Six New Constituents from an Ascomycete, *Chaetomium quadrangulatum*, Found in a Screening Study Focused on Monoamine Oxidase Inhibitory Activity

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A screening study focusing on monoamine oxidase inhibitory activity on the EtOAc extract of an Ascomycete *Chaetomium quadrangulatum*, which previously gave five unique chromones possessing this activity (chaetoquadrins A—E (1—5)), this time afforded six new constituents termed chaetoquadrins F—K (6—11) in addition to 1—5. The structures of 6—11 have been deduced on the basis of spectral and chemical data, and 7 and 8 have shown appreciable monoamine oxidase inhibitory activity.

Key words *Chaetomium quadrangulatum*; chromone; 2-pyrone; monoamine oxidase (MAO) inhibitory activity; chaetoquadrin; Ascomycete

In our screening program on monoamine oxidase (MAO) inhibitory constituents from fungi, five new chromones having MAO inhibitory activity called chaetoquadrins A—E (tentative name: CQ-1—5) (**1**—**5**) were isolated from the EtOAc extract of an Ascomycete, *Chaetomium quadrangulatum* CHIVERS, and their structures including absolute configuration were elucidated.[1)] Successive study on the extract of *C. quadrangulatum* guided by MAO inhibitory activity has this time afforded six new constituents tentatively termed CQ-6—11 (**6**—**11**) in addition to **1**—**5**. This paper deals with the structures and MAO inhibitory activity of these new compounds.

The EtOAc extract of *C. quadrangulatum* strain 71-NG-22[2)] cultivated on sterilized rice medium inhibited mouse liver MAO by 30.8% at 1.0×10^{-4} g/ml. When the EtOAc extract was partitioned into *n*-hexane, EtOAc, and water layers, the EtOAc layer showed higher MAO inhibitory activity than the other two layers. Chromatographic fractionation of the EtOAc layer focused on MAO inhibitory activity gave six novel constituents tentatively called CQ-6—11 (**6**—**11**) in addition to **1**—**5**. The yields of **6**—**11** from the EtOAc extract were 0.22, 0.12, 0.25, 0.011, 0.13, and 0.38%, respectively.

CQ-6 (**6**), $C_9H_{12}O_4$, was obtained as an optically active white powder, IR ν_{max}^{KBr} cm^{-1}: 3109 (OH), 1678 (C=O), 1655, 1591 (C=C), 1429, 1383, 1257, 1124, 1076 (C–O), UV λ_{max}^{MeOH} nm (log ε): 204 (4.51), 230 (3.37), and 290 (4.02). These spectral data suggested the presence of an α,β-unsaturated carbonyl system in **6**. The ^{1}H- and ^{13}C-NMR data showed the presence of two methyls [$\underline{CH_3}$–CH<, $\underline{CH_3}$–C=], one methylene [>CH–$\underline{CH_2}$–C=], two methines [>$\underline{CH}$–O, –$\underline{CH}$=], and four quaternary carbons [>$\underline{C}$=, =$\underline{C}$(–O)–, =$\underline{C}$(–O)–O, >$\underline{C}$=O] in **6** (see Table 1). The ^{1}H- and ^{13}C-NMR data including spin-decoupling ^{1}H-NMR, two dimensional ^{1}H–^{1}H shift correlation (COSY), ^{1}H-detected single-bond heteronuclear correlation through multiple quantum coherence (HSQC), and ^{1}H-detected heteronuclear multiple-bond correlation (HMBC) NMR data suggested a 2-pyrone-type structure (**6**) or a 4-pyrone-type structure (**6a**) as the candidate molecular structure of CQ-6 (without stereochemistry). Here, **6** possessed a phenolic OH at position 4 and an alcoholic OH at position 2′, meanwhile, **6a** possessed a phenolic OH at position 2 and an alcoholic OH at position 2′ (see Chart 1). On methylation with CH_2N_2, the phenolic OH in CQ-6 was methylated to give a monomethylether (**12**) [^{1}H-NMR δ (ppm) in CD_3OD: 4.10 (3H, s, C$\underline{H_3}$O–), UV λ_{max}^{MeOH} nm (log ε): 210 (4.40) and 263 (4.01)]. In the HMBC NMR spectrum of the monomethylether, it was found that C$\underline{H_3}$O (δ_H 4.10) had significant correlation with C-2 (δ_C 165.7) which possessed no correlation with H-5 (δ_H 6.21), indicating that the plane structure of the monomethylether was expressed as **12**. It was already known that 2- and 4-pyrone-type compounds give their typical UV absorptions at 280—314 and 240—276 nm, respectively.[3)] The fact that CQ-6 and **12** gave their respective typical UV absorptions at nm (log ε): 290 (4.02) and 263 (4.01) as mentioned above suggested the possibility that CQ-6 and **12** might be 2-pyrone-type and 4-pyrone-type compounds, respectively. This possibility was also supported by the ^{13}C-NMR spectral data. Namely, comparison of the ^{13}C-NMR spectrum of **12** with that of CQ-6 showed that the signal of C-4 was shifted to δ_C 183.6 (+15.9) ppm (see Table 1), indicating that C-4, which was an aromatic carbon bearing a phenolic OH in CQ-6, was converted into a carbonyl carbon in **12** during the methylation. Therefore, the plane structure of CQ-6 was deduced not to be **6a**, but to be **6**. On treatment with (*R*)-(+)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acids [(*R*)- and (*S*)-MTPA acids], both hydroxyls at positions 2 and 2′ in **6** were esterified to give di-(*R*)- and di-(*S*)-MTPA esters (**13**, **14**), respectively. To apply the modified Mosher's method[4)] to **6**, the $\Delta\delta$ values ($\delta_{14}-\delta_{13}$) were calculated as shown in Chart 1, indicating that the absolute configuration at position 2′ in **6** was (*S*), though the $\Delta\delta$ value at position 2′ was not 0.00 but −0.02. Accordingly, CQ-6 was deduced to be (2′*S*)-4-hydroxy-3-methyl-6-(2′-hydroxypropyl)-2-pyrone (**6**), as shown in Chart 1. To our knowledge, this is the first time that **6** has been isolated from a natural source. Thus we propose to name CQ-6 chaetoquadrin F (**6**).

CQ-7 (**7**), $C_{20}H_{22}O_6$, was obtained as an optically active white powder, circular dichroism (CD) (1.12 mM, MeOH) $\Delta\varepsilon$ (nm): −1.2 (317), −0.51 (295), −6.1 (262), −6.1 (258), +1.3 (230), +0.56 (224), +0.72 (221), −0.51 (213), −0.15 (210), −1.7 (205), IR ν_{max}^{KBr} cm^{-1}: 3447 (OH), 1654 (C=O), 1597 (C=C), 1448, 1401, 1345, 1207, 1130 (C–O), UV

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Table 1. ^{1}H- and ^{13}C-NMR Data for Chaetoquadrin F (**6**), Its Monomethylether (**12**), Di-(*R*)-MTPA Ester (**13**), and Di-(*S*)-MTPA Ester (**14**)

Position	**6**		**12**		**13**	**14**
	in CD_3OD		in CD_3OD		in $CDCl_3$	in $CDCl_3$
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_H
2		169.1 (s)		165.7 (s)		
2-OCH_3			4.10 (3H, s)	56.8 (q)		
3		99.3 (s)		101.4 (s)		
3-CH_3	1.85 (3H, s)	8.2 (q)	1.85 (3H, s)	6.7 (q)	1.82 (3H, s)	1.82 (3H, s)
4		167.7 (s)		183.6 (s)		
5	6.05 (s)	102.8 (d)	6.21 (s)	113.6 (d)	5.85 (s)	5.95 (s)
6		162.0 (s)		163.4 (s)		
1′	2.52 (dd, 14.8, 6.8)	43.9 (t)	2.68 (dd, 14.4, 8.0)	43.1 (t)	2.75 (2H, br d, 6.4)	2.80 (2H, br d, 6.8)
	2.57 (dd, 14.8, 5.4)		2.79 (dd, 14.4, 4.4)			
2′	4.10 (m)	66.2 (d)	4.19 (m)	66.3 (d)	5.47 (m)	5.45 (m)
3′	1.21 (3H, d, 6.4)	23.4 (q)	1.31 (3H, d, 6.0)	23.4 (q)	1.45 (3H, d, 6.4)	1.39 (3H, d, 6.4)
–OCOC(CF_3)(OCH_3)C_6H_5					3.48 (3H, s), 3.60 (3H, s)	3.44 (3H, s), 3.58 (3H, s)
–OCOC(CF_3)(OCH_3)C_6H_5					7.28—7.59 (10H, m)	7.29—7.58 (10H, m)

δ (ppm) from TMS as an internal standard [coupling constants (Hz) in parentheses].

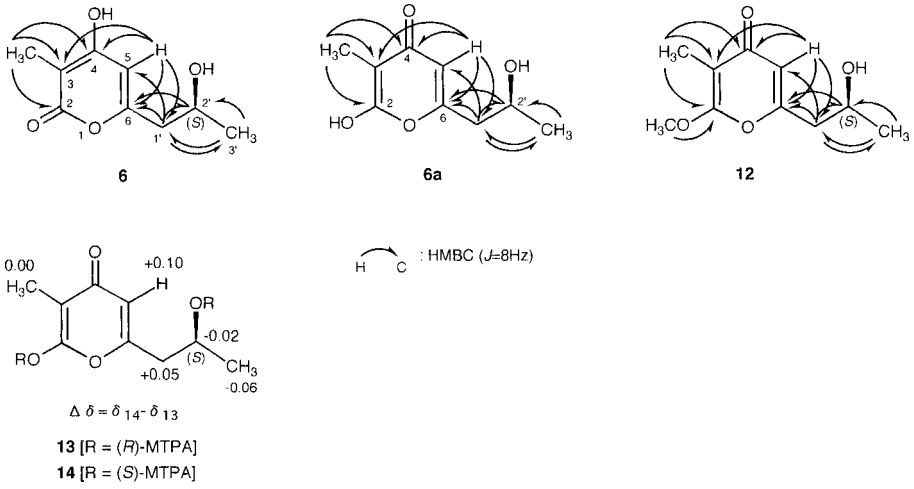


Chart 1

λ_{max}^{MeOH} nm (log ε): 208 (4.46), 233 (4.33), and 260 (4.45). The ^{1}H- and ^{13}C-NMR data showed the presence of four methyls [$\underline{CH_3}$–CH<×2, $\underline{CH_3}$–C=, $\underline{CH_3}$O–], two methylenes [CH–$\underline{CH_2}$–×2], five methines [>$\underline{CH}$–O, >$\underline{CH}$–C=, –$\underline{CH}$=×3], and nine quaternary carbons [>$\underline{C}$=×2, =$\underline{C}$(–O)–×5, >$\underline{C}$=O×2] in **7** (see Table 2). The ^{1}H- and ^{13}C-NMR data including spin-decoupling ^{1}H-NMR, COSY, HSQC, and HMBC data suggested that CQ-7 was composed of three partial structures *a*, *b*, and *c*. Connection of *a* with *b* and *c* was attained by the aid of the HMBC data to provide a chromone-type structure (**7**) as the molecular structure of CQ-7 (without stereochemistry) (see Chart 2). The provided structure **7** was quite similar to the molecular structure of chaetoquadrins A ((2′*R*,3′*R*,5′*R*,7′*S*)-6-[(5,3′:3′,7′-diepoxy-5′-hydroxy-2′-methyl)octyl]-7-methoxy-2-methylchromone) (**1**) and B ((5′*S*)-isomer of **1**) (**2**)[1] except for the substituents at positions 5, 3′(4′), and 5′. On oxidation with CrO_3-pyridine complex, both **1** and **2** gave the same product, which was identical with **7** in terms of ^{1}H-NMR and CD spectra. This fact and comparison of the ^{1}H- and ^{13}C-NMR data of CQ-7 with those of **1** and **2** indicated that the structure of CQ-7 was (2′*R*,7′*S*)-5-hydroxy-7-methoxy-6-[(3′,7′-epoxy-2′-methyl-5′-oxo)-3′-octenyl]-2-methylchromone (**7**), as shown in Chart 2. To our knowledge, this is the first time that **7** has been isolated from a natural source. Thus we propose to name CQ-7 chaetoquadrin G (**7**).

CQ-8 (**8**), $C_{20}H_{22}O_6$, was obtained as an optically active white powder, CD (1.12 mM, MeOH) $\Delta\varepsilon$ (nm): −1.5 (317), +0.47 (290), −2.9 (269), +5.3 (254), −1.7 (233), −0.76 (223), −0.87 (220), −0.57 (216), −1.4 (210), +1.4 (203), IR ν_{max}^{KBr} cm^{-1}: 3447 (OH), 1654 (C=O), 1588 (C=C), 1448, 1402, 1344, 1206, 1130 (C–O), UV λ_{max}^{MeOH} nm (log ε): 210 (4.41), 233 (4.28), and 259 (4.40). The ^{1}H- and ^{13}C-NMR data of **8** were quite similar to those of **7**, showing that **8** might be a stereoisomer of **7** (see Table 2). On oxidation with CrO_3-pyridine complex, chaetoquadrin C ((2′*S*,3′*R*,5′*S*,7′*S*)-6-[(5,3′:3′,7′-diepoxy-5′-hydroxy-2′-methyl)octyl]-7-methoxy-2-methylchromone) (**3**)[1] gave a product which was identical with **8** in terms of TLC and HPLC. This fact and comparison of the ^{1}H- and ^{13}C-NMR data of CQ-8 with those of **3** suggested that the structure of CQ-8 was 5-hydroxy-7-methoxy-6-[(3′,7′-epoxy-2′-methyl-5′-oxo)-3′-octenyl]-2-methylchromone (**8**), as shown in Chart 2 (we assume **8** may be (2′*S*)-isomer of **7**). To our knowledge, this is the first time

Table 2. ^{1}H- and ^{13}C-NMR Data for Chaetoquadrins G (**7**), H (**8**), I (**9**), and A (**1**)[1)]

Position	**7**		**8**		**9**		**1**[1)]	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2		166.4 (s)		166.5 (s)		166.5 (s)		162.9 (s)
2-CH_3	2.35 (3H, s)	20.4 (q)	2.35 (3H, s)	20.4 (q)	2.35 (3H, s)	20.4 (q)	2.28 (3H, s)	19.8 (q)
3	6.04 (s)	108.9 (d)	6.04 (s)	108.9 (d)	6.04 (s)	109.0 (d)	5.94 (s)	111.8 (d)
4		182.4 (s)		182.5 (s)		182.5 (s)		177.4 (s)
4a		105.0 (s)		105.0 (s)		105.1 (s)		108.3 (s)
5		159.1 (s)		159.0 (s)		158.9 (s)		151.3 (s)
6		110.6 (s)		110.6 (s)		111.1 (s)		107.3 (s)
7		163.3 (s)		163.2 (s)		163.0 (s)		161.4 (s)
7-OCH_3	3.86 (3H, s)	55.8 (q)	3.86 (3H, s)	55.8 (q)	3.88 (3H, s)	55.9 (q)	3.89 (3H, s)	55.7 (q)
8	6.35 (s)	89.3 (d)	6.34 (s)	89.3 (d)	6.36 (s)	89.4 (d)	6.42 (s)	91.2 (d)
8a		156.8 (s)		156.8 (s)		156.8 (s)		158.0 (s)
1′	2.75 (dd, 12.4, 7.2), 2.93 (dd, 12.4, 6.8)	27.2 (t)	2.70 (dd, 12.0, 6.4), 2.97 (dd, 12.0, 7.6)	27.1 (t)	2.92 (2H, m)	19.4 (t)	2.39 (dd, 16.9, 3.2), 2.91 (dd, 16.9, 6.6)	24.2 (t)
2′	2.73 (m)	38.5 (d)	2.73 (m)	38.9 (d)	2.46 (2H, ddd, 7.8, 7.8, 2.8)	33.6 (t)	2.11 (qdd, 7.1, 6.6, 3.2)	32.5 (d)
2′-CH_3	1.12 (3H, d, 6.8)	17.2 (q)	1.17 (3H, d, 6.8)	17.4 (q)			1.00 (3H, d, 7.1)	15.6 (q)
3′		181.4 (s)		181.1 (s)		177.6 (s)		101.4 (s)
4′	5.22 (s)	102.5 (d)	5.11 (s)	103.1 (d)	5.21 (s)	104.1 (d)	1.32 (dd, 12.7, 11.2), 2.43 (ddd, 12.7, 4.8, 1.7)	39.4 (t)
5′		193.5 (s)		193.6 (s)		193.3 (s)	4.67 (ddd, 12.0, 11.2, 4.8)	64.5 (d)
6′	2.33 (2H, m)	42.7 (t)	2.32 (2H, m)	42.7 (t)	2.34 (2H, m)	42.7 (t)	1.25 (ddd, 12.0, 12.0, 12.0) 2.04 (ddd, 12.0, 3.0, 1.7)	42.4 (t)
7′	4.42 (m)	75.4 (d)	4.37 (m)	75.6 (d)	4.45 (m)	75.6 (d)	4.00 (dqd, 12.0, 6.8, 3.0)	66.6 (d)
8′	1.42 (3H, d, 6.0)	20.3 (q)	1.44 (3H, d, 6.4)	20.3 (q)	1.44 (3H, d, 6.0)	20.4 (q)	1.08 (3H, d, 6.8)	21.4 (q)

δ (ppm) from TMS as an internal standard in $CDCl_3$ [coupling constants (Hz) in parentheses].

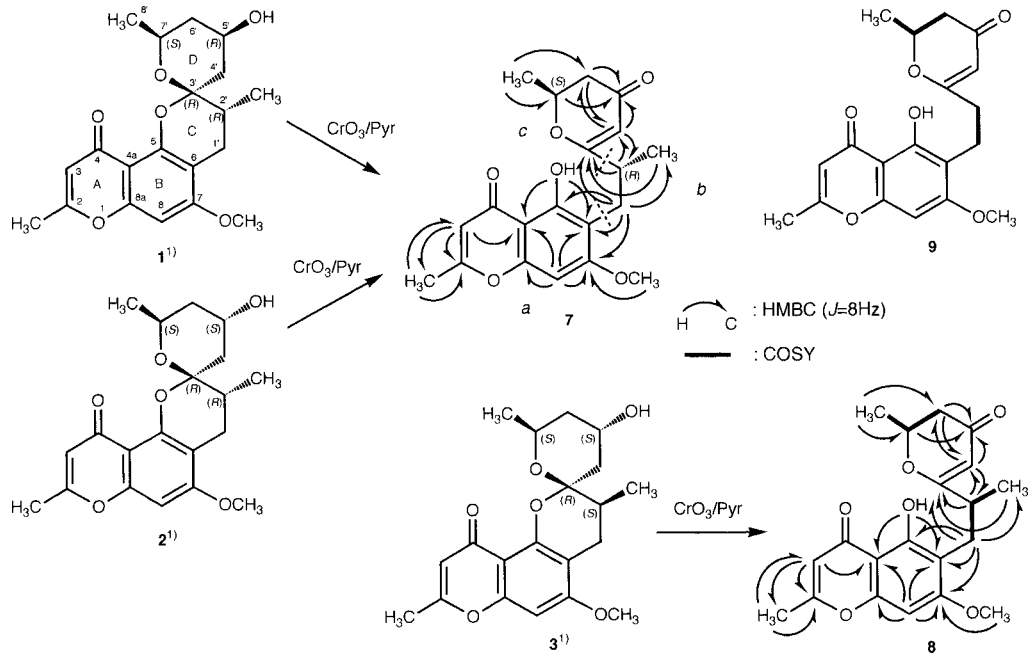


Chart 2

that **8** has been isolated from a natural source. Thus, we propose to name CQ-8 chaetoquadrin H (**8**).

CQ-9 (**9**), $C_{19}H_{20}O_6$, was obtained as an optically active colorless amorphous, UV λ_{max}^{MeOH} nm (log ε): 208 (4.36), 232 (4.21), and 259 (4.32). The UV spectrum of **9** was quite similar to those of **7** and **8**. Comparison of the ^{1}H- and ^{13}C-NMR data of **9** with those of **7** and **8** indicated that the –CH(CH_3)– group at position 2′ in **7** and **8** was replaced with the –CH_2– group in **9** (see Table 2). This fact was also supported by comparison of the molecular formula of **9** with those of **7** and **8**. Accordingly, the structure of CQ-9 was estimated to be 5-hydroxy-7-methoxy-6-[(3′,7′-epoxy-5′-oxo)-3′-octenyl]-2-methylchromone (**9**), as shown in Chart 2. To our knowledge, this is the first time that **9** has been isolated from a natural source. Thus we propose to name CQ-9 chaetoquadrin I (**9**).

CQ-10 (**10**), $C_{23}H_{22}O_8$, was obtained as an optically active white powder, IR ν_{max}^{KBr} cm^{-1}: 3431 (OH), 1660 (C=O), 1620 (C=C), 1491, 1444, 1341, 1313, 1201, 1130, 1108 (C–O), UV λ_{max}^{MeOH} nm (log ε): 211 (4.29), 230 (4.21), 259 (4.05), 275

(3.92). The ^{1}H- and ^{13}C-NMR data showed the presence of four methyls [$\underline{CH_3}$–CH<, $\underline{CH_3}$–C=×2, $\underline{CH_3}$–O], two methylenes [>CH–$\underline{CH_2}$–C=, =C–$\underline{CH_2}$–C=], three methines [>$\underline{CH}$–O, –$\underline{CH}$=×2], and fourteen quaternary carbons [>$\underline{C}$=×6, =$\underline{C}$(–O)–×6, >$\underline{C}$=O×2] in **10** (see Table 3). The ^{1}H- and ^{13}C-NMR data suggested that CQ-10 might be composed of two partial structures *d* (chromone part) and *e* (dihydroisocoumarin part) (see Chart 3). Connection of *d* with *e* was attained with the aid of HMBC data to give the plane structure of CQ-10 (**10**), as shown in Chart 3. To our knowledge, this is the first time that **10** has been isolated from a natural source. Thus we propose to name CQ-10 chaetoquadrin J (**10**).

Table 3. ^{1}H- and ^{13}C-NMR Data for Chaetoquadrins J (**10**) and K (**11**)

Position	**10**		**11**	
	δ_H	δ_C	δ_H	δ_C
2		167.3 (s)		166.5 (s)
2-CH_3	2.37 (3H, s)	20.5 (q)	2.35 (3H, s)	20.4 (q)
3	6.10 (s)	108.9 (d)	6.06 (s)	109.0 (d)
4		182.4 (s)		182.5 (s)
4a		105.1 (s)		105.0 (s)
5		157.6 (s)		159.2 (s)
5-OH	14.01 (s)		12.82 (s)	
6		110.0 (s)		110.2 (s)
7		162.5 (s)		163.5 (s)
7-OCH_3	3.91 (3H, s)	56.1 (q)	3.85 (3H, s)	55.8 (q)
8	6.43 (s)	90.5 (d)	6.36 (s)	89.4 (d)
8a		156.9 (s)		157.0 (s)
9	3.82 (2H, s)	18.8 (t)		
1′		171.0 (s)	2.87 (dd, 12.8, 8.4) 3.03 (dd, 12.8, 5.6)	25.9 (t)
2′			2.85 (m)	38.4 (d)
2′-COOH				181.9 (s)
3′	4.61 (m)	75.0 (d)	1.14 (3H, d, 6.8)	16.2 (q)
3′-CH_3	1.57 (3H, d, 6.0)	21.1 (q)		
4′	2.82 (dd, 16.4, 12.0) 3.53 (dd, 16.4, 3.0)	32.5 (t)		
4a′		136.5 (s)		
5′		113.4 (s)		
6′		160.3 (s)		
6′-OH	8.11 (s)			
7′		111.0 (s)		
7′-CH_3	2.08 (3H, s)	8.0 (q)		
8′		161.0 (s)		
8′-OH	11.57 (s)			
8a′		100.9 (s)		

δ (ppm) from TMS as an internal standard in $CDCl_3$ [coupling constants (Hz) in parentheses].

CQ-11 (**11**), $C_{15}H_{16}O_6$, was obtained as an optically active white powder, IR ν_{max}^{KBr} cm^{-1}: 3437 (OH), 1701, 1662 (C=O), 1620 (C=C), 1496, 1448, 1345, 1204, 1137 (C–O), UV λ_{max}^{MeOH} nm (log ε): 209 (4.29), 232 (4.15), 253 (4.08), 259 (4.09), 293 (3.78). The ^{1}H- and ^{13}C-NMR data showed the presence of three methyls [$\underline{CH_3}$–CH<, $\underline{CH_3}$–C=, $\underline{CH_3}$–O], one methylene [>CH–$\underline{CH_2}$–C=], three methines [>$\underline{CH}$–, –$\underline{CH}$=×2], and eight quaternary carbons [>$\underline{C}$=×2, =$\underline{C}$(–O)–×4, >$\underline{C}$=O×2] in **11** (see Table 3). The ^{1}H- and ^{13}C-NMR data suggested that CQ-11 might be 5-hydroxy-6-(2′-carboxy)propyl-7-methoxy-2-methylchromone (**11**), as shown in Chart 3. To our knowledge, this is the first time that **11** has been isolated from a natural source. Thus we propose to name CQ-11 chaetoquadrin K (**11**).

The mouse liver MAO inhibitory activities of chaetoquadrins F—H (**6**—**8**), J (**10**), and K (**11**) were calculated as shown in Table 4. Among these compounds, both **7** and **8** displayed higher MAO inhibitory activity than the others. However, comparison of the activity of **7** and **8** (IC_{50} of **7** and **8**: 4.5×10^{-4} and 2.3×10^{-4} M, respectively) with those of chaetoquadrin D (**4**) (IC_{50}: 3.8×10^{-5} M),[1] luteusin A (IC_{50}: 6.6×10^{-6} M),[5—9] GP-A (IC_{50}: 2.7×10^{-6} M),[10] monankarin A (IC_{50}: 1.6×10^{-5} M),[11] and coniochaeton A (IC_{50}: 2.9×10^{-5} M),[12] which we previously isolated from fungi, suggested that both **7** and **8** display somewhat low activity.

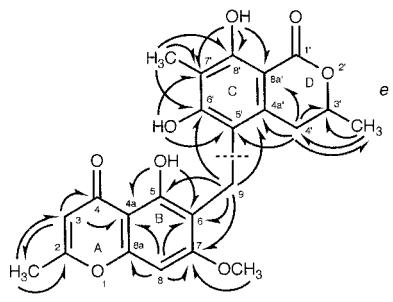
Experimental

Optical rotations and CD spectra were measured with a JASCO DIP-140 digital polarimeter and a JASCO J-500 spectropolarimeter, respectively. UV and IR spectra were recorded on Hitachi U-3200 and JASCO FT/IR-230 spectrophotometers, respectively. Electron impact (EI)-MS and high-resolution (HR)-FAB-MS spectra were measured with Hitachi M-60 and JEOL JMX-HX-110A spectrometers using *m*-nitrobenzyl alcohol (*m*-NBA) as a

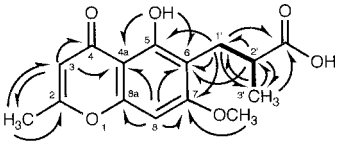
Table 4. Mouse Liver MAO Inhibitory Activities of Chaetoquadrins F—H (**6**—**8**), J (**10**), and K (**11**)

Compound	Inhibitory ratio (%)		
	1.0×10^{-4}	2.5×10^{-5}	1.0×10^{-5} g/ml
Chaetoquadrin F (**6**)	0.5	3.8	−1.7
Chaetoquadrin G (**7**)	48.0	23.5	12.1
Chaetoquadrin H (**8**)	56.0	28.0	13.7
Chaetoquadrin J (**10**)	4.5	1.9	3.6
Chaetoquadrin K (**11**)	8.6	5.3	4.8
Chaetoquadrin G (**7**): $IC_{50}=4.5\times10^{-4}$ M			
Chaetoquadrin H (**8**): $IC_{50}=2.3\times10^{-4}$ M			

Chaetoquadrin I (**9**) was not tested because it was in short supply.



10



11

H C : HMBC (*J*=8Hz)

: COSY

Chart 3

matrix, respectively. ^{1}H- and ^{13}C-NMR spectra were measured with JEOL JNM-A400 (^{1}H, 399.65; ^{13}C, 100.40 MHz) and -A500 (^{1}H, 500.00; ^{13}C, 125.65 MHz) spectrometers using chemical shifts, δ (ppm) values from tetramethylsilane (TMS) as an internal standard. TLC and preparative TLC were performed using silica gel 60F_{254} plates (Merck). The procedure for the evaluation of inhibitory activity of samples against mouse liver MAO was the same as described previously.[5—9)]

Isolation of Chaetoquadrins F (6)—K (11) *C. quadrangulatum* strain 71-NG-22[2)] was cultivated on sterilized rice (200 g/flask×100) at 25 °C for 33 d. The moldy rice was extracted with EtOAc (30 l) two times to give an EtOAc extract (61.2 g), which inhibited MAO by 30.8% at 1.0×10^{-4} g/ml. The EtOAc extract (41.5 g) was partitioned into *n*-hexane layer (after evaporation *in vacuo*, 15.89 g), EtOAc layer (16.07 g), and aqueous layer (7.60 g), which inhibited MAO by 10.3, 29.6, and 21.9% at 1.0×10^{-4} g/ml, respectively. The AcOEt layer (14.80 g) was chromatographed on a silica gel column to give the five fractions I—V. Fraction IV (6.38 g), which inhibited MAO by 36% at 1.0×10^{-4} g/ml, was further chromatographed to give the six fractions IVa—f. Fractions IVb (667 mg) and IVc (1.76 g) were chromatographed repeatedly to afford **1** (55 mg), **2** (12.5 mg), **3** (9.4 mg), **4** (29 mg), and **5** (83 mg), as we described recently.[1)] Fraction IVd (1.71 g), which inhibited MAO by 8% at 2.5×10^{-5} g/ml, was further chromatographed on a silica gel column with *n*-hexane–acetone (4 : 1), (4 : 1), (2 : 1), (1 : 1), and MeOH to give the five fractions IVd1—5, respectively. Fraction IVd3 (366 mg) was treated with $CHCl_3$ to afford **6** (32 mg) as precipitates. Fraction III (1.79 g), which inhibited MAO by 24% at 1.0×10^{-4} g/ml, was chromatographed on a silica gel column with $CHCl_3$, $CHCl_3$, $CHCl_3$–MeOH (50 : 1), (30 : 1), (20 : 1), and MeOH to give the six fractions IIIa—f, respectively. Fraction IIIb (59 mg) was treated with MeOH to afford **10** (19 mg) as precipitates. Fraction IIIc (179 mg) was further chromatographed on a silica gel column with *n*-hexane–acetone (3 : 1), (3 : 1), (2 : 1), and MeOH to give the four fractions IIIc1—4, respectively. Fraction IIIc2 (60 mg) was chromatographed on an HPLC octadecyl silica gel (ODS) column with CH_3CN–H_2O (50 : 50) at a flow rate of 8 ml/min to afford **9** (1.7 mg), **7** (17 mg), and **8** (37 mg). Fraction IIId (590 mg) was chromatographed on a silica gel column with $CHCl_3$, $CHCl_3$–MeOH (30 : 1), (20 : 1), and (10 : 1) to give the four fractions IIId1—4, respectively. Fraction IIId3 (407 mg) was treated with CH_3CN to afford **11** (56 mg) as precipitates.

Chaetoquadrin F (**6**): White powder from $CHCl_3$, mp 139—141 °C. $[\alpha]_D^{20}$ +35.0° (c=0.2, MeOH). HR-FAB-MS *m/z*: 185.0809 ($C_9H_{13}O_4$ requires 185.0814 [(M+H)$^+$]).

Chaetoquadrin G (**7**): White powder from aqueous CH_3CN, mp 108—110 °C. $[\alpha]_D^{20}$ −131.4° (c=0.2, $CHCl_3$). HR-FAB-MS *m/z*: 359.1472 ($C_{20}H_{23}O_6$ requires 359.1494 [(M+H)$^+$]).

Chaetoquadrin H (**8**): White powder from aqueous CH_3CN, mp 108—110 °C. $[\alpha]_D^{20}$ −57.2° (c=0.2, $CHCl_3$). HR-FAB-MS *m/z*: 359.1465 ($C_{20}H_{23}O_6$ requires 359.1495 [(M+H)$^+$]).

Chaetoquadrin I (**9**): Colorless amorphous. $[\alpha]_D^{20}$ −40.8° (c=0.05, $CHCl_3$). HR-FAB-MS *m/z*: 345.1349 ($C_{19}H_{21}O_6$ requires 345.1338 [(M+H)$^+$]).

Chaetoquadrin J (**10**): White powder from MeOH, mp 253—255 °C. $[\alpha]_D^{20}$ −30.9° (c=0.2, $CHCl_3$). HR-FAB-MS *m/z*: 427.1382 ($C_{23}H_{23}O_8$ requires 427.1393 [(M+H)$^+$]).

Chaetoquadrin K (**11**): White powder from CH_3CN, mp 166—169 °C. $[\alpha]_D^{20}$ −2.5° (c=0.3, $CHCl_3$). HR-FAB-MS *m/z*: 293.1015 ($C_{15}H_{17}O_6$ requires 293.1025 [(M+H)$^+$]).

Chaetoquadrin F Monomethylether (12) To a solution of **6** (9.1 mg) in MeOH (400 μl), 400 μl of 10% solution of trimethylsilyldiazomethane in *n*-hexane (Nacalai) was added, and the solution was stirred at room temperature for 30 min. The reaction mixture was evaporated *in vacuo* to give a crude product, which was purified on a preparative TLC with $CHCl_3$–MeOH (10 : 1) to afford **12** (3.1 mg) as a colorless amorphous substance. EI-MS *m/z* (%): 198 (88.7, M$^+$), 165 (10.2), 139 (38.3), 95 (40.3), 83 (100.0).

(*R*)- and (*S*)-MTPA Esters of Chaetoquadrin F (13, 14) A solution of **6** (3 mg), (*R*)-MTPA acid (15 mg), and dicyclohexylcarbodiimide (DCC) (9 mg) in pyridine (25 μl) and CH_2Cl_2 (1.0 ml) was allowed to stand at room temperature for 3 h, and then at 40 °C for 2 h. The reaction mixture was evaporated *in vacuo* to give a resinous residue, which was purified on a preparative TLC with $CHCl_3$–MeOH (10 : 1) to afford **13** (4 mg) as a colorless amorphous substance. A solution of **6** (3 mg), (*S*)-MTPA acid (15 mg), and DCC (9 mg) in pyridine (25 μl) and CH_2Cl_2 (1.0 ml) was treated in the way described for the preparation of **13** from **6** to afford **14** (4 mg) as a colorless amorphous substance.

Formation of Chaetoquadrin G (7) from Chaetoquadrins A (1) and B (2) A solution of **1** (4 mg) in pyridine (50 μl) was added to a suspension of CrO_3 (25 mg)–pyridine (150 μl) complex under ice-cooling, and then the reaction mixture was stirred continuously at 40 °C for 5 h. After addition of 1 drop of MeOH, the mixture was diluted with water and extracted with $CHCl_3$. A product mixture obtained from evaporation of the $CHCl_3$ layer was purified on a preparative TLC with $CHCl_3$–MeOH (20 : 1) and then on an HPLC ODS column with CH_3CN–H_2O (60 : 40) at a flow rate of 2 ml/min to afford white powder (1 mg), which was identical with **7** in terms of the ^{1}H-NMR ($CDCl_3$) and CD (MeOH) spectra. A solution of **2** (2 mg) in pyridine (50 μl) was added to a suspension of CrO_3 (25 mg)–pyridine (150 μl) complex under ice-cooling, and then the reaction mixture was stirred continuously at 40 °C for 36 h. The reaction mixture was treated in the way described for the formation of **7** from **1** to afford white powder (1 mg), which was also identical with **7** in terms of the ^{1}H-NMR ($CDCl_3$) and CD (MeOH) spectra.

Formation of Chaetoquadrin H (8) from Chaetoquadrin C (3) A solution of **3** (1 mg) in pyridine (50 μl) was added to a suspension of CrO_3 (30 mg)–pyridine (250 μl) complex under ice-cooling, and then the reaction mixture was treated as described for the formation of **7** from **2** to afford a very small amount of a substance, which was identical with **8** in terms of TLC with $CHCl_3$–MeOH (20 : 1) and HPLC [column: ODS, eluent: CH_3CN–H_2O (60 : 40), flow rate: 2 ml/min].

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References and Notes

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