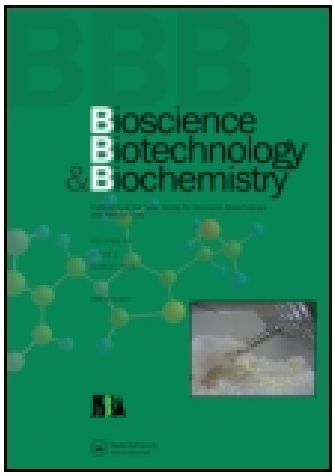


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# Transformation of Schizandrin into Gomisin A by Use of Microbial *O*-Demethylation and Chemical Reactions

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Received October 21, 1993

**The transformation of schizandrin (I) into gomisin A (II) was accomplished by use of a combination of biotransformation and chemical reactions. The biotransformation, microbial *O*-demethylation of I by *Cunninghamella echinulata* var. *elegans* (ATCC 9245) produced two novel metabolites [3-norschizandrin (IV) and 2-norschizandrin (VI)] and two known metabolites [gomisin T (III) and 13-norschizandrin (V)]. Among those metabolites, compound III was derived to II by the *O*-demethylation with a Lewis acid in the presence of an acid scavenger, followed by methylenation.**



Schizandrin (**I**)[1] and gomisin A (TJN-101, **II**)[2,3] are lignans isolated from the fruits of *Schisandra chinensis* BAILL. It has been reported that **II** has an inhibitory effect on some chemical-induced liver injuries[4–9] and an antitussive effect.[4,5] The synthetic study of gomisin A has been already reported by a collaborator, M. Tanaka *et al.*,[13] but the efficiency of synthesis was not satisfactory. In this study, we designed the synthesis of **II** by the conversion of **I**, which has a same structure as **II** except for a methylenedioxyl group as shown in Fig. 1. However, it was not easy to do the specific *O*-demethylation of two methoxyl groups at the C-12 and C-13 positions among six methoxyl groups in **I** by chemical reactions.

To solve this problem, we did the microbial *O*-demethylation of **I**. The fungus *Cunninghamella echinulata* var. *elegans* (ATCC 9245) was selected for this study, because it has been reported that it had a faculty for the *O*-demethylation of 10,11-dimethoxyaporphine.[10]

The fungus was grown with shizandrin in Erlenmeyer's flaks for 15 days. The analysis of the culture broth by high pressure liquid chromatography (HPLC) suggested the existence of four main metabolites (Fig. 2). The filtrate was chromatographed on Diaion HP-20, silica gel, and reversed phase silica gel to give four main metabolites, **III**, **IV**, **V**, and **VI**.

Compound **III** and **V** were identified as Gomisin T[11] and the 13-*O*-demethylated derivative of **I**,[12] respectively, by their spectral data.

Compound **IV** was obtained as a white amorphous powder, $[\alpha]_D$ +105° ($CHCl_3$), and its molecular formula was found to be $C_{23}H_{30}O_7$ from the high-resolution mass spectrum (high-resolution MS). Its ultraviolet (UV), infrared (IR), and $^1$H-nuclear magnetic resonance ($^1$H-NMR) spectra (Table I) and $^{13}$C-NMR spectrum (Table II) indicated that **IV** has a phenolic hydroxyl group and five methoxyl groups on the aromatic rings. The position of the phenolic hydroxyl group in **IV** was identified by measurement of the two-dimensional nuclear Overhauser effects spectroscopy (NOESY) and the correlation spectroscopy *via* long-range coupling (COLOC, the measurement was done under three conditions, the $J_{CH}$ parameter = 5.5, 7.14, and 10.0 Hz). In the NOESY spectrum, a singlet methyl signal (C-7 methyl) at $\delta$ 1.24 had a weak cross peak with a methine signal at $\delta$ 2.33. The methine signal had a strong cross peak with a lower-field aromatic proton signal at $\delta$ 6.69. A doublet methyl signal (C-8 methyl) at $\delta$ 0.82 had a cross peak with a higher-field aromatic proton signal at $\delta$ 6.54 (Fig. 3, thick arrow). These facts indicate that the signal at $\delta$ 6.69 is assigned to the aromatic proton signal

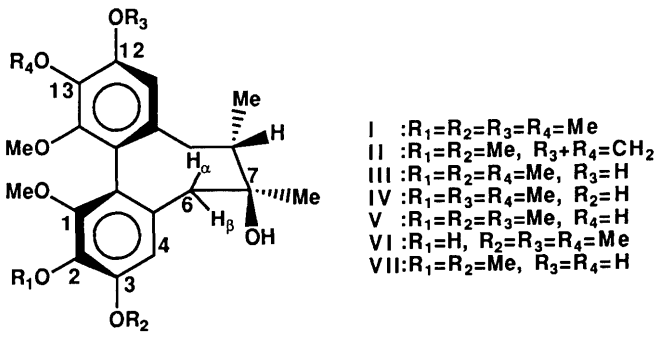



**Fig. 1.** Structures of Compound I–VII.

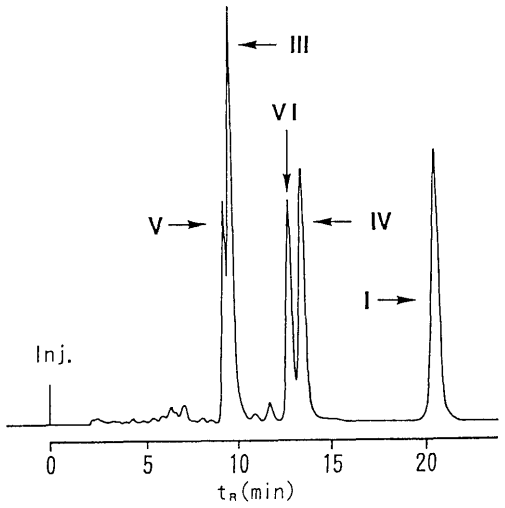



**Fig. 2.** Chromatogram of Culture Broth by *C. echinulata* var. *elegans*, ATCC 9245.

Column, YMC A-312; mobile phase; $CH_3CN$–MeOH–$H_2O$ (10:9:16); detection, UV 254 nm; flow rate, 1 ml/min.

**Table I.** $^1$H-NMR Spectral Data for **I**, **III**–**VI** ($\delta$ in $CDCl_3$, 500 MHz)

| Compd. | H-4, s<br>H-11, s | H-6α<br>d<br>($J$=Hz) | H-6β<br>d<br>($J$=Hz) | H-9α<br>dd<br>($J$=Hz) | H-9β<br>dd<br>($J$=Hz) | H-C$_{(8)}$-Me<br>m | <br>d<br>($J$=Hz) | HO-C$_{(7)}$-Me<br>s | <br>s | OMe<br>s | HO-Ar<br>br. s |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **I**[a] | 6.60<br>6.53 | 2.70<br>(14) | 2.32<br>(14) | 2.33<br>(14, 7) | 2.68<br>(14, 2) | 1.80 | 0.82<br>(7) | 1.86 | 1.25 | 3.59 (×2),<br>3.90 (×2),<br>3.92 (×2) | |
| **III**[b] | 6.63<br>6.62 | 2.68<br>(13.7) | 2.37<br>(13.7) | 2.34<br>(14.2, 7.3) | 2.61<br>(14.2, 1.5) | 1.87 | 0.82<br>(7.3) | 1.87 | 1.26 | 3.55 (×2)<br>3.90, 3.91,<br>3.92 | 5.78 |
| **IV**[b] | 6.69<br>6.54 | 2.63<br>(13.7) | 2.33<br>(13.7) | 2.37<br>(14.2, 7.8) | 2.71<br>(14.2, 1.5) | 1.87 | 0.82<br>(7.3) | 1.91 | 1.24 | 3.54, 3.56,<br>3.89 (×2),<br>3.94 | 5.86 |
| **V**[b] | 6.63<br>6.55 | 2.68<br>(13.2) | 2.38<br>(13.2) | 2.36<br>(14.2, 7.3) | 2.65<br>(14.2, 2.0) | 1.88 | 0.82<br>(7.3) | 1.88 | 1.26 | 3.43, 3.54,<br>3.90, 3.91,<br>3.92 | 5.59 |
| **VI**[b] | 6.63<br>6.55 | 2.66<br>(13.7) | 2.36<br>(13.7) | 2.38<br>(14.2, 7.8) | 2.66<br>(14.2, 1.5) | 1.89 | 0.83<br>(7.3) | —[c] | 1.26 | 3.41, 3.55,<br>3.89 (×2),<br>3.94 | —[c] |

[a] This compound was measured at 200 MHz.
[b] These assignments were based on the $^1$H–$^1$H correlation spectroscopy (COSY) and NOESY spectra.
[c] These signals were not measured.
[d] *Abbreviations*: br. = broad; d = doublet; m = multiplet; s = singlet.

**Table II.** $^{13}$C-NMR Spectral Data for **I**, **III**–**VI** ($\delta$ in $CDCl_3$, 125 MHz)

| Carbon | **I**[a] | **III** | **IV** | **V** | **VI** |
|---|---|---|---|---|---|
| 1 | 151.9[b] | 152.1[b] | 151.6[b] | 152.0 | 151.6 |
| 2 | 140.8[c] | 140.9 | 138.5 | 141.1 | 137.1 |
| 3 | 152.3 | 152.4 | 148.5 | 152.6 | 146.7 |
| 4 | 110.5[d] | 110.2 | 112.7 | 110.3 | 109.8 |
| 5 | 131.8 | 132.1 | 132.7 | 132.0 | 127.5 |
| 6 | 40.9 | 40.9 | 40.7 | 40.8 | 40.5 |
| 7 | 71.8 | 72.0 | 71.9 | 71.9 | 71.7 |
| 8 | 41.8 | 41.9 | 41.7 | 41.9 | 41.9 |
| 9 | 34.4 | 34.0 | 34.6 | 33.9 | 34.3 |
| 10 | 133.8 | 134.6 | 134.2 | 129.6 | 134.1 |
| 11 | 110.1[d] | 113.1 | 110.6 | 110.2 | 110.6 |
| 12 | 152.0 | 147.8 | 151.9 | 146.3 | 152.1 |
| 13 | 140.3[c] | 137.8 | 140.3 | 136.4 | 140.5 |
| 14 | 151.6[b] | 150.4[b] | 151.0[b] | 145.2 | 145.6 |
| 15 | 122.8 | 122.0 | 122.8 | 122.1 | 122.6 |
| 16 | 124.2 | 124.1 | 123.3 | 124.0 | 123.4 |
| 17 | 15.9 | 15.8 | 15.8 | 15.8 | 15.9 |
| 18 | 29.7 | 29.8 | 29.9 | 29.9 | 29.8 |
| OMe | | | | | |
| C-1, 14 | 60.5 (×2) | 60.1[c], 60.6[c] | 60.1[c], 60.6[c] | 60.7, 60.3 | 60.8, 60.3 |
| C-2, 13 | 60.9 (×2) | 60.9, 61.0 | 60.9, 61.0 | 61.0, | 61.0 |
| C-3, 12 | 56.0 (×2) | 56.0 | 56.0 | 56.2 56.1 | 56.2 56.0 |

[a] This compound was measured at 50 MHz.
[b–d] The assignments within any column may be reversed.

(H-4) at the C-4 position. The COLOC spectrum (the $J_{CH}$ parameter was set at 5.5 Hz: two- or three-bond correlation) showed a strong cross peak between the H-4 signal ($\delta$ 6.69) and the quaternary aromatic carbon signal at $\delta$ 138.5, and a weak cross peak between the H-4 signal and the quaternary aromatic carbon signal at $\delta$ 148.5. The aromatic carbon signal at $\delta$ 148.5 had no cross peak with the methoxyl proton, in spite of the presence of a cross peak between the aromatic carbon signal at $\delta$ 138.5 and the methoxyl proton (Fig. 3, thin arrow). These facts indicate that the aromatic carbon signals at $\delta$ 138.5 and $\delta$ 148.5 are assigned to the C-2 and C-3, respectively, and the phenolic hydroxyl group is linked to C-3.

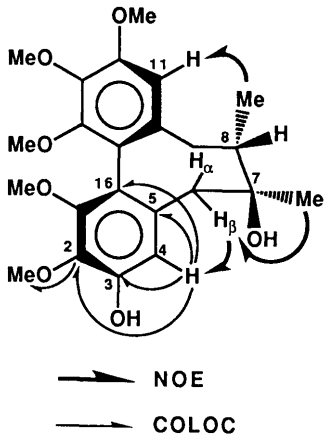


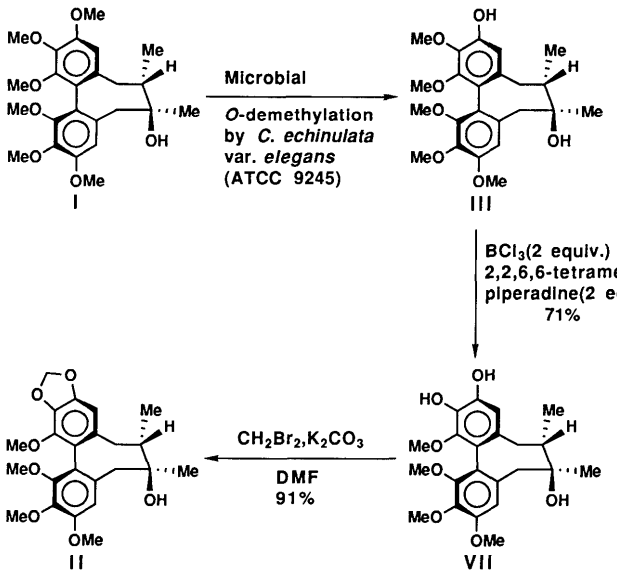

**Fig. 3.** Significant Correlations Observed in NOESY and COLOC Experiments of **IV**.

On the basis of the above observations, **IV** was identified as the 3-*O*-demethylated derivative of schizandrin.

Compound **VI** was obtained as a white amorphous powder, $[\alpha]_D$ +106° ($CHCl_3$), and its molecular formula was found to be $C_{23}H_{30}O_7$ from the high-resolution MS. Its UV, IR, $^1$H-NMR (Table I), and $^{13}$C-NMR spectra (Table II) indicated that **VI** had a phenolic hydroxyl group and five methoxyl groups on the aromatic rings. The position of the phenolic hydroxyl group in **VI** was identified by detailed analysis of the NOESY and the COLOC spectra as well as **IV**.

On the basis of the above observations, **VI** was identified as the 2-*O*-demethylated derivative of schizandrin.

In the above study, four mono-*O*-demethylated metabolites of schizandrin were isolated from the culture broth of the fungus, but 12,13-di-*O*-demethylated schizandrin (**VII**),[12] which is the most suitable intermediate for the synthesis of **II** from **I** was not obtained. Therefore, we tried




**Scheme** Transformation of Gomisin A (**II**) from Schizandrin (**I**).

the transformation of **VII** by the chemical *O*-demethylation of the methoxyl group at the C-13 position of **III** with a hydroxyl group at the C-12 position. Among the numerous *O*-demethylation methods,[14] Lewis acid catalyzed reaction was adopted taking advantage of the chelation of the *O*-hydroxyl group of **III** to Lewis acid for the regioselective reaction at the C-13 position. At the same time, to avoid the dehydrative rearrangement of eight-membered ring, which might be caused by the influence of protic acid,[15] the reaction was done in the presence of the acid scavenger.[16] After extensive attempts using various organic or inorganic bases, 2,2,6,6-tetramethylpiperidine was found to offer the best result. In the presence of the base, the treatment of **III** with boron trichloride in dichloromethane at room temperature afforded **VII** in 71% yield. Finally, the conversion of **VII** to **II** proceeded uneventfully by methylation using methylene dibromide and potassium carbonate in dimethyl formamide in 91% yield.

In this study, the synthesis of **II** from **I** was accomplished by the combination of biotransformation and chemical reactions (Scheme). The structures of **III** and **VII** were confirmed by a chemical transformation of **VII** to **II** (Gomisin A) the chemical and biological properties of which are known. In this biotransformation, the efficiency of transformation was not satisfactory because of the simultaneous production of by-products, **IV**, **V**, and **VI**. Further study to improve the efficiency of biotransformation is in progress.

## Experimental

The UV spectra were recorded with a Hitachi U-3200 spectrophotometer and the IR spectra with a Hitachi 270-30 infrared spectrophotometer. The $^1$H-NMR and $^{13}$C-NMR spectra were recorded with JEOL JNM-FX-200 and Bruker AM-500 NMR spectrometers using tetramethyl silane (TMS) as an internal standard. The specific rotations were measured with a JASCO DIP-30 digital polarimeter and the MS spectra were measured with a JEOL JMS-DX 300 mass spectrometer.

*Microorganism.* We used commercial fungi (*Cunninghamella echinulata* var. *elegans*, ATCC 9254) from ATCC.

*Schizandrin* (*substrate*). Schizandrin was obtained from the fruits of *Schisandra chinensis* BAILL.[3]

*Fermentation and isolation of metabolites.* The microbial transformation was done in a submerged medium consisting of (grams per liter of distilled water): Potato Dextrose Broth, 5.0; glucose, 20.0; Yeast extract, 5.0; NaCl, 5.0; $K_2HPO_4$, 5.0; pH, 7.0.

*Cunninghamella echinulata* var. *elegans* (ATCC 9245) was grown in thirty-four 100-ml Erlenmeyer's flasks each containing 20 ml of medium at 28°C on a reciprocating shaker (120 rpm). After incubation for 5 days, 20 mg of schizandrin dissolved in 50 $\mu$l of ethanol was added to each flask and fermentation was continued for 15 days.

The fungal mycelia were removed by filtration with suction after the culture medium was sterilized in an autoclave at 121°C for 15 min. The filtrate was absorbed on Diaion HP-20 and eluted with methanol after washing with water. The methanol eluate was evaporated *in vacuo* to give 0.72 g of residue. This residue was chromatographed on a column of silica gel (Kieselgel 60, Merck) using a mixture of *n*-hexane and acetone (80 : 20 to 75 : 25). The eluate was combined to two fractions according to the results of TLC analysis.

These fractions were also chromatographed on a column of reversed-phase silica gel (ODS, S-343, YMC) using a mixture of $H_2O$, methanol and acetonitrile (8 : 5 : 5). In the result, four main metabolites, gomisin T (**III**, 51.2 mg), 3-norschizandrin (**IV**, 45.5 mg), 13-norschizandrin (**V**, 15.8 mg), and 2-norschizandrin (**VI**, 43.6 mg) were obtained.

*Gomisin T* (**III**). A white amorphous powder, $[\alpha]_D$ +93.6° (*c* 1.95, $CHCl_3$). IR $\nu_{max}$ (KBr) cm$^{-1}$: 3432 (OH), 1584, 1488, 1454 (aromatic ring). UV $\lambda_{max}$ (EtOH) nm (log $\varepsilon$): 252 (4.20), 278 (3.82), 288 (3.80). High-resolution MS, Calcd. for $C_{23}H_{30}O_7$ ($M^+$): 418.1992. Found: 418.1996. MS *m/z* (%): 418 ($M^+$, 100), 400 (31), 375 (18), 347 (13), 344 (28), 343 (29), 316 (39), 315 (15). $^1$H-NMR and $^{13}$C-NMR: see Tables I and II.

*3-Norschizandrin* (**IV**). A white amorphous powder, $[\alpha]_D$ +105.1° (*c* 1.32, $CHCl_3$). IR $\nu_{max}$ (KBr) cm$^{-1}$: 3424 (OH), 1586, 1488, 1454 (aromatic ring). UV $\lambda_{max}$ (EtOH) nm (log $\varepsilon$): 252 (4.15), 277 (3.54), 288 (3.41). High-resolution MS, Calcd. for $C_{23}H_{30}O_7$ ($M^+$): 418.1992. Found: 418.1986. MS *m/z* (%): 418 ($M^+$, 100), 400 (15), 375 (9), 347 (11), 344 (13), 343 (24), 316 (30), 315 (43). $^1$H-NMR and $^{13}$C-NMR: see Tables I and II.

*13-Norschizandrin* (**V**). A white amorphous powder, $[\alpha]_D$ +109.6° (*c* 1.76, $CHCl_3$). IR $\nu_{max}$ (KBr) cm$^{-1}$: 3444 (OH), 1596, 1496, 1462 (aromatic ring). UV $\lambda_{max}$ (EtOH) nm (log $\varepsilon$): 252 (4.12), 277 (3.61), 288 (3.53). High-resolution MS, Calcd for $C_{23}H_{30}O_7$ ($M^+$): 418.1992. Found: 418.1990. MS *m/z* (%): 418 ($M^+$, 100), 400 (15), 347 (27), 344 (13), 343 (18), 334 (21), 316 (47), 315 (23). $^1$H-NMR and $^{13}$C-NMR: see Tables I and II.

*2-Norschizandrin* (**VI**). A white amorphous power, $[\alpha]_D$ +106.0° (*c* 0.53, $CHCl_3$). IR $\nu_{max}$ (KBr) cm$^{-1}$: 3724, 3568 (OH), 1600, 1496, 1462 (aromatic ring). UV $\lambda_{max}$ (EtOH) nm (log $\varepsilon$): 250 (4.14), 277 (3.52), 286 (3.40). High-resolution MS, Calcd for $C_{23}H_{30}O_7$ ($M^+$): 418.1992. Found: 418.1999. MS *m/z* (%): 418 ($M^+$, 100), 400 (9), 375 (15), 347 (11), 344 (16), 343 (24), 316 (25), 315 (14). $^1$H-NMR and $^{13}$C-NMR: see Tables I and II.

*Demethylation of* **III**. Compound **III** (1.0 g; 2.4 mmol) and 2,2,6,6-tetramethylpiperidine (0.89 ml; 5.28 mmol) were dissolved in dry dichloromethane (10 ml) under an atmosphere of argon. The solution was cooled to 0°C and stirred for 10 min. The boron trichloride (1.0 M solution in dichloromethane, 4.8 ml; 4.8 mmol) was added to an ice-cold solution and the resultant solution was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated sodium bicarbonate (50 ml) and extracted with ethyl acetate (40 ml × 3). The ethyl acetate extract was washed with 1 N hydrochloric acid and saturated sodium chloride. The organic layer, dried over $MgSO_4$, was evaporated *in vacuo*, and the chromatography (silica gel, 60 g, ethyl acetate : *n*-hexane = 2 : 3) of the residue followed by the recrystallization from *n*-hexane–ethyl acetate afforded 685.3 mg (71.0%) of met B (**VII**)[12] as colorless prisms, mp 194.4–195.6°C, IR $\nu_{max}$ (KBr) cm$^{-1}$: 3384, 1590. MS *m/z*: 404 ($M^+$). $^1$H-NMR $\delta_H$ ($CDCl_3$): 0.82 (3H, d, $J$=7 Hz), 1.27 (3H, s), 1.84 (1H, br. s), 2.32 (1H, dd, $J$=7, 13 Hz), 2.38 (1H, d, $J$=13 Hz), 2.58 (1H, dd, $J$=2, 13 Hz), 2.71 (1H, d, $J$=13 Hz), 3.29 (3H, s), 3.47 (3H, s), 3.91 (6H, s), 5.35 (1H, s), 5.56 (1H, s), 6.62 (1H, s), 6.66 (1H, s).

*Methylenation of* **VII**. Compound **VII** (100 mg, 0.25 mmol) was dissolved in DMF (1 ml), potassium carbonate (247.5 mg, 2.5 mmol) and dibromomethane (0.18 ml, 2.5 mmol) were added, and the mixture was stirred at 60°C for 1.5 h. The reaction mixture was taken up into ethyl acetate, washed with water and brine, then dried over magnesium sulfate. The evaporation of the solvent and chromatography of the residue (silica gel, ethyl acetate : *n*-hexane = 2 : 5) gave gomisin A (**II**) as colorless solid (93.4 mg, 91%), IR $\nu_{max}$ (KBr) $cm^{-1}$: 3512, 1160, 1502. MS *m/z*: 416 ($M^+$). $^1$H-NMR $\delta_H$ ($CDCl_3$): 0.82 (3H, d, $J$ = 7 Hz), 1.25 (3H, s), 1.78–1.89 (2H, m), 2.34 (1H, dd, $J$ = 7, 14 Hz), 2.35 (1H, d, $J$ = 14 Hz), 2.59 (1H, dd, $J$ = 14, 1.7 Hz), 2.69 (1H, d, $J$ = 14 Hz), 3.52 (3H, s), 3.84 (3H, s), 3.91 (6H, s), 5.96 (1H, d, $J$ = 1.5 Hz), 5.97 (1H, d, $J$ = 1.5 Hz), 6.48 (1H, s), 6.62 (1H, s).

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