May 1993 Notes Chem. Pharm. Bull. 41(5) 971—974 (1993)

Chemical Modification of Antitumor Alkaloids, 20(*S*)-Camptothecin and 7-Ethylcamptothecin: Reaction of the E-Lactone Ring Portion with Hydrazine Hydrate

Takashi YAEGASHI,[a] Seigo SAWADA,*,[a] Tomio FURUTA,[a] Teruo YOKOKURA,[a]
Kentaro YAMAGUCHI[b] and Tadashi MIYASAKA[b]

Yakult Central Institute for Microbiological Research,[a] Yaho, Kunitachi-shi, Tokyo 186 and School of Pharmaceutical Sciences, Showa University,[b] Hatanodai 1–5–8, Shinagawa-ku, Tokyo 142, Japan. Received September 24, 1992

The structure of the *N*-amino pyridone (4a) obtained by the reaction of camptothecin (1a) with hydrazine was determined by X-ray crystallography. A mixture of 7-ethylcamptothecin (1b) and hydrazine hydrate was stirred at room temperature, and the hydrazide (2b) was isolated as its diacetate 2c. Treatment of the 17-*O*-acetyl amide (5a) with hydrazine gave 1b (74% yield) and the *N*-amino lactam 6 (11% yield). Compounds with bulky acyl groups, 5c—e, gave 6 in modest yields. The *N*-amino lactam 6 was smoothly dehydrated into the pyridone 4d by refluxing in hydrazine hydrate.

Keywords 20(*S*)-camptothecin; 7-ethylcamptothecin; hydrazine; *N*-amino pyridone; X-ray crystallography; L1210

20(*S*)-Camptothecin (**1a**) is an antitumor alkaloid which was first isolated from *Camptotheca acuminata* (Nyssaceae) by Wall and coworkers in 1966.[1)] The E-ring lactone of the alkaloid containing the 20-hydroxyl group is said to be the moiety responsible for the antitumor activity.[2)]

There are many reports concerning E-ring modified derivatives.[3)] For example, Adamovics and Hutchinson reported that reaction of camptothecin with isopropylamine gave the E-ring-cleaved amide (**2a**),[3a)] while the reaction with sodium azide resulted in direct replacement at the 17-carbon followed by decarboxylation to the ketone (**3a**).[3c)]

We are conducting a program to establish derivatizations utilizing the reactive lactone to improve the water-solubility of camptothecins, while retaining the activities. We have already reported the synthesis of E-ring-modified 17-*O*-acyl amide derivatives of 7-ethylcamptothecin (**1b**) and their significant activity.[4)] In this paper, we wish to describe an attempt to obtain the hydrazide form of the E-ring-opened compounds, as an alternative derivatization applicable to alkyl or halogenocamptothecins.

When **1a** was refluxed in hydrazine hydrate for 2 h, the major product (**4a**) consisted of orange-yellow needles, mp 325—330 °C (dec.), which showed *m*/*z* 344 as the largest ion peak and 20 carbon signals in its ^{13}C-NMR spectrum. The structure of **4a** was determined by a single crystal X-ray crystallographic study (Fig. 1). The observed cell parameters for a crystal of **4a** (0.25 × 0.05 × 0.50 mm) recrystallized from methanol–chloroform (1 : 9) were as follows: $C_{20}H_{16}N_4O_2 \cdot 1/2CHCl_3$, $M_w = 404.06$, monoclinic, $C2/C$, $a = 22.421(2)$, $b = 9.883(1)$, $c = 16.665(1)$ Å, $\beta = 105.359(5)$ Å, $V = 3563.1(6)$ Å^3, $Z = 8$, $D_x = 1.506$ Mgm^{-3}, $\lambda(\mathrm{Cu}K_{\alpha_1}) = 1.54050$ Å. $\mu = 2.791$ mm^{-1}, $F(000) = 1672$, $T = 296$ K, final $R = 0.063$, $R_w = 0.066$ for 2192 reflections. Atomic coordinates and isotropic thermal parameters are given in Experimental (Table III). The crystal of **4a** has 1/2 mol of chloroform as solvent of crystallization, confirmed by its NMR spectrum, though its exact position could not be determined due to irregular existence. The pyridone **4d** was also obtained from **1b** by means of the reaction described above. The diacetyl compound **4b** was obtained in a usual manner and saponified to obtain the monoacetate (**4c**).

A mixture of **1b** and hydrazine hydrate was stirred at room temperature for 30 min, then the precipitate was collected and acetylated to furnish the diacetate **2c**. Attempts to isolate the hydrazide **2b** failed due to its ready conversion to **1b**.

In an attempt to obtain the 17-hydrazino compound, the amide **5a** was treated with hydrazine hydrate in refluxing

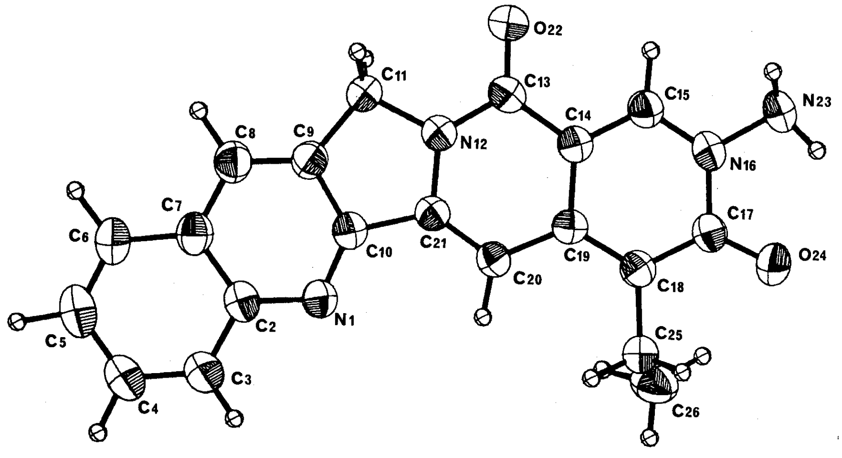
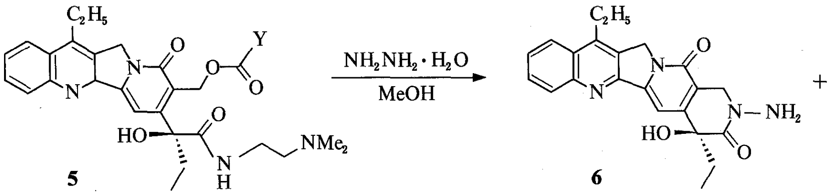


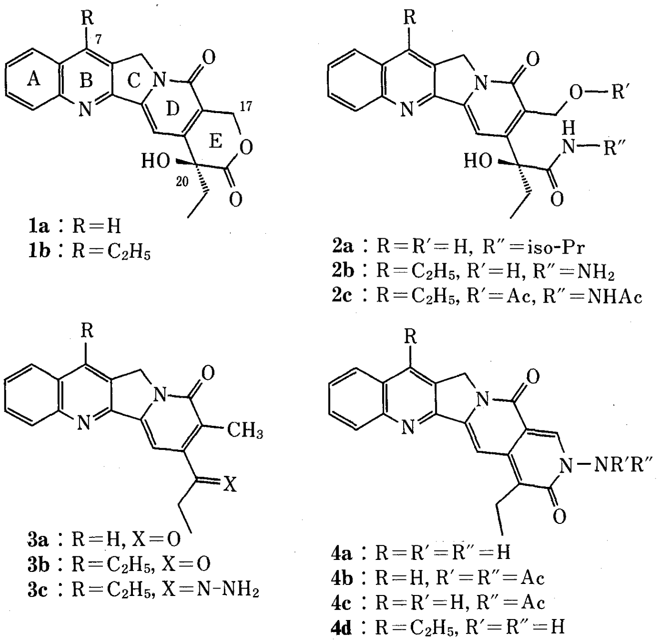
Fig. 1. ORTEP Drawing of Compound **4a**

TABLE I. Reaction of the Amide **5** with Hydrazine Yielding the *N*-Amino Lactam **6**



Compound No.	Y	**6** (Yield %)$^{a)}$	**1b** (Yield %)$^{a)}$
5a	CH_3	$11^{b)}$	$74^{b)}$
5b	$C(CH_3)_3$	16	10
5c	C_6H_5	36	38
5d	C_6H_4–CN(*p*)	46	42
5e	C_6H_4–OMe(*p*)	46	20

a) Determined by HPLC. Column: inertsil ODS-2, 4 mm × 25 cm. Temperature: 40 °C. Detection: 254 nm. Eluent: 0.01 M KH_2PO_4–CH_3CN–MeOH (3 : 1 : 1). *b*) Isolated yield.



1a : R=H
1b : R=C_2H_5

2a : R=R′=H, R″=iso-Pr
2b : R=C_2H_5, R′=H, R″=NH_2
2c : R=C_2H_5, R′=Ac, R″=NHAc

3a : R=H, X=O
3b : R=C_2H_5, X=O
3c : R=C_2H_5, X=N-NH_2

4a : R=R′=R″=H
4b : R=H, R′=R″=Ac
4c : R=R′=H, R″=Ac
4d : R=C_2H_5, R′=R″=H

Fig. 2

methanol. However, the *N*-amino lactam **6** (11% yield) and **1b** (74% yield) were obtained instead of the desired compound. Other results are summarized in Table I. Compound **6** was thought to be formed through substitution of hydrazine at the 17-carbon followed by cyclization, while hydrazinolysis of the acetyl group of **5a** gave the hydroxyamide, which was easily converted to **1b** as described in the preceding paper.[4a)] Hydrazinolysis was predominant with **5a** and **5b**, whereas formation of **6** was predominant with the bulkier acyl compounds **5c**—**e**.

The *N*-amino lactam **6** was smoothly converted to the pyridone **4d** by refluxing in hydrazine hydrate. Upon reaction of camptothecins (**1a** or **1b**) with hydrazine, the hydrazide (**2b**) was first formed. Under accelerated conditions **2b** was dehydrated to the exomethylene intermediate, as pointed by Adamovic and Hutchinson,[3a)] and cyclized to the *N*-amino lactam **6**, followed by aromatization to **4** (**a** or **d**).

The ketone **3b** was treated with hydrazine to give an approximately 5 : 3 mixture of two products, both of which were geometric isomers of the hydrazone **3c**, as confirmed by the NMR and mass spectra (Experimental). HPLC detected a trace amount of **3c** (about 0.1%) in the reaction mixture of **1b** with hydrazine.

In conclusion, **1** reacted with hydrazine, as with isopropylamine, mainly at the lactone carbonyl carbon to give the unstable hydrazide **2b**. Direct attack at the 17-poisiton of the lactone, as reported with sodium azide,[3c)] was also observed but to a far lesser extent. Under the conditions described above, the hydrazide was cyclized and aromatized to **4** (**a** or **d**).

Compounds **4a**, **4c** and **6** were inactive against mouse leukemia L1210 *in vivo*, as detailed in Experimental (Table II).

Experimental

Melting points (with decomposition) are uncorrected. ^1H-NMR and ^{13}C-NMR spectra were determined with a JEOL GX-400 (400 MHz) spectrometer with tetramethylsilane as the internal standard. Infrared (IR) and ultraviolet (UV) spectra were recorded on Shimadzu IR 435 and UV-240 spectrophotometers, respectively. Mass spectra (MS) were measured with a Hitachi M-80B Mass Spectrometer. The X-ray diffraction study was carried out using a Rigaku AQFC-5 diffractometer. The structure was solved by the direct method and refined by the full-matrix least-squares method.

2-Amino-4-ethylpyrido[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(2*H*,12*H*)-dione (4a) A suspension of **1a** (1.0 g, 2.87 mmol) in $NH_2NH_2 \cdot H_2O$ (30 ml) was refluxed for 2 h under an N_2 atmosphere. The mixture was allowed to stand at room temperature, and the precipitate was collected by suction. The solid was recrystallized from dimethyl sulfoxide (DMSO) to give 540 mg (55% yield) of the title compound as orange-yellow needles. IR (KBr): 1665, 1645, 1615 cm^{-1}. ^1H-NMR (recrystallized from a 1 : 9 mixture of MeOH–$CHCl_3$, in DMSO-d_6) δ: 1.15 (3H, t, $J=7$ Hz), 2.86 (2H, q, $J=7$ Hz), 5.27 (2H, s), 6.80 (2H, s), 7.24 (1H, s), 7.67—7.91 (2H, m), 8.08—8.25 (2H, m), 8.32 (0.5H, $CHCl_3$), 8.65 (1H, s), 8.73 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 13.44, 19.43, 48.94, 93.72, 106.61, 121.33, 127.51, 128.10, 128.37, 128.89, 129.94, 130.23, 131.36, 135.45, 138.83, 143.51, 147.97, 152.69, 158.12, 159.13. MS *m*/*z*: 344 $(M)^+$. UV λ_{max}^{MeOH} nm (ε): 210 (23200), 258 (31700), 292 (21000), 340 (10600), 360 (12000), 402 (9300). *Anal*. Calcd for $C_{20}H_{16}N_4O_2 \cdot 1/4H_2O$: C, 68.86; H, 4.77; N, 16.06. Found: C, 69.19; H, 4.70; N, 16.23.

4d: **1b** (1.0 g, 2.66 mmol) was treated as described above to give **4d** (639 mg, 64% yield). Orange-yellow needles, mp 322—324 °C (DMSO). IR (KBr): 1665, 1640, 1620 cm^{-1}. ^1H-NMR (DMSO—d_6) δ: 1.15 (3H, t, $J=7$ Hz), 1.31 (3H, t, $J=8$ Hz), 2.84 (2H, q, $J=7$ Hz), 3.18 (2H, q, $J=8$ Hz), 5.28 (2H, s), 6.78 (2H, s), 7.19 (1H, s), 7.67—7.90 (2H, m), 8.15—8.31 (2H, m), 8.72 (1H, s). MS *m*/*z*: 372 $(M)^+$. *Anal*. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.21; H, 5.51; N, 15.37.

4b: A suspension of **4a** (600 mg, 1.74 mmol) in pyridine (120 ml) and

Table II. Antitumor Activity of **4a**, **4c** (Na Salt) and **6** against L1210 in Mice

Total dose (mg/kg)	Compd. No.		
	4a	**4c**	**6**
3.13	100[a]	89	93
6.25	100	95	89
12.5	100	102	95
25	102	98	89
50	102	98	93
100	100	100	84
200	105	100	91

[a] $T/C\%$ = (mean survival time of the tested animals)/(mean survival time of the control animals) × 100. Values of $T/C \geq 125\%$ are evaluated as active compound.

Table III. Fractional Atomic Coordinates and Isotopic Thermal Parameters of Compound **4a**

Atom	x	y	z	B_{eq}
N(1)	−0.0347 (1)	0.5110 (3)	−0.1692 (1)	0.045 (1)
C(2)	−0.0814 (1)	0.5706 (4)	−0.2291 (2)	0.041 (1)
C(3)	−0.1232 (1)	0.4888 (5)	−0.2864 (2)	0.052 (1)
C(4)	−0.1691 (1)	0.5435 (5)	−0.3482 (2)	0.057 (1)
C(5)	−0.1756 (1)	0.6859 (5)	−0.3565 (3)	0.064 (1)
C(6)	−0.1367 (1)	0.7690 (5)	−0.3006 (2)	0.058 (1)
C(7)	−0.0888 (1)	0.7151 (4)	−0.2358 (2)	0.049 (1)
C(8)	−0.0483 (1)	0.7963 (4)	−0.1768 (2)	0.053 (1)
C(9)	−0.0031 (1)	0.7360 (4)	−0.1173 (2)	0.046 (1)
C(10)	0.0016 (1)	0.5937 (4)	−0.1174 (2)	0.041 (1)
C(11)	0.0456 (2)	0.7945 (4)	−0.0471 (3)	0.053 (1)
N(12)	0.0795 (1)	0.6722 (3)	−0.0090 (2)	0.045 (1)
C(13)	0.1317 (1)	0.6768 (4)	0.0561 (2)	0.048 (1)
C(14)	0.1588 (1)	0.5449 (4)	0.0836 (2)	0.043 (1)
C(15)	0.2099 (1)	0.5433 (4)	0.1499 (2)	0.046 (1)
N(16)	0.2357 (1)	0.4260 (3)	0.1801 (2)	0.046 (1)
C(17)	0.2146 (1)	0.2985 (4)	0.1457 (2)	0.045 (1)
C(18)	0.1618 (1)	0.3005 (3)	0.0758 (2)	0.042 (1)
C(19)	0.1334 (1)	0.4207 (3)	0.0450 (2)	0.039 (1)
C(20)	0.0792 (1)	0.4310 (4)	−0.0243 (2)	0.041 (1)
C(21)	0.0545 (1)	0.5534 (3)	−0.0488 (2)	0.040 (1)
O(22)	0.1521 (1)	0.7864 (3)	0.0870 (2)	0.065 (1)
N(23)	0.2904 (1)	0.4297 (4)	0.2466 (2)	0.053 (1)
O(24)	0.2433 (1)	0.1972 (2)	0.1799 (1)	0.057 (1)
C(25)	0.1800 (2)	0.1172 (6)	−0.0199 (3)	0.068 (2)

acetic anhydride (60 ml) was warmed at 50 °C for 2 h with stirring. The mixture was evaporated *in vacuo*, and the residue was recrystallized from n-C_6H_{14}–$CHCl_3$ to give **4b** (720 mg, 97% yield) as yellow needles, mp 241—243 °C. IR (KBr): 1740, 1675, 1635, 1215 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7 Hz), 2.30 (6H, s), 2.84 (2H, q, J=7 Hz), 5.26 (2H, s), 7.20 (1H, s), 7.68—7.92 (2H, m), 8.09—8.25 (2H, m), 8.66 (1H, s), 8.98 (1H, s). MS m/z: 428 $(M)^+$. UV λ_{max}^{MeOH} nm (ε): 210 (34700), 258 (36700), 264 (37800), 294 (29300), 320 (16300), 338 (14300), 354 (12200), 396 (10500), 416 (15100), 440 (11700). *Anal.* Calcd for $C_{24}H_{20}N_4O_4 \cdot 1/4H_2O$: C, 66.58; H, 4.77; N, 12.94. Found: C, 66.62; H, 4.68; N, 13.15.

4c: A suspension of **4b** (120 mg, 0.28 mmol) in MeOH (2 ml) containing 1.0 ml of 1 N NaOH was stirred at room temperature for 10 min. To this mixture, 1 N HCl (2.0 ml) was added and the whole was evaporated under reduced pressure. The residue was washed with water, dried and then recrystallized from 10% MeOH–$CHCl_3$ to give **4c** (106 mg, 98% yield) as yellow needles, mp 333—335 °C. IR (KBr): 3200, 1710, 1675, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7 Hz), 2.11 (3H, s), 2.80 (2H, q, J=7 Hz), 5.20 (2H, s), 7.12 (1H, s), 7.64—7.90 (2H, m), 8.02—8.21 (2H, m), 8.47 (1H, s), 8.60 (1H, s), 11.48 (1H, s). MS m/z: 386 $(M)^+$. UV λ_{max}^{MeOH} nm (ε): 210 (33900), 257 (40200), 262 (39500), 294 (30700), 320 (16600), 338 (15000), 354 (13600), 394 (10500), 412 (14300), 436 (11400). *Anal.* Calcd for $C_{22}H_{18}N_4O_3 \cdot 1/2H_2O$: C, 66.83; H, 4.84; N, 14.17. Found: C, 67.07; H, 4.69; N, 14.56.

The *N*-Amino Lactam 6, General Procedure A solution of **5** (700 mg) in MeOH (70 ml) containing $NH_2NH_2 \cdot H_2O$ (4 ml) was refluxed for 2.5 h. The mixture was evaporated *in vacuo*, and the residue was purified through silica gel column chromatography with 10% MeOH–$CHCl_3$ as the eluent. The fractions containing **6** were combined and evaporated to dryness. The residue was recrystallized from n-C_6H_{14}–$CHCl_3$ to give the title compound as pale yellow needles. The yields are presented in Table I. **6**: mp 228—290 °C. IR (KBr): 3360, 1660, 1650, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.71 (3H, t, J=7 Hz), 1.33 (3H, t, J=8 Hz), 1.78 (1H, dq, J=14, 7 Hz), 1.96 (1H, dq, J=14, 7 Hz), 3.23 (2H, q, J=8 Hz), 4.45 (1H, d, J=18 Hz), 4.56 (1H, d, J=18 Hz), 5.27 (2H, s), 5.33 (2H, s), 6.01 (1H, s), 7.29 (1H, s), 7.70—7.90 (2H, m), 8.17 (1H, d, J=8 Hz), 8.29 (1H, d, J=8 Hz). ^{13}C-NMR (DMSO-d_6) δ: 7.93, 13.99, 22.26, 34.19, 48.93, 49.38, 72.72, 97.50, 119.41, 124.08, 126.56, 127.48, 127.86, 129.89, 129.98, 144.98, 145.59, 148.54, 149.20, 152.19, 157.55, 167.28. MS m/z: 390 $(M)^+$, 361 $(M-29)^+$, 332 $(M-58)^+$. *Anal.* Calcd for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.67; H, 5.61; N, 14.41.

Reaction of 6 with Hydrazine, Yielding 4d **6** (30 mg) was refluxed in $NH_2NH_2 \cdot H_2O$ (3 ml) for 30 min. The mixture was cooled in an ice bath and the precipitate was collected by suction. The pyridone **4d** (24 mg, 84% yield) was obtained.

2c: A suspension of **1b** (1.0 g, 2.66 mmol) in $NH_2NH_2 \cdot H_2O$ (30 ml) was stirred at room temperature for 30 min. The precipitates were collected by suction and dried under reduced pressure. The solid was dissolved in pyridine (30 ml) and acetic anhydride (10 ml) was slowly added to the mixture in an ice-bath, followed by stirring at room temperature for 1 h. The mixture was purified through silica gel column chromatography with 5% MeOH–$CHCl_3$ to give the title compound as a pale yellow solid (800 mg, 61% yield), mp 221—223 °C [EtOH–Et_2O]. IR (KBr): 1710, 1645, 1595, 1255 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7 Hz), 1.32 (3H, t, J=8 Hz), 1.83 (3H, s), 1.99 (3H, s), 2.07—2.29 (2H, m), 3.22 (2H, q, J=8 Hz), 5.30 (2H, s), 5.34 (1H, d, J=11 Hz), 5.40 (1H, d, J=11 Hz), 6.32 (1H, s), 7.50 (1H, s), 7.69—7.89 (2H, m), 8.18 (1H, d, J=8 Hz), 8.28 (1H, d, J=8 Hz), 9.67 (1H, d, J=2 Hz), 9.82 (1H, d, J=2 Hz). MS (SIMS) m/z: 493 $(M+1)^+$. *Anal.* Calcd for $C_{26}H_{28}N_4O_6$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.41; H, 5.76; N, 11.46.

3b: A solution of **1b** (2.0 g, 5.32 mmol) and NaN_3 (450 mg, 6.92 mmol) in *N*,*N*-dimethylformamide (DMF) (200 ml) containing 18-crown-6 (1.82 g) was heated at 120 °C for 4 h under an N_2 atmosphere. The mixture was evaporated to dryness under reduced pressure and the residue was purified through silica gel column chromatography with 1% MeOH–$CHCl_3$ as the eluent. Yield 345 mg, 20%, mp 213—215 °C (EtOH). IR (KBr): 1700, 1650, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.41 (3H, t, J=8 Hz), 2.30 (3H, s), 2.91 (2H, q, J=7 Hz), 3.21 (2H, q, J=8 Hz), 5.26 (2H, s), 7.24 (1H, s), 7.62—7.85 (2H, m), 8.13 (1H, d, J=8 Hz), 8.20 (1H, d, J=8 Hz). MS m/z: 332 $(M)^+$, 317 $(M-15)^+$, 303 $(M-29)^+$, 275 $(M-57)^+$. *Anal.* Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.59; H, 6.11; N, 8.41.

3c: A mixture of **3b** (200 mg, 0.60 mmol) and $NH_2NH_2 \cdot H_2O$ (0.5 ml) in EtOH (20 ml) was refluxed for 24 h. The mixture was evaporated to dryness under reduced pressure, and the residue was purified through silica gel column chromatography using 5% MeOH–$CHCl_3$. **3c**-1 (*syn*-form, 62 mg, 30% yield, TLC: *Rf*=0.28, 5% MeOH–$CHCl_3$), mp 238—241 °C (EtOH). IR (KBr): 3350, 3200, 1650, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.05 (3H, t, J=7 Hz), 1.32 (3H, t, J=8 Hz), 2.01 (3H, s), 2.44 (2H, q, J=7 Hz), 3.22 (2H, q, J=8 Hz), 5.22 (1H, d, J=19 Hz), 5.30 (1H, d, J=19 Hz), 5.65—5.94 (2H, br), 6.84 (1H, s), 7.65—7.88 (2H, m), 8.05—8.30 (2H, m). MS m/z: 346 $(M)^+$, 331 $(M-15)^+$, 330 $(M-16)^+$. *Anal.* Calcd for $C_{21}H_{22}N_4O \cdot 1/4H_2O$: C, 71.87; H, 6.46; N, 15.96. Found: C, 71.99; H, 6.36; N, 15.87. **3c**-2 (*anti*-form, 108 mg, 52% yield, TLC: *Rf*=0.16, 5% MeOH–$CHCl_3$), mp 216—220 °C (EtOH). IR (KBr): 3390, 3210, 1650, 1600, 1585, 1555 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.99 (3H, t, J=8 Hz), 1.32 (3H, t, J=8 Hz), 2.11 (3H, s), 2.58 (2H, q, J=8 Hz), 3.21 (2H, q, J=8 Hz), 5.26 (2H, s), 6.35—6.82 (2H, br), 6.97 (1H, s), 7.65—7.87 (2H, m), 8.07—8.30 (2H, m). Positive differential nuclear Overhauser effect (NOE) was observed between CH_2 of the ethyl group and NH_2 of the hydrazone. MS m/z: 346 $(M)^+$, 331 $(M-15)^+$. *Anal.* Calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.81; H, 6.47; N, 15.95.

Antitumor Activity L1210 leukemia cells (10^5) were implanted intraperitoneally (i.p.) into 7-week-old BDF_1 female mice on day 0. Six mice were used for each dose. The sample was dissolved (**4c** as Na salt) or suspended (**4a** and **6**) in saline and administered i.p. on days 1, 5 and 9. Control mice were injected with saline.

References and Notes

1) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail

and G. A. Sim, *J. Am. Chem. Soc.*, **88**, 3888 (1966).

2) Review; J.-C. Cai and C. R. Hutchinson, "The Alkaloids," Vol. 21, ed. by A. Brossi, Academic Press, New York, 1983, p. 101.

3) *a*) J. A. Adamovics and C. R. Hutchinson, *J. Med. Chem.*, **22**, 310 (1979); *b*) R. P. Hertzberg, M. Jo Caranfa, K. G. Holden, D. R. Jakas, J. O'Leary Bartus, R. K. Johnson and W. D. Kingsbury, *ibid.*, **32**, 715 (1989); *c*) W. D. Kingsbury, *Tetrahedron Lett.*, **29**, 6847 (1988); *d*) A. W. Nicholas, M. C. Wani, G. Manikumar, M. E. Wani, K. W. Kohn and Y. Pommier, *J. Med. Chem.*, **33**, 972 (1990).

4) *a*) Previous papers; S. Sawada, T. Yaegashi, T. Furuta, T. Yokokura and T. Miyasaka, *Chem. Pharm. Bull.*, **41**, 310 (1993); *b*) S. Sawada, K. Nokata, T. Furata, T. Yokokura and T. Miyasaka, *Chem. Pharm. Bull.*, **39**, 2574 (1991); Uehara, H. Baba, M. Takeuchi, T. Yokokura, S. Sawada, T. Miyasaka and M. Mutai, *J. Pharmacobio-Dyn.*, **10**, 481 (1987); H. Nagata, N. Kaneda, T. Furuta, S. Sawada, T. Yokokura, T. Miyasaka, M. Fukuda and K. Notake, *Cancer Treat. Rep.*, **71**, 341 (1987).