activity. Mdm2, a ubiquitin E3 ligase, binds to p53, ubiquitinates, and induces p53 degradation by proteasome.[2] Because inhibition of p53 degradation promotes p53 transcriptional activity and induces cell death, compounds that induce p53 activation are being developed to suppress the growth of tumor cells. Nutlin-3, MI-63, AM8553, and their derivatives inhibit p53-Mdm2 interaction, induce p53-dependent cell death *in vitro*, and suppress osteosarcoma tumor growth in the xenograft model.[3−7] JNJ-26854165, an Mdm2 ubiquitin ligase inhibitor, also induces growth suppression in a p53-dependent manner.[8] Some of these compounds are progressing to clinical trial in cancer patients.[5,9] Therefore, inducers of p53-dependent cell death may be attractive lead compounds for a new cancer therapy.

To discover new inducers of p53-dependent cell death, we have developed a screening system using glioblastoma LNZTA3 cells. These cells are engineered to express wild-type p53 in a tetracycline-regulated system.[10] The production of p53 is induced in the absence of tetracycline, while the production of p53 is suppressed in its presence. Using this screening system, we screened microbial metabolites to find cytotoxic compounds that preferentially act under p53-producing conditions. As the results of this screening, we have isolated five novel natural compounds, namely, quinofuracins A−E, from *Staphylotrichum boninense* PF1444 (Figure 1). Quinofuracins A−E (**1**−**5**) are anthraquinone derivatives containing a β-D-galactofuranose moiety. These quinofuracins induced p53-depedent growth suppression in human glioblastoma LNZTA3 cells. In this report, we describe the isolation and structural elucidation of **1**−**5** along with their ability to induce p53-dependent growth suppression in LNZTA3 cells.

RESULTS AND DISCUSSION

The fungus *S. boninense* PF-1444 was cultured in a solid rice medium (2 kg). Aqueous acetone extracts of solid cultures were partitioned between H_2O and EtOAc. The organic fraction was concentrated to give an oily material. The resulting material was subjected to silica gel chromatography followed by HPLC to give five novel compounds, **1**−**5**.

Quinofuracin D (**4**), the predominant quinofuracin, was isolated as a red, amorphous solid. The UV spectrum of **4** exhibited absorption maxima at 223, 263, 290, 314, and 460 nm and was very similar to that of averantin.[11] The molecular formula of **4** was determined to be $C_{26}H_{28}O_{13}$ based on HRMS analysis and NMR spectroscopic data. The ^1H and ^{13}C NMR

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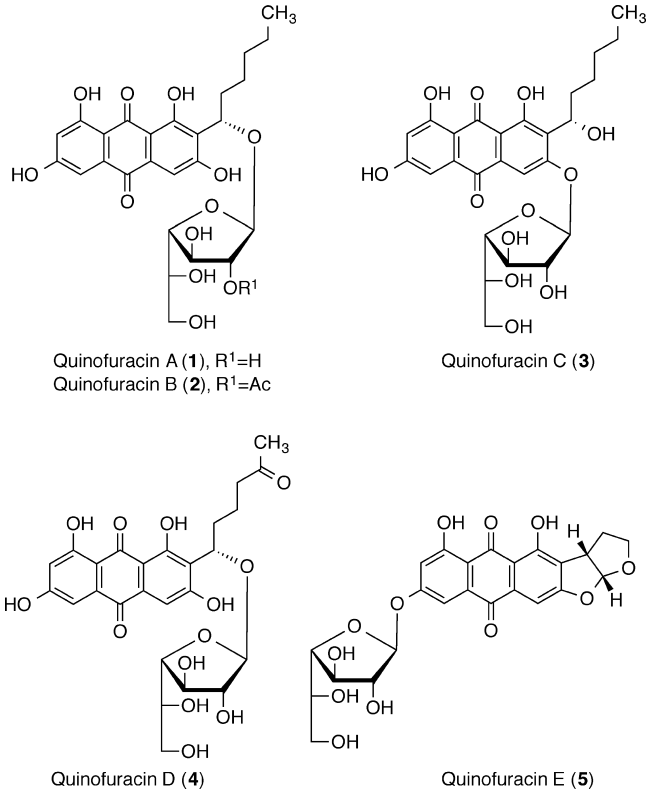

Figure 1. Structures of quinofuracins A–E (**1**–**5**).

spectroscopic data of **4** are shown in Table 1. Analysis of ^{13}C NMR and DEPT, along with HMQC spectra, revealed the presence of 26 carbons in **4**, which were categorized as one methyl, four methylene, six oxymethine, three sp^2 methine, nine sp^2 quaternary, and three carbonyl carbons. **4** was elucidated primarily using two-dimensional NMR experiments ($^1H-^1H$ COSY and HMBC) as illustrated in Figure 2. In the HMBC spectrum, correlations between aromatic protons at H-2, H-4, H-6, and an oxymethine proton at H-1′ and relevant carbons in the anthraquinone skeleton suggested that **4** was a pentasubstituted anthraquinone. In the $^1H-^1H$ COSY spectrum, a spin network was observed from the oxymethine proton at H-1′ to the methylene protons at H_2-4′ through two methylenes at H_2-2′ and H_2-3′. In the HMBC spectrum, methyl protons at H_3-6′ showed correlations with the methylene carbon at C-4′ and the carbonyl carbon at C-5′, and methylene protons at H_2-4′ showed correlations with the carbonyl carbon at C-5′ and the methyl carbon at C-6′, suggesting the presence of 5′-oxoaverantin as an aglycone.[12,13]

In addition, a proton spin network from protons on the anomeric proton at H-1″ to methylene protons at H_2-6″ through four oxymethines (H-2″ to H-5″) were evident in the $^1H-^1H$ COSY. In addition, HMBC correlations were observed from the anomeric proton at H-1″ to the methine carbon at C-4″ and from the methine proton at H-4″ to the anomeric carbon at C-1″. These observations implied the presence of a furanose-type sugar moiety. Furthermore, HMBC correlations were observed between methine proton/carbon (H/C-1′) and anomeric carbon/proton (C/H-1″). These results suggested that the furanose moiety was linked to oxymethine C-1′ through a glycosidic bond. Consequently, **4** was characterized to be the novel 5′-oxoaverantin derivative containing a furanose as the sugar moiety.

The nature of the sugar moiety and the absolute configuration of **4** were determined after chemical degradation (Scheme 1). The treatment of **4** with hydrogen chloride in methanol at room temperature afforded anthraquinone **6** and methyl glycoside **7**. NMR spectroscopic analysis revealed that compound **6** was averufin.[14,15] 5′-Oxoaverantin, the aglycone of **4**, has been known to be readily dehydrated to **6** by nonenzymatic means.[12,13] Therefore, the formation of **6** confirmed that **4** was a derivative of 5′-oxoaverantin. In addition, the absolute configuration of **6** was determined to be 1′*S* and 5′*R*, because its circular dichroism (CD) spectrum was consistent with that of (1′*S*, 5′*R*)-averufin (Figure S1).[16] Thus, the configuration at position 1′ in **4** was determined to be *S*. Meanwhile, the methyl glycoside **7** was *p*-bromobenzoylated to afford tetra-*O*-*p*-bromobenzoates **8a** and **8b**. NMR chemical shifts, coupling constants, and optical behavior of **8a** were identical to those of methyl 2,3,4,6-tetra-*O*-*p*-bromobenzoyl-α-D-galactopyranoside (i.e., the α-anomer),[17] whereas the NMR data and specific rotation data of **8b** were identical to those of the β-anomer.[17] The structures of **8a** and **8b** were further confirmed by chemical synthesis.[18]

^{13}C NMR chemical shifts of the D-galactofuranoside moiety in **4** were consistent with those of methyl β-D-galactofuranoside.[18−20] The coupling constants ($J_{1″,2″}$ = 1.8 Hz and $J_{2″,3″}$ = 3.8 Hz) indicated that the anomeric carbon of the galactofuranoside has a β configuration in **4**.[21] Taken together, the structure of **4** was determined to be (1′*S*)-1′-*O*-β-D-galactofuranosyl-5′-oxoaverantin (Figure 1).

Quinofuracin A (**1**) was isolated as a red, amorphous solid. The similarity in the physicochemical and the NMR data of **1** with those of **4** (Table 1) indicated that **1** had a related structure. The molecular formula of **1** was established as $C_{26}H_{30}O_{12}$ based on the HRMS and NMR data, indicating that **1** had two additional hydrogen atoms and one less oxygen atom than **4**; the absence of a carbonyl carbon signal in the ^{13}C NMR spectrum of **1** supported this observation. From detailed NMR analysis, it was evident that the carbonyl group (C-5′) of **4** was replaced by a methylene (δ_H 1.35, δ_C 23.7) in **1**, suggesting that **1** has averantin[11] as an aglycone (Figure 3). Methanolysis of **1** gave the methyl glycoside **7** (as in the case of **4**) and the methylated aglycone **9** (Scheme S1). Methyl glycoside **7** was characterized using methods described for the identification of degradation products of **4**, i.e., *p*-bromobenzoylation, followed by NMR analysis and specific rotation data determination. NMR analysis of methylated aglycone **9** revealed its identity as 1′-*O*-methylaverantin.[14,22] However, the specific rotation of **9**, $[\alpha]^{27}_D$ 0 (*c* 0.10, $CHCl_3$–MeOH = 5:1), suggested the likelihood of racemization at position 1′ during methanolysis. Therefore, by comparing the CD spectra of **4** and **1**, the absolute configuration at C-1′ in **1** was established to be *S* as shown in Figure S2. The structure of **1** was determined to be (1′*S*)-1′-*O*-β-D-galactofuranosylaverantin (Figure 1).

Quinofuracin B (**2**) was isolated as a red, amorphous solid, with physicochemical properties and spectroscopic data similar to those of **1** (Table 1). The determined molecular formula of **2**, $C_{28}H_{32}O_{13}$, suggested that **2** could be the acetyl derivative of **1**. ^1H and ^{13}C NMR spectra of **2** supported the presence of an acetyl group (δ_H 1.98, δ_C 20.6 and 172.1). The methine proton at δ 4.99 (H-2″) in **2** was shifted downfield when compared with that in **1**, and HMBC correlations between the methine proton (H-2″) and the carbonyl carbon at δ_C 172.1 revealed that the 2″-OH was acetylated (Figure 4). In addition, the CD spectrum of **2** was similar to that of **1**, suggesting that **2** has the

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Table 1. ^{13}C (150 MHz) and ^{1}H (600 MHz) NMR Spectroscopic Data for Quinofuracins A–E (1–5)

	1[a]			2[a]			3[b]			4[a]			5[b]		
position	δ_C	type	δ_H (mult., J in Hz)	δ_C	type	δ_H (mult., J in Hz)	δ_C	type	δ_H (mult., J in Hz)	δ_C	type	δ_H (mult., J in Hz)	δ_C	type	δ_H (mult., J in Hz)
1	166.3	C		166.5	C		166.0	C		166.4	C		165.3	C	
2	109.2	CH	6.49 (br s)	109.4	CH	6.46 (br s)	109.5	CH	6.96 (br s)	109.4	CH	6.49 (d, 2.2)	110.0	CH	7.21 (br s)
3	167.0	C		168.5	C		168.6	C		168.2	C		164.2	C	
4	110.1	CH	7.10 (br s)	110.9	CH	7.10 (br s)	111.1	CH	7.69 (br s)	110.7	CH	7.12 (d, 2.2)	110.0	CH	7.71 (d, 1.8)
4a	136.5	C		136.5	C		136.5	C		136.5	C		135.6	C	
5	182.9	C		183.3	C		182.1	C		183.3	C		181.7	C	
5a	135.3	C		135.4	C		133.8	C		135.4	C		136.7	C	
6	110.1	CH	7.14 (s)	110.2	CH	7.14 (s)	106.3	CH	8.04 (s)	110.3	CH	7.16 (s)	102.2	CH	7.44 (s)
7	164.7	C		164.1	C		160.1	C		165.3	C		166.3	C	
8	120.6	C		120.2	C		128.1	C		120.3	C		120.8	C	
9	163.8	C		165.3	C		161.9	C		164.0	C		165.9	C	
9a	110.2	C		109.9	C		111.3	C		109.8	C		112.2	C	
10	190.8	C		190.4	C		189.6	C		190.5	C		191.7	C	
10a	110.0	C		109.7	C		109.1	C		109.9	C		111.1	C	
11													113.9	CH	6.61 (d, 6.0)
12													44.8	CH	4.13 (m)
13													31.0	CH_2	2.15 (m)
															2.32 (m)
14													67.9	CH_2	3.72 (m)
															4.11 (m)
1′	72.9	CH	5.42 (dd, 5.6, 8.0)	72.3	CH	5.42 (dd, 5.8, 8.2)	66.3	CH	5.79 (dd, 6.0, 8.0)	72.2	CH	5.41 (dd, 5.4, 8.0)			
2′	34.8	CH_2	1.87 (m)	34.6	CH_2	1.86 (m)	36.6	CH_2	2.18 (m)	33.9	CH_2	1.83 (m)			
			2.06 (m)			2.09 (m)			2.37 (m)			2.10 (m)			
3′	26.6	CH_2	1.38 (m)	26.8	CH_2	1.37 (m)	26.6	CH_2	1.53 (m)	21.3	CH_2	1.64 (m)			
			1.52 (m)			1.52 (m)			1.76 (m)			1.75 (m)			
4′	32.7	CH_2	1.35 (m)	32.7	CH_2	1.35 (m)	32.1	CH_2	1.35 (m)	43.8	CH_2	2.58 (br t, 7.0)			
5′	23.7	CH_2	1.35 (m)	23.7	CH_2	1.35 (m)	22.9	CH_2	1.25 (m)	212.3	C				
6′	14.4	CH_3	0.91 (t, 7.0)	14.4	CH_3	0.90 (t, 7.4)	14.2	CH_3	0.80 (t, 7.2)	29.9	CH_3	2.13 (s)			
1″	107.7	CH	4.85 (overlap with solvent)	104.9	CH	4.92 (br s)	105.7	CH	6.61 (br s)	107.7	CH	4.83 (br s)	108.1	CH	6.34 (br s)
2″	83.1	CH	4.00 (dd, 1.4, 3.8)	86.2	CH	4.99 (dd, 1.2, 3.4)	81.2	CH	4.96 (br s)	83.2	CH	4.00 (dd, 1.8, 3.8)	83.6	CH	5.16 (dd, 1.8, 4.2)
3″	79.0	CH	4.04 (dd, 3.8, 6.4)	76.9	CH	4.18 (dd, 3.4, 7.0)	79.2	CH	5.02 (br s)	79.1	CH	4.01 (dd, 3.8, 6.4)	78.3	CH	5.21 (dd, 4.2, 6.4)
4″	85.6	CH	4.06 (dd, 3.4, 6.4)	84.5	CH	4.07 (dd, 3.4, 7.0)	89.7	CH	5.11 (br s)	85.4	CH	4.05 (dd, 3.8, 6.4)	86.5	CH	5.09 (dd, 3.2, 6.4)
5″	72.4	CH	3.78 (dd, 3.4, 7.0)	72.0	CH	3.77 (dt, 3.4, 6.8)	72.9	CH	4.45 (m)	72.5	CH	3.72 (m)	72.4	CH	4.58 (dd, 3.2, 6.2)
6″	64.8	CH_2	3.68 (d, 7.0)	64.9	CH_2	3.69 (d, 6.8)	63.8	CH_2	4.22 (d, 6.2)	64.6	CH_2	3.65 (dd, 7.0, 11.6)	64.3	CH_2	4.36 (dd, 6.2, 10.0)
												3.68 (dd, 6.0, 11.6)			4.38 (dd, 6.2, 10.0)
2″-$COCH_3$				172.1	C										
2″-$COCH_3$				20.6	CH_3	1.98 (s)									

[a] ^{13}C NMR spectra were measured in CD_3OD solvent. [b] ^{13}C NMR spectra were measured in C_5D_5N solvent.

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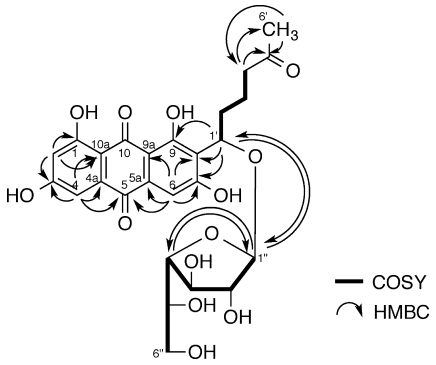


Figure 2. Key correlations of **4** obtained by $^{1}H-^{1}H$ COSY and HMBC spectroscopy.

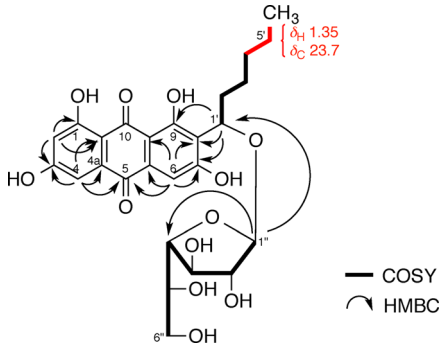


Figure 3. Key correlations of **1** obtained by $^{1}H-^{1}H$ COSY and HMBC spectroscopy.

same configuration as **1** (Figure S2). Thus, the structure of **2** was determined to be 1′-*O*-(2″-*O*-acetyl-*β*-D-galactofuranosyl)-averantin (Figure 1).

Quinofuracin C (**3**) was isolated as a red, amorphous solid. The molecular formula of **3** was established as $C_{26}H_{30}O_{12}$ based on the HRMS and NMR data and was elucidated to be the same as that of **1**. However, several NMR chemical shifts and the physicochemical behavior of **3** were distinct from those of **1** (Table 1). In particular, the anomeric proton at *δ* 6.61 (H-1″) in **3** was shifted downfield when compared with that in **1** and showed a correlation with the carbon at C-7 in the HMBC spectrum, indicating that *β*-D-galactofuranose was bound at the C-7 position of the aglycone (Figure 5). In addition, the CD spectrum of **3** was similar to that of **1**, suggesting that **3** might have the same configuration as **1** (Figure S2). Therefore, the structure of **3** was determined to be 7-*O*-*β*-D-galactofuranosyl-averantin (Figure 1).

Quinofuracin E (**5**) was isolated as an orange-yellow, amorphous solid. The features in the UV spectrum of **5** were distinct from those of **1**–**4**, whereas they were similar to those of versicolorin B.[23] The molecular formula of **5** was established as $C_{24}H_{22}O_{12}$ by HRMS and NMR spectroscopic data. NMR analysis indicated the presence of pentasubstituted anthraquinone and galactofuranose moieties. In the $^{1}H-^{1}H$ COSY spectrum, a proton spin network from the dioxymethine proton at H-11 to oxymethylene protons at H_2-14 through H-12 and H_2-13 was observed. In the HMBC spectrum, correlations between C-11 and C-14 suggested the presence of a fused

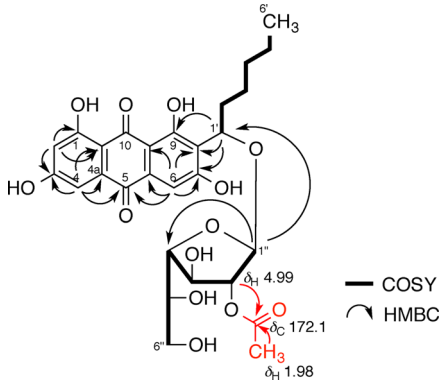
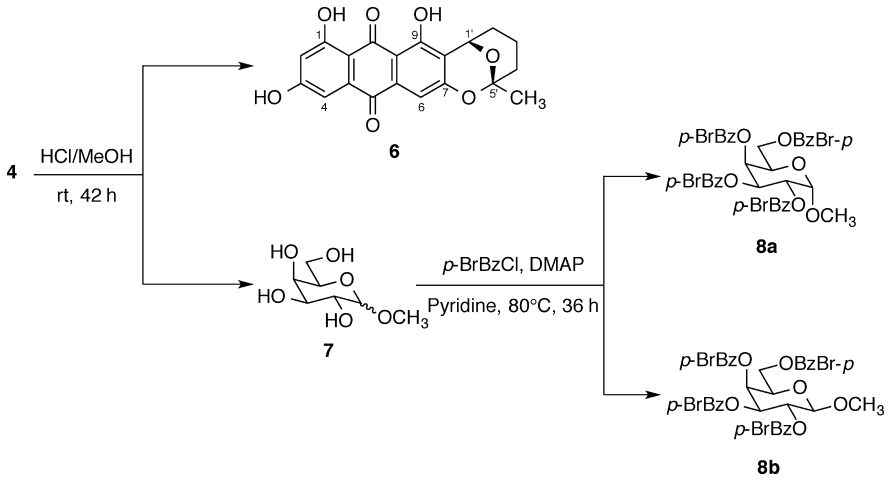


Figure 4. Key correlations of **2** obtained by $^{1}H-^{1}H$ COSY and HMBC spectroscopy.

tetrahydrofuran ring (Figure 6). In addition, the methine proton H-11 showed a correlation with C-7, and the methine proton H-12 showed a correlation with C-8, suggesting that **5** possesses the versicolorin B skeleton as the aglycone.[23,24] The protons H-11 and H-12 were determined to be in a *cis* configuration on the basis of NOE interactions. The coupling constants ($J_{1'',2''}$ = 1.8 Hz and $J_{2'',3''}$ = 4.2 Hz) revealed that the anomeric carbon (C-1″) of the galactofuranoside moiety has a *β* configuration. Moreover, the anomeric proton exhibited a correlation with an aromatic carbon at C-3, suggesting that *β*-galactofuranose was linked to the C-3 carbon by a glycosidic bond.

Scheme 1. Degradation Study of 4



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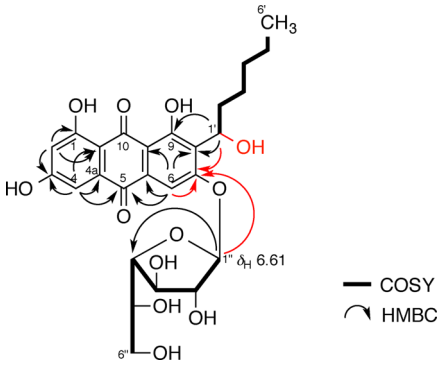

Figure 5. Key correlations of **3** obtained by $^{1}H-^{1}H$ COSY and HMBC spectroscopy.

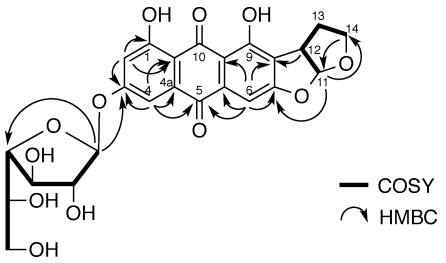

Figure 6. Key correlations of **5** obtained by $^{1}H-^{1}H$ COSY and HMBC spectroscopy.

The absolute configuration of **5** was determined after characterizing the products of methanolysis, i.e., the aglycone **10** and the methyl sugar **7** (Scheme S2). Compound **10** was identified as versicolorin B by analysis of its NMR spectra. In addition, the specific rotation of **10** $\{[\alpha]^{26}_{D}$ −230 (*c* 0.07, dioxane)} was identical to that of (1′*R*,2′*S*)-(−)-versicolorin B.[23] Therefore, the aglycone of **5** possessed the same absolute configuration as (1′*R*, 2′*S*)-versicolorin B. Meanwhile, the structure of the methyl sugar **7** was identical to the corresponding degradation product of **4**. The structure of **5** was therefore determined to be (1′*R*,2′*S*)-3-*O*-*β*-D-galactofuranosylversicolorin B (Figure 1).

To examine the p53-dependent growth suppression by quinofuracins, we used human glioblastoma LNZTA3 cells. These cells contain a wild-type p53 encoding sequence controlled by tetracycline. Wild-type p53 is produced in the absence of tetracycline; however, p53 is not produced in the presence of tetracycline. LNZTA3 cells were treated with quinofuracins in the presence or absence of tetracycline. After treatment for 72 h, the cell viability was determined by MTT assay (Figure 7). Nutlin-3, an Mdm2 inhibitor, induced p53-dependent growth suppression in LNZTA3 cells.[3] Compound **1** inhibited growth in LNZTA3 cells with IC_{50} values of 6.2 μM (presence of p53) and 32 μM (absence of p53), respectively. The IC_{50} values of **2** were similar to **1**. Growth suppression by **3** was weaker than that of **1** or **2**. An aglycone of **1**−**3**, (1′*S*)-averantin showed p53-dependent growth suppression, although the p53 dependency was low (Figure S3). Compound **4** displayed growth suppression in the presence of p53 in LNZTA3 cells; however, growth suppression by **4** was not observed in the absence of p53 even at doses of >100 μM. Compound **5** inhibited the growth of LNZTA3 cells more strongly in the presence of p53 than in its absence. The IC_{50} values of all quinofuracins were lower in the presence of p53 than that in its absence. These compounds exhibited preferential cytotoxicity to LNZTA3 cells expressing wild-type p53. In addition, quinofuracins also induce p53-dependent growth suppression on various wild-type p53 cancer cells (MKN45, RKO, HCT-116, and MCF-7) and mutant p53 cancer cells (MKN-7, HCT-15, and MDA-MB-23) (data not

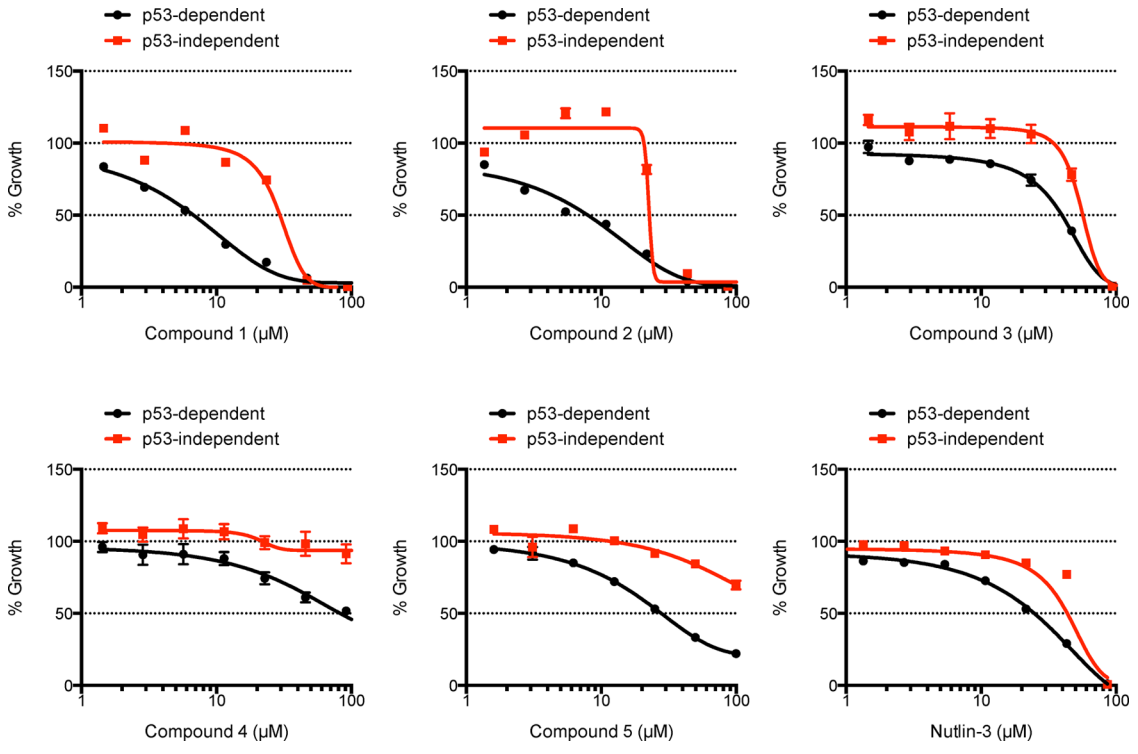

Figure 7. p53-dependent growth suppression of quinofuracins.

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shown). Further investigations into the biological activities of quinofuracins and the molecular mechanism of p53 dependency are currently under way.

In this study, we have identified novel bioactive compounds produced by the fungal strain PF1444. This strain, isolated from a soil sample collected in Fukuoka prefecture, has been identified as *S. boninense,* a fungus that has been recently reported as a new hyphomycete belonging to the Chaetomiaceae (Ascomycota) family.[25] *S. boninense* has been reported to produce averufin and its derivatives. We found that *S. boninense* strain PF1444 produces five novel compounds (**1**−**5**), named quinofuracins A−E. Quinofuracins consist of an anthraquinone aglycone and the sugar β-D-galactofuranose. On the basis of the nature of the aglycone, quinofuracins are classified into three groups: those containing averantin (e.g., **1**−**3**), those containing 5′-oxoaverantin (e.g., **4**), and those containing versicolorin B (e.g., **5**). Averantin, 5′-oxoaverantin, and versicolorin B are known intermediates in the biosynthesis of afratoxin.[26] Whereas a few derivatives of these aglycones have been reported,[22,27] this study constitutes the first report of D-galactofuranosylated derivatives. Furthermore, although over 10 000 fungal secondary metabolites have been reported,[28] only five other galactofuranosylated glycosides are in the literature;[18,29,30] quinofuracins are the sixth case. Glycosylation is expected to enhance the physicochemical properties of the compounds such as improved solubility. Quinofuracins may be promising candidates for pharmaceutical development.

EXPERIMENTAL SECTION

General Experimental Procedures. NMR spectra were acquired on a JNM-A400 (JEOL, Tokyo, Japan) and a JNM-ECA (JEOL). For ^{1}H NMR, chemical shifts are reported as δ in parts per million downfield from tetramethylsilane and are referenced to residual protons in the NMR solvent. For ^{13}C NMR, chemical shifts are reported in the scale relative to the NMR solvent as an internal reference. NMR data are reported as follows: integration, chemical shifts, multiplicity, coupling constant (Hz), and position. Infrared (IR) spectra were recorded on an FT-210 Fourier transform infrared spectrophotometer (Horiba, Kyoto, Japan). Optical rotation was measured using a P-1030 polarimeter (JASCO, Tokyo, Japan). CD spectra were recorded using a J-720 spectrometer (JASCO). HRESIMS spectra were measured on a Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA). Silica gel column chromatography was performed using silica gel 60 (Merck, Darmstadt, Germany). TLC analysis was performed on precoated plates (silica gel 60F_{254}, Merck; $CHCl_3$−MeOH−AcOH = 10:1:0.03). HPLC analysis was conducted on an HPLC system equipped with a reversed-phase column (CapcellPak UG120, Φ 0.45 cm × 25 cm, Shiseido, Tokyo, Japan; 40% aqueous CH_3CN containing 0.1% AcOH; flow rate, 1 mL/min; detection, 455 nm).

Microorganism. The fungal strain PF-1444 was isolated from a soil sample collected in Fukuoka Prefecture, Japan. This strain was deposited as NITE BP-1450 at the NITE Patent Microorganisms Depository, Japan.

Taxonomy. The following media were used to identify strain PF-1444: potato dextrose agar, 2% malt agar, oatmeal agar, and LCA (Miura's) medium. The formed colonies were observed during the 2 to 7-week incubation period at 25 °C. The 28S rRNA-D1/D2 and ITS-5.8S rRNA sequences of strain PF-1444 were identical to those of *Staphylotrichum boninense* JCM17909 (100%). Therefore, this strain was designated as *Staphylotrichum boninense* PF-1444. These sequence data of *S. boninense* PF-1444 were deposited in GenBank as LC004917 and LC004918.

Fermentation and Isolation. A slant culture of *S. boninense* PF-1444 was inoculated into a 100 mL Erlenmeyer flask containing seed medium (20 mL) consisting of soluble starch (2.0%), glucose (1.0%), polypeptone (0.5%), wheat germ (0.6%), yeast extract (0.3%), and $CaCO_3$ (0.2%) in deionized water with the pH adjusted to 7.0 with NaOH solution before sterilization. The flask was incubated at 25 °C for 4 days on a rotary shaker at 220 rpm. Aliquots (3 mL) of this seed culture were transferred into 500 mL Erlenmeyer flasks containing a mixture of oatmeal (2 g) and water-absorbed rice (80 g) as a solid production medium. The flasks were cultured at 25 °C for 14 days (no shaking), following which the obtained culture (2 kg) was extracted with aqueous acetone (67%; 4 L) and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was partitioned between H_2O (2 L) and EtOAc (2 L). The organic fraction was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed using a silica gel column with $CHCl_3$−MeOH to give a crude material. This material was then applied to a reversed-phase HPLC column (CapcellPak UG120, Φ 20 mm × 250 mm) and eluted with aqueous CH_3CN (30% or 40%) containing 0.1% acetic acid. Consequently, five novel compounds, **1** (30 mg), **2** (5 mg), **3** (10 mg), **4** (60 mg), and **5** (25 mg), were isolated.

*Quinofuracin A (**1**):* red, amorphous solid; UV (MeOH) λ_{max} (log ε) 223 (4.38), 262 (4.16), 295 (4.27), 314 (4.23), 469 (3.78) nm; IR (KBr) ν_{max} 620, 770, 1070, 1170, 1210, 1260, 1400, 1470, 1620, 2930, 3430 cm^{-1}; HRESIMS *m*/*z* 557.1614 (calcd for $C_{26}H_{30}O_{12}Na$, 557.1629); TLC R_f = 0.15; HPLC t_R = 10.8 min. Specific rotation of quinofuracins is undetectable due to red-colored solutions.

*Quinofuracin B (**2**):* red, amorphous solid; UV (MeOH) λ_{max} (log ε) 223 (4.37), 263 (4.11), 294 (4.23), 314 (4.09), 460 (3.75) nm; IR (KBr) ν_{max} 630, 780, 1070, 1170, 1210, 1260, 1380, 1450, 1620, 2930, 3430 cm^{-1}; HRESIMS *m*/*z* 599.1724 (calcd for $C_{28}H_{32}O_{13}Na$, 599.1735); TLC R_f = 0.39; HPLC t_R = 15.2 min.

*Quinofuracin C (**3**):* red, amorphous solid; UV (MeOH) λ_{max} (log ε) 223 (4.42), 261 (4.22), 290 (4.25), 314 (4.16), 455 (3.85) nm; IR (KBr) ν_{max} 650, 770, 1080, 1170, 1210, 1280, 1400, 1470, 1620, 2930, 3430 cm^{-1}; HRESIMS *m*/*z* 557.1616 (calcd for $C_{26}H_{30}O_{12}Na$, 557.1629); TLC R_f = 0.16; HPLC t_R = 15.4 min.

*Quinofuracin D (**4**):* red, amorphous solid; UV (MeOH) λ_{max} (log ε) 223 (4.39), 263 (4.14), 290 (4.30), 314 (4.12), 460 (3.82) nm; IR (KBr) ν_{max} 620, 770, 1090, 1160, 1210, 1260, 1400, 1470, 1620, 2930, 3430 cm^{-1}; HRESIMS *m*/*z* 571.1422 (calcd for $C_{26}H_{28}O_{13}Na$, 571.1422); TLC R_f = 0.11; HPLC t_R = 4.2 min.

*Quinofuracin E (**5**):* orange-yellow, amorphous solid; UV (MeOH) λ_{max} (log ε) 222 (4.41), 251 (sh) (4.10), 266 (sh) (4.20), 287 (4.35), 317 (3.84), 442 (3.89) nm; IR (KBr) ν_{max} 650, 770, 950, 1070, 1160, 1190, 1250, 1320, 1390, 1470, 1630, 2930, 3430 cm^{-1}; HRESIMS *m*/*z* 503.1173 (calcd for $C_{24}H_{23}O_{12}$, 503.1184); TLC R_f = 0.25; HPLC t_R = 6.0 min.

Methanolysis of 4. A solution of **4** (19.2 mg) in 5% HCl−MeOH (1.92 mL) was stirred for 42 h at room temperature. The reaction mixture was extracted with EtOAc (80 mL) and H_2O (80 mL). The organic layer was washed with water (80 mL) and saturated NaCl solution (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent $CHCl_3$−MeOH = 50:1) to give **6** (10.8 mg). The aqueous layer was concentrated *in vacuo* to give **7** (6.7 mg).

*Averufin (**6**):* red, amorphous solid; ^{1}H NMR (CD_3OD, 600 MHz) δ 7.11 (1H, s, H-6), 7.09 (1H, d, *J* = 2.0 Hz, H-4), 6.38 (1H, d, *J* = 2.0 Hz, H-2), 5.30 (1H, br d, *J* = 5.6 Hz, H-1′), 2.09 (1H, m, H-2′a), 2.04 (1H, m, H-4′a), 1.88 (1H, m, H-2′b), 1.86 (1H, m, H-4′b), 1.68 (1H, m, H-3′a), 1.59 (1H, m, H-3′b), 1.53 (3H, s, H-6′); ^{13}C NMR (CD_3OD, 150 MHz) δ 189.9 (C-10), 183.8 (C-5), 172.4 (C-3), 167.0 (C-1), 161.3 (C-7), 159.9 (C-9), 136.4 (C-4a), 135.1 (C-5a), 117.5 (C-8), 113.2 (C-4), 110.3 (C-9a), 109.8 (C-2), 108.4 (C-6, C-10a), 102.3 (C-5′), 68.3 (C-1′), 36.9 (C-4′), 28.6 (C-2′), 28.2 (C-6′), 17.0 (C-3′); HRESIMS *m*/*z* 369.0968 (calcd for $C_{20}H_{17}O_7$, 369.0969).

***p*-Bromobenzoylation of Methyl D-Galactopyranoside (7).** To a solution of **7** (10.8 mg) in pyridine (2 mL) were added *p*-bromobenzoyl chloride (200 mg) and DMAP (10 mg), and the mixture was stirred for 36 h at 80 °C. The reaction mixture was

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quenched with H_2O and extracted with EtOAc (50 mL). The organic layer was sequentially washed with HCl (0.2 N), H_2O, saturated $NaHCO_3$, H_2O, and saturated NaCl (50 mL each) and dried over Na_2SO_4. The organic filtrate was concentrated under reduced pressure, and the resulting residue was purified over an HPLC column (CapcellPak UG120, ⌀ 20 mm × 250 mm, 80% aqueous acetonitrile) to give **8a** (5.4 mg) and **8b** (1.4 mg).

*Methyl 2,3,4,6-tetra-O-p-bromobenzoyl-α-D-galactopyranoside (**8a**):* colorless, amorphous solid; $[\alpha]^{25}_D$ +177.5 (*c* 0.29, $CHCl_3$) {lit.[17] $[\alpha]^{25}_D$ +178.1 (*c* 1.16, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0−7.4 (16H, *p*-bromobenzoyl × 4), 5.96 (1H, d, *J* = 3.2 Hz, H-4), 5.93 (1H, dd, *J* = 3.2, 10.8 Hz, H-3), 5.62 (1H, dd, *J* = 3.6, 10.8 Hz, H-2), 5.28 (1H, d, *J* = 3.6 Hz, H-1), 4.58 (2H, m, H-5, H-6a), 4.38 (1H, m, H-6b), 3.48 (3H, s, OCH_3-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3 (ester), 165.3 (ester), 164.9 (ester), 164.7 (ester), 132.1−127.8 (aromatic carbons), 97.5 (C-1), 69.3 (C-4), 69.2 (C-2), 68.5 (C-3), 66.5 (C-5), 62.5 (C-6), 55.8 (OCH_3); HRESIMS *m*/*z* 944.8142 (calcd for $C_{35}H_{26}O_{10}Br_4Na$, 944.8152).

*Methyl 2,3,4,6-tetra-O-p-bromobenzoyl-β-D-galactopyranoside (**8b**):* colorless, amorphous solid; $[\alpha]^{25}_D$ +149.3 (*c* 0.06, $CHCl_3$) {lit.[17] $[\alpha]^{25}_D$ +132.6 (*c* 1.16, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0−7.4 (16H, *p*-bromobenzoyl × 4), 5.93 (1H, dd, *J* = 1.0, 3.6 Hz, H-4), 5.70 (1H, dd, *J* = 7.8, 10.8 Hz, H-2), 5.55 (1H, dd, *J* = 3.6, 10.8 Hz, H-3), 4.73 (1H, d, *J* = 7.8 Hz, H-1), 4.67 (1H, dd, *J* = 6.8, 11.0 Hz, H-6a), 4.40 (1H, d, *J* = 7.0, 11.0 Hz, H-6b), 4.30 (1H, br dd, *J* = 6.8, 7.0 Hz, H-5), 3.60 (3H, s, OCH_3-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3 (ester), 164.9 (ester), 164.8 (ester), 164.6 (ester), 132.1−127.4 (aromatic carbons), 102.2 (C-1), 71.8 (C-3), 71.0 (C-5), 69.8 (C-2), 68.2 (C-4), 61.9 (C-6), 57.4 (OCH_3); HRESIMS *m*/*z* 944.8143 (calcd for $C_{35}H_{26}O_{10}Br_4Na$, 944.8152).

Preparation of Authentic Methyl 2,3,4,6-Tetra-*O*-*p*-bromobenzoyl-α-D- galactopyranoside (8a). To a solution of methyl α-D-galactopyranoside (10 mg) in pyridine (1 mL) were added *p*-bromobenzoyl chloride (200 mg) and DMAP (5 mg), and the mixture was stirred for 12 h at 80 °C. The reaction mixture was quenched with H_2O and extracted with EtOAc (50 mL). The organic layer was sequentially washed with HCl (0.2 N), H_2O, saturated $NaHCO_3$, H_2O, and saturated NaCl (50 mL, each) and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography (*n*-hexane−EtOAc = 10:1) to give an authentic sample of **8a** (37.8 mg): colorless, amorphous solid; $[\alpha]^{26}_D$ +189.0 (*c* 0.88, $CHCl_3$); HRESIMS *m*/*z* 944.8164 (calcd for $C_{35}H_{26}O_{10}Br_4Na$, 944.8152).

Preparation of Authentic Methyl 2,3,4,6-Tetra-*O*-*p*-bromobenzoyl-β-D- galactopyranoside (8b). In a procedure similar to that used in the synthesis of **8a**, methyl β-D-galactopyranoside was used to generate an authentic sample of **8b** (44.9 mg): colorless, amorphous solid; $[\alpha]^{26}_D$ +139.7 (*c* 1.05, $CHCl_3$); HRESIMS *m*/*z* 944.8169 (calcd for $C_{35}H_{26}O_{10}Br_4Na$, 944.8152).

Methanolysis of 1. A solution of **1** (16.7 mg) in 5% HCl−MeOH (1.67 mL) was stirred for 18 h at room temperature. The reaction mixture was extracted with EtOAc (84 mL) and H_2O (84 mL). The organic layer was washed with H_2O (80 mL) and saturated NaCl solution (80 mL) and dried over Na_2SO_4. The organic filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent $CHCl_3$) to give **9** (10.7 mg). The aqueous layer was concentrated *in vacuo* to give **7** (6.0 mg). Methyl D-galactopyranoside (**7**) was *p*-bromobenzoylated and purified in a manner similar to that described above to afford **8a** {7.1 mg; $[\alpha]^{27}_D$ +173.6 (*c* 0.34, $CHCl_3$)} and **8b** {1.1 mg; $[\alpha]^{27}_D$ +147.5 (*c* 0.06, $CHCl_3$)}.

*1′-O-Methylaverufin (**9**):* red, amorphous solid; $[\alpha]^{27}_D$ 0 (*c* 0.1, $CHCl_3$/MeOH = 5:1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.82 (OH), 12.14 (OH), 11.20 (OH), 7.20 (1H, s, H-6), 7.08 (1H, d, *J* = 2.6 Hz, H-4), 6.56 (1H, d, *J* = 2.6 Hz, H-2), 4.81 (1H, dd, *J* = 6.4, 7.2 Hz, H-1′), 3.20 (3H, s, OCH_3-1′), 2.00 (1H, m, H-2′a), 1.80 (1H, m, H-2′b), 1.30 (1H, m, H-3′a), 1.24 (4H, m, H_2-4′, H_2-5′), 1.20 (1H, m, H-3′b), 0.84 (3H, s, H-6′); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 188.9 (C-10), 181.3 (C-5), 165.2 (C-1), 164.2 (C-3), 163.7 (C-7), 163.1 (C-9), 134.8 (C-4a), 133.3 (C-5a), 119.3 (C-8), 108.7 (C-2, C- 10a), 108.5 (C-4), 108.1 (C-6, C-9a), 74.7 (C-1′), 56.2 (OCH_3-1′), 32.5 (C-2′), 31.2 (C-4′), 25.4 (C-3′), 22.0 (C-5′), 13.9 (C-6); HRESIMS *m*/*z* 385.1295 (calcd for $C_{21}H_{21}O_7$, 385.1282).

Methanolysis of 5. A solution of **5** (3.6 mg) in 5% HCl−MeOH (1.0 mL) was stirred for 42 h at room temperature. The reaction mixture was extracted with EtOAc (80 mL) and H_2O (80 mL). The organic layer was washed with saturated NaCl solution (80 mL) and dried over Na_2SO_4. The organic filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent $CHCl_3$) to give **10** (1.8 mg). The aqueous layer was concentrated *in vacuo* to give **7** (2.5 mg). Methyl D-galactopyranoside (**7**) was *p*-bromobenzoylated and purified in a manner similar to that described above to afford **8a** (0.8 mg; $[\alpha]^{24}_D$ +182.9 (*c* 0.04, $CHCl_3$) and **8b** (<0.1 mg).

*Versicolorin B (**10**):* orange-yellow, amorphous solid; $[\alpha]^{26}_D$ −230 (*c* 0.07, dioxane); ^{1}H NMR ($CDCl_3$/CH_3OD = 1:1, 400 MHz) δ 7.53 (1H, d, *J* = 2.6 Hz, H-4), 7.22 (1H, s, H-6), 6.59 (1H, d, *J* = 2.6 Hz, H-2), 6.49 (1H, d, *J* = 5.8 Hz, H-11), 4.17 (2H, m, H-12, H-14a), 3.86 (1H, m, H-14b), 2.37 (1H, m, H-13a), 2.30 (1H, m, H-13b); ^{13}C NMR ($CDCl_3$/CH_3OD = 1:1, 100 MHz) δ 190.4 (C-10), 182.6 (C-5), 166.2 (C-7), 166.0 (C-9), 165.4 (C-1), 160.2 (C-3), 136.5 (C-5a), 135.6 (C-4a), 120.3 (C-8), 113.6 (C-11), 111.9 (C-9a), 110.2 (C-4), 109.4 (C-10a), 108.9 (C-2), 102.8 (C-6), 48.2 (C-14), 44.7 (C-12), 31.0 (C-13); HRESIMS *m*/*z* 341.0655 (calcd for $C_{18}H_{13}O_7$, 341.0656).

Cell Culture. LNZTA3 cells, stably transfected human glioblastoma LN-Z308 cells that express wild-type p53 by a tetracycline-regulated system, were obtained from the American Type Culture Collection (Rockville, MD, USA).[9] LNZTA3 cells were grown at 37 °C with 5% CO_2 in Opti-MEM (Life Technologies, Carlsbad, CA, USA) supplemented with 1% heat-inactivated fetal bovine serum (Nichirei Biosciences, Tokyo, Japan), penicillin G (100 units/mL), and tetracycline (2.3 μM).

p53-Dependent Growth Suppression Assay. LNZTA3 cells in the presence or absence of tetracycline (2.3 μM) were plated into 96-well plates (8 × 10^3 cells/well) and precultured for 12 h. Various amounts of quinofuracins were added to the wells, and the cells were subsequently cultured for 3 days. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; 10 μL; 12 mM) was added to the treated cells, and the incubation at 37 °C continued for 6 h. After incubation, cells were supplemented with sodium dodecyl sulfate and incubated at 37 °C for 12 h. Absorbance was measured at 570 nm using a spectrophotometer.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

CD, ^{1}H NMR, and ^{13}C NMR spectra for quinofuracins are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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