FL-120A～D′, NEW PRODUCTS RELATED TO KINAMYCIN FROM *Streptomyces chattanoogensis* subsp. *taitungensis* subsp. nov.

II. ISOLATION AND STRUCTURE DETERMINATION

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Six new kinamycin antibiotics have been isolated from the culture filtrate of *Streptomyces chattanoogensis*. The structures of six related components were determined employing 1D and 2D NMR spectroscopy and mass spectrometry. These structures represent the first reported epoxide kinamycin (**2, 3**) and propionyl derivative of kinamycin (**5**), and new isobutyryl derivatives of kinamycin (**1, 4, 6**).

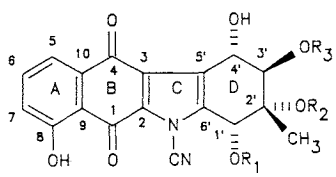
The kinamycin antibiotics were first isolated and characterized by ŌMURA *et al.*[1～4] in 1970. They are mainly active against Gram-positive bacteria, but less active against Gram-negative organisms. Weak antitumor activity was exhibited by kinamycin C against Ehrlich ascites carcinoma and against sarcoma-180[2]. The biosynthesis pathway was investigated by GOULD *et al.*[5～6] and established the carbon assignments by long-range HETCOR[7]. In the course of our screening program for new antibiotics, six new antibiotics (**1～6**) have been isolated from the culture filtrate of *Streptomyces chattanoogensis* IY2-13 cont. The producing strain was isolated from a soil sample collected in Taitung, Taiwan. We report here the isolation and structure determination for FL-120A～D′ (**1～6**) (Fig. 1). The taxonomy, fermentation and biological properties of these compounds are discussed in the previous paper[8].

Results

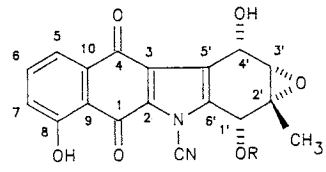
Isolation

The filtered culture broth (505 liters) from a 150-liter fermentor was extracted with an equal volume of EtOAc three times at pH 7.0 and the organic layer was concentrated to one liter at 32°C under reduced

Fig. 1. Structures of FL-120A～D′ (**1～6**) and kinamycin D (**7**).

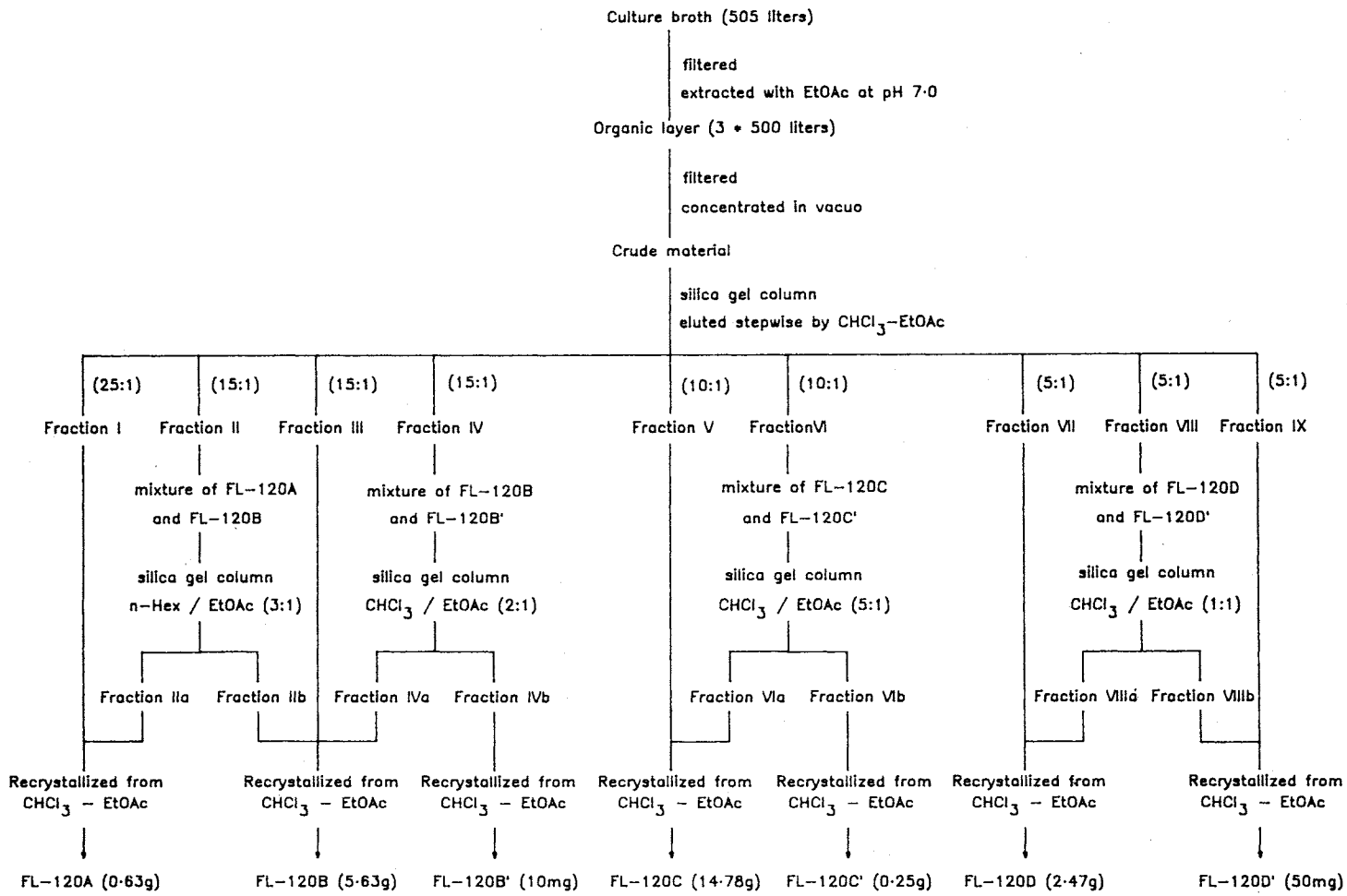


1 R_1=Ac, R_2=$COCH(CH_3)_2$, R_3=Ac
4 R_1=$COCH(CH_3)_2$, R_2=H, R_3=Ac
5 R_1=$COCH_2CH_3$, R_2=H, R_3=Ac
6 R_1=$COCH(CH_3)_2$, R_2=H, R_3=H
7 R_1=R_3=Ac, R_2=H



2 R=$COCH(CH_3)_2$
3 R=Ac

Fig. 2. Isolation procedure of FL-120A~D' (**1**~**6**) and kinamycin D (**7**).



pressure. Then the crude extract was separated by column chromatography on silica gel (Merck art. No 7734) which was developed stepwise with $CHCl_3$-EtOAc (25:1, 15:1, 10:1, 5:1) to elute sequentially FL-120A (**1**), FL-120B (**2**), FL-120B′ (**3**), FL-120C (**4**), FL-120C′ (**5**), kinamycin D (FL-120D, **7**), FL-120D′ (**6**). Each mixture fraction was evaporated to dryness and subjected to a second silica gel column with a solvent mixture of $CHCl_3$ and EtOAc. After chromatography, each kinamycin was further purified by recrystallization using a solvent mixture of $CHCl_3$ and EtOAc which gave three major products **2** (5.63 g), **4** (14.78 g), **7** (2.47 g) and four minor products **1** (0.63 g), **3** (10 mg), **5** (0.25 g), **6** (50 mg). The detailed purification scheme is outlined in Fig. 2.

Structure Determination

We have determined the structures of FL-120A~D′ (**1**~**6**). The ^1H and ^{13}C NMR spectra data are presented in Tables 1 and 2, respectively. All carbon assignments at **1**~**6** were furnished from HETCOR and long-range HETCOR spectra. These ^{13}C NMR spectra are very similar to kinamycin D (**7**), which was reported by GOULD *et al.* for biosynthetic studies[5,6]. All six have similar UV spectra and exhibit a red shift in their absorption in alkaline solution. The IR spectra show only hydrogen-bonding quinone

Table 1. ^1H NMR spectra data of FL-120A~D′ (**1**~**6**) and kinamycin D (**7**).[a]

	1	**2**	**3**	**4**
1′-H	6.57 (s)	6.38 (d, 1.2)	6.39 (d, 1.2)	5.42 (s)
2′-CH_3	1.54 (s)	1.49 (s)	1.51 (s)	1.22 (s)
3′-H	5.89 (d, 8.1)	3.59 (d, 2.7)	3.61 (d, 2.7)	5.60 (d, 8.1)
4′-H	4.79 (dd, 8.1, 1.5)	5.08 (m)	5.12 (m)	4.79 (d, 8.1)
4′-OH	5.45 (d, 1.5)	5.93 (s)	6.01 (br s)	5.49 (br s)
5-H	7.70 (dd, 8.0, 1.1)	7.64 (dd, 7.9, 1.2)	7.71 (dd, 8.0, 0.9)	7.68 (dd, 7.8, 1.1)
6-H	7.57 (t, 8.0)	7.55 (t, 7.9)	7.58 (t, 8.0)	7.57 (t, 7.8)
7-H	7.22 (dd, 8.0, 1.1)	7.19 (dd, 7.9, 1.2)	7.22 (dd, 8.0, 0.9)	7.21 (dd, 7.8, 1.1)
8-OH	12.17 (s)	12.07 (s)	12.12 (s)	12.13 (s)
CH_3CO–	2.09 (s)	—	2.30 (s)	2.27 (s)
	2.24 (s)	—	—	—
$(CH_3)_2CHCO$–	1.15 (d, 6.9)	1.31 (d, 6.9)	—	1.20 (d, 7.1)
	1.15 (d, 6.9)	1.34 (d, 6.9)	—	1.25 (d, 7.1)
$(CH_3)_2CHCO$–	2.50 (m, 6.9)	2.81 (m, 6.9)	—	2.69 (m, 7.1)
CH_3CH_2CO–	—	—	—	—
CH_3CH_2CO–	—	—	—	—

	5	**6**	**7**
1′-H	5.43 (s)	5.55 (s)	5.43 (s)
2′-CH_3	1.24 (s)	1.27 (s)	1.22 (s)
3′-H	5.60 (d, 8.1)	4.26 (d, 7.8)	5.59 (d, 7.9)
4′-H	4.75 (dd, 8.1, 1.5)	4.62 (d, 7.8)	4.78 (d, 7.9)
4′-OH	5.45 (d, 1.5)	5.77 (br s)	5.50 (br s)
5-H	7.60 (dd, 8.1, 1.8)	7.67 (dd, 7.9, 1.3)	7.67 (dd, 7.8, 1.0)
6-H	7.55 (t, 8.1)	7.58 (t, 7.9)	7.57 (t, 7.8)
7-H	7.19 (dd, 8.1, 1.8)	7.22 (dd, 7.9, 1.3)	7.22 (dd, 7.8, 1.0)
8-OH	12.03 (s)	12.13 (s)	12.12 (s)
CH_3CO–	2.27 (s)	—	2.19 (s)
	—	—	2.26 (s)
$(CH_3)_2CHCO$–	—	1.18 (d, 6.9)	—
	—	1.23 (d, 6.9)	
$(CH_3)_2CHCO$–	—	2.65 (m, 6.9)	
CH_3CH_2CO–	1.19 (t, 7.5)	—	—
CH_3CH_2CO–	2.46, 2.52 (qABq[b], 7.5, 17)	—	—

[a] Recorded at 300 MHz in $CDCl_3$, chemical shifts in ppm referenced to TMS at 0 ppm as internal standard; δ_H (multiplicity, J=Hz).

[b] qABq: quartet of AB quartet.

Table 2. ^{13}C NMR data of FL-120A~D′ (**1**~**6**) and kinamycin D (**7**).[a]

Carbon	**1**	**2**	**3**	**4**	**5**	**6**	**7**[b]
C-1	183.1	182.9	182.9	182.7	183.4	183.5	183.6
C-2	132.5	132.6	132.6	132.0	132.6	132.6	132.8
C-3	128.3	129.8	129.8	128.4	129.0	129.3	129.0
C-4	180.2	180.7	180.8	179.9	180.6	180.8	180.8
C-5	120.0	120.4	120.4	119.8	120.2	120.3	120.3
C-6	136.1	136.2	136.2	136.0	136.2	136.2	136.2
C-7	124.5	124.7	124.7	124.4	124.7	124.7	124.3
C-8	162.1	162.2	162.2	162.0	162.4	162.4	162.4
C-9	115.4	115.3	115.3	115.1	115.6	115.6	115.6
C-10	133.5	133.6	133.6	133.3	133.8	133.9	133.8
C-1′	67.1	68.2	68.6	70.9	71.1	70.1	71.3
C-2′	80.9	57.8	57.7	73.8	73.8	73.6	73.7
C-3′	73.3	61.3	61.4	75.6	75.7	74.8	75.7
C-4′	67.1	63.5	63.5	67.1	67.3	69.7	67.3
C-5′	131.5	129.6	129.6	131.7	132.1	132.7	132.1
C-6′	126.9	129.3	129.1	128.3	128.2	128.6	127.8
CH_3–	15.4	19.0	19.0	18.1	18.3	18.5	18.6
CH_3CO–	20.6	—	20.1	20.9	21.1	—	21.0
	21.0	—	—	—	—	—	21.2
CH_3CO–	169.6	—	170.8	172.1	172.2	—	171.3
	170.6	—	—	—	—	—	172.3
$(CH_3)_2CHCO$–	18.7	18.8	—	18.6	—	18.8	—
	18.9	19.4	—	18.9	—	19.0	—
$(CH_3)_2CHCO$–	34.9	34.0	—	33.9	—	34.1	—
$(CH_3)_2CHCO$–	175.6	177.2	—	176.9	—	177.2	—
CH_3CH_2CO–	—	—	—	—	8.9	—	—
CH_3CH_2CO–	—	—	—	—	27.5	—	—
CH_3CH_2CO–	—	—	—	—	174.5	—	—

[a] Recorded at 75.4 MHz in $CDCl_3$, chemical shifts in ppm referenced to $CDCl_3$ at 77.7 ppm as internal standard.
[b] From ref 6.

carbonyl suggesting all of them possess a free hydroxy group at the C-4′ position[3,4] and the IR absorption band also indicates the existence of a cyanamide group. The absolute configuration has been determined by X-ray crystallography of kinamycin C *p*-bromobenzoate[13].

Structure Determination of FL-120A (**1**)

FL-120A has a molecular formula of $C_{26}H_{24}N_2O_{10}$ as established by HREI-MS and elemental analysis. The ultraviolet and visible spectra bear resemblance to those of kinamycin D[2]. A red shift in their absorption in 0.1 N sodium hydroxide-methanol solution suggests the presence of a phenolic hydroxy group[3,4]. The IR absorption band at 2160 and 1741 cm^{-1} indicates the existence of cyanamide and ester carbonyl groups, respectively. The ^1H NMR and FAB-MS spectra showed the presence of one isobutyryl group and two acetyl groups. Those acyl group positions were assigned as shown in Fig. 1 by two dimensional ^1H-^{13}C long-range HETCOR[9,10]. That is, the two acetyl carbonyl carbons at δ 169.9 and 170.6 had long-range coupling with 1′-H and 3′-H proton, respectively (Fig. 3-a). NOESY spectra of **1** showed 2′-CH_3 had a nuclear overhauser effect with 1′-H and 4′-H[11,12], suggesting that they must be on the same side of the D-ring and possess the same stereochemistry as kinamycin D.

Structure Determination of FL-120C (**4**) and FL-120C′ (**5**)

According to the ^1H NMR spectra **4** and **5** showed the presence of isobutyryl and propionyl groups, respectively. The chemical shift of the methine protons indicated that they had a similar structure to that of kinamycin D except for an acyl group (Table 1). From ^1H-^{13}C long-range HETCOR, the 3′-H protons

Fig. 3. Carbonyl region of long-range HETCOR spectrum.

(a) FL-120A (**1**); (b) FL-120C (**4**); (c) FL-120C′ (**5**).

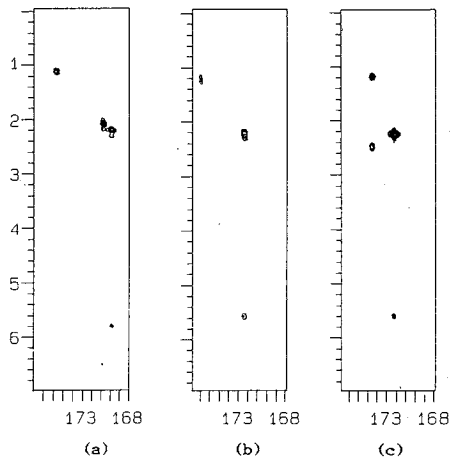
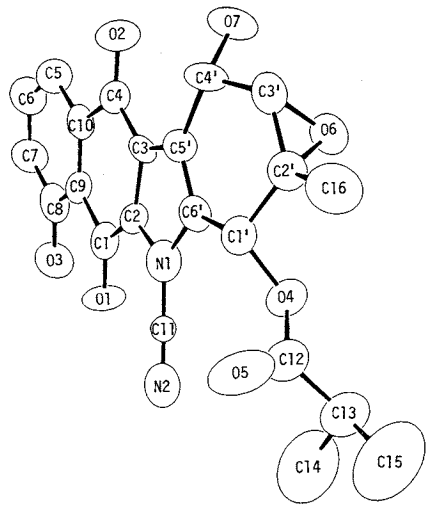


Fig. 4. X-ray crystal structure of FL-120B (**2**) and hydrogens are omitted for clarity.



of **4** and **5** showed long-range coupling with the acetyl carbonyl carbon at δ 172.1 and 172.2, respectively (Fig. 3-b, c). From the comparison of the chemical shift of 2′-CH_3 protons, **4** and **5** were considered to have a free *tert*-OH at C-2′ position[3,4]. It was thus concluded that isobutyrate and propionate residues are located at C-1′. FL-120C has a molecular formula of $C_{24}H_{22}N_2O_9$ as established by HREI-MS. Elemental analysis of FL-120C′ gave a formula of $C_{23}H_{20}N_2O_9$. NOESY spectra of **4** and **5** suggest that they possess the same stereochemistry as kinamycin D.

Structure Determination of FL-120D′ (**6**)

The IR spectra of FL-120D′ (**6**) show only hydrogen-bonding quinone carbonyl absorption at 1619 cm^{-1} suggesting a process free hydroxy group at the C-4′ position. According to the FAB-MS spectra and the chemical shift from ^1H NMR the presence of only one isobutyrate residue at the C-1′ position was indicated, and had a molecular formula of $C_{22}H_{20}N_2O_8$. The coupling constant between 3′-H and 4′-H (J=7.8 Hz) and NOESY spectra showed the process to have the same stereochemistry as kinamycin D.

Structure Determination of FL-120B (**2**) and FL-120B′ (**3**)

FL-120B (**2**) has a molecular formula of $C_{22}H_{18}N_2O_7$, which corresponds to the molecular formula of FL-120D′ (**6**) minus the atoms of a water molecular. This difference in molecular structure is attributed to dehydration in FL-120B (**2**) at C-2′, C-3′. From ^1H NMR of **2**, the smaller coupling constant between 3′-H and 4′-H (J=2.7 Hz) than kinamycin D (J=8.1 Hz) suggest that there is a novel oxirane structure between C-2′ and C-3′. Comparing the ^1H NMR of **2** with **3** indicates that they had a similar structure except that in place of an isobutyryl group was an acetyl group (Table 1). FL-120B′ (**3**) has a molecular formula of $C_{20}H_{14}N_2O_7$ as established by HREI-MS. The structure and absolute stereochemistry of **2** was finally confirmed by X-ray crystallographic analysis (Fig. 4). Crystal data: $C_{22}H_{18}N_2O_7$, M=422.1, monoclinic, space group $P2_1$, Z=2, a=5.321(3), b=16.783(3), c=10.463(3) Å, β=92.43(4)°, V=933.5(6) $Å^3$ and $D_{(calc.)}$=1.431 g/cm^3. 1703 independent reflections were measured of which 1230 were considered observed [$I>2\sigma(I)$]. Intensity data were collected on a Nonius CAD4 diffractometer, using

the $\theta \sim 2\theta$ scan mode. The structure was solved by direct methods to present a R value of 0.062, All calculations were performed on a Micro Vax III system.

Discussion

The chemical shift of methine protons (1'-H, 3'-H and 4'-H) and 3'-CH_3 were influenced by the substituted position and the number of acyl groups. Different kinds of acyl groups placed at the same position produced only little effect on the chemical shift. The skeleton of FL-120B (**2**) and FL-120B' (**3**) has a novel oxirane structure, which is the reduced product of "keto-anhydrokinamycin"[12], and the biosynthesis intermediate proposed by SATO *et al.*[6]. The propionyl derivative of kinamycin FL-120C' (**5**) is first reported here.

Experimental

General

MP's were determined on an Electrothermal melting point apparatus and are uncorrected. UV spectra were recorded on a Varian Cary4 spectrophotometer and FT-IR spectra were obtained with a Bio-Rad FTS-60 spectrometer. FAB-MS and HREI-MS were measured on a JEOL JMS-HX110 spectrometer. Elemental analyses were performed on a Heraeus CHN-O-RAPID elemental analyzer. All 1D and 2D NMR spectra were acquired on a Varian Unity 300 spectrometer, ^1H and ^{13}C NMR spectra are reported as ppm at 300 and 75.4 MHz, respectively and data are collected in tables within the text. Rf values reported were acquired on Merck Kieselgel $60F_{254}$ precoated TLC plates.

Physico-chemistry Properties

FL-120A (**1**): Orange powder; MP 62~63°C (dec) and Rf 0.4 in $CHCl_3$-EtOAc (20:1); UV λ_{max} (MeOH) nm (ε) 207 (20,800), 246 (23,900), 274 (14,200), 294 (sh, 9,100), 309 (sh, 6,900), 393 (8,000), 441 (8,700); UV λ_{max} (NaOH-MeOH) nm (ε) 217 (20,900), 240 (23,100), 274 (14,500), 309 (8,400), 389 (6,300), 549 (5,900); IR ν_{max} (KBr) cm^{-1} 3391, 2979, 2165, 1747, 1625, 1461, 1235; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); FAB-MS *m/z* (abundance) 525 ($M+H^+$, 100%), 507 (41%), 465 (25%), 436 (30%), 419 (28%), 377 (42%), 349 (58%), 335 (42%), 136 (85%); HREI-MS *m/z* 524.1461 (M^+ Calcd for $C_{26}H_{24}N_2O_{10}$ 524.1431).

Anal Calcd for $C_{26}H_{24}N_2O_{10}$: C 59.54, H 4.61, N 5.34.
Found: C 59.48, H 4.60, N 5.38.

FL-120B (**2**): Orange needle; MP 185~190°C (dec) and Rf 0.35 in $CHCl_3$-EtOAc (10:1); UV λ_{max} (MeOH) nm (ε) 206 (12,500), 243 (10,600), 274 (7,600), 294 (sh, 4,600), 308 (sh, 3,200), 394 (3,400), 445 (3,700); UV λ_{max} (NaOH-MeOH) nm (ε) 218 (14,300), 238 (14,800), 275 (14,100), 308 (6,400), 389 (3,900), 539 (4,000); IR ν_{max} (KBr) cm^{-1} 3375, 2981, 2160, 1739, 1624, 1453, 1234; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); FAB-MS *m/z* (abundance) 423 ($M+H^+$, 88%), 405 (100%), 335 (85%), 289 (36%), 279 (30%), 136 (72%); HREI-MS *m/z* 422.1110 (M^+ Calcd for $C_{22}H_{18}N_2O_7$ 422.1114).

Anal Calcd for $C_{22}H_{18}N_2O_7$: C 62.56, H 4.30, N 6.63.
Found: C 62.49, H 4.28, N 6.64.

FL-120B' (**3**): Orange powder; MP 155~160°C (dec) and Rf 0.32 in $CHCl_3$-EtOAc (10:1); UV λ_{max} (MeOH) nm (ε) 207 (14,000), 247 (15,300), 275 (10,300), 295 (sh, 6,500), 309 (sh, 5,300), 394 (5,700), 445 (4,200); UV λ_{max} (NaOH-MeOH) nm (ε) 218 (11,600), 240 (15,400), 274 (13,900), 309 (7,600), 392 (5,300), 545 (5,000); IR ν_{max} (KBr) cm^{-1} 3405, 2980, 2152, 1738, 1620, 1457, 1236; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); FAB-MS *m/z* (abundance) 395 ($M+H^+$, 62%), 377 (45%), 335 (43%), 289 (46%), 136 (100%); HREI-MS *m/z* 394.0806 (M^+ Calcd for $C_{20}H_{14}N_2O_7$ 394.0801).

FL-120C (**4**): Orange powder; MP 135~141°C (dec) and Rf 0.36 in $CHCl_3$-EtOAc (3:1); UV λ_{max} (MeOH) nm (ε) 207 (19,800), 246 (22,600), 274 (12,900), 294 (sh, 9,300), 309 (sh, 6,800), 394 (7,900), 442 (8,600); UV λ_{max} (NaOH-MeOH) nm (ε) 218 (19,800), 239 (21,900), 274 (16,600), 309 (8,400), 391 (6,000), 540 (5,700); IR ν_{max} (KBr) cm^{-1} 3409, 2978, 2159, 1736, 1619, 1458, 1233; ^1H NMR (see Table 1); ^{13}C

NMR (see Table 2); FAB-MS *m/z* (abundance) 483 ($M+H^+$, 63%), 465 (34%), 391 (79%), 377 (72%), 335 (65%), 136 (100%); HREI-MS *m/z* 482.1325 (M^+ Calcd for $C_{24}H_{22}N_2O_9$ 482.1325).

FL-120C′ (**5**): Orange powder; MP 140~150°C (dec) and Rf 0.23 in $CHCl_3$-EtOAc (3:1); UV λ_{max} (MeOH) nm (ε) 207 (20,700), 246 (22,600), 274 (12,900), 294 (sh, 8,300), 309 (sh, 6,500), 394 (7,700), 447 (8,000); UV λ_{max} (NaOH-MeOH) nm (ε) 218 (17,600), 240 (23,000), 273 (14,900), 310 (8,700), 387 (6,700), 549 (6,100); IR ν_{max} (KBr) cm^{-1} 3431, 2985, 2157, 1740, 1620, 1459, 1234; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); FAB-MS *m/z* (abundance) 469 ($M+H^+$, 95%), 451 (42%), 425 (16%), 408 (17%), 395 (19%), 377 (49%), 349 (16%), 335 (49%), 136 (100%);

Anal Calcd for $C_{23}H_{20}N_2O_9$: C 58.98, H 4.30, N 5.98.
Found: C 58.95, H 4.28, N 5.94.

FL-120D′ (**6**): Orange powder; MP 105~110°C (dec) and Rf 0.3 in $CHCl_3$-EtOAc (1:1); UV λ_{max} (MeOH) nm (ε) 209 (16,400), 246 (18,000), 274 (12,200), 294 (sh, 7,900), 309 (sh, 5,900), 394 (6,800), 447 (7,400); UV λ_{max} (NaOH-MeOH) nm (ε) 218 (16,200), 239 (20,700), 274 (16,100), 309 (8,300), 388 (6,000), 539 (5,800); IR ν_{max} (KBr) cm^{-1} 3417, 2978, 2168, 1726, 1622, 1455, 1240; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); FAB-MS *m/z* (abundance) 441 ($M+H^+$, 54%), 335 (100%), 279 (73%), 265 (33%).

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