Syntheses and Antifungal Activity of *dl*-Griseofulvin and Its Congeners. III[1a-c)]

Yasuo TAKEUCHI,* Ikuo WATANABE, Keiji MISUMI, Mari IRIE, Yoko HIROSE, Kazumi HIRATA, Masatoshi YAMATO, and Takashi HARAYAMA

Faculty of Pharmaceutical Sciences, Okayama University,[a] Tsushima-naka 1-1-1, Okayama 700, Japan.
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Several congeners (1b—g), with novel substituents on the benzene ring of griseofulvin, were prepared by the application of a synthetic method developed by us. Antifungal activity of these congeners decreased in order of *dl*-griseofulvin (1a) = 1d > 1b, c ≫ 1e-f (inactive). The relationship between the antifungal activity and the position or kind of substituents on the benzene ring of griseofulvin is discussed.

Key words griseofulvin; thiogriseofulvin; 3(2*H*)-benzofuranone; antifungal activity

Griseofulvin (*d*-**1a**) acts at the level of tubulin polymerization to exhibit antifungal activity.[2)] We have previously reported that *dl*-griseofulvin (**1a**) exhibited the highest activity among congeners in which the methyl group at the 6′ position of **1a** was replaced with other substituents.[1b,c)] In this paper, we describe the synthesis and antifungal activity of congeners with modified substituents at the **4**, **5**, or **6** position on the benzene ring of **1a**. It has already been reported that dechlorogriseofulvin lacking a chlorine substituent at the 7 position shows very weak activity.[3a,b)]

Synthesis Congeners (**1b—g**) of **1a** could be synthesized by the application of our method[1a)] shown in Chart 1. The reaction of corresponding benzofuranones (**2**) with sulfinylketones (**3**)[1a)] proceeded with elimination of the sulfinyl group to give hexylidenebenzofuranones (**4**), but we could not determine the configuration of the *exo* olefin of **4** from the spectral data. The ring-closure reaction of **4** could be achieved with a high diastereoselectivity by using alumina to afford *dl*-thiogriseofulvins (**5**). Griseofulvin congeners (**1b—g**) were obtained successfully by oxidation of 2′-thiogriseofulvin congeners (**5**) with *m*-chloroperbenzoic acid (*m*-CPBA) followed by addition–elimination reaction with sodium methoxide. Yields, physical constants, and spectral data of those compounds (**1b—g**, **4b—g**, and **5b—g**) are summarized in Tables 1 and 2.

The synthesis of 3(2*H*)-benzofuranones (**2b—g**), the starting materials for the griseofulvin congeners (**1b—g**), is illustrated in Chart 2. The key reaction is a carbon–carbon bond formation reaction between the **3** and **3a** positions (see **2b—g** in Chart 1) in **2**. We obtained 7-chloro-6-methoxy-3(2*H*)-benzofuranone (**2d**) and 7-chloro-4,6-dimethoxy-5-methyl-3(2*H*)-benzofuranone (**2f**) by using the Friedel–Crafts reaction. Friedel–Crafts reaction of **6d** produced a demethylated product, while that of compound **6f** gave **7f** instead of the demethylated product. We think that this demethylation reaction may involve chelation of the Lewis acid ($AlCl_3$) between the oxygen atoms of the chloroacetyl group and methoxyl group,[4)] and so may be dependent on the structure of the starting material rather than reaction conditions. From 2-chloro-5-methoxyphenol, we obtained **2b** in a one-pot reaction of 5 steps, *i.e.*, methoxymethylation, *ortho*-lithiation, acetylation, α-bromination, and ring-closure reaction. Compounds **2c** and **2e** could be successfully prepared by using Dieckmann condensation. 5,7-Dichloro-4,6-dimethoxy-3(2*H*)-benzofuranone (**2g**) could be prepared easily by chlorination of **6g**.

Antifungal Activity and Discussion The antifungal activity of griseofulvin congeners was examined and the minimum inhibitory concentration (MIC) values against *Trichophyton mentagrophytes* are listed in Table 1. All compounds (**1e—g**) having an additional substituent at the 5 position of *dl*-griseofulvin lacked antifungal activity, suggesting that the steric factor at the 5 position is important. On the other hand, among the congeners (**1b—d**) having one methoxy group on the benzene ring, the 6-methoxy congener (**1d**) exhibited the same activity as **1a**. These results indicate that the 4-methoxy group of **1a** is essential for the antifungal activity.

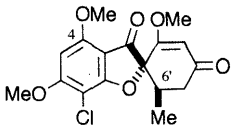

Fig. 1. Griseofulvin (*d*-**1a**)

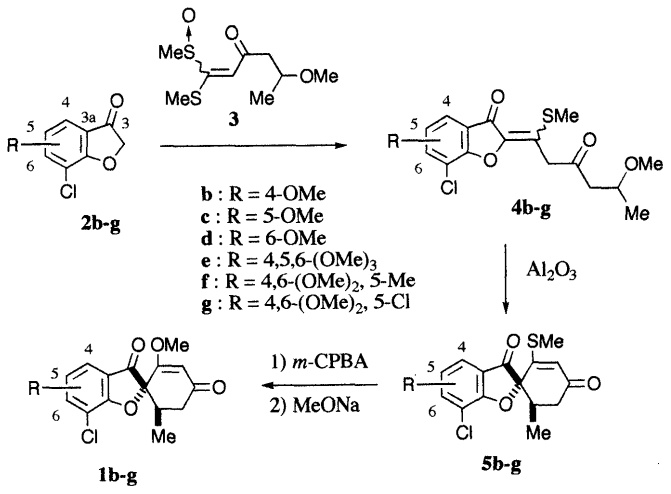

Chart 1

* To whom correspondence should be addressed.

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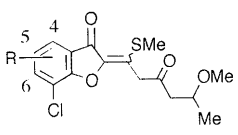
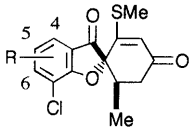
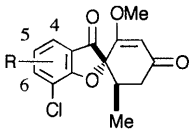
Table 1. Characteristics of **4b—g**, **5b—g**, and **1b—g**



4b-g



5b-g



1b-g

Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H
4b	4-OMe	50	128—129	$C_{17}H_{19}ClO_5S$	55.06 (54.80	5.16 5.06)
4c	5-OMe	50	138—140	$C_{17}H_{19}ClO_5S$	55.06 (55.15	5.16 5.16)
4d	6-OMe	69	102—103	$C_{17}H_{19}ClO_5S$	55.06 (54.52	5.16 5.07)
4e	4,5,6-$(OMe)_3$	61	63—64	$C_{19}H_{23}ClO_7S$	52.96 (53.05	5.38 5.46)
4f	4,6-$(OMe)_2$, 5-Me	67	82—84	$C_{19}H_{23}ClO_6S$	55.00 (54.99	5.59 5.51)
4g	4,6-$(OMe)_2$, 5-Cl	29	103—105	$C_{18}H_{20}Cl_2O_6S$	49.66 (49.51	4.63 4.57)
5b	4-OMe	33	205—206	$C_{16}H_{15}ClO_4S$	56.72 (56.62	4.46 4.41)
5c	5-OMe	53	193—196	$C_{16}H_{15}ClO_4S$	56.72 (57.08	4.46 4.60)
5d	6-OMe	77	194—195	$C_{16}H_{15}ClO_4S$	56.72 (56.35	4.46 4.42)
5e	4,5,6-$(OMe)_3$	74	135—137	$C_{18}H_{19}ClO_6S$	54.20 (54.17	4.80 4.81)
5f	4,6-$(OMe)_2$, 5-Me	65	171—173	$C_{18}H_{19}ClO_5S$	56.47 (56.57	5.00 5.05)
5g	4,6-$(OMe)_2$, 5-Cl	38	171—173	$C_{17}H_{16}Cl_2O_5S$	50.63 (50.75	4.00 3.96)
1b	4-OMe	80	189—191	$C_{16}H_{15}ClO_5 \cdot 1/4H_2O$	58.72 (58.50	4.74 4.69)
1c	5-OMe	80	177—180	$C_{16}H_{15}ClO_5$	59.54 (59.86	4.68 4.73)
1d	6-OMe	77	153—155	$C_{16}H_{15}ClO_5 \cdot 1/2H_2O$	57.92 (58.01	4.86 4.74)
1e	4,5,6-$(OMe)_3$	65	125—128	$C_{18}H_{19}ClO_7$	56.48 (56.39	5.00 4.92)
1f	4,6-$(OMe)_2$, 5-Me	60	155—157	$C_{18}H_{19}ClO_6$	58.94 (58.62	5.22 5.28)
1g	4,6-$(OMe)_2$, 5-Cl	66	158—160	$C_{17}H_{16}Cl_2O_6$	52.73 (52.34	4.16 3.97)

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a VG-70SE spectrometer. ^{1}H-NMR spectra were run on a Hitachi R-1500 (60 MHz) or a Varian VXR-500 (500 MHz) spectrometer. Merck silica gel 60 (230—400 mesh) was employed for column chromatography. Extracts were dried over anhydrous $MgSO_4$.

7-Chloro-4-methoxy-3(2*H*)-benzofuranone (2b) Sodium hydride (60% in mineral oil, 0.13 g, 3.3 mmol) and methoxymethyl chloride (0.26 ml, 3.8 mmol) were successively added dropwise to a solution of 2-chloro-5-methoxyphenol[5] (**6b**, 0.40 g, 2.5 mmol) in *N*,*N*-dimethylformamide (DMF, 6.3 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and poured into ice water. The whole was extracted with Et_2O. The Et_2O layer was washed with water, dried, and evaporated *in vacuo*. *n*-Butyllithium (1.11 M in hexane, 2.5 ml, 2.9 mmol) was added dropwise to a solution of the residue in dry tetrahydrofuran (THF, 9.2 ml) at −10 °C. The reaction mixture was stirred at −10 °C for 30 min. Acetic anhydride (0.58 ml, 6.0 mmol) was added dropwise at −10 °C, and the whole was stirred at −10 °C for 40 min, then poured into saturated NH_4Cl solution, and with Et_2O. The Et_2O layer was washed with water, dried, and evaporated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$) to give crude 2-acetyl-6-chloro-3-methoxyphenol (about 0.47 g). Tetrabutylammonium tribromide (TBABr) (1.01 g, 2.1 mmol) was added to a solution of this compound in CH_2Cl_2 (23 ml) and MeOH (9.2 ml). The mixture was stirred at room temperature for 40 min, refluxed for 15 min, then concentrated. The residue was treated with AcONa (500 mg, 6.0 mmol) and EtOH (10 ml).

This mixture was concentrated, poured into water, and extracted with AcOEt. The AcOEt layer was washed with water, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2 : hexane = 1 : 1) to give **2b** (0.17 g, 33%), mp 130—131 °C (AcOEt–hexane). IR (Nujol) cm^{-1}: 1715. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.90 (3H, s), 4.61 (2H, s), 6.42, 7.45 (each 1H, each s, each J = 8.0 Hz). FAB-MS (positive ion mode) *m/z*: 201 [$(M+1)^+ + 2$], 199 [$(M+1)^+$]. *Anal.* Calcd for $C_9H_7ClO_3$: C, 54.42; H, 3.55. Found: C, 53.97; H, 3.57.

Methyl 3-Chloro-2-hydroxy-5-methoxybenzoate (7c) *N*-Chlorosuccinimide (3.66 g, 27.5 mmol) was added to a solution of methyl 2-hydroxy-5-methoxybenzoate[6] (**6c**, 5.00 g, 27.5 mmol) in dry DMF (38 ml) at room temperature. Under an Ar atmosphere, the mixture was stirred at room temperature for 2.5 h and poured into water. The whole was extracted with Et_2O. The Et_2O layer was washed with brine,

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Table 2. Spectral Data for **4b—g**, **5b—g**, and **1b—g**

Compd. No.	IR (Nujol) cm^{-1} (C=O)	^{1}H-NMR (60 MHz, $CDCl_3$) δ	FAB-MS (positive ion mode) *m/z*
4b	1715, 1680	1.18 (3H, d, J=6.0 Hz), 2.40—2.85 (2H, m), 2.57 (3H, s), 3.30 (3H, s), 3.65—4.05 (1H, m), 3.90 (3H, s), 4.15—4.50 (2H, m), 6.48, 7.44 (each 1H, each d, each J=8.0 Hz)	373 [(M+1)$^+$+2] 371 [(M+1)$^+$]
4c	1715, 1670	1.20 (3H, d, J=6.5 Hz), 2.56 (3H, s), 2.62 (1H, dd, J=15.9, 5.1 Hz), 2.86 (1H, dd, J=15.9, 7.6 Hz), 3.32 (3H, s), 3.80 (3H, s), 3.85 (1H, dqd, J=7.6, 6.5, 5.1 Hz), 4.20, 4.38 (each 1H, each d, each J=17.3 Hz), 7.03, 7.21 (each 1H, each d, each J=2.6 Hz)[a]	373 [(M+1)$^+$+2] 371 [(M+1)$^+$]
4d	1710, 1675	1.19 (3H, d, J=6.0 Hz), 2.29—2.95 (2H, m), 2.57 (3H, s), 3.30 (3H, s), 3.69—4.09 (1H, m), 3.98 (3H, s), 4.19—4.34 (2H, m), 6.77, 7.57 (each 1H, each d, each J=8.0 Hz)	373 [(M+1)$^+$+2] 371 [(M+1)$^+$]
4e	1720, 1670	1.18 (3H, d, J=7.0 Hz), 2.52 (3H, s), 2.60 (1H, dd, J=16.0, 5.0 Hz), 2.83 (1H, dd, J=16.0, 7.5 Hz), 3.30 (3H, s), 3.81 (3H, s), 3.83 (1H, dqd, J=7.5, 7.0, 5.0 Hz), 4.02, 4.12 (each 3H, each s), 4.13, 4.32 (each 1H, each d, each J=17.5 Hz)[a]	432 (M$^+$+2) 430 (M$^+$)[b]
4f	1710, 1685	1.20 (3H, d, J=6.1 Hz), 2.15 (3H, s), 2.54 (3H, s), 2.62 (1H, dd, J=15.9, 5.0 Hz), 2.86 (1H, dd, J=16.0, 7.5 Hz), 3.32 (3H, s), 3.86 (1H, dqd, J=7.6, 6.1, 5.0 Hz), 3.90, 4.06 (each 3H, each s), 4.17, 4.36 (each 1H, each d, each J=17.3 Hz)[a]	416 [(M+1)$^+$+2] 414 [(M+1)$^+$]
4g	1710, 1680	1.21 (3H, d, J=6.1 Hz), 2.38—2.82 (2H, m), 2.56 (3H, s), 3.31 (3H, s), 3.66—4.08 (1H, m), 3.97, 4.13 (each 3H, each s), 4.24 (2H, dd, J=17.6, 21.0 Hz)	439 [(M+1)$^+$+4] 437 [(M+1)$^+$+2] 435 [(M+1)$^+$]
5b	1720, 1660	0.92 (3H, d, J=6.0 Hz), 2.20 (3H, s), 2.24—3.10 (3H, m), 3.93 (3H, s), 5.92 (1H, s), 6.53, 7.60 (each 1H, each d, each J=8.0 Hz)	341 [(M+1)$^+$+2] 339 [(M+1)$^+$]
5c	1720, 1660	0.89 (3H, d, J=6.5 Hz), 2.23 (3H, s), 2.49 (1H, dd, J=15.5, 2.8 Hz), 2.94—3.04 (2H, m), 3.82 (3H, s), 5.95 (1H, s), 6.99, 7.35 (each 1H, each d, each J=2.8 Hz)[a]	340 (M$^+$+2) 338 (M$^+$)[b]
5d	1715, 1650	0.86 (3H, d, J=6.0 Hz), 2.20 (3H, s), 2.20—2.91 (3H, m), 4.00 (3H, s), 5.90 (1H, s), 6.76, 7.64 (each 1H, each d, each J=8.0 Hz)	341 [(M+1)$^+$+2] 339 [(M+1)$^+$]
5e	1710, 1650	0.93 (3H, d, J=7.0 Hz), 2.23 (3H, s), 2.47 (1H, dd, J=16.6, 4.6 Hz), 2.93 (1H, dqd, J=13.6, 6.5, 4.6 Hz), 3.00 (1H, dd, J=16.6, 13.6 Hz), 3.84, 4.11, 4.14 (each 3H, each s), 5.93 (1H, s)[a]	400 (M$^+$+2) 398 (M$^+$)[b]
5f	1720, 1660	0.92 (3H, d, J=6.4 Hz), 2.15 (3H, s), 2.24 (3H, s), 2.48 (1H, dd, J=16.6, 4.0 Hz), 2.94 (1H, dqd, J=13.8, 6.4, 4.0 Hz), 3.00 (1H, dd, J=16.4, 13.8 Hz), 3.97, 4.06 (each 3H, each s), 5.94 (1H, s)[a]	384 (M$^+$+2) 382 (M$^+$)[b]
5g	1700, 1650	0.94 (3H, d, J=6.1 Hz), 2.26 (3H, s), 2.37—3.08 (3H, m), 4.06, 4.15 (each 3H, each s), 5.95 (1H, s)	407 [(M+1)$^+$+4] 405 [(M+1)$^+$+2] 403 [(M+1)$^+$]
1b	1717, 1662	0.98 (3H, d, J=6.2 Hz), 2.24—3.05 (3H, m), 3.63 (3H, s), 3.96 (3H, s), 5.63 (1H, s), 6.46, 7.58 (each 1H, each d, each J=8.0 Hz)	325 [(M+1)$^+$+2] 323 [(M+1)$^+$]
1c	1715, 1660	0.90 (3H, d, J=7.0 Hz), 2.46 (1H, dd, J=16.5, 4.5 Hz), 2.85 (1H, dqd, J=13.0, 7.0, 4.5 Hz), 2.96 (1H, dd, J=16.5, 13.0 Hz), 3.60 (3H, s), 3.80 (3H, s), 5.54 (1H, s), 6.95, 7.31 (each 1H, each d, each J=3.0 Hz)[a]	324 (M$^+$+2) 322 (M$^+$)[b]
1d	1710, 1655	0.90 (3H, d, J=6.0 Hz), 2.19—3.00 (3H, m), 3.60 (3H, s), 4.00 (3H, s), 5.53 (1H, s), 6.76, 7.56 (each 1H, each d, each J=8.0 Hz)	325 [(M+1)$^+$+2] 323 [(M+1)$^+$]
1e	1705, 1660	0.96 (3H, d, J=7.0 Hz), 2.45 (1H, dd, J=16.6, 4.5 Hz), 2.84 (1H, dqd, J=13.3, 7.0, 4.5 Hz), 2.98 (1H, dd, J=16.6, 13.3 Hz), 3.64 (3H, s), 3.84, 4.10, 4.14 (each 3H, each s), 5.56 (1H, s)[a]	384 (M$^+$+2) 382 (M$^+$)[b]
1f	1720, 1670	0.95 (3H, d, J=6.7 Hz), 2.15 (3H, s), 2.45 (1H, dd, J=16.6, 4.4 Hz), 2.86 (1H, dqd, J=13.5, 6.7, 4.4 Hz), 2.98 (1H, dd, J=16.6, 13.5 Hz), 3.64 (3H, s), 3.96, 4.05 (each 3H, each s), 5.57 (1H, s)[a]	368 (M$^+$+2) 366 (M$^+$)[b]
1g	1710, 1660	0.98 (3H, d, J=6.2 Hz), 2.29—3.07 (3H, m), 3.67 (3H, s), 4.06, 4.16 (each 3H, each s), 5.59 (1H, s)	391 [(M+1)$^+$+4] 389 [(M+1)$^+$+2] 387 [(M+1)$^+$]

a) 500 MHz. *b*) EI-MS.

dried, and evaporated *in vacuo*. The residue was purified by column chromatography (AcOEt : hexane = 1 : 10) to give **7c** (4.38 g, 74%), as colorless needles, mp 77—79 °C (AcOEt–hexane). IR (Nujol) cm^{-1}: 1670. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.77 (3H, s), 3.97 (3H, s), 7.14—7.28 (2H, m), 10.85 (1H, s). FAB-MS (positive ion mode) *m/z*: 219 [(M+1)$^+$+2], 217 [(M+1)$^+$]. *Anal.* Calcd for $C_9H_9ClO_4$: C, 49.90; H, 4.19. Found: C, 49.85; H, 4.09.

Methyl 7-Chloro-3-hydroxy-5-methoxy-2-benzofurancalboxylate (8c) Sodium hydride (62.7% in mineral oil, 3.45 g, 90.0 mmol) was added portionwise at 0 °C to a solution of **7c** (13.0 g, 60.0 mmol) in dry DMF (300 ml). Under an Ar atmosphere, the mixture was stirred at the same temperature for 20 min, then methyl bromoacetate (8.52 ml, 90.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 3.5 h, then sodium hydride (62.7% in mineral oil, 3.45 g, 90.0 mmol) was added portionwise at 0 °C. The whole was stirred at room temperature for 12 h, then poured into water, and made acidic with 10% HCl solution. The precipitate was collected by filtration and washed with water. Recrystallization from benzene gave **8c** (11.8 g, 76%), as yellow needles, mp 178—180 °C. IR (Nujol) cm^{-1}: 3350, 1690. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.85 (3H, s), 4.01 (3H, s), 7.02, 7.14 (each 1H, each d, J=2.3 Hz), 8.07 (1H, s). FAB-MS (positive ion mode) *m/z*: 259 [(M+1)$^+$+2], 257 [(M+1)$^+$]. *Anal.* Calcd for $C_{11}H_9ClO_5$: C, 51.48;

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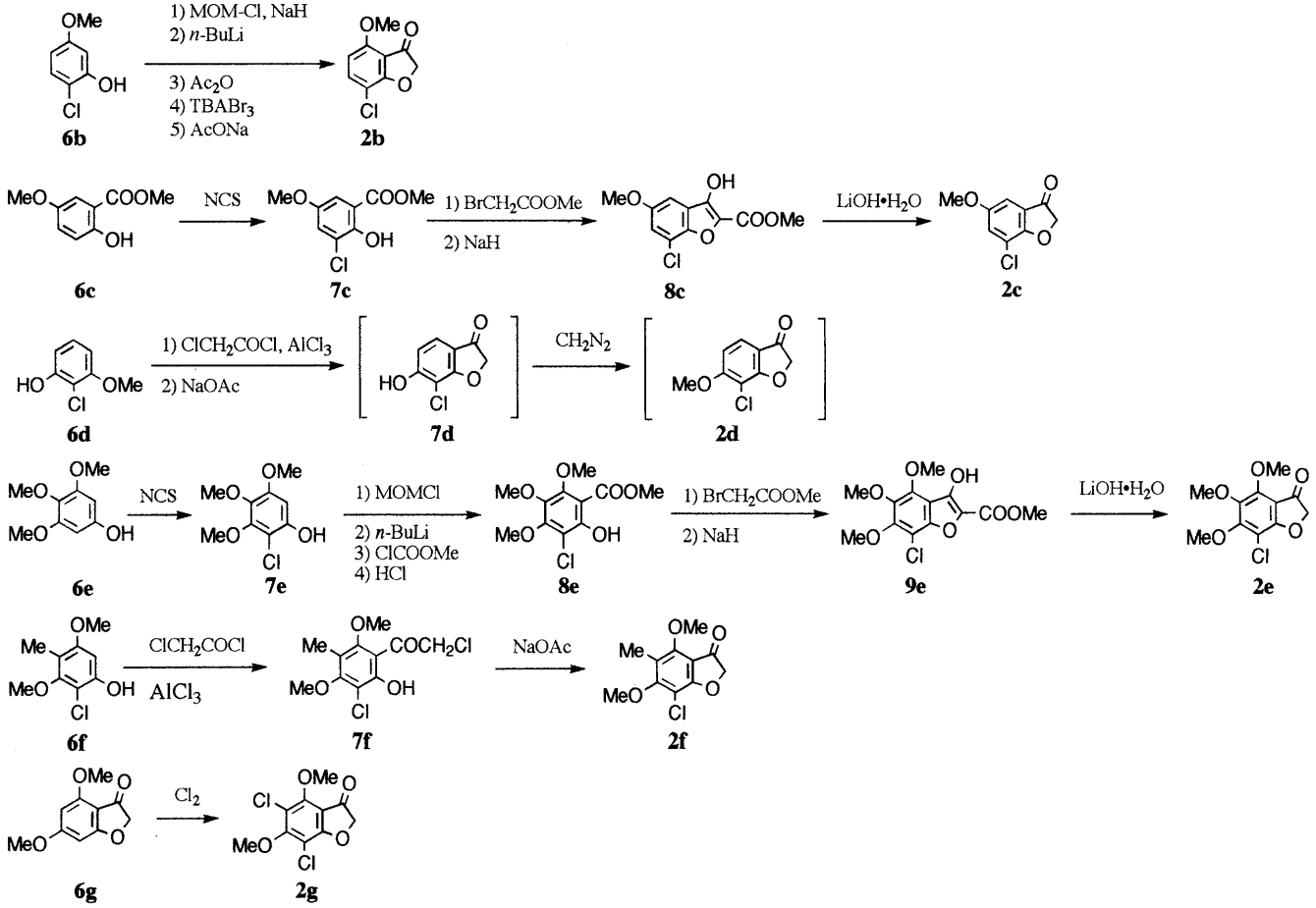

Chart 2

Table 3. Antifungal Activities of Griseofulvin Derivatives (*in Vitro*)

Compound	MIC (mg/ml)	
	T.m. T-14[a]	*T.m.* T-16[b]
d-Griseofulvin	3.13	1.56
1a (*dl*-Griseofulvin)	6.25	3.13
1b	12.5	6.25
1c	25	6.25
1d	6.25	3.13
1e	>100	>100
1f	>100	>100
1g	>100	>100

a) *T.m.* T-14 = *Trichophyton mentagrophytes* T-14. *b*) *T.m.* T-16 = *Trichophyton mentagrophytes* T-16.

H, 3.53. Found: C, 51.79; H, 3.53.

7-Chloro-5-methoxy-3(2*H*)-benzofuranone (2c) A mixture of **8c** (10.0 g, 39.0 mmol), $LiOH \cdot H_2O$ (95%, 8.17 g, 185 mmol), *N*,*N*-dimethyl sulfoxide (DMSO, 50 ml), and H_2O (87 ml) was stirred at 70 °C for 40 min and poured into 10% HCl solution. The precipitates were collected by filtration and washed with water. Recrystallization from Et_2O gave **2c** (6.29 g, 81%) as yellow needles, mp 136—141 °C. IR (Nujol) cm^{-1}: 1715. ^1H-NMR (60 MHz, $CDCl_3$) δ: 3.81 (3H, s), 4.73 (2H, s), 7.00, 7.29 (each 1H, each d, J = 2.3 Hz). EI-MS *m/z*: 200 ($M^+ + 2$), 198 (M^+). *Anal.* Calcd for $C_9H_7ClO_3$: C, 54.43; H, 3.55. Found: C, 54.79; H, 3.60.

7-Chloro-6-methoxy-3(2*H*)-benzofuranone (2d) Aluminum chloride (10.2 g, 76 mmol) and chloroacetyl chloride (2.3 ml, 28.5 mmol) were added to a solution of 2-chloro-3-methoxyphenol[7] (**6d**, 3.0 g, 19 mmol) in nitrobenzene (3 ml). The mixture was stirred at room temperature for 10 h and poured into ice water. The whole was extracted with AcOEt. The AcOEt layer was washed with water, dried, and evaporated *in vacuo*. A mixture of the residue, AcONa (10.2 g, 66.5 mmol), and EtOH (50 ml) was stirred at reflux for 40 min. After removal of the solvent, the residue was poured into water. The aqueous layer was extracted with AcOEt. The AcOEt layer was washed with 5% aqueous K_2CO_3 and the aqueous layer was made acidic with 10% HCl solution. The whole was extracted with AcOEt. The combined AcOEt layer was washed with water, dried, and evaporated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$) to give crude 7-chloro-6-hydroxy-3(2*H*)-benzofuranone (**7d**, about 2 g). Excess diazomethane in Et_2O was added to a solution of the above product in THF (150 ml). After standing for 3 d, the mixture was treated with AcOH and evaporated *in vacuo* to give crude **2d**. The residue was chromatographed with $CHCl_3$ to give **2d** (about 2.1 g). This compound was used for the next reaction without futher purification.

2-Chloro-3,4,5-trimethoxyphenol (7e) *N*-Chlorosuccinimide (3.33 g, 25.0 mmol) was added to a solution of 3,4,5-trimethoxyphenol[8] (**6e**, 4.18 g, 22.7 mmol) in dry DMF (35 ml) at 0 °C. Under an Ar atmosphere, the mixture was stirred at 0 °C for 3.5 h, then at room temperature for 2.5 h. It was poured into ice water and the precipitate was removed by filtration. The filtrate was extracted with Et_2O. The Et_2O layer was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (AcOEt : hexane = 1 : 7) to give **7e** (3.48 g, 70%), as colorless plates, mp 48—49 °C (AcOEt–hexane). IR (Nujol) cm^{-1}: 3250. ^1H-NMR (60 MHz, $CDCl_3$) δ: 3.82 (6H, s), 3.94 (3H, s), 5.50 (1H, s, OH), 6.42 (1H, s). EI-MS *m/z*: 220 ($M^+ + 2$), 218 (M^+). *Anal.* Calcd for $C_9H_{11}ClO_4$: C, 49.44; H, 5.07. Found: C, 49.14; H, 5.00.

Methyl 3-Chloro-2-hydroxy-4,5,6-trimethoxybenzoate (8e) A mixture of **7e** (9.52 g, 43.5 mmol) and dry DMF (30 ml) was added dropwise at 0 °C to a suspension of NaH (62.7% in mineral oil, 3.33 g, 87.1 mmol) in dry DMF (40 ml) under an Ar atmosphere. The reaction mixture was stirred at the same temperature for 25 min. Methoxymethyl chloride (5.26 g, 65.3 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred at the same temperature for 1 h, then poured into ice water. The whole was extracted with Et_2O. The Et_2O layer was

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washed with brine, dried, and evaporated *in vacuo* to give crude 2-chloro-3,4,5-trimethoxy-1-methoxymethoxybenzene. *n*-Butyllithium (1.43 M in hexane, 45.7 ml, 65.3 mmol) was added dropwise at −15 °C during 45 min to a solution of the above product in dry THF (120 ml). The reaction mixture was stirred at −10 °C for 15 min. Methyl chloroformate (5.05 ml, 65.3 mmol) was added dropwise at −10 °C during 20 min to the mixture. The mixture was stirred at 0 °C for 2 h, then poured into ice water. The whole was extracted with Et_2O. The Et_2O layer was washed with brine, dried, and evaporated *in vacuo*. A solution of the residue in MeOH (240 ml) and 10% HCl solution (95 ml) was stirred at 60 °C for 2.5 min. After removal of the solvent, the mixture was poured into ice water. The whole was extracted with Et_2O. The Et_2O layer was washed with brine, dried, and evaporated *in vacuo*. Recrystallization from petroleum ether gave **8e** (10.4 g, 87%) as colorless needles, mp 54—56 °C (AcOEt–hexane). IR (Nujol) cm^{-1}: 1660. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.83, 3.90, 4.00, 4.03 (each 3H, each s), 11.68 (1H, s). EI-MS *m/z*: 278 [$M^+ + 2$], 276 [M^+]. *Anal.* Calcd for $C_{11}H_{13}ClO_6$: C, 47.75; H, 4.74. Found: C, 48.02; H, 4.82.

Methyl 7-Chloro-3-hydroxy-4,5,6-trimethoxy-2-benzofurancalboxylate (9e) Sodium hydride (62.7% in mineral oil, 1.66 g, 43.4 mmol) was added portionwise at 0 °C to a solution of **8e** (8.00 g, 28.9 mmol) in dry DMF (80 ml). Under an Ar atmosphere, the mixture was stirred at 0 °C for 20 min, then methyl bromoacetate (4.09 ml, 43.2 mmol) was added dropwise at 0 °C. The whole was stirred at 0 °C for 3.5 h. Sodium hydride (62.7% in mineral oil, 1.66 g, 43.4 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h and poured into cold 10% HCl solution. The precipitates were collected by filtration and washed with water. Recrystallization from CH_2Cl_2 gave **9e** (6.93 g, 76%), as yellow needles, mp 134—136 °C. IR (Nujol) cm^{-1}: 3350, 1685. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.92, 4.11 (each 3H, each s), 4.00 (6H, s), 8.38 (1H, s). EI-MS *m/z*: 318 ($M^+ + 2$), 316 (M^+). *Anal.* Calcd for $C_{13}H_{13}ClO_7$: C, 49.30; H, 4.14. Found: C, 49.55; H, 4.20.

7-Chloro-5-4,5,6-trimethoxy-3(2*H*)-benzofuranone (2e) A mixture of **9e** (1.20 g, 3.8 mmol), $LiOH \cdot H_2O$ (95%, 0.80 g, 18 mmol), in DMSO (8 ml), and H_2O (12 ml) was stirred at 75 °C for 45 min. The whole was poured into 10% HCl solution. The precipitates were collected by filtration and washed with water. Recrystallization from a mixture of CH_2Cl_2, Et_2O, and petroleum ether gave **2e** (0.88 g, 90%), as yellow needles, mp 109—110 °C. IR (Nujol) cm^{-1}: 1695. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.83, 4.06, 4.16 (each 3H, each s), 4.67 (2H, s). EI-MS *m/z*: 260 [$M^+ + 2$], 258 [M^+]. *Anal.* Calcd for $C_{11}H_{11}ClO_5$: C, 51.08; H, 4.29. Found: C, 51.22; H, 4.14.

2,3′-Dichloro-2′-hydroxy-4′,6′-dimethoxy-5′-methylacetophenone (7f) A mixture of 2-chloro-3,5-dimethoxy-4-methylphenol[9] (**6f**, 200 mg, 0.99 mmol) in dry Et_2O (1.0 ml) was added dropwise at 0 °C to $AlCl_3$ (500 mg, 3.7 mmol) in dry Et_2O (1.0 ml), then chloroacetyl chloride (150 mg, 1.3 mmol) was added at the same temperature under an Ar atmosphere. The mixture was stirred at room temperature for 0.5 h, then refluxed for 3 h. Water and 10% HCl solution were added. The precipitates were collected by filtration and washed with water. Recrystallization from a mixture of Et_2O and petroleum ether gave **7f** (93 mg, 90%) as yellow needles, mp 144—146 °C. IR (Nujol) cm^{-1}: 1640. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.20 (3H, s), 3.82, 3.93 (each 3H, each s), 4.88 (2H, s), 12.74 (1H, s). EI-MS *m/z*: 282 ($M^+ + 4$), 280 ($M^+ + 2$), 278 (M^+). *Anal.* Calcd for $C_{11}H_{12}Cl_2O_4$: C, 47.34; H, 4.33. Found: C, 47.57; H, 4.42.

7-Chloro-4,6-dimethoxy-5-methyl-3(2*H*)-benzofuranone (2f) A mixture of **7f** (0.70 g, 2.5 mmol) and $AcONa \cdot 3H_2O$ (1.20 g, 8.8 mmol) in EtOH (18 ml) was stirred at room temperature for 1.5 h under an Ar atmosphere, then poured into water. The precipitates were collected by filtration and washed with water. Recrystallization from a mixture of EtOH and water gave **2f** (0.60 g, 98%) as colorless needles, mp 144—146 °C. IR (Nujol) cm^{-1}: 1720. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.14 (3H, s), 3.92, 4.09 (each 3H, each s), 4.69 (2H, s). EI-MS *m/z*: 244 ($M^+ + 2$), 242 (M^+). *Anal.* Calcd for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57. Found: C, 54.38; H, 4.63.

5,7-Dichloro-4,6-dimethoxy-5-methyl-3(2*H*)-benzofuranone (2g) Chlorine solution (0.3 M in CCl_4, 10.3 ml, 3.08 mmol) was added dropwise at 0 °C to a solution of 4,6-dimethoxy-5-methyl-3(2*H*)-benzofuranone[10] (**6g**, 300 mg, 1.54 mmol) in dry $CHCl_3$ (10 ml). The mixture was stirred at 0 °C, then washed with 10% sodium sulfite solution, water, and brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (AcOEt : hexane = 1 : 5) to give **2g** (170 mg, 48%) as colorless plates, mp 140—142 °C (AcOEt–hexane). IR (Nujol) cm^{-1}: 1710. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.45, 4.16 (each 3H, each s), 4.60 (2H, s). FAB-MS (positive ion mode) *m/z*: 231 [$(M+1)^+ + 2$], 229 [$(M+1)^+$]. *Anal.* Calcd for $C_{10}H_9ClO_4$: C, 52.53; H, 3.97. Found: C, 52.23; H, 3.88.

4-Chloro-2-[5-methoxy-1-(methylthio)-3-oxohexylidene]-3(2*H*)-benzofuranones (4b—g) General Procedure: *m*-Chloroperbenzoic acid (80%, 1.30 g, 6.03 mmol) was added portionwise at 0 °C to a solution of 1,1-bis(methylthio)-5-methoxy-1-hexen-3-one[1a] (**3**, 1.10 g, 4.99 mmol) in CH_2Cl_2 (110 ml). The mixture was stirred at 0 °C for 50 min, then washed with 10% sodium sulfite solution, saturated $NaHCO_3$ solution, and brine, dried, and evaporated *in vacuo* to give crude 5-methoxy-1-(methylsulfinyl)-1-(methylthio)-1-hexen-3-one. The synthesis of **4e** is described as representative example. Potassium *tert*-butoxide (0.50 g, 4.47 mmol) was added portionwise at 0 °C to a solution of **2e** (1.05 g, 4.06 mmol) in dry THF (15 ml). The mixture was stirred at 0 °C for 20 min under an Ar atmosphere. The solution of the above product in dry THF (5 ml) was added to the mixture dropwise at 0 °C. The mixture was stirred at the same temperature for 20 min and poured into 10% HCl solution. The whole was extracted with AcOEt. The AcOEt layer was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (AcOEt : hexane = 1 : 5) to give **4e** (1.07 g, 61%).

Yields, physical constants, and spectral data of **4b—g** were shown in Tables 1 and 2.

***dl*-2′-Demethoxy-2′-methylthiogriseofulvins (5b—g)** General Procedure: The synthesis of **5e** is described as a representative example. A mixture of **4e** (0.80 g, 1.86 mmol), dry THF (50 ml), and Al_2O_3 (1.89 g, 18.6 mmol, for column chromatography) was stirred at reflux for 12 h under an Ar atmosphere. The Al_2O_3 was removed by filtration and the filtrate was evaporated *in vacuo*. Recrystallization of the residue from a mixture of Et_2O and petroleum ether gave **5e** (0.55 g, 74%).

Yields, physical constants, and spectral data of **5b—g** are shown in Tables 1 and 2.

***dl*-2′-Demethoxy-2′-methylthiogriseofulvins (1b—g)** General Procedure: The synthesis of **1e** is described as a representative example. *m*-CPBA (80%, 0.26 g, 1.2 mmol) was added portionwise at 0 °C to a solution of **5e** (0.40 g, 1.0 mmol) in CH_2Cl_2 (16 ml). The mixture was stirred at 0 °C for 20 min, then washed with 10% sodium sulfite solution, saturated $NaHCO_3$ solution, and brine, dried, and evaporated *in vacuo* to give crude *dl*-2′-demethoxy-5-methoxy-2′-(methylsulfinyl)griseofulvin. Sodium methoxide (0.30 M in MeOH, 4.0 ml, 1.2 mmol) was added dropwise at 0 °C to a solution of the above product in dry benzene (4 ml). The mixture was stirred at 0 °C for 15 min under an Ar atmosphere and poured into 10% HCl solution. The whole was extracted with Et_2O. The Et_2O layer was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (AcOEt : hexane = 1 : 4) to give **1e** (0.25 g, 65%).

Yields, physical constants, and spectral data of **1b—g** are shown in Tables 1 and 2.

Antifungal Activity Assays and evaluation of antifungal activities were carried out according to the methods described previously.[1b]

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