NOVEL ANTIBIOTICS, FURAQUINOCINS C, D, E, F, G AND H

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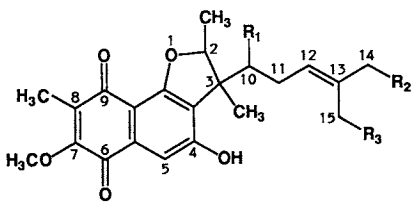
Furaquinocins C, D, E, F, G and H, congeners of furaquinocins A and B, were isolated from the culture broth of *Streptomyces* sp. KO-3988 and their structures have been determined on the basis of their spectroscopical and chemical properties. These antibiotics showed cytocidal activities against HeLa S3 and B16 melanoma cells *in vitro*.

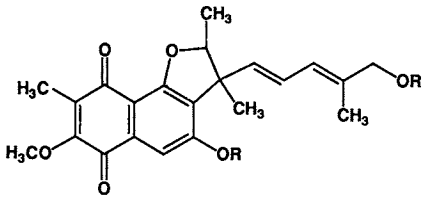
In the preceding paper,[1] we reported the production, isolation, physico-chemical properties and biological activities of furaquinocins A (**1**) and B (**2**), together with the taxonomy of the producing organism, *Streptomyces* sp. KO-3988. Structural elucidation and biosynthetic studies on furaquinocins A (**1**) and B (**2**) have also been described.[2,3] Through careful fractionation of the fermentation broth from which **1** and **2** were isolated, six other compounds, designated as furaquinocins C~H (**3**~**8**), were obtained. This paper deals with the isolation and structural elucidation of furaquinocins C~H (**3**~**8**).

Isolation of Furaquinocins C~H

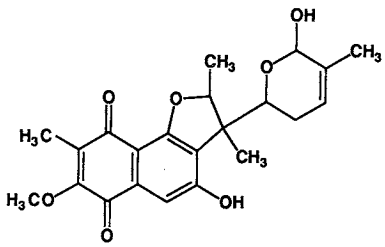
The isolation, characterization, and structural elucidation of furaquinocins A (**1**) and B (**2**) were described in the preceding papers.[1,2] The same fermentation procedure employed for **1** and **2** was used for the production of furaquinocins C~H (**3**~**8**). Separation of furaquinocins C~H (**3**~**8**) was performed



	R_1	R_2	R_3
1	OH	H	OH
2	OH	OH	H
3	H	H	H
4	OH	H	H
6	H	OH	H
8	OH	OH	OH



5 R=H
9 R=$COCH_3$



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by repeated silica gel column chromatogtaphies along with gel filtration on Sephadex LH-20. Preparative HPLC on ODS column was used to obtain furaquinocins E (**5**), F (**6**), and G (**7**). The details on the isolation procedure were described in the Experimental Section. Rf values on TLC of furaquinocin A~H (**1**~**8**) are given in Table 1.

Physico-chemical Properties of Furaquinocins C~H

The physico-chemical properties of furaquinocins C~H (**3**~**8**) are summarized in Table 2. The UV and IR spectra of these compounds were quite similar and suggested that the chromophore of naphtho[1,2b]furan-6,9-dione, which was present in the structures of furaquinocins A (**1**) and B (**2**), was also common to all these compounds. HR mass spectra revealed all of furaquinocins C~H (**3**~**8**) possessed 22 carbons and ^{1}H and ^{13}C NMR spectra, presented in Tables 3 and 4, respectively, indicated that the structural difference among these compounds lies in the part of the isoprenoid side chain.

Table 1. Chromatographic behavior of furaquinocins A~H (**1**~**8**) on TLC (Kieselgel 60 F_{254} DC-fertigplatten, Merck).

Solvent system	Rf value							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
$CHCl_3$ - MeOH (19 : 1)	0.48	0.31	0.96	0.96	0.42	0.49	0.90	0.16
Benzene - acetone (2 : 1)	0.53	0.40	0.91	0.88	0.58	0.58	0.75	0.12

Table 2. Physico-chemical properties of furaquinocins C~H (**3**~**8**).

	3	**4**	**5**
Appearance	Yellow needle	Yellow powder	Yellow powder
MP (°C)	213~215	177~179	184~186
Optical rotation	$[\alpha]_D^{19}$ −38° (*c* 0.55, $CHCl_3$)	$[\alpha]_D^{19}$ −95° (*c* 0.53, $CHCl_3$)	$[\alpha]_D^{18}$ −79° (*c* 0.26, MeOH)
UV λ_{max}^{MeOH} nm	221, 267, 298, 406	221, 267, 292, 402	215, 240 (sh), 265, 296, 400
IR ν_{max} (KBr) cm^{-1}	3260, 1655, 1615, 1555, 1390, 1280, 1195	3350, 1660, 1630, 1575, 1400, 1275, 1160	3400, 1665, 1630, 1570, 1440, 1295, 1200
MW	370	386	384
Molecular formula	$C_{22}H_{26}O_5$	$C_{22}H_{26}O_6$	$C_{22}H_{24}O_6$
EI-MS (*m/z*)	370 (M^+), 287, 273, 259	386 (M^+), 287, 273, 259	384 (M^+), 351, 327, 299
HR-MS Calcd (*m/z*):	370.1781	386.1729	384.1573
Found:	370.1795	386.1737	384.1588

	6	**7**	**8**
Appearance	Yellow powder	Yellow powder	Yellow powder
MP (°C)	115~118	121~124	75~78
Optical rotation	$[\alpha]_D^{18}$ −13° (*c* 0.35, MeOH)	$[\alpha]_D^{19}$ +12° (*c* 0.33, MeOH)	$[\alpha]_D^{19}$ +52° (*c* 0.25, MeOH)
UV λ_{max}^{MeOH} nm	218, 266, 294, 400	219, 266, 297, 406	220, 268, 290, 405
IR ν_{max} (KBr) cm^{-1}	3400, 1660, 1635, 1575, 1440, 1290, 1195	3350, 1660, 1635, 1580, 1400, 1285, 1165	3350, 1660, 1630, 1575, 1400, 1290, 1165
MW	386	400	418
Molecular formula	$C_{22}H_{26}O_6$	$C_{22}H_{24}O_7$	$C_{22}H_{26}O_8$
EI-MS (*m/z*)	386 (M^+), 287, 273, 259	400 (M^+), 382, 299, 287	420 $(M+2)^+$,[a] 402, 287, 273
HR-MS Calcd (*m/z*):	386.1729	400.1522	420.1784
Found:	386.1735	400.1533	420.1792[a]

[a] Instead of the molecular ion, the (M+2) ion was predominantly observed.[2)]

Table 3. ^{1}H NMR spectra (δ ppm) of furaquinocins A~H (**1~8**).

Position	**1**[a]	**2**[a]	**3**[a]	**4**[a]
2	4.67 q	4.69 q	4.55 q	4.67 q
2-CH_3	1.30 d	1.32 d	1.51 d	1.30 d
3-CH_3	1.31 s	1.37 s	1.47 s	1.34 s
5	7.12 s	7.15 s	7.32 s	7.14 s
7-OCH_3	3.98 s	4.00 s	3.99 s	3.98 s
8-CH_3	2.03 s	2.04 s	2.08 s	2.03 s
10	3.95 dd	4.07 dd	1.95 m (2H)	4.01 dd
11	2.61 ddd, 2.13 dt	2.57 dt, 2.19 ddd	1.80 m (2H)	2.48 dt, 2.15 ddd
12	5.50 m	5.52 m	4.98 m	5.17 m
14	1.86 br s (3H)	4.09 s (2H)	1.60 br s (3H)	1.76 br s (3H)
15	4.00 d, 4.41 d	1.74 br s (3H)	1.48 br s (3H)	1.69 br s (3H)

Position	**5**[b]	**6**[b]	**7**[a]	**8**[c]
2	4.57 q	4.49 q	4.65 q	4.61 q
2-CH_3	1.36 d	1.51 d	1.35 d	1.33 d
3-CH_3	1.58 s	1.46 s	1.34 s	1.32 s
5	7.07 s	7.07 s	7.16 s	7.07 s
7-OCH_3	3.99 s	3.99 s	4.00 s	3.93 s
8-CH_3	1.99 s	1.99 s	2.04 s	1.99 s
10	6.06 m	na	4.39 dd	3.91 d
11	5.60 m	na	2.43 m, 2.00 m	2.56 m, 2.19 m
12	6.06 m	5.27 m	5.70 br dd	5.61 dd
14	3.94 s (2H)	3.81 s (2H)	5.44 s	4.10 d, 4.05 d
15	1.64 br s (3H)	1.49 br s (3H)	1.78 br s (3H)	4.18 d, 4.04 d

[a] In $CDCl_3$. [b] in CD_3OD. [c] in $CDCl_3$-CD_3OD (3:1).
na: Not assigned.

Table 4. ^{13}C NMR spectra (δ ppm) of furaquinocins A~H (**1~8**).

Position	**1**[a]	**2**[a]	**3**[a]	**4**[a]	**5**[b]	**6**[b]	**7**[a]	**8**[c]
2	88.9 d	88.9 d	91.7 d	88.9 d	93.4 d	93.0 d	89.1 d	90.3 d
2-CH_3	16.1 q	16.1 q	13.6 q	16.0 q	15.8 q	13.9 q	16.2 q	16.1 q
3	52.8 s	52.4 s	46.6 s	52.3 s	50.5 s	48.0 s	51.4 s	53.3 s
3-CH_3	18.9 q	18.9 q	22.7 q	18.9 q	22.8 q	23.6 q	19.3 q	19.6 q
3a	124.6 s	124.5 s	127.9 s	124.6 s	127.7 s	128.7 s	124.9 s	125.4 s
4	158.9 s	158.4 s	158.0 s	158.5 s	161.0 s	161.1 s	158.2 s	159.6 s
5	111.0 d	110.7 d	109.6 d	110.8 d	110.2 d	110.1 d	110.4 d	111.0 d
5a	134.0 s	134.1 s	133.1 s	134.0 s	135.3 s	135.0 s	133.7 s	134.4 s
6	180.8 s	180.7 s	181.3 s	180.7 s	182.3 s	182.3 s	180.8 s	181.6 s
7	156.9 s	156.9 s	157.0 s	156.9 s	158.7 s	158.8 s	156.9 s	157.6 s
7-OCH_3	60.6 q	60.7 q	60.7 q	60.6 q	61.4 q	61.4 q	60.7 q	61.1 q
8	133.6 s	133.7 s	134.1 s	133.6 s	134.1 s	134.1 s	132.0 s	134.3 s
8-CH_3	9.3 q	9.3 q	9.4 q	9.3 q	9.6 q	9.6 q	9.3 q	9.7 q
9	183.8 s	183.7 s	184.2 s	183.7 s	185.6 s	185.8 s	183.7 s	184.6 s
9a	108.8 s	109.2 s	109.3 s	109.1 s	109.8 s	114.0 s	109.3 s	109.2 s
9b	160.6 s	160.4 s	161.6 s	160.5 s	162.8 s	162.9 s	160.4 s	161.6 s
10	71.4 d	73.0 d	23.8 t	73.1 d	134.3 d	24.9 t	68.5 d	72.8 d
11	32.4 t	31.9 t	35.0 t	32.1 t	127.8 d	36.0 t	26.1 t	32.2 t
12	124.9 d	120.1 d	124.1 d	118.7 d	125.6 d	126.8 d	122.2 d	126.4 d
13	138.3 s	140.0 s	131.6 s	138.2 s	138.5 s	136.2 s	134.0 s	141.6 s
14	23.2 q	68.0 t	25.6 q	26.0 q	68.7 t	69.2 t	92.8 d	65.7 t
15	61.4 t	14.3 q	17.6 q	18.2 q	14.4 q	14.1 q	18.8 q	58.2 t

[a] In $CDCl_3$. [b] in CD_3OD. [c] in $CDCl_3$-CD_3OD (3:1).

Sturucture Elucidation of Furaquinocins C~H

Furaquinocin C (**3**) was shown to have the molecular formula $C_{22}H_{26}O_5$ by HREI-MS, indicating that furaquinocin C (**3**) lacks two oxygen atoms from those ($C_{22}H_{26}O_7$) of furaquinocin A (**1**) or B (**2**). ^1H and ^{13}C NMR data (Tables 3 and 4) as well as the characteristic EI-MS ion at m/z 287 (M^+ −side chain (C-10~C-15))[2] revealed the structure of naphtoquinone nucleus was the same as that of **1** or **2**. Since furaquinocin A (**1**) or B (**2**) possesses two oxygen atoms on the side chain, furaquinocin C (**3**) was inferred to possess no oxygen atom in the side chain part. ^1H and ^{13}C NMR spectra revealed the presence of two methylene, one sp^2 methine, one quarternary sp^2 carbon, and two olefinic methyls for the C-10~C-15 moiety and the ^1H-^1H COSY spectrum showed the 4-methyl-3-pentenyl group for the structure of this part.

Furaquinocin D (**4**), $C_{22}H_{26}O_6$, possessed one more oxygen atom than furaquinocin C (**3**). The position of the oxygen was deduced to be at C-10 by the ^1H and ^{13}C NMR data (δ_H 4.01, dd, J=9.5 and 2 Hz; δ_C 73.1, d), leading to 1-hydroxy-4-methyl-3-pentenyl group for the structure of the side chain. Other spectral data were also consisitent with structure **4** for furaquinocin D.

The molecular formula of furaquinocin E (**5**), $C_{22}H_{24}O_6$, implied that **5** lacks one water molecule from furaquinocin A (**1**) or B (**2**). The presence of the terminal olefinic methyl (δ_C 14.4, q) and hydroxymethyl (δ_C 68.7, t) was shown by ^{13}C NMR spectrum and those ^{13}C chemical shifts indicated *E*-configuration of the $\Delta^{12,13}$-double bond.[2] For C-10 and C-11, two sp^2 methine carbons (δ_C 127.8, d and 134.3, d) were observed, indicating the side chain structure to be 5-hydroxy-4-methyl-1,3-pentadienyl group. In the UV spectrum of **5**, a shoulder was observed at 240 nm due to the diene. Although the ^1H signals for 10-H~12-H of **5** were heavily overlapped, those signal in the ^1H NMR of the diacetate (**9**) were well resolved to indicate 10*E*-configuration by the coupling constant ($J_{10,11}$=14.5 Hz).

Furaquinocin F (**6**), $C_{22}H_{26}O_6$, possessed the same molecular formula as furaquinocin D (**4**). The structural difference between **4** and **6** was the position of the hydroxyl group in the side chain. The ^1H and ^{13}C NMR of **6** showed the presence of two methylene (δ_C 24.9, t and 36.0, t), one hydroxymethyl (δ_C 69.2, t), and one olefinic methyl group (δ_C 14.1, q), giving rise to 5-hydroxy-4-methyl-3-pentenyl group for the side chain structure. The ^{13}C chemical shifts for the terminal methyl and hydroxymethyl groups implied 12*E*-configuration.[2]

Furaquinocin G (**7**) possessed the molecular formula, $C_{22}H_{24}O_7$, which suggested that **7** lacks one hydrogen molecule from furaquinocin A (**1**) or B (**2**). Compound **7** also possessed the same naphtho-[1,2b]furan-6,9-dione nucleus and the structural difference was expected to be found only in the side chain. ^{13}C NMR revealed, for the side chain, the presence of one oxymethine (δ_C 68.5, d), one methylene (δ_C 26.1, t), one sp^2 methine (δ_C 122.2, d), one sp^2 quarternary carbon (δ_C 134.0, s), one olefinic methyl (δ_C 18.8, q), and one hemiacetal carbon (δ_C 92.8, d). A hemiacetal proton signal appeared at δ_H 5.44, s. These observations along with the ^1H-^1H and ^1H-^{13}C COSY spectra allowed to assign the structure of the side chain to be 1,5-epoxy-5-hydroxy-4-methyl-3-pentenyl group.

Furaquinocin H (**8**) possessed the molecular formula, $C_{22}H_{26}O_8$, having one more oxygen atom than furaquinocin A (**1**) or B (**2**). The ^1H and ^{13}C NMR spectra revealed the presence of two hydroxymethyl groups and the absence of the terminal olefinic methyl group in the side chain. For other part of the molecule, **8** gave very similar ^1H and ^{13}C NMR results to those of furaquinocin A (**1**) or B (**2**). These observations showed the structure of the C-10~C-15 part of **8** to be 1,5-dihydroxy-4-hydroxymethyl-3-pentenyl group.

From all of the observations described above, the structures of furaquinocins C~H were concluded to be **3**~**8**, respectively. Cytocidal activities (IC_{50} value, μg/ml) of furaquinocins A~H against B16 melanoma cells and HeLa S3 cells are shown in Table 5. Among these compounds, furaquinocin H (**8**) possessed the most potent cytocidal activity against both cell lines.

Table 5. IC_{50} value of furaquinocins (μg/ml).

	B16	HeLa S3
A (**1**)	>19.9	>21.9
B (**2**)	5.58	1.33
C (**3**)	0.63	1.22
D (**4**)	6.87	5.05
E (**5**)	2.56	1.30
F (**6**)	>25	>25
G (**7**)	1.88	0.92
H (**8**)	0.08	0.22

Experimental

General Procedures

MP's were determined using a Yanagimoto MP-3 hot stage microscope and are uncorrected. Optical rotations were measured with a Jasco DIP-181 polarimeter. IR spectra were recorded on a Jasco A-102 spectrophotometer and UV spectra were measured with a Shimadzu UV 200S double beam spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian XL-400 spectrometer and mass spectra were recorded on a Jeol JMS DX 300 or JMA 3100 spectrometer. Kieselgel 60 F_{254} DC-fertigplatten (Merck) was used for TLC analyses, and Kieselgel 60 (Merck) was used for silica gel column chromatographies. TRI Rotar-V (Jasco) and UVIDEC-100 (Jasco) instruments were used for HPLC with a column of YMC D-ODS-5 (Yamamura Chemical Lab., 2.2×27 cm; eluant: MeOH-H_2O (70:30); flow rate: 9.0 ml/minute; detection: UV at 254 or 300 nm).

Isolation of Furaquinocins

The fermentation of *Streptomyces* sp. KO-3988 was carried out by the same conditions previously described.[1] The fermentation broth (300 liters) was extracted with EtOAc (180 liters) and the EtOAc layer was concentrated *in vacuo* to about 5 liters and dried over anhydrous Na_2SO_4. Concentration of the EtOAc layer gave a brown oil (445 g).

The brown oil (445 g) was subjected to a silica gel column chromatography (9×25 cm; column I) eluted successively with 6 liters of $CHCl_3$, 6 liters of $CHCl_3$-MeOH (9:1), and 3 liters of $CHCl_3$-MeOH (1:1). The fraction eluting from 6 to 9 liters (fraction 3, 43 g) was separated by a silica gel column (5.0×32 cm; column II) eluted with benzene-ethyl acetate (1:1, 1.4 liters and 1:2, 0.6 liter) to give furaquinocin A (**1**, 2.3 g) in the 1,020~1,540 ml fraction. The 120~340 ml fraction of column II (25 g) was further purified with a silica gel column (3.3×42 cm; column III) eluted with benzene-ethyl acetate (9:1, 1 liter and 4:1, 0.5 liter). The 240~560 ml fraction of column III (11 g) was separated again by a silica gel column (5.0×36 cm; column IV) eluted with hexane-ethyl acetate (2:1). The fraction eluting from 180 to 460 ml (5.2 g) of column IV contained mainly piericidine A_1,[4] and the 460~800 ml fraction (3.2 g) was recrystallized from hexane-ethyl acetate (2:1) to afford furaquinocin C (**3**, 540 mg). The 660~1,100 ml fraction of column III (8 g) was purified with a Sephadex LH-20 column chromatography (3.1×53 cm; column V) and the 135~255 ml fraction of column V (6 g) was further separated by a silica gel column (3.3×50 cm; column VI) eluted with chloroform-ethyl acetate (9:1) to give furaquinocin D (**4**, 2.2 g) in the 180~525 ml fraction together with antimycin complex[5] (1.8 g) in the 525~1,050 ml fraction.

The 500~920 ml fraction of column II (2.4 g) was separated by a Sephadex LH-20 column (3.1×53 cm; column VII) eluted with chloroform-methanol (1:1) and the 100~150 ml fraction of column VII (1.6 g) was further purified with a silica gel column chromatography (3.1×53 cm; column VIII) eluted with chloroform-ethyl acetate (4:1, 1 liter and 3:2, 1 liter). The 690~810 ml fraction of column VIII (163 mg) was then separated by a silica gel column (2.2×40 cm; column IX) eluted with hexane-acetone (2:1). The 90~150 ml fraction of column IX (36 mg) was subjected to HPLC separation to give furaquinocin G (**7**, 8.0 mg, Rt 25.0 minutes). The 900~1,125 ml fraction of column VIII (246 mg) was also subjected to HPLC separation to afford furaquinocin E (**5**, 30.5 mg, Rt 22.1 minutes) and furaquinocin F (**6**, 16.7 mg, Rt 26.0 minutes).

On the other hand, the fraction of column I eluting from 9 to 12 liters (fraction 4, 17 g) was separated by a silica gel column chromatography (4.5 × 25 cm; column X) eluted with chlorofrom - methanol (19 : 1). The 675 ~ 945 ml fraction of column IX (7 g) was then purified with a silica gel column chromatogtaphy (4.5 × 32 cm; column XI) eluted with benzene - ethyl acetate (1 : 2) to afford furaquinocin B (**2**, 2.7 g) in the 1,180 ~ 2,400 ml fraction. The 800 ~ 1,080 ml fraction of column XI was further separated with a Sephadex LH-20 column (1.7 × 128 cm; column XII) eluted with 100% methanol to give furaquinocin A (**1**, 0.9 g) in the 152 ~ 208 ml fraction.

The 945 ~ 1,380 ml fraction of column X (5.9 g) was separated with a Sephadex LH-20 column (2.4 × 50 cm; column XIII) eluted with 100% methanol. The 130 ~ 300 ml fraction of column XIII (1.8 g) was then purified with a silica gel column chromatography (2.4 × 50 cm; column XIV) eluted with chloroform - methanol (9 : 1). The 315 ~ 465 ml fraction of column XIV (460 mg) was further separated by a silica gel column (2.2 × 43 cm) eluted with benzene - acetone (2 : 3) to give furaquinocin H (**8**, 50 mg) in the 210 ~ 315 ml fraction.

Furaquinocin E Acetate (**9**)

Furaquinocin E (**5**, 29 mg, crude sample) was treated with acetic anhydride (0.5 ml) and pyridine (0.5 ml) at room temperature for 23 hours. After evaporation of the solvent, the residue was purified with a gel column chromatography (1.5 × 20 cm) eluted with hexane - ethyl acetate (2 : 1) to afford the diacetate (**9**, 5 mg): ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, d, J=6.5 Hz, 2-CH_3), 1.53 (3H, s, 3-CH_3), 1.70 (3H, s, 15-H_3), 2.08 (3H, s, 8-CH_3), 2.22 (3H, s, Ac), 2.27 (3H, s, Ac), 4.05 (3H, s, 7-OCH_3), 4.49 (2H, s, 14-H_2), 4.70 (1H, q, J=6.5 Hz, 2-H), 5.66 (1H, d, J=14.5 Hz, 10-H), 6.03 (1H, d, J=11 Hz, 12-H), 6.09 (1H, dd, J=14.5 and 11 Hz, 11-H), and 7.39 (1H, s, 5-H); EI-MS m/z 468 (M^+), 426, 408, 383, 365, and 287.

Cytocidal Activity Test of **1** ~ **8** against B16 Melanoma and HeLa S3 Cells

B16 melanoma and HeLa S3 cells were maintained in monolayers in EAGLE's minimum essential medium supplemented with 10% bovine serum and kanamycin (60 μg/ml) at 37°C. To determine the cytotoxicity of **1** ~ **8**, 5×10^3 of B16 melanoma cells or HeLa S3 cells in a medium (0.2 ml) were plated into 96-well culture plate (Falcon). One day after the cultivation at 37°C in a 5% CO_2/95% air atmosphere, to each culture was added 5 μl of the MeOH solution of a different concentration of **1** ~ **8**, and they were reincubated. After further 3 days of incubation, the cell growth was evaluated by the method of MIRABELLI *et al.*[6]

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