Effect of Several *d*-Morphinans on Ascites Tumors in Mice

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Accepted March 27, 1987

Abstract—Dextromethorphan and its analogues (DM 16, DM 34, DM 72, DM 75 and DM 96) were examined for their effect on Ehrlich ascites carcinoma or ascites sarcoma-180 in female mice of the ddY strain. The suspension of Ehrlich carcinoma cells or sarcoma-180 cells was prepared from mice at 10 days after i.p. inoculation of the cells, using Hanks' balanced salt solution, and the cell suspension was inoculated i.p. into mice (2×10^6 viable cells/mouse). The chemicals dissolved in physiological saline containing 5% HCO-60 were then injected i.p. into the mice once daily for 5 successive days (5–40 mg/kg/day). In addition, mice given the tumor cells were treated with the saline containing 5% HCO-60 alone for 5 days (untreated mice). In groups of mice bearing Ehrlich ascites carcinoma or ascites sarcoma-180, the mean survival time of mice treated with 20–40 mg/kg/day of DM 96 was more than twice that of the corresponding untreated mice. The mean survival time of mice treated with 20 mg/kg/day of DM 96 was also longer than that of mice treated with 40 mg/kg/day of the other chemicals, irrespective of the ascites tumors. Concerning these survival times, the LD50 (i.p.) of DM 96 in mice differed slightly from that of other chemicals (88 mg/kg and 77–106 mg/kg). These results indicate that DM 96 is more active than the other chemicals against the ascites tumors in mice.

Recently, certain derivatives of morphine such as naloxone, naltrexone and dextromethorphan have been reported to inhibit the growth of experimental tumors (1–4). However, the antitumor activity of these agents appears to be less potent than that of antitumor drugs used in chemotherapy (5).

Many studies on the derivatives of morphine have established that modifications in the chemical structure of morphine, particularly modifications in the structure of the side chain at the 3rd or 17th position of the morphinan molecule, result in changes in the pharmacological properties; and they indicate that the pharmacological properties of *d*-isomers of morphinan such as dextromethorphan markedly differ from those of *l*-morphinans including morphine, naloxone or naltrexone (6). These facts suggest that there may be some compounds with potent antitumor activity among the derivatives of morphine or dextromethorphan when the

derivatives differ from the known opioid drugs in the structure of the side chain at the 3rd or 17th position of the morphinan molecule.

The present study deals with the effect of several *d*-morphinans, new analogues of dextromethorphan (*d*-3-methoxy-N-methylmorphinan), on Ehrlich carcinoma cells and sarcoma-180 cells in vitro or in vivo.

Materials and Methods

The chemicals used were as follows: dextromethorphan hydrobromide (Nippon Roche Co., Japan), *d*-3-allyloxy-N-methylmorphinan (DM 16), *d*-3-cinnamyloxy-N-methylmorphinan (DM 34), *d*-3-(2,4-pentadienyloxy)-N-methylmorphinan (DM 72), *d*-3-(5-phenyl-2,4-pentadienyloxy)-N-methylmorphinan (DM 75) and *d*-3-(7-phenyl-3-methyl-2,6-heptadienyloxy)-N-methylmorphinan (DM 96) (Table 1). These compounds were dissolved in physiological

Table 1. Structure of dextromethorphan and its analogues

Chemicals	R
Dextromethorphan	CH ₃ -
<i>d</i> -3-Allyloxy-N-methylmorphinan (DM 16)	CH ₂ CH=CH ₂ -
<i>d</i> -3-Cinnamyloxy-N-methylmorphinan (DM 34)	-CH=CHCH ₂ -
<i>d</i> -3-(2,4-Pentadienyloxy)-N-methylmorphinan (DM 72)	CH ₂ =CHCH=CHCH ₂ -
<i>d</i> -3-(5-Phenyl-2,4-pentadienyloxy)-N-methylmorphinan (DM 75)	-CH=CHCH=CHCH ₂ -
<i>d</i> -3-(7-Phenyl-3-methyl-2,6-heptadienyloxy)-N-methylmorphinan (DM 96)	-CH=CHCH ₂ CH ₂ C(CH ₃)=CHCH ₂ -

saline containing 5% HCO-60 (Nikko Chemicals Co., Japan). In addition, cyclophosphamide (Shionogi & Co., Japan) and fluorouracil (Kyowa Hakko Kogyo Co., Ltd., Japan) were used in this study.

The *in vitro* or *in vivo* effect of chemicals on ascites tumor cells was examined as described previously (4). Animals used were 7–8 weeks old female mice of the ddY strain (Shizuoka Laboratory Animal Center, Japan). Ehrlich carcinoma cells or sarcoma-180 cells were obtained from mice at 10 days after *i.p.* inoculation of the cells, and they were suspended in Hanks' balanced salt solution (HBSS) supplemented with 2% bovine albumin fraction V (Armour Pharmaceut. Co., U.S.A.). For testing the *in vitro* effect of chemicals, 20 ml of the tumor cell suspension (2×10^6 cells/ml) in 50-ml test tubes was incubated at 37°C for 120 min in the presence or absence of chemicals, and the proportion of viable tumor cells in the cell suspension was examined by the trypan blue test

thereafter.

The *in vivo* effect of chemicals was examined against Ehrlich ascites carcinoma and ascites sarcoma-180 in mice. Groups of 10 mice each were inoculated *i.p.* with Ehrlich carcinoma cells or sarcoma-180 cells suspended in HBSS without bovine albumin (2×10^6 viable cells/mouse). The *i.p.* injection of chemicals into mice (5–40 mg/kg/day) was begun 24 hr after inoculation of the tumor cells and was continued once daily for 5 successive days. As a control, mice given the tumor cells were treated with the saline containing 5% HCO-60 alone for 5 days (untreated mice). These mice were observed for 60 days. To evaluate the antitumor activity of chemicals, the mean survival time of mice treated with chemicals (T) was compared with that of untreated control mice (C): $T/C (\%) = T/C \times 100$.

In addition, the 50% lethal dose (LD₅₀) of chemicals in mice was examined according to the method of Litchfield and Wilcoxon (7).

Briefly, groups of 8 mice each were injected i.p. with graded doses of chemicals, and their survival was observed for 72 hr. The LD₅₀ (i.p.) of chemicals in mice was then calculated from the number of mice that died within 72 hr and the number of survivors at the respective doses.

Results

First, dextromethorphan and its analogues were examined for their *in vitro* effect on Ehrlich carcinoma cells or sarcoma-180 cells. Tables 2 and 3 show the proportion of viable tumor cells after incubation for 120 min with various concentrations of chemicals.

In Ehrlich carcinoma cells and sarcoma-180 cells, the proportion of viable cells was 80–83% after incubation for 120 min without chemicals. When Ehrlich carcinoma cells or sarcoma-180 cells were incubated with 0.1–1.0 mM of three analogues of dextromethorphan (DM 34, DM 75 and DM 96), the proportion of viable cells was reduced

markedly (less than 1% in both tumor cells). The incubation of these tumor cells with 1.0 mM of DM 16, DM 72 or dextromethorphan also resulted in a significant decrease in the proportion of viable cells (less than 1% in Ehrlich cells and 1–24% in sarcoma-180 cells). However, the change in the proportion of viable cells was only slight in Ehrlich carcinoma cells and sarcoma-180 cells when these tumor cells were incubated with 0.1 mM of DM 16, DM 72 or dextromethorphan (52–64% in Ehrlich cells and 66–79% in sarcoma-180 cells). Thus, it is apparent that DM 34, DM 75 and DM 96 are more cytotoxic to Ehrlich carcinoma cells or sarcoma-180 cells than dextromethorphan.

In the following experiments, dextromethorphan and its analogues were examined for their *in vivo* effect on Ehrlich ascites carcinoma or ascites sarcoma-180 in mice. Tables 4 and 5 show the mean survival time of mice, which were inoculated with Ehrlich carcinoma cells or sarcoma-180 cells and

Table 2. Proportion of viable Ehrlich carcinoma cells treated with several *d*-morphinans

Chemicals	Proportion of viable tumor cells (%)			
	Concentration of chemicals (mM)			
	1.0	0.1	0.01	0
Dextromethorphan	0.6±0.1	54.2±3.6	78.3±1.8	81.1±0.9
DM 16	0.6±0.3	52.4±2.9	74.3±1.2	81.6±0.8
DM 34	0.1±0.1	0.9±0.4	72.8±2.0	81.4±0.6
DM 72	0.1±0.1	63.8±0.8	77.2±1.7	80.5±1.3
DM 75	0	0.1±0	48.8±1.9	80.7±1.9
DM 96	0	0.2±0.2	78.1±2.8	83.3±1.0

Tumor cells suspended in Hank's balanced salt solution supplemented with 2% bovine albumin were incubated at 37°C for 120 min with various concentrations of chemicals, and the proportion of viable cells was examined thereafter. Each value represents the mean±S.E. of 6 experiments.

Table 3. Proportion of viable sarcoma-180 cells treated with several *d*-morphinans

Chemicals	Proportion of viable tumor cells (%)			
	Concentrations of chemicals (mM)			
	1.0	0.1	0.01	0
Dextromethorphan	23.8±2.9	76.1±2.1	80.6±0.7	81.9±1.1
DM 16	4.7±0.6	78.9±1.4	80.1±1.3	80.4±1.5
DM 34	0	0.5±0.2	76.0±1.2	81.9±1.4
DM 72	0.6±0.2	66.4±1.2	80.1±1.8	82.6±1.3
DM 75	0	0.4±0.2	71.4±1.8	82.4±1.6
DM 96	0	0.2±0.1	80.8±1.4	81.1±1.4

Each value represents the mean±S.E. of 6 experiments.

Table 4. Antitumor effect of several *d*-morphinans on Ehrlich ascites carcinoma in mice

Chemicals	LD50 (i.p.) of chemicals (mg/kg)	Doses of chemicals (mg/kg/day)	No. of survivors at 60 days	Mean survival time of mice (days)	T/C (%)
Dextromethorphan	94	40	0/10	21.8±2.5	119.1
		20	0/10	19.7±1.4	107.7
		10	0/10	19.0±0.7	103.8
		0	0/10	18.3±0.9	
DM 16	104	40	0/10	20.1±2.1	110.4
		20	0/10	18.3±1.3	100.5
		10	0/10	18.4±1.9	101.1
		0	0/10	18.2±2.1	
DM 34	77	40	0/10	33.4±1.7*	184.5
		20	0/10	26.4±2.3*	145.9
		10	0/10	20.4±1.8	112.7
		0	0/10	18.1±1.8	
DM 72	N.D.	40	0/10	20.4±1.2	112.7
		20	0/10	19.7±1.0	108.8
		10	0/10	18.7±1.4	103.3
		0	0/10	18.1±0.8	
DM 75	106	40	0/10	35.0±2.2*	202.3
		20	0/10	28.3±1.4*	163.6
		10	0/10	21.4±1.7	123.7
		0	0/10	17.3±1.0	
DM 96	88	40	2/10	42.2±4.2*	245.3
		20	0/10	35.1±2.5*	204.1
		10	0/10	27.0±2.1*	157.0
		5	0/10	20.5±1.7	118.5
		0	0/10	17.2±1.0	

Chemicals were dissolved in physiological saline containing 5% HCO-60, and tumor cells were suspended in Hanks' balanced salt solution. Mice were inoculated i.p. with tumor cells (2×10^6 viable cells/mouse), and they were injected i.p. with various doses of chemicals once daily for 5 successive days. Mice given tumor cells were also treated with saline containing 5% HCO-60 alone for 5 days (control mice). The survival time of these mice was observed for 60 days. When mice given tumor cells and treated with chemicals survived for 60 days after inoculation of the cells, the survival time of these mice was defined as 60 days. Each value of the survival time represents the mean±S.E. of 10 mice. T/C (%) was calculated from the mean survival time of mice treated with chemicals (T) and that of control animals (C): $T/C (\%) = T/C \times 100$. N.D.: not determined. *Significantly different from the values of control mice ($P < 0.01$).

injected with various doses of chemicals for 5 days.

The mean survival time of untreated mice was 17–18 days for Ehrlich ascites carcinoma and 13–14 days for ascites sarcoma-180, respectively. When mice bearing Ehrlich carcinoma or sarcoma-180 were treated with 20–40 mg/kg/day of DM 96, the mean survival time of these mice was increased pronouncedly (35–42 days for Ehrlich carcinoma and 30–37 days for sarcoma-180)

(Fig. 1). The treatment with 40 mg/kg/day of DM 34 or DM 75 also resulted in a significant increase in the mean survival time of the tumor-bearing mice (33–35 days for Ehrlich carcinoma and 21–23 days for sarcoma-180). On the other hand, there was a slight increase in the mean survival time of mice treated with 40 mg/kg/day of DM 16, DM 72 or dextromethorphan, irrespective of the ascites tumors (20–22 days for Ehrlich carcinoma and 14–17 days for sarcoma-180).

Table 5. Antitumor effect of several *d*-morphinans on ascites sarcoma-180 in mice

Chemicals	LD50 (i.p.) of chemicals (mg/kg)	Doses of chemicals (mg/kg/day)	No. of survivors at 60 days	Mean survival time of mice (days)	T/C (%)
Dextromethorphan	94	40	0/10	17.3±1.9	129.1
		20	0/10	15.4±1.1	114.9
		10	0/10	13.4±0.7	100.0
		0	0/10	13.4±0.6	
DM 16	104	40	0/10	13.7±0.9	106.2
		20	0/10	13.5±1.1	104.7
		10	0/10	13.1±0.8	101.6
		0	0/10	12.9±1.0	
DM 34	77	40	0/10	22.5±1.6*	171.8
		20	0/10	18.0±1.4*	137.4
		10	0/10	14.1±0.8	107.6
		0	0/10	13.1±0.6	
DM 72	N.D.	40	0/10	16.6±1.2	124.8
		20	0/10	15.1±0.8	113.5
		10	0/10	13.8±0.7	103.8
		0	0/10	13.3±1.0	
DM 75	106	40	0/10	20.9±2.4*	167.2
		20	0/10	17.6±1.3*	140.8
		10	0/10	14.4±0.7	115.2
		0	0/10	12.5±1.0	
DM 96	88	40	1/10	37.0±3.0*	270.1
		20	0/10	30.0±3.6*	219.0
		10	0/10	22.3±1.8*	162.8
		5	0/10	16.0±0.7	116.8
		0	0/10	13.7±1.0	

Mice given tumor cells i.p. (2×10^6 viable cells/mouse) were injected i.p. with various doses of chemicals once daily for 5 successive days, and their survival time was observed for 60 days. When mice given tumor cells and treated with chemicals survived for 60 days after inoculation of the cells, the survival time of these mice was defined as 60 days. Each value of the survival time represents the mean $\pm$ S.E. of 10 mice. T/C (%) was calculated as described in Table 4. N.D.: not determined. *Significantly different from the values of control mice ($P < 0.01$).

These results indicate that DM 34, DM 75 and DM 96 are effective in prolonging the survival time of the tumor-bearing mice, as compared with dextromethorphan.

In this connection, comparisons were made of the antitumor effect on the ascites tumors in mice among three analogues of dextromethorphan (DM 34, DM 75 and DM 96). In groups of mice bearing Ehrlich ascites carcinoma, the T/C value of mice treated with 10 mg/kg/day of DM 96 was nearly equal to that of mice treated with 20 mg/kg/day of DM 34 or DM 75 (T/C: about 160% and 150–160% respectively), and the

T/C value of mice treated with 20 mg/kg/day of DM 96 was similar to that of animals treated with 40 mg/kg/day of the other analogues (T/C: about 200% and 180–200% respectively) (Table 4). In groups of mice bearing ascites sarcoma-180, there was a slight difference in the T/C values between mice treated with 10 mg/kg/day of DM 96 and animals treated with 40 mg/kg/day of DM 34 or DM 75 (T/C: about 160% and about 170%, respectively) (Table 5). These strongly suggest that DM 96 is more active than DM 34 and DM 75 against Ehrlich ascites carcinoma or ascites sarcoma-180

Fig. 1. Changes in the body weight of mice given tumor cells and treated with DM 96. DM 96 was dissolved in physiological saline containing 5% HCO-60, and tumor cells were suspended in Hanks' balanced salt solution. Groups of 10 mice each were inoculated i.p. with Ehrlich carcinoma cells (A) or sarcoma-180 cells (B), and these mice were injected i.p. with 20 ($\blacktriangle$) or 40 ($\bullet$) mg/kg/day of DM 96 once daily for 5 successive days. As a control, mice given the tumor cells were treated with the saline containing 5% HCO-60 alone for 5 days ($\circ$). Each value represents the mean of 2–10 mice.

Fig. 2. T/C (%) in groups of mice given tumor cells and treated with DM 34, DM 75 or DM 96. Mice receiving Ehrlich carcinoma cells or sarcoma-180 cells were injected i.p. with various doses of DM 34 ($\blacktriangle$), DM 75 ($\bullet$) or DM 96 ($\circ$) once daily for 5 successive days. As a control, mice given the tumor cells were treated with the saline containing 5% HCO-60 alone for 5 days. T/C (%) was calculated from the mean survival time of mice treated with chemicals (T) and that of control animals (C), as described in Table 4.

(Fig. 2).

Concerning the above experiments, the LD50 (i.p.) of dextromethorphan and its analogues in mice was examined by the method of Litchfield and Wilcoxon. As can be seen in Table 4 or 5, the LD50 (i.p.) of DM 75 and DM 96 was similar to that of dextromethorphan. Thus it appears that DM 75 and DM 96 differ slightly from dextromethorphan in the acute toxicity in mice although there is a marked difference in the antitumor effect between these two analogues and dextromethorphan.

In addition, the antitumor effect of DM 96 on the ascites tumors in mice was compared with that of two antitumor drugs, cyclophosphamide and fluorouracil (Tables 6 and 7). In groups of mice bearing Ehrlich ascites carcinoma or ascites sarcoma-180, the T/C values of mice treated with 20–40 mg/kg/day of DM 96 were larger than those of mice treated with the corresponding doses of cyclophosphamide (T/C: more than 200%

and less than 120% for Ehrlich carcinoma, 220–280% and 170–200% for sarcoma-180, respectively). On the contrary, the T/C values of mice treated with 10–20 mg/kg/day of DM 96 were smaller than those of animals treated with the corresponding doses of fluorouracil, irrespective of the ascites tumors (T/C: 160–220% and 220–310%). Thus it appears that DM 96 is more active than cyclophosphamide against Ehrlich ascites carcinoma and ascites sarcoma-180 in mice, but less active than fluorouracil against these ascites tumors (Fig. 3).

Discussion

The present results clearly indicate that DM 96, an analogue of dextromethorphan, prolongs significantly the survival time of mice bearing Ehrlich ascites carcinoma or ascites sarcoma-180, as compared with dextromethorphan. In groups of mice bearing these ascites tumors, the T/C values of mice treated with 10 and 20 mg/kg/day of DM 96

Table 6. Antitumor effect of DM 96, cyclophosphamide or fluorouracil on Ehrlich ascites carcinoma in mice

Chemicals	Doses of chemicals (mg/kg/day)	No. of survivors at 60 days	Mean survival time of mice (days)	T/C (%)
DM 96	40	5/20	41.3±2.0*	241.5
	20	2/20	35.1±2.8*	205.3
	10	0/20	28.1±1.4*	164.3
	5	0/20	20.2±0.9	118.1
	0	0/20	17.1±1.1	
Cyclophosphamide	40	0/20	21.3±1.1	113.9
	20	0/20	18.4±1.2	98.4
	10	0/20	18.4±1.1	98.4
	5	0/20	19.1±1.2	102.1
	0	0/20	18.7±0.9	
Fluorouracil	40	3/20	28.7±3.3*	144.9
	20	12/20	52.4±2.3*	264.5
	10	7/20	44.5±3.6*	224.7
	5	3/20	38.3±3.0*	193.4
	2.5	1/20	29.8±1.7*	150.5
	0	0/20	19.8±1.6	

Mice given tumor cells i.p. (2×10^6 viable cells/mouse) were injected i.p. with various doses of chemicals once daily for 5 successive days, and their survival time was observed for 60 days. When mice given tumor cells and treated with chemicals survived for 60 days after inoculation of the cells, the survival time of these mice was defined as 60 days. Each value of the survival time represents the mean±S.E. of 20 mice. T/C (%) was calculated as described in Table 4. *Significantly different from the values of control mice ($P < 0.01$).

were about 160% and 200–220%, respectively, whereas the T/C values of mice treated with 40 mg/kg/day of dextromethorphan were less than 130%. On the other hand, the

Table 7. Antitumor effect of DM 96, cyclophosphamide or fluorouracil on ascites sarcoma-180 in mice

Chemicals	Doses of chemicals (mg/kg/day)	No. of survivors at 60 days	Mean survival time of mice (days)	T/C (%)
DM 96	40	2/20	38.4±2.5*	280.3
	20	1/20	30.6±2.4*	223.4
	10	0/20	22.9±1.3*	167.2
	5	0/20	15.1±1.0	110.2
	0	0/20	13.7±0.8	
Cyclophosphamide	40	0/20	25.8±1.2*	201.6
	20	0/20	21.2±0.8*	165.6
	10	0/20	17.0±0.9*	132.8
	5	0/20	14.4±0.6	112.5
	0	0/20	12.8±0.6	
Fluorouracil	40	1/20	31.2±3.1*	213.7
	20	7/20	44.8±2.8*	306.8
	10	3/20	37.0±3.0*	253.4
	5	0/20	27.1±2.7*	185.6
	2.5	0/20	18.6±1.3*	128.0
	0	0/20	14.6±0.6	

Each value of the survival time represents the mean±S.E. of 20 mice. T/C (%) was calculated as described in Table 4. *Significantly different from the values of control mice ($P<0.01$).

Fig. 3. T/C (%) in groups of mice given tumor cells and treated with DM 96, cyclophosphamide or fluorouracil. Mice receiving Ehrlich carcinoma cells or sarcoma-180 cells were injected i.p. with various doses of DM 96 (○), cyclophosphamide (▲) or fluorouracil (●) once daily for 5 successive days. As a control, mice given the tumor cells were treated with the saline containing 5% HCO-60 alone for 5 days. T/C (%) was calculated from the mean survival time of mice treated with chemicals (T) and that of control animals (C), as described in Table 4.

LD50 (i.p.) of DM 96 in mice was similar to that of dextromethorphan (LD50: 88 mg/kg and 94 mg/kg, respectively). Therefore, it may be concluded that DM 96 exhibits a strong antitumor effect on Ehrlich ascites carcinoma and ascites sarcoma-180 in mice, as compared with dextromethorphan.

The present results also show that DM 96 differs markedly from dextromethorphan in the cytotoxicity on Ehrlich carcinoma cells or sarcoma-180 cells *in vitro*. A significant decrease in the proportion of viable cells was observed in the tumor cells treated with 0.1 mM of DM 96, but not in the tumor cells treated with 0.1 mM of dextromethorphan (proportion of viable tumor cells after the 120-min incubation with these agents: less than 0.5% and more than 50%, respectively).

In this connection, the incubation of Ehrlich carcinoma cells or sarcoma-180 cells at 37°C for 120 min with 0.1–1.0 mM of DM 96 resulted in degenerative changes such as cell swelling and vesiculation of the cytoplasm in the cells, followed by cell lysis. Thus, DM 96 appears to be lytic to these tumor cells *in vitro*, although the mechanism responsible for the antitumor activity of DM 96 remains to be elucidated.

Chemically, DM 96 differs from dextromethorphan in the structure of the side chain at the 3-position of the morphinan molecule. Differences in the chemical structure between dextromethorphan and DM 96 can be summarized as follows: The presence or absence of a phenyl radical in the side chain and the difference in the chain length. Concerning these, many *d*-morphinans without a phenyl radical in the side chain at the 3-position, such as DM 16 or DM 72, had little or a slight effect on the survival time of mice bearing Ehrlich ascites carcinoma or ascites sarcoma-180; and several *d*-morphinans, which differ from dextromethorphan in the structure of the side chain at the 17-position of the morphinan molecule, showed no antitumor effect on these ascites tumors in mice (data not presented). In *d*-morphinans, therefore, the antitumor activity may be closely related to the chemical structure of the side chain at the 3-position.

Comparative studies on the antitumor activity between DM 96 and two antitumor

drugs, cyclophosphamide and fluorouracil, indicated that DM 96 is more active than cyclophosphamide against Ehrlich ascites carcinoma or ascites sarcoma-180 in mice, but less active than fluorouracil against these ascites tumors. The LD50 (i.p.) of these antitumor drugs in mice was reported to be about 440 mg/kg for cyclophosphamide and about 240 mg/kg for fluorouracil, respectively (8). On the other hand, the LD50 (i.p.) of DM 96 in mice was 88 mg/kg, as described above. Thus it appears that the margin of safety between the effective and toxic dose of DM 96 is smaller than that of cyclophosphamide or fluorouracil. Nevertheless, it might be of great interest that DM 96, an analogue of dextromethorphan, exhibits a strong antitumor activity against ascites tumors in mice, because the chemical structure of DM 96 is quite different from those of known antitumor drugs such as cyclophosphamide or fluorouracil.

Acknowledgment: The authors thank Dr. K. Mita and Mr. Y. Ueda, Toyo Pharmar Co., Ltd., for synthesizing the analogues of dextromethorphan, and we would like to thank Ms. N. Yamada for secretarial assistance.

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