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Endoplasmic Reticulum Stress Suppressive Compounds from the Edible Mushroom *Mycoleptodonoides aitchisonii*

Jae-Hoon Choi,[†,#] Tomohiro Suzuki,[†,#] Hiroshi Okumura,[‡] Keiichi Noguchi,[§] Mitsuru Kondo,[†] Kaoru Nagai,[⊥] Hirofumi Hirai,[†,‡] and Hirokazu Kawagishi*[,†,‡,∥]

[†]Research Institute of Green Science and Technology, Shizuoka University, 836 Ohya, Suruga-ku, Shizuoka 422-8529, Japan

[‡]Graduate School of Agriculture, Shizuoka University, 836 Ohya, Suruga-ku, Shizuoka 422-8529, Japan

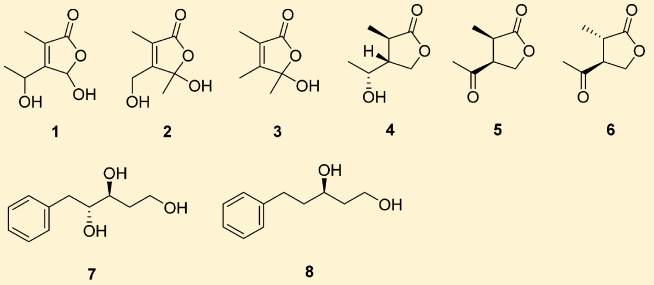
[§]Instrumentation Analysis Center, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

[⊥]Department of Epigenetic Medicine, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi 409-3898, Japan

[∥]Graduate School of Science and Technology, Shizuoka University, 836 Ohya, Suruga-ku, Shizuoka 422-8529, Japan

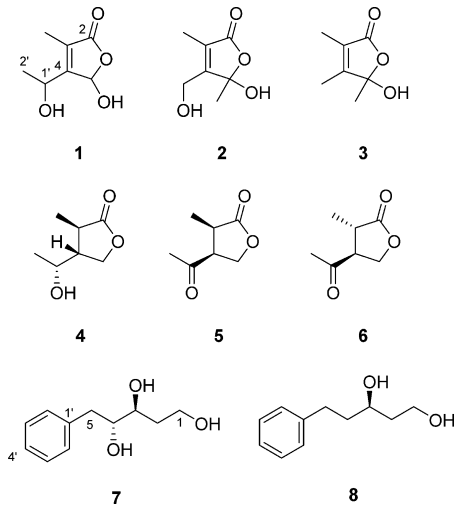
Supporting Information

ABSTRACT: Two novel compounds, **1** and **7**, along with six known compounds (**2**−**6** and **8**), were isolated from the edible mushroom *Mycoleptodonoides aitchisonii* (bunaharitake in Japanese). The structures of the new compounds were determined by the interpretation of spectroscopic data. Compounds **1**−**4** and **6**−**8** showed protective activity against endoplasmic reticulum stress-dependent cell death.



Endoplasmic reticulum (ER) stress is caused by disturbances in the structure and function of the ER with the accumulation of misfolded proteins and alterations in calcium homeostasis. In the case of prolonged or aggravated ER stress, cellular signals leading to cell death are activated. ER stress has been suggested to be involved in some human neuronal diseases, such as Parkinson's, Alzheimer's, and prion diseases.[1−3] ER stress has been reported to cause not only neurodegenerative diseases but also some other diseases, such as diabetes, atherosclerosis, and heart and liver disease.[4] Therefore, protective activity against ER stress is possibly an important target for addressing these diseases, and the demand for new lead compounds prompted us to screen the protective activity of mushroom extracts. We have reported new ER stress protective compounds from the mushrooms *Hericium erinaceum*,[5,6] *Termitomyces titanicus*,[7] and *Leccinum extremiorientale*.[8] Three furanones and a phenylpentanone from the edible mushroom *Mycoleptodonoides aitchisonii* have also been reported as protective compounds.[9] In the course of our continuing search for ER stress protecting compounds from the mushroom *M. aitchisonii*, we found the active compounds described below.

Fresh fruiting bodies of *M. aitchisonii* were extracted with EtOH and acetone, successively. After the solutions were combined and concentrated under reduced pressure, the concentrate was divided into a CH_2Cl_2-soluble fraction, an EtOAc-soluble fraction, and a water-soluble fraction. Compounds **1**, **2**, and **5** were purified from the EtOAc-soluble part, and compounds **3**, **4**, and **6**−**8** were obtained from the CH_2Cl_2-soluble part. By comparison of the NMR data, mass spectra, and specific rotation of compounds **2**−**6** and **8** with those reported previously,[10−16] the six known compounds were identified as shown. Although **5** and **8** have been synthesized,[14−16] this is the first report of the isolation of these compounds from nature.



Compound **1** was purified as a colorless oil. Its molecular formula was determined as $C_7H_{10}O_4$ by HRESIMS (*m*/*z*

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159.0687 $[M + H]^+$; calcd for $C_7H_{11}O_4$, 159.0657), indicating the presence of three degrees of unsaturation in the molecule. The structure of **1** was elucidated by interpretation of 2D NMR spectra including COSY, HMBC, and HMQC (Figure 1). The

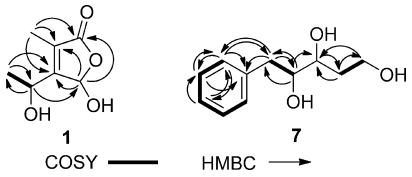

Figure 1. COSY and HMBC correlations of **1** and **7**.

DEPT experiment and the molecular formula indicated the presence of two methyls, two methines, two quaternary carbons, and a carboxy. The complete assignment of all the protons and carbons was accomplished as shown in Table 1.

Table 1. ^{1}H and ^{13}C NMR Data for 1 and 7

	1 (in CD_3OD)			**7** (in $CDCl_3$)	
position	δ_C, type	δ_H, mult (J in Hz)	position	δ_C, type	δ_H, mult (J in Hz)
1			1	61.1, CH_2	3.86, m
2	174.9, C		2	33.1, CH_2	1.81, m
3	126.4, C		3	73.8, CH	3.83, m
4	162.7, C		4	75.3, CH	3.83, m
5	99.6, CH	6.08, s	5a	38.4, CH_2	2.86, dd (13.7, 2.8)
			5b		2.71, dd (13.7, 9.2)
1′	64.9, CH	4.75, m	1′	138.2, C	
2′	21.8, CH_3	1.42, d (7.0)	2′, 6′	129.3, C_2H_2	7.22, d (7.5)
3-Me	8.8, CH_3	1.89, s	3′, 5′	128.6, C_2H_2	7.30, dd (7.0, 7.5)
			4′	126.6, CH	7.23, t (7.0)

The furanone moiety was determined by the HMBC correlations (H-5/C-2, H-5/C-3, H-5/C-4) and the chemical shifts of the two quaternary carbons (δ_C 126.4, 162.7) and the carboxy carbon (δ_C 174.9). A methyl was determined to be connected to C-3 by the HMBC correlations (C-3−Me/C2, C-3−Me/C3, C-3−Me/C-4). The linkage between the hydroxyethyl group [COSY (H-1′/H-2′), HMBC (H-1′/C-2′, H-2′/C-1′)] and the furanone ring was determined by the HMBC correlations (H-2′/C-4, H-1′/C-5). The presence of the hydroxy group at C-5 was suggested by the molecular formula and the chemical shift [δ_H 6.08 (1H, s) and δ_C 99.6]. All the data allowed us to conclude that **1** was 5-hydroxy-4-(1-hydroxyethyl)-3-methylfuran-2(5*H*)-one. Its stereochemistry remains undetermined.

Compound **7** was isolated as a colorless oil. Its molecular formula was determined as $C_{11}H_{16}O_3$ by HRESIMS. The structure of **7** was elucidated by interpretation of 2D NMR spectra including COSY, HMBC, and HMQC. The complete assignment of all the protons and carbons was accomplished as shown in Table 1. The presence of the benzene ring was suggested by the COSY correlations (bold line in Figure 1) and the HMBC correlations (H-2′/C-1′, H-2′/C-3′, H-2′/C-4′, H-3′/C-1′, H-3′/C-2′, H-4′/C-2′, H-4′/C-3′). The pentane-1,3,4-triol moiety was elucidated by the COSY correlations (H-1/H-2, H-4/H-5), the HMBC correlations (H-1/C-3, H-2/C-1, H-2/C-3, H-3/C-2, H-4/C-3, H-4/C-5, H-5/C-3, H-5/C-4), and the molecular formula. The connection between the benzene and pentane moieties was determined by the HMBC correlations (H-5/C-1′, H-5/C-2′, H-2′/C-5). As a result, the planar structure of **7** was determined to be 5-phenylpentane-1,3,4-triol. The absolute configuration of **7** was determined as 3*S*, 4*R* by X-ray crystallography analysis on its *p*-bromobenzoate (Figure 2).

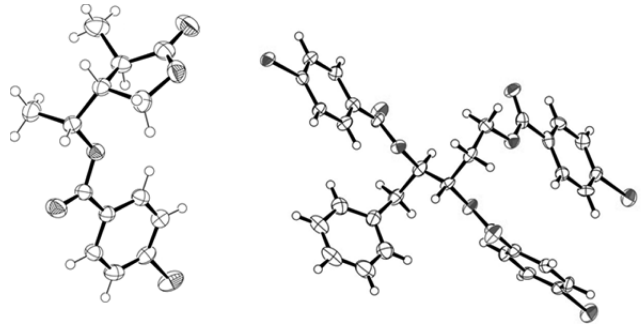

Figure 2. ORTEP drawing of *p*-bromobenzoates of **4** (left) and **7** (right) with ellipsoids at the 50% probability level. Hydrogen atoms are shown as small spheres of arbitrary radii.

The stereochemistry of compound **4** has not been previously reported.[12] In this study, the absolute configuration of **4** was determined as 3*R*, 4*R*, 1′*R* by X-ray crystallography analysis of its *p*-bromobenzoate (Figure 2).

Compounds **1**−**8** were subjected to the protective-activity assay against ER stress-dependent cell death caused by tunicamycin (TM) or thapsigargin (TG). ER stress was induced by the addition of TM or TG into the culture medium of Neuro2a cells in the presence or absence of each compound. TM is an inhibitor of N-linked glycosylation and the formation of N-glycosidic protein−carbohydrate linkages.[17] It specifically inhibits dolichol pyrophosphate-mediated glycosylation of asparaginyl residues of glycoproteins and induces ER stress.[18] TG, an inhibitor of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase, also induces ER stress by disrupting the homeostatic balance of the Ca^{2+} concentration in the ER.[19] None of the compounds showed protective activity against TM toxicity. On the other hand, in the assay using TG, all the compounds except for **5** showed protective activity at more than 50 μM. Compounds **5** and **6** are diastereomers of each other, suggesting that the stereochemistry played an important role in the activity. Similar γ-lactones and a phenylpentanol having protective activity against TM or TG toxicity have been reported previously.[9] Sodium valproate, which is known as an ER stress protector *in vivo*, showed a similar protective effect to these compounds (Figure S11, Supporting Information).[20]

EXPERIMENTAL SECTION

General Experimental Procedures. ^{1}H NMR spectra (one- and two-dimensional) were recorded on a Jeol Lambda-500 spectrometer at 500 MHz, while ^{13}C NMR spectra were recorded on the same instrument at 125 MHz. The HRESIMS spectra were measured on a JMS-T100LC mass spectrometer. A Jasco grating infrared spectrophotometer was used to record the IR spectra, and the specific rotation values were measured by a Jasco DIP-1000 polarimeter. HPLC separations were performed with a Jasco Gulliver system using normal-phase HPLC columns (Senshu Pak AQ, Senshu Scientific Co., Ltd., Japan; Develosil Silica-HILIC, Nomura Chemical, Japan; Cosmosil

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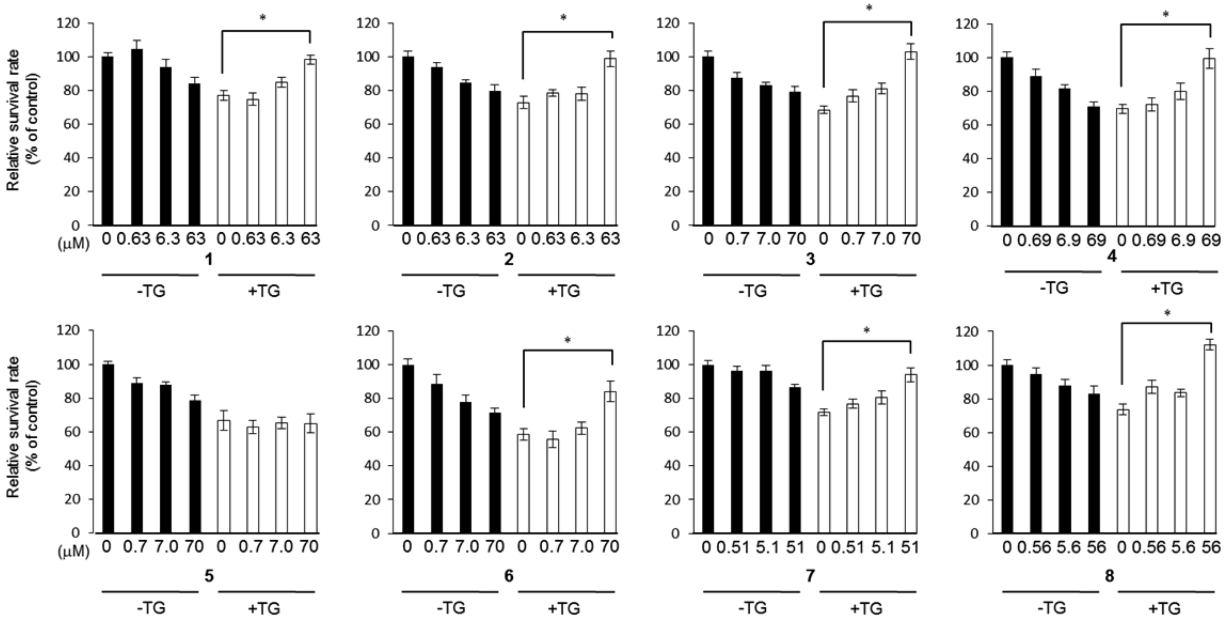

Figure 3. Protective activity of **1**–**8** against ER stress-dependent cell death. Neuro2a cells were incubated with various concentrations of compounds in the absence or presence of 10 nM thapsigargin (TG) for 24 h. The cell viabilities were analyzed by MTT assay, and the values were represented as the mean ± SE of the relative percentage of surviving cells compared with the untreated cells (n = 10–12). (*) $p < 0.01$, Tukey–Kramer multiple comparisons tests.

5SL-II, Nacalai Tesque, Japan) and a reversed-phase HPLC column (Develosil C30-UG-5, Nomura Chemical, Japan). Silica gel plates (Merck F_{254}), ODS gel plates (Merck F_{254}), and silica gel 60 N (Kanto Chemical, Japan) were used for analytical TLC and for flash column chromatography, respectively.

Fungal Material. Mature fruiting bodies of *Mycoleptodonoides aitchisonii* were collected at Narusawa Village, Yamanashi Prefecture, in Japan, in August 2006, and identified by one of the authors (H.K.). A voucher specimen of the organism is located in Shizuoka University (voucher specimen no. SU2006MA).

Extraction and Isolation. The fresh fruiting bodies of *M. aitchisonii* (13.0 kg) were extracted with EtOH (21 L, three times) and then acetone (10 L, once). After the solutions were combined and concentrated under reduced pressure, the concentrate was partitioned between CH_2Cl_2 and H_2O and then between EtOAc and H_2O. The CH_2Cl_2-soluble part (73.6 g) was fractionated by silica gel flash column chromatography (hexane–CH_2Cl_2, 7:3, hexane–EtOAc, 9:1, 5:5, CH_2Cl_2–MeOH, 8:2, 5:5, 0:10, 2 L each) to obtain 25 fractions (fractions 1–25), and fraction 19 (6.9 g) was further separated by silica gel flash column chromatography (CH_2Cl_2–acetone, 9:1, 7:3, 3:7, acetone–MeOH, 5:5, and MeOH, 1 L each), and 24 fractions were obtained (fractions 19-1 to 19-24). Fraction 19-12 (1.0 g) was further separated by silica gel flash column chromatography (CH_2Cl_2–acetone, 9:1, 8:2, CH_2Cl_2–MeOH, 9:1, 8:2, and EtOH, 1 L each) to obtain nine fractions (fractions 19-12-1 to 1-12-9). Fraction 19-12-6 (613.2 mg) was further separated by normal-phase HPLC (Develosil Silica-HILIC, $CHCl_3$–MeOH, 98:2) to afford 21 fractions (fractions 19-12-6-1 to 19-12-6-21). Compound **8** (2.5 mg) was purified from fraction 19-12-6-16 (6 mg) by normal-phase HPLC (Develosil Silica-HILIC, $CHCl_3$–MeOH, 98:1). Fraction 19-8 (4.2 g) was further separated by silica gel flash column chromatography (CH_2Cl_2–acetone, 9:1, 8:2, 5:5, CH_2Cl_2–MeOH, 9:1, 8:2, 1 L each) to obtain seven fractions (fractions 19-8-1 to 19-8-7), and then fraction 19-8-2 (3.3 g) was further separated by normal-phase HPLC (Develosil Silica-HILIC, $CHCl_3$–MeOH, 98:1) to obtain 11 fractions (fractions 19-8-2-1 to 19-8-2-11). Fraction 19-8-2-10 (27 mg) was separated by normal-phase HPLC (Senshu Pak AQ, $CHCl_3$–MeOH, 99:1) to afford compound **4** (7.5 mg). Fraction 19-15 (751 mg) was separated by silica gel flash column chromatography (CH_2Cl_2, CH_2Cl_2–MeOH, 99:1, 95:5, 9:1, 1:1, and MeOH, 1 L each) to obtain 11 fractions (fractions 19-15-1 to 19-15-11), and then fraction 19-15-6 (92.7 mg) was further separated by normal-phase HPLC (Senshu Pak AQ, $CHCl_3$–MeOH, 98:2) to obtain 15 fractions (fractions 19-15-6-1 to 19-15-6-15). Compound **7** (10.2 mg) was purified by a normal-phase HPLC (Senshu Pak AQ, $CHCl_3$–MeOH, 96:4) from fraction 19-15-6-10 (16.9 mg). Fraction 18 (374 mg) was separated by preparative silica TLC (CH_2Cl_2–MeOH, 9:1) to obtain six fractions (fractions 18-1 to 18-6), and then fraction 18-5 (72 mg) was further separated by preparative ODS TLC (90% MeOH) to afford compound **6** (21.6 mg). Compound **3** (1.6 mg) was purified by normal-phase HPLC (Senshu Pak AQ, $CHCl_3$–MeOH, 99:1) from fraction 18-3 (37 mg). Similarly, the EtOAc-soluble part (25.0 g) was fractionated by silica gel flash column chromatography (CH_2Cl_2, CH_2Cl_2–MeOH, 9:1, 7:3, 5:5, and MeOH, 1 L each), and 10 fractions were obtained (fractions 1 to 10). Fraction 6 (12.0 g) was further separated by silica gel flash column chromatography (CH_2Cl_2, CH_2Cl_2–MeOH, 99:1, 98:2, 95:5, 8:2, 1:1, 1 L each) to obtain nine fractions (fractions 6-1 to 6-9), and then fraction 6-3 (53.9 mg) was further separated by normal-phase HPLC (Cosmosil 5SL-II, $CHCl_3$–hexane, 9:1) to give compound **5** (2.2 mg). Compounds **1** (2.0 mg) and **2** (3.8 mg) were purified from fraction 6-6 (63.5 mg) by reversed-phase HPLC (Develosil C30-UG-5, 25% MeOH).

*5-Hydroxy-4-(1-hydroxyethyl)-3-methylfuran-2(5H)-one (**1**):* colorless oil; $[\alpha]_D^{26}$ −16 (c 0.12, MeOH); IR (neat) 3290, 1749 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS m/z 159.0687 $[M + H]^+$ (calcd for $C_7H_{11}O_4$, 159.0657).

*(3R,4R)-4-((R)-1-Hydroxyethyl)-3-methyldihydrofuran-2(3H)-one (**4**):* colorless oil; $[\alpha]_D^{31}$ +27 (c 0.50, $CHCl_3$); IR (neat) 3446, 1763m^{-1}; ^1H NMR (500 MHz, in $CDCl_3$) δ 4.28 (1H, dd, J = 8.9, J = 8.9, H-5a), 3.94 (1H, dd, J = 8.9, J = 8.9, H-5b), 3.84 (1H, m, H-1′), 2.56 (1H, m, H-4), 2.19 (1H, m, H-3), 1.33 (3H, d, J = 7.3, C-3–Me, 1.20 (3H, d, J = 6.4, H-2′); ^{13}C NMR (125 MHz, in $CDCl_3$) δ 180.4 (C-2), 68.4 (C-1′), 67.9 (C-5), 49.8 (C-3), 36.9 (C-4), 21.7 (C-2′), 16.3 (C-4–Me); ESIMS m/z 167 $[M + Na]^+$.

*(3S,4R)-5-Phenylpentane-1,3,4-triol (**7**):* colorless oil; $[\alpha]_D^{25}$ +63 (c 0.10, MeOH); IR (neat) 3364, 1456 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS m/z 219.1019 $[M + Na]^+$ (calcd for $C_{11}H_{16}NaO_3$, 219.0997).

Preparation of *p*-Bromobenzoates of (3*R*,4*R*)-4-((*R*)-1-Hydroxyethyl)-3-methyldihydrofuran-2(3*H*)-one and (3*S*,4*R*)-5-Phenylpentane-1,3,4-triol. (3*R*,4*R*)-4-((*R*)-1-Hydroxyethyl)-3-

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methyldihydrofuran-2(3*H*)-one (**4**) (2.1 mg) was dissolved in 0.25 mL of anhydrous pyridine in a 4 mL vial, and *p*-bromobenzoyl chloride (16 mg) was added to the solution. After shaking at 50 °C for 3 days, the reaction mixture was evaporated to dryness under reduced pressure. The products were then purified by normal-phase HPLC (Senshu Pak AQ, $CHCl_3$−MeOH, 96:4) to give the *p*-bromobenzoate (1.5 mg) of **4**. *p*-Bromobenzoate of **4**: ^{1}H NMR (500 MHz, in $CDCl_3$) δ 7.85 (2H, d, J = 8.5, *p*-Br−COC_6H_4), 7.56 (2H, d, J = 8.5, *p*-Br−COC_6H_4), 5.26 (1H, m, H-1′), 4.39 (1H, dd, J = 8.2, J = 9.2, H-5a), 3.99 (1H, dd, J = 8.6, J = 9.2, H-5b), 2.60 (1H, m, H-3), 2.51 (1H, m, H-4), 1.51 (3H, s, C-3−Me), 1.35 (3H, d, J = 6.7, H-2′); ESIMS m/z 349 $[M + Na]^+$. (3*S*,4*R*)-5-Phenylpentane-1,3,4-triol (**7**) (1.3 mg) was dissolved in 0.25 mL of anhydrous pyridine in a 4 mL vial, and *p*-bromobenzoyl chloride (7.3 mg) was added to the solution. After shaking at 50 °C for 2 days, the reaction mixture was evaporated to dryness under reduced pressure. The products were then purified by normal-phase HPLC (Senshu Pak AQ, hexane−$CHCl_3$, 1:1) to give the *p*-bromobenzoate (1.9 mg) of **7**. *p*-Bromobenzoate of **7**: ^{1}H NMR (500 MHz, in $CDCl_3$) δ 7.81 (6H, m), 7.56 (6H, m), 7.28 (5H, m), 5.72 (1H, m), 5.60 (1H, m), 4.54 (1H, m), 4.38 (1H, m), 3.14 (2H, m), 2.36 (2H, m).

X-ray Crystallography Analysis. Crystal data for *p*-bromobenzoate of **4**: $C_{14}H_{15}Br_1O_4$, M = 327.17, orthorhombic, a = 6.2502(1) Å, b = 7.1121(1) Å, c = 31.0868(6) Å, V = 1381.87(4) Å^3, T = 193 K, $P2_12_12_1$, Z = 4, λ = 1.541 87 Å, $\mu(\lambda = 1.541\ 87)$ = 4.14 mm^{-1}, $F(000)$ = 664. The size of the crystal used for measurements was 0.60 × 0.10 × 0.05 mm. Diffraction data were collected on a Rigaku *R*-AXIS-RAPID diffractometer with imaging plate detector; 25 210 reflections were collected in the range 4.3° < θ < 68.2°, of which 2543 were unique (R_{int} = 0.0420). The structure was refined by full-matrix least-squares on F^2 values using all unique reflections. The final R indices were $R(F)$ = 0.0254, $wR(F^2)$ = 0.0612 (all reflections) with goodness of fit = 1.089. The Flack parameter was −0.02(2) with 1022 Friedel pairs. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 978569. Crystal data for *p*-bromobenzoate of **7**: $C_{32}H_{25}Br_3O_6$, M = 745.26, monoclinic, a = 14.899(3) Å, b = 5.6970(11) Å, c = 17.092(5) Å, V = 1447.7(6) Å^3, T = 173 K, Z = 2, $\mu(\lambda = 0.71075)$ = 4.24 mm^{-1}, $F(000)$ = 740. The size of the crystal used for measurements was 0.14 × 0.03 × 0.01 mm. Diffraction data were collected on a Rigaku Saturn724 diffractometer with imaging plate detector; 23 580 reflections were collected in the range θ < 29.0°, of which 7620 were unique (R_{int} = 0.0812). The structure was refined by full-matrix least-squares on F^2 values using all unique reflections. The final R indices were $R(F)$ = 0.0660, $wR(F^2)$ = 0.1287 (all reflections) with goodness of fit = 1.001. The Flack parameter was 0.008 with 3420 Friedel pairs. The single crystal was mounted on a loop using oil. Diffraction data were collected at −100 °C under a cold nitrogen stream on a Rigaku VariMax with a Satrun diffractometer using a multilayer mirror monochromated Mo Ka radiation source (λ = 0.710 75 Å). Eighteen preliminary data frames were measured at 0.5° increments of ω, to assess the crystal quality and preliminary unit cell parameters. The intensity images were also measured at 0.5° intervals of ω. The intensity images were integrated using the Crystal Clear program package. The structure was solved by direct methods (SHELX-97). All non-hydrogen atoms were refined anisotropically by full-matrix least-squares technique. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 978780. The data can be obtained free of charge via www.ccdc.cam.ac.uk/products/csd/request.

Bioassay. Neuro2a cells were obtained from the Health Science Research Resources Bank, Japan, and maintained in Dulbecco's modified Eagle's medium (D-MEM) (Sigma, USA) supplemented with 10% fetal bovine serum (FBS), unless particularly noted. Cell viability analysis was performed by the 3-(4,5-dimethyl-2-thiazolyl) 2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay. The MTT assay was performed as follows: Neuro2a cells were cultured for 24 h in 96-well plates, starting at a cell density of 2000 cells/well. The cells were pretreated with varying concentrations of test compounds or sodium valproate in D-MEM without serum for 6 h, and then ER stressor (final concentration 0.5 μg/mL of TM or 10 nM TG) was applied to the medium and incubated for additional 24 h. After treatment, the cell viability was measured by the MTT assay as described previously.[21] Briefly, 0.25 mg/mL of MTT in D-MEM without FBS was added to the cells and incubated for 2 h. The incubation was terminated by the addition of 20% SDS (v/w) and 50% *N*,*N*-dimethylformamide in water. The absorbance at 570 nm of the reaction mixture was measured by a microplate reader (Molecular Devices, USA).

Statistical Analysis. Data collected were analyzed statistically using Tukey−Kramer multiple comparisons tests to determine significant differences in the data among the groups. p values less than 0.01 or 0.05 were considered significant. The values are expressed as mean ± SE.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and 2D NMR spectra of compounds **1** and **7**, X-ray crystallographic data for *p*-bromobenzoates of **4** and **7**, and effect of sodium valproate on ER stress-dependent cell death are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel/Fax: +81-54-238-4885. E-mail: achkawa@ipc.shizuoka.ac.jp.

Author Contributions

#J.-H. Choi and T. Suzuki contributed equally to this work.

Notes

The authors declare no competing financial interest.

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