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Chemistry of renieramycins. Part 6: Transformation of renieramycin M into jorumycin and renieramycin J including oxidative degradation products, mimosamycin, renierone, and renierol acetate☆

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Abstract—The transformation of renieramycin M (**1m**) into renieramycin J (**1j**) and jorumycin (**2**) is presented along with the results of antiproliferative assay data. The chemical stability and the oxidative degradation of **2** and renieramycin E (**1e**) to generate simple isoquinoline alkaloids, such as mimosamycin (**7**), renierol acetate (**12**), and renierone (**8**) are also described.

Renieramycins are isoquinoline marine natural products that are related structurally to other isoquinoline natural products including saframycins, naphthyridinomycin, and ecteinascidins.[2] Renieramycins are isolated from marine sponges belonging to genera *Reniera*,[3a] *Xestospongia*,[3b] *Haliclona*,[3c] *Cribrochalina*,[3d] and *Neopetrosia*.[3e] The ring systems of these natural products including their relative stereochemistry are identical with those of saframycins that exhibit strong cytotoxicity against cultured cells and antitumor activity against several experimental tumors. Many biochemists are interested in these antineoplastic active compounds; however, it is difficult to determine whether the renieramycins have promising antitumor activity because of the scarcity of availability from natural sources. We have recently reported the isolation and structure elucidation of renieramycin M (**1m**) with gram-scale supply from a Thai sponge, *Xestospongia* sp., that was pretreated with potassium cyanide.[1b] The availability of **1m** has enabled us to prepare and evaluate new members of this class of compounds. We present herein the successful transformation of **1m** into jorumycin (**2**) and renieramycin J (**1j**).[4] The chemical stability and the oxidative degradation of **2** and renieramycin E (**1e**) to generate simple isoquinoline alkaloids are also discussed (Fig. 1).

In 2000, **2** was discovered in very minute quantities from the mantle and mucus of the Pacific nudibranch (India), *Jorunna funebris* (Mollusca: Nudibranchia: Doridina: Kentrodoridae).[4] Its structure was elucidated on the grounds of ESMS data and extensive 2D NMR analysis. We became interested in the structure of **2** because this is the only example of this series of marine natural products possessing an acetyl ester side chain, and its cytotoxicity against various human cancer cell lines has been evaluated. The crucial step of this transformation involves the removal of the angeloyl group of **1m**. It is well known that the angeloyl ester can be easily hydrolyzed with potassium cyanide in aqueous alcohol, and that the initial Michael-type addition of HCN saturates the angelates and the basic medium thereby generated causes the hydrolysis of the saturated esters.[5] Treatment of **1m** with potassium cyanide in aqueous methanol gave an inseparable mixture of polymeric material because it has vinylogous esters in both quinone rings. Catalytic hydrogenation of the unsaturated ester residue in **1m** followed by alkaline hydrolysis also gave unsatisfactory results.[6] Furthermore, numerous attempts at the hydrolysis of the ester side chain of **1m** under acidic conditions were unsuccessful.[7] By contrast, the reduction of **1m** with lithium aluminium hydride in THF at 0 °C for 1 h gave the alcohol **3** (25.8%) along with restored the starting material **1m** (15.0%). The reduction of **1m** with less bulky reagent, such as aluminium hydride in THF gave the completely

☆ See Ref. 1.

Keywords: Renieramycin M; Jorumycin; Transformation; Antitumor activity; Oxidative degradation.
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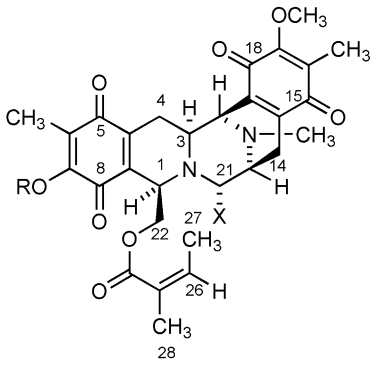
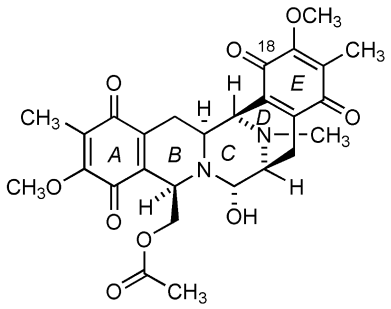
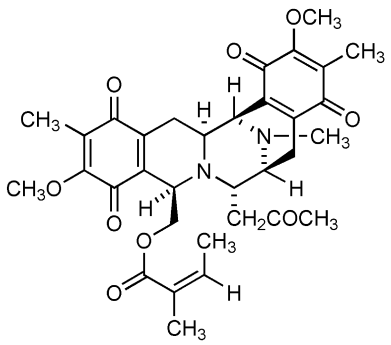


renieramycins
E (**1e**): R = CH_3, X = OH
M (**1m**): R = CH_3, X = CN
S (**1s**): R = H, X = CN



jorumycin (**2**)



renieramycin J (**1j**)

Figure 1.

disappearance of the starting material **1m**, albeit the yield of **3** was still low (26.0%). Accordingly, the following sequence of reactions was studied. Hydrogenation of **1m** with 20% $Pd(OH)_2/C$ in ethyl acetate for 3 h gave the leuco compound **4**, which was subsequently treated with aluminium hydride in THF at −20 °C for 4 h and oxidized in air to provide **3** in 53.3% overall yield along with the decyanated compound **5**[8] (14.1%) and the recovered **1m** (20.5%).[9] With **3** in hand, the reaction of **3** with acetyl chloride, triethylamine, and 4-dimethylaminopyridine in dichloromethane afforded the acetate **6** in 72.9% yield. Compound **6** was easily transformed into **2** in 82.9% yield by treatment with silver nitrate in aqueous acetonitrile at 40 °C for 2 h, which had identical data upon comparison with those of a natural sample (see Table 1) (Chart 1).[4]

Next, we turn our attention to the preparation of renieramycin J (**1j**), which was discovered in our preliminary extraction the Thai sponge, *Xestospongia* sp., and it was found to have an acetone residue at C-21.[1b] Encouraged by our recent results of model transformation,[10] we successfully applied the procedure to the preparation of **1j** from **1m**. A two-step transformation of **1m** into **1j** via **1e** was unsuccessful because the intermediate **1e** was unstable. Treatment of **1m** with silver nitrate in acetone at 50 °C for 1 h gave **1j** in 69.6% yield, which gave spectral data that were in full agreement with those of the isolated compound (Chart 2).

To assess the biological activity of **2**, antiproliferative assays using three human cancer cell lines, HCT116 (colon carcinoma), QG56 (lung carcinoma), and DU145 (prostate cancer), were run in parallel against a range of drug concentrations (Table 2). The data revealed that **2**, **3**, **1e**, and **6** have very similar cytotoxic activities. In addition, the data suggested that renieramycin derivatives have activities similar to those of saframycins,[11] and **5** and **1j**, which lack a leaving group at C-21 position, have much less activities. To realize good cytotoxic activity, a cyano or a hydroxyl group at C-21 position is essential, suggesting that the elimination of this functional group under physiological conditions results in the formation of a reactive iminium species that is responsible for covalent bond formation with the target.

He and Faulkner suggested that **1e** undergoes oxidative cleavage to generate mimosamycin (**7**) and renierone (**8**).[3a] During the course of our research, we also observed the decomposition of that **1e**. Treatment of **1e** with trifluoroacetic acid in chloroform under reflux for 3 h gave **7**[12] (11.7%), **8**[13] (15.8%), **9**[14] (18.4%), and **10**[15] (4.4%). Furthermore, oxidation of **1e** with selenium oxide and

Table 1. ^{1}H and ^{13}C NMR assignment for jorumycin (**2**) in $CDCl_3$

Atom No.	^{13}C NMR, δ (multi., original[a])			^{1}H NMR, δ (multi., integral, J in Hz)			HMBC correlation	NOE correlation
1	52.7	52.6	d		4.36	(ddd, 1H, 3.6, 3.4, 2.7)	22-H_2, 21-H, 3-H	22-H_2
3	51.1	50.8	d		3.16	(ddd, 11.2, 2.7, 2.1)	1-H, 11-H, 21-H	4-Hα
4	25.6	25.5	t	α	2.84	(dd, 1H, 16.8, 2.1)		4-Hβ, 3-H, 11-H
				β	1.29	(ddd, 1H, 16.8, 11.2, 2.7)		4-Hα
5	185.8	185.5	s				4-Hα, 6-CH_3	
6	128.3	128.4	s				6-CH_3	
7	155.7	155.7	s				6-CH_3, 7-OCH_3	
8	181.3	181.0	s					
9	137.3	141.7	s				22-H_2, 4-H_2	
10	141.8	141.9	s				3-H, 4-H_2	
11	54.2	54.4	d		3.91	(d, 1H, 2.7)	4-Hβ, 13-H, NCH_3	4-Ha, 13-H, NCH_3
13	57.5	54.4	d		3.18	(m, 1H)	11-H, NCH_3, 14-H_2 H-14α, NCH_3	11-H, 21-H
14	20.4	20.6	t	α	2.66	(dd, 1H, 21.1, 7.9)		14-Hβ, 13-H
				β	2.25	(d, 1H, 21.1)		14-Hα, 21-H
15	186.5	185.7	s				16-CH_3	
16	128.7	128.8	s				16-CH_3	
17	155.3	155.1	s				16-CH_3, 17-OCH_3	
18	182.6	181.3	s				11-H	
19	134.5	137.2	s				3-H, 11-H, 14-H_2	
20	141.9	141.9	s				11-H, 14-H_2	
21	83.0	83.0	d		4.44	(br s, 1H)	1-H, 14-H_2	13-H, 14-Hβ
22	64.3	64.2	t		4.43	(dd, 1H, 11.3, 3.4)		1-H, 22-H
					3.82	(dd, 1H, 11.3, 3.6)		1-H, 22-H
CO	170.0	170.0	s				$COCH_3$, 22-H_2	
$CO\mathit{CH_3}$	20.5	20.7	s		1.76	(s, 3H)		
6-CH_3	8.6	8.7	q		1.94	(s, 3H)		
16-CH_3	8.7	8.7	q		1.96	(s, 3H)		
7-OCH_3	61.0	61.0	q		3.99	(s, 3H)		
17-OCH_3	61.0	61.0	q		4.01	(s, 3H)		
NCH_3	41.4	41.3	q		2.27	(s, 3H)		11-H, 13-H

[a] Ref. 4.

p-toluenesulfonic acid in 1,4-dioxane at 80 °C for 14 h afforded **7** (43.9%), **8** (46.4%), and **11**[16] (21.8%). It is interesting to note that products **7**–**11** were isolated together with renieramycins from *Reniera* sp.[3a] In contrast, treatment of **2** under the same conditions generated **7** and renierol acetate (**12**)[17] in 20.5 and 37.2% yields, respectively. These observations are evidence that such simple isoquinolinequinones as **7**–**12** may be oxidative degradation products and/or artifacts of isolation procedures (Fig. 2).

In summary, we have prepared of jorumycin (**2**) from **1m** via **3** and showed that all the simple isoquinolinequinones from the marine organisms may be oxidative degradation products. The biological and stability data revealed that **6** is much promising than jorumycin. Although the relationship between the difference in side chain and cytotoxicity varied among the ester derivatives, some correlation should be apparent among them. Further studies are required to solve these problems.

1. Experimental

1.1. General

All melting points were determined using a Yanagimoto micromelting point apparatus and were uncorrected. Optical rotations were measured using a Horiba-SEPA polarimeter. CD was obtained using a JASCO J-720WI spectropolarimeter. IR spectra were obtained with a Hitachi 260-10 spectrophotometer. UV spectra were determined with a Hitachi 340 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125.65 MHz, respectively, on a JEOL-JNM-LA 500 FT NMR spectrometer and at 270 and 67.5 MHz, respectively, on a JEOL-JNM-EX 270 spectrometer (ppm, J in Hz with TMS as internal standard). Mass spectra were recorded on JMS-DX 302 and JMS-700 instruments with a direct inlet system operating at 70 eV. Elemental analyses were conducted on Perkin–Elmer Model 240B and Yanaco MT-6 CHN CORDER elemental analyzers.

1.1.1. 7-Cyano-6,7,9,14,14a,15-hexahydro-9-(hydroxymethyl)-2,11-dimethoxy-3,12,16-tri-methyl-(6*S*,7*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocine-1,4,10,13(9*H*)-tetrone (3).

Direct transformation of **1m** *into* **3** ($LiAlH_4$). A stirred solution of **1m** (57.5 mg, 0.1 mmol) in dry THF (4 ml) was cooled with ice water. A THF solution of lithium aluminium hydride (0.6 M, 0.6 ml, 0.6 mmol) was added dropwise over 10 min, and stirring was continued at 0 °C for 1 h. After quenching by the addition of brine (30 ml), the reaction mixture was extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (48.7 mg), the purification of which by silica gel column chromatography (hexane–ethyl acetate, 3:1) afforded the alcohol (**3**: 13.2 mg, 26.8%) and **1m** (8.6 mg, 15.0% recovery).

Direct transformation of **1m** *into* **3** (AlH_3). A stirred solution of **1m** (23.7 mg, 0.05 mmol) in dry THF (2 ml) was cooled with ice water. A THF solution of aluminium

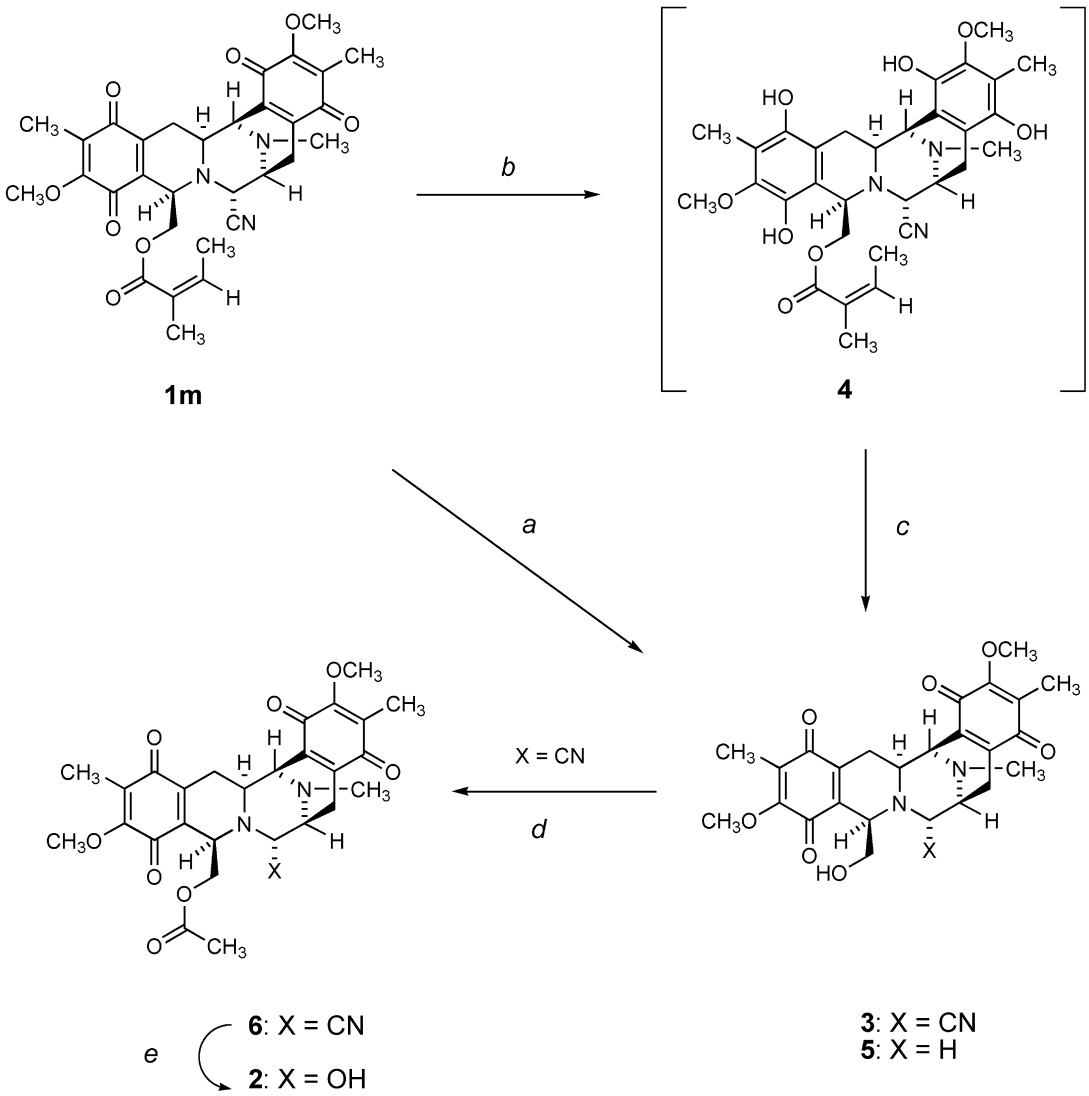


Chart 1. *a*: AlH_3, THF, 26.0% (compound **3**); *b*: H_2, 20% $Pd(OH)_2$/C, EtOAc; *c*: AlH_3, THF, 53.3% (compound **3**), 14.1% (compound **5**); *d*: AcCl, TEA, DMAP, CH_2Cl_2, 72.9%; *e*: $AgNO_3$, CH_3CN/H_2O, 82.9%.

hydride (0.5 M, 0.6 ml, 0.3 mmol) was added dropwise over 10 min, and stirring was continued at 0 °C for 1 h. After quenching by the addition of brine (30 ml), the reaction mixture was extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (28.1 mg), the purification of which by silica gel column chromatography (hexane–ethyl acetate, 3:1) afforded the alcohol (**3**: 6.4 mg, 26.0%) as a yellow amorphous powder.

Two-step transformation of **1m** *into* **3** *via* **4**. *Procedure A*. A solution of renieramycin M (**1m**, 86.3 mg, 0.15 mmol) in

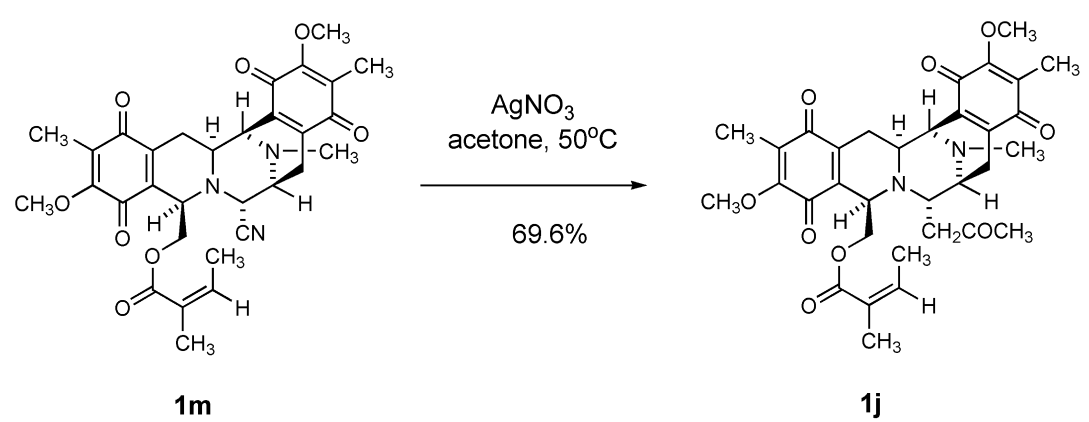


Chart 2.

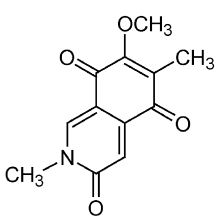
Table 2. Cytotoxicity of jorumycin and derivatives against antiproliferative activity

Compound	IC_{50} (nM)		
	HCT116	QG56	DU145
Renieramycin M (**1m**)	7.9	11.0	NT[a]
Compound **3**	0.38>	2.9	2.6
Compound **5**	32.0	130.0	10.0
Compound **6**	0.38>	0.68	0.38>
Jorumycin (**2**)	0.57	0.76	0.49
Renieramycin E (**1e**)	0.38>	1.0	0.38>
Renieramycin J (**1j**)	730.0	510.0	370.0
5-Fluorouracil	2.0	2.6	3.5

HCT116=human colon carcinoma; QC56=human lung carcinoma; DU145=human prostate cancer.
[a] NT: not tested.

ethyl acetate (8 ml) was hydrogenated over 20% $Pd(OH)_2/C$ (43.2 mg) at 1 atm for 3 h. The catalyst was removed by filtration and washed with ethyl acetate (200 ml). The combined filtrates were concentrated in vacuo to give the leuco compound (**4**, 115.8 mg) as a colorless amorphous powder, which was used in the next step without further purification. A stirred solution of **4** in dry THF (6 ml) was cooled with ice water. A THF solution of aluminium hydride (0.5 M, 2.4 ml, 1.2 mmol) was added dropwise over 10 min at −20 °C, and stirring was continued at −20 °C for 4 h. After quenching by the addition of water (1 ml) and chloroform (10 ml), stirring was continued at room temperature overnight. The reaction mixture was diluted with brine (30 ml) and extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (87.6 mg) that was subjected to chromatography on a silica gel (2.5 g) column with hexane–ethyl acetate (3:1) as the eluent to give the alcohol (**3**: 39.4 mg, 53.3%) and **1m** (17.7 mg, 20.5% recovery). Further elution with ethyl acetate gave the decyanated compound **5** (9.9 mg, 14.1%) as a yellow amorphous powder, which gave spectral data (IR, ^1H NMR, ^{13}C NMR, IR, HREIMS) that were in complete agreement with those of the racemic **5**.[8]

Two-step transformation of **1m** *into* **3** *via* **4**. *Procedure B*. A solution of renieramycin M (**1m**, 16.0 mg, 0.028 mmol) in ethyl acetate (3 ml) was hydrogenated over 20% $Pd(OH)_2/C$ (8.0 mg) at 1 atm for 3 h. The catalyst was removed by filtration and washed with ethyl acetate (50 ml). The combined filtrates were concentrated in vacuo to give the leuco compound (**4**, 19.2 mg) as a colorless amorphous powder, which was used in the next step without further purification. A stirred solution of **4** in dry THF (1.5 ml) was cooled with ice water. A THF solution of lithium aluminium



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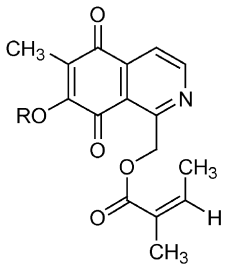
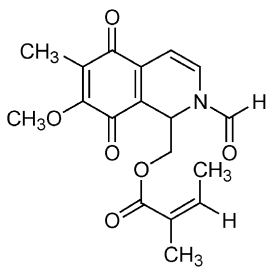


8: R = CH_3
11: R = H



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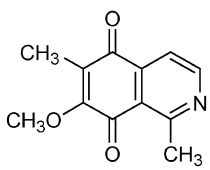

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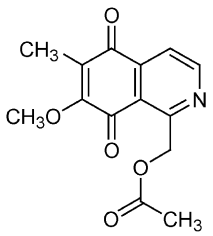

12

		product (%)					
renieramycin	condition	**7**	**8**	**9**	**10**	**11**	**12**
1e	TFA, $CHCl_3$, reflux, 3 h	11.7	15.8	18.4	4.4	0	
1e	*p*-TsOH, SeO_2, dioxane, 80°C, 14 h	43.9	46.4	0	0	21.8	
2	*p*-TsOH, SeO_2, dioxane, 80°C, 12 h	20.5					37.2

Figure 2.

hydride (1.0 M, 0.2 ml, 0.2 mmol) was added dropwise over 10 min at −20 °C, and stirring was continued at −20 °C for 4 h. After quenching by the addition of water (0.1 ml) and chloroform (10 ml), stirring was continued at room temperature overnight. The reaction mixture was diluted with brine (30 ml) and extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (19.2 mg) that was subjected to chromatography on a silica gel (1.5 g) column with hexane–ethyl acetate (3:1) as the eluent to give the alcohol (**3**: 4.7 mg, 34.3%) and **1m** (3.4 mg, 21.3% recovery).

Compound **3**. $[\alpha]_D^{25}=-270.6$ (*c* 1.0, $CHCl_3$); CD Δ ε nm (*c* 103.3 μM, methanol, 24 °C) −2.9 (352), −1.5 (300), −10.2 (280), +3.2 (257), −1.8 (230); IR ($CHCl_3$) 3631, 3368, 3015, 2945, 2840, 1656, 1449, 1375, 1311, 1189 cm^{-1}; UV λ_{max} (log ε) 269 (4.61), 370 (3.11) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.15 (1H, d, *J*=2.4 Hz, 21-H), 4.07 (1H, d, *J*=2.6 Hz, 11-H), 4.03, 3.98 (each, 3H, s, 7-OCH_3 and 17-OCH_3), 3.89 (1H, ddd, *J*=3.7, 3.1, 2.4 Hz, 1-H), 3.71 (1H, dd, *J*=11.3, 3.1 Hz, 22-H), 3.48 (1H, dd, *J*=11.3, 3.7 Hz, 22-H), 3.41 (1H, dd, *J*=7.6, 2.4 Hz, 13-H), 3.17 (1H, ddd, *J*=11.6, 2.6, 2.4 Hz, 3-H), 2.92 (1H, dd, *J*=17.4, 2.4 Hz, 4-Hα), 2.82 (1H, dd, *J*=21.1, 7.6 Hz, 14-Hα), 2.30 (3H, s, NCH_3), 2.27 (1H, d, *J*=21.1 Hz, 14-Hβ), 1.93 (6H, s, 6-CH_3 and 16-CH_3), 1.42 (1H, ddd, *J*=17.4, 11.6, 2.4 Hz, 4-Hβ); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.3 (s, C-15), 185.5 (s, C-5), 182.3 (s, C-18), 181.4 (s, C-8), 155.5 (s, C-7), 155.4 (s, C-17), 141.7 (s, C-20), 141.4 (s, C-10), 136.1 (s, C-9), 135.6 (s, C-19), 128.8 (s, C-6), 128.6 (s, C-16), 116.9 (s, CN), 64.2 (t, C-22), 61.1 (q, OCH_3), 61.0 (q, OCH_3), 59.1 (d, C-21), 58.0 (d, C-1), 54.5 (d, C-13), 54.3 (d, C-3), 54.2 (d, C-11), 41.5 (q, NCH_3), 25.4 (t, C-4), 21.5 (t, C-14), 8.7 (q, 6-CH_3), 8.7 (q, 16-CH_3); FAB-MS (Magic bullet) *m*/*z* (%) 494 (M^++1, 8), 309 (20), 220 (15), 155 (59), 154 (17), 152 (13), 137 (10), 135 (24), 121 (13), 118 (100), 102 (42), 101 (14), 89 (15), 87 (12), 85 (77), 69 (12), 55 (14); HR-FABMS *m*/*z* 494.1910 [M^++1] (calcd for $C_{26}H_{28}N_3O_7$, 494.1927).

1.1.2. 6,7,9,14,14a,15-Hexahydro-9-(hydroxymethyl)-2,11-dimethoxy-3,12,16-trimethyl-(6*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocine-1,4,10,13(9*H*)-tetrone (5). $[\alpha]_D^{25}=-109.8$ (*c* 0.2, $CHCl_3$); CD Δ ε nm (*c* 129.6 μM, methanol, 24 °C) −2.5 (346), −1.4 (300), −9.1 (281), +1.9 (254), −1.3 (230), −0.6 (223); IR ($CHCl_3$) 2943, 1656, 1615, 1450, 1376, 1311, 1237, 1153 cm^{-1}; UV λ_{max} (log ε) 269 (4.35), 370 (3.14) nm; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.06 (1H, dd, *J*=2.7, 0.5 Hz, 11-H), 4.01, 3.96 (each, 3H, s, 7-OCH_3 and 17-OCH_3), 3.75 (1H, dd, *J*=11.2, 3.7 Hz, 22-H), 3.52 (1H, dd, *J*=11.2, 1.0 Hz, 22-H), 3.51 (1H, ddd, *J*=3.7, 2.9, 1.0 Hz, 1-H), 3.18 (1H, m, 13-H), 3.03 (1H, dd, *J*=11.0, 2.4 Hz, 21-Hβ), 2.81 (1H, ddd, *J*=11.7, 2.7, 2.4 Hz, 3-H), 2.81 (1H, dd, *J*=18.1, 2.4 Hz, 4-Hα), 2.80 (1H, dd, *J*=11.0, 2.4 Hz, 21-Hα), 2.80 (1H, dd, *J*=21.0, 7.6 Hz, 14-Hα), 2.26 (3H, s, NCH_3), 2.24 (1H, d, *J*=21.0 Hz, 14-Hβ), 1.94, 1.92 (each 3H, s, 6-CH_3 and 16-CH_3), 1.41 (1H, ddd, *J*=18.1, 11.7, 2.9 Hz, 4-Hβ); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 185.9 (s, C-15), 185.8 (s, C-5), 182.6 (s, C-18), 182.1 (s, C-8), 155.6 (s, C-7), 155.5 (s, C-17), 142.8 (s, C-20), 142.0 (s, C-10), 137.3 (s, C-9), 136.3 (s, C-19), 128.8 (s, C-6), 128.6 (s, C-16), 61.5 (t, C-22), 61.0 (q, OCH_3), 60.9 (q, OCH_3), 58.7 (t, C-21), 58.7 (d, C-1), 57.2 (d, C-13), 54.8 (d, C-3), 52.2 (d, C-11), 41.1 (q, NCH_3), 26.2 (t, C-4), 22.7 (t, C-14), 8.7 (q, 6-CH_3), 8.7 (q, 16-CH_3); FAB-MS (*m*-nitrobenzyl alcohol) *m*/*z* (%) 469 (M^++1, 6), 437 (3), 391 (3), 307 (17), 289 (12), 220 (30), 218 (20), 154 (100), 136 (72); HR-FABMS *m*/*z* 469.1970 [M^++1] (calcd for $C_{25}H_{29}N_2O_7$, 469.1975).

1.1.3. 9-[Acetoxymethyl]-7-cyano-6,7,9,14,14a,15-hexahydro-2,11-dimethoxy-3,12,16-tri-methyl-(6*S*,7*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocine-1, 4,10,13(9H)-tetrone (6). Acetyl chloride (9.4 μl, 0.13 mmol) was added to a solution of **3** (16.4 mg, 0.033 mmol), triethylamine (9.2 μl, 0.0066 mmol), and 4-dimethylaminopyridine (8.1 mg, 0.0066 mmol) in dichloromethane (4 ml) at 0 °C, and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (20 ml) and extracted with dichloromethane (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated in vacuo to give a residue (18.7 mg), the purification of which by flash silica gel column chromatography (hexane–ethyl acetate 5:1) afforded the acetate (**6**, 12.9 mg, 72.9%) as an amorphous powder. $[\alpha]_D^{25}=-94.5$ (*c* 0.2, $CHCl_3$); CD Δ ε nm, (*c* 94.3 μM, methanol, 24 °C) −3.5 (351), −1.5 (300), −7.0 (280), +4.5 (256), −1.3 (230), −0.6 (222); IR ($CHCl_3$) 3026, 2964, 2854, 1741, 1656, 1615, 1449, 1375, 1310, 1233, 1162 cm^{-1}; UV λ_{max} (log ε) 269 (4.59), 370 (3.13) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.44 (1H, d, *J*=2.4 Hz, 21-H), 4.43 (1H, dd, *J*=11.3, 3.4 Hz, 22-H), 4.36 (1H, ddd, *J*=3.7, 3.1, 2.4 Hz, 1-H), 4.01 (3H, s 17-OCH_3), 3.99 (3H, s, 7-OCH_3), 3.91 (1H, d, *J*=2.7 Hz, 11-H), 3.82 (1H, dd, *J*=11.3, 3.6 Hz, 22-H), 3.18 (1H, dd, *J*=7.9, 2.4 Hz, 13-H), 3.16 (1H, ddd, *J*=11.2, 2.7, 2.1 Hz, 3-H), 2.84 (1H, dd, *J*=16.8, 2.1 Hz, 4-Hα), 2.66 (1H, dd, *J*=21.1, 7.9 Hz, 14-Hα), 2.27 (3H, s, NCH_3), 2.25 (1H, d, *J*=21.1 Hz, 14-Hβ), 1.96 (3H, s, 16-CH_3), 1.94 (3H, s, 6-CH_3), 1.76 (3H, s, $COCH_3$), 1.29 (1H, ddd, *J*=16.8, 11.2, 2.7 Hz, 4-Hβ); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.1 (s, C-15), 185.4 (s, C-5), 182.5 (s, C-18), 181.0 (s, C-8), 169.9 (s, CO), 155.5 (s, C-7), 155.2 (s, C-17), 142.2 (s, C-20), 141.8 (s, C-10), 135.4 (s, C-9), 134.9 (s, C-19), 128.7 (s, C-6), 128.7 (s, C-16), 116.9 (s, CN), 63.6 (t, C-22), 61.1 (q, OCH_3), 61.0 (q, OCH_3), 59.7 (d, C-21), 55.8 (d, C-1), 54.6 (d, C-13), 54.5 (d, C-3), 54.3 (d, C-11), 41.5 (q, NCH_3), 25.3 (t, C-4), 21.3 (t, C-14), 20.5 (q, $COCH_3$), 8.8 (q, 6-CH_3), 8.6 (q, 16-CH_3); EIMS *m*/*z* (%) 535 (M^+, 7), 260 (8), 243 (6), 221 (19), 220 (100), 218 (24), 204 (12); HR-EIMS *m*/*z* 535.1953 [M^+] (calcd for $C_{28}H_{29}N_3O_8$, 535.1955).

1.1.4. 9-[(Acetoxy)methyl]-6,7,9,14,14a,15-hexahydro-7-hydroxy-2,11-dimethoxy-3,12,16-trimethyl-(6*S*,7*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]-benzazocine-1,4,10,13(5H)-tetrone (jorumycin: 2). Compound **6** (28.5 mg, 0.053 mmol) was dissolved in a mixture of acetonitrile and water [3:2 (v/v), 5 ml], and silver nitrate (225.1 mg, 1.33 mmol) was added. After stirring at 40 °C for 2 h, the reaction mixture was filtered and then washed with chloroform (50 ml), and the combined filtrates were concentrated in vacuo. The residue was diluted with water (20 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with brine (20 ml),

dried, and concentrated in vacuo to give a residue (28.7 mg), the purification of which by flash silica gel column chromatography (hexane–ethyl acetate 2:1) afforded jorumycin (**2**, 23.1 mg, 82.9%) as a pale yellow amorphous powder. $[\alpha]_D^{25}=-82.0$ (*c* 0.31, $CHCl_3$) [lit.[2] −57 (*c* 0.05, $CHCl_3$)]; CD Δ ε nm (*c* 112.8 μM, methanol, 24 °C) −2.2 (351), −0.6 (303), −4.6 (280), +2.5 (256), +0.5 (247), −1.9 (230), −1.9 (230); IR ($CHCl_3$) 2929, 2854, 1735, 1656, 1616, 1375, 1310, 1233 cm^{-1}; UV λ_{max} (log ε) 269 (4.59), 370 (3.13) nm; ^1H NMR and ^{13}C NMR spectral data: see Table 1; EIMS *m/z* (%) 526 (M^+, 3), 508 (2), 437 (3), 369 (26), 368 (26), 313 (15), 262 (13), 236 (16), 232 (12), 220 (100); HR-FABMS *m/z* 509.1916 [M^++1−H_2O] (calcd for $C_{27}H_{29}N_2O_8$, 509.1924).

1.1.5. Transformation of renieramycin M (1m) into J (1j). Silver nitrate (144.1 mg, 0.80 mmol) was added to a stirred solution of **1m** (24.4 mg, 0.04 mmol) in acetone (4 ml) at 25 °C, and the mixture was stirred at 50 °C for 1 h. After the solvent was removed in vacuo, the residue was diluted with water (20 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated in vacuo to give a solid (31.3 mg), the purification of which by silica gel column chromatography (hexane–ethyl acetate, 2:1) afforded renieramycin J (**1j**: 17.9 mg, 69.6%) as a yellow amorphous powder, which gave spectral data (IR, ^1H NMR, ^{13}C NMR, IR, HREIMS) that were in complete agreement with those of the authentic standard:[1b] $[\alpha]_D^{20}=-708.8$ (*c* 0.1, $CHCl_3$); CD Δ ε nm (*c* 83.5 μM, methanol, 24 °C) −2.9 (367), −0.4 (316), −0.9 (303), −7.6 (284), +6.3 (259), −3.4 (230), +8.1 (209).

1.1.6. Oxidative degradation of 1e. *Method A*. Trifluoroacetic acid (28 μl, 0.36 mmol) was added to a stirred solution of **1e** (12.5 mg, 0.022 mmol) in chloroform (2 ml), and the mixture was heated under reflux for 3 h. The reaction mixture was diluted with water (10 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (10 ml×3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (11.3 mg) was subjected to chromatography on preparative layer silica gel (Merck 5715, solvent ethyl acetate–hexane, 2:1) to give **7** (0.6 mg, 11.7%), **8** (1.1 mg, 15.8%), **9** (1.4 mg, 18.4%), and **10** (0.2 mg, 4.4%).

Method B. *p*-Toluenesulfonic acid (5.1 mg, 0.027 mmol) was added to a stirred solution of **1e** (15.5 mg, 0.027 mmol) and selenium oxide (30.4 mg, 0.27 mmol) in 1,4-dioxane (5 ml), and the mixture was stirred for 14 h at 80 °C. The reaction mixture was filtered and then washed with chloroform (50 ml). The combined filtrates were concentrated in vacuo and the residue was diluted with water (10 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (10 ml×3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo to give a residue (10.6 mg), the purification of which by silica gel column chromatography (ethyl acetate–hexane, 1:3) afforded **7** (2.8 mg, 43.9%). Further elution with ethyl acetate–hexane (1:2) gave **8** (4.0 mg, 46.4%). The pH was carefully brought to approximately 6–7 with acetic acid and further extraction was carried out with chloroform (10 ml×3). The combined extracts were washed with brine (10 ml), dried, and concentrated in vacuo to give **11** (1.8 mg, 21.8%) as pale yellow needles.

7-Methoxy-2,6-dimethyl-3,5,8(2H)isoquinolinetrione (*mimosamycin*, **7**). Mp 223–224 °C (dichloromethane–CH_3OH, yellow prisms) (lit.[12a] mp 223–227 °C); IR (KBr) 1680, 1650, 1640, 1590 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.27 (1H, s), 7.10 (1H, s), 4.17 (3H, s, OCH_3), 3.67 (3H, s, NCH_3), 2.06 (3H, s, 5-CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 183.5 (s), 177.3 (s), 162.8 (s), 159.5 (s), 142.1 (s), 138.9 (s), 133.1 (s), 116.7 (s), 111.3 (s), 61.3 (q, OCH_3), 38.4 (q, NCH_3), 9.5 (q, 5-CH_3); EIMS *m/z* (%) 233 (M^+, 100), 218 (33), 204 (10), 190 (16), 177 (12), 149 (11); HR-EIMS *m/z* 233.0682 [M^+] (calcd for $C_{12}H_{11}NO_3$, 233.0688).

(Z)-2-Methyl-2-butenoic acid (5,8-dihydro-7-methoxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*renierone*, **8**). Mp 89–90 °C (ethyl acetate–ether) (lit.[13] mp 91.5–92 °C); IR (KBr) 2950, 2930, 1710, 1660, 1640, 1560 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.92 (1H, d, *J*=4.9 Hz, 3-H), 7.88 (1H, d, *J*=4.9 Hz, 4-H), 6.12 (1H, qq, *J*=7.3, 1.3 Hz, CH), 5.79 (2H, s, 1-H_2), 4.15 (3H, s, OCH_3), 2.09 (3H, s, 6-CH_3), 2.01 (3H, dq, *J*=7.3, 1.5 Hz, 15-CH_3), 1.98 (3H, dq, *J*=1.5, 1.3 Hz, 14-CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 184.5 (s, C-5), 181.7 (s, C-8), 167.8 (s, CO), 158.5 (s, C-1), 156.8 (s, C-7), 153.9 (d, C-3), 138.5 (s, C-10), 138.0 (d, C-15), 130.5 (s, C-14), 128.0 (s, C-9), 122.6 (s, C-6), 118.3 (d, C-4), 65.3 (t, C-11), 61.2 (q, OCH_3), 20.6 (q, 14-CH_3) 15.7 (q, 15-CH_3), 9.0 (q, 6-CH_3); EIMS *m/z* (%) 315 (M^+, 100), 232 (26), 216 (32), 83 (58), 82 (76), 55 (43); HR-EIMS *m/z* 315.1113 [M^+] (calcd for $C_{17}H_{17}NO_5$, 315.1107).

(Z)-2-Methyl-2-butenoic acid (2-formyl-1,2,5,8-tetrahydro-7-methoxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*N-formyl-1,2-dihydrorenierone*, **9**). Dark red amorphous powder; IR ($CHCl_3$) 1715, 1650 cm^{-1}; ^1H NMR (270 MHz) major isomer δ 8.43 (1H, s, CHO), 6.91 (1H, d, *J*=7.5 Hz, 3-H), 6.05 (1H, qq, *J*=7.3, 1.5 Hz, CH), 6.03 (1H, d, *J*=7.5 Hz, C-4), 5.99 (1H, dd, *J*=4.5, 3.1 Hz, C-1), 4.36 (1H, dd, *J*=12.0, 4.5 Hz, H-11), 4.20 (1H, dd, *J*=12.0, 3.1 Hz, H-11), 4.07 (3H, s, OCH_3), 1.95 (3H, s, 6-CH_3), 1.91 (1H, qd, *J*=7.3, 1.3 Hz, 15-CH_3), 1.77 (1H, qd, *J*=1.5, 1.3 Hz, 14-CH_3); minor isomer δ 8.22 (1H, s, CHO), 7.44 (1H, d, *J*=7.5 Hz, 3-H), 6.23 (1H, d, *J*=7.5 Hz, C-4), 6.15 (1H, qq, *J*=7.2, 1.5 Hz, CH), 5.36 (1H, dd, *J*=5.0, 4.3 Hz, C-1), 4.21 (1H, dd, *J*=12.5, 5.0 Hz, H-11), 4.06 (3H, s, OCH_3), 3.90 (1H, dd, *J*=11.5, 4.3 Hz, H-11), 2.00 (1H, qd, *J*=7.3, 1.3 Hz, 14-CH_3), 1.98 (3H, s, 6-CH_3), 1.87 (1H, qd, *J*=1.5, 1.3 Hz, 15-CH_3); EIMS *m/z* (%) 345 (M^+, 6), 315 (15), 232 (100), 204 (79), 117 (10), 83 (21); HR-EIMS *m/z* 345.1226 (calcd for $C_{18}H_{19}NO_6$, 345.1212).

1,6-Dimethyl-7-methoxy-5,6-dihydroisoquinoline-5,8-dione (**10**). Mp 189–190 °C (lit.[15] mp 188–190 °C); IR (KBr) 2920, 2850, 1670, 1615, 1570, 1400, 1380, 1340, 1300, 1205, 905 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.84 (1H, d, *J*=5.0 Hz), 7.80 (1H, d, *J*=5.0 Hz), 4.14 (3H, s, OCH_3), 2.99 (3H, s, $-CH_3$), 2.08 (3H, s, C$-CH_3$); EIMS *m/z* (%) 217 (M^+, 100), 202 (13), 187 (17), 174 (18), 146 (7), 130 (10), 118 (11); HR-EIMS *m/z* 217.0748 [M^+] (calcd for $C_{12}H_{11}NO_3$, 217.0739).

(Z)-2-Methyl-2-butenoic acid (5,8-dihydro-7-hydroxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*demethylrenierone*, **11**). Mp 134.5–136 °C (dichloromethane–hexane) (lit.[16] mp 135–136 °C); IR (KBr) 2950, 2930, 1710, 1660, 1640, 1560 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.97 (1H, d, J=5.0 Hz), 7.95 (1H, d, J=5.0 Hz), 6.12 (1H, qq, J=7.2, 1.5 Hz), 5.80 (2H, s), 2.12 (3H, s, C–CH_3), 2.01 (3H, dq, J=7.2, 1.5 Hz), 1.98 (3H, dq, J=1.5, 1.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 184.5 (s), 181.7 (s), 167.8 (s, CO), 158.5 (s), 156.8 (s), 153.9 (d), 138.5 (s), 138.0 (s), 130.5 (s), 128.0 (s), 122.6 (s), 118.3 (d), 65.3 (t), 61.2 (q, OCH_3), 20.6 (q) 15.7 (q), 9.0 (q); EIMS m/z (%) 301 (M^+, 100), 218 (14), 203 (10), 202 (19), 83 (44), 82 (74), 55 (33); HR-EIMS m/z 301.0943 [M^+] (calcd for $C_{16}H_{15}NO_5$, 301.0950).

1.1.7. Oxidative degradation of 2. *p*-Toluenesulfonic acid (16.7 mg, 1.09 mmol) was added to a stirred solution of **2** (23.1 mg, 0.044 mmol) and selenium oxide (58.6 mg, 0.53 mmol) in 1,4-dioxane (7 ml), and the mixture was stirred for 12 h at 80 °C. The reaction mixture was filtered and then washed with chloroform (50 ml). The combined filtrates were concentrated in vacuo, and the residue was diluted with water (20 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 ml×3). The combined extracts were washed with water (20 ml), dried, and concentrated in vacuo to give a residue (14.6 mg), the purification of which by silica gel column chromatography (ethyl acetate–hexane, 1:5) afforded **12** (4.5 mg, 37.2%). Further elution with ethyl acetate–hexane (1:2) gave **10** (2.1 mg, 20.5%).

Acetic acid (5,8-Dihydro-7-methoxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*renierol acetate*, **12**). Pale yellow amorphous powder; IR ($CHCl_3$) 2940, 1738, 1660, 1650, 1570, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (1H, d, J=5.0 Hz, 3-H), 7.90 (1H, d, J=5.0 Hz, 4-H), 5.71 (2H, s, 1-H_2), 4.15 (3H, s, OCH_3), 2.22 (3H, s, $COCH_3$), 2.09 (3H, s, 6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4 (s, C-5), 181.7 (s, C-8), 171.0 (s, CO), 158.5 (s, C-1), 156.6 (s, C-7), 153.8 (d, C-3), 139.1 (s, C-10), 130.6 (s, C-14), 128.0 (s, C-9), 122.8 (s, C-6), 118.6 (d, C-4), 65.5 (t, C-11), 61.3 (q, OCH_3), 20.9 (q, COCH_3) 9.1 (q, 6-CH_3); EIMS m/z (%) 275 (M^+, 1), 234 (13), 233 (100), 218 (8), 215 (10), 204 (10), 190 (18), 187 (14); HR-EIMS m/z 275.0793 [M^+] (calcd for $C_{14}H_{13}NO_5$, 275.0794).

1.2. Assay for cytotoxicity

A single-cell suspension of each cell (2×10^3 cells/well) was added to the serially diluted test compounds in a microplate. The cells were then cultured for 4 days. Cell growth was measured with a cell counting kit (DOJINDO, Osaka, Japan). IC_{50} was expressed as the concentration at which cell growth was inhibited by 50% compared with untreated control.

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References and notes

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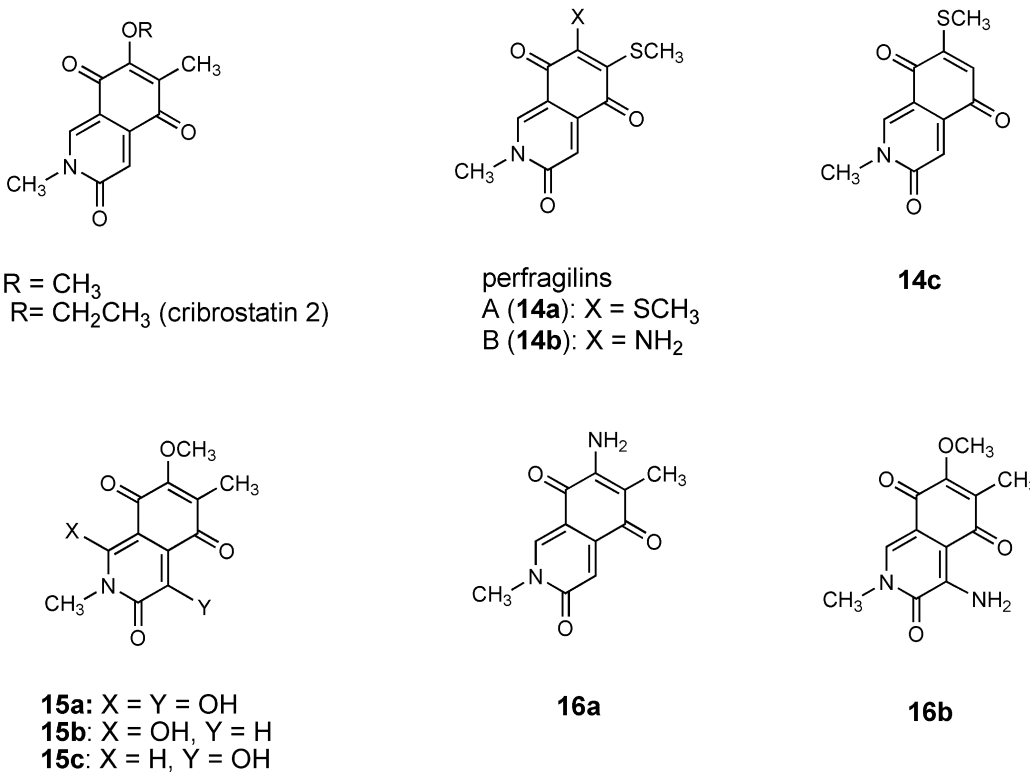

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