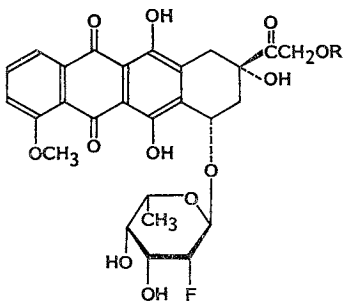
SYNTHESIS AND ANTITUMOR ACTIVITIES OF 14-*O*-ACYL DERIVATIVES OF 7-*O*-(2,6-DIDEOXY-2-FLUORO-α-L-TALOPYRANOSYL) ADRIAMYCINONE

Sir:

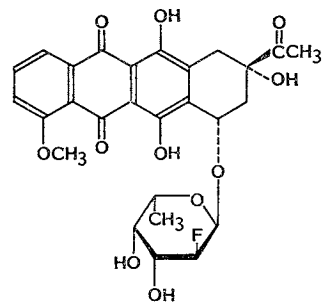
Doxorubicin is a clinically important antitumor antibiotic but its use (especially for the long-term use) is restricted by the cardiotoxicity and other undesirable side effects. In previous papers,[1,2] we reported the synthesis of a new fluorine-containing anthracycline glycoside, 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone (**1**) which exhibits strong antitumor activity and weak toxicity[1]. These desired characteristics of **1** may be, in portion, due to the presence of the 2′-fluoro atom which strengthens the glycoside bond. However, the 2′-epifluoro derivative† (**2**) showed no antitumor activity, suggesting the importance of the disposition of the fluoro atom as well. The fluoro compound (**1**), however, is sparingly soluble in water due to the lack of the 3′-amino group of doxorubicin, thus limiting its effectiveness for intravenous administration.

To increase the solubility of **1**, one possible device would be attachment of a hydrophilic group at the 14-OH. Water-soluble sodium salt of the 14-*O*-sulfuric hemiester†† (**3**) of **1** was thus prepared, but this compound was found to be devoid of activity. ISRAEL *et al.*[3] prepared *N*-trifluoroacetyladriamycin 14-valerate, more effective and less toxic than doxorubicin at more than a 10-fold greater dose than that of doxorubicin, but this compound was sparingly soluble in water. Then they prepared the water-soluble 14-hemiadipate[4] (soluble *ca.* 60 mg/ml in buffered water of pH 7.4) retaining the antitumor activity and low toxicity similar to the 14-valerate. In this paper we wish to report the preparation, solubility and activity of 14-hemisuccinate (**4**), -hemiglutarate (**5**), -hemiadipate (**6**), -hemipimelate (**7**), and -hemisuberate (**8**) of the compound **1**.

A solution of 14-bromo-7-*O*-(2,6-dideoxy-2-fluoro-3,4-*O*-isopropylidene-α-L-talopyranosyl)-daunomycinone[1,2] (**9**, 100 mg) and the mono sodium salt of pimelic acid (490 mg) in Me_2CO - water (4 : 1, 12 ml) was stirred for 14 hours at room temp. After evaporation, the residue was extracted with $CHCl_3$. The solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel with benzene - Me_2CO (5 : 1) to give a red solid of the 3′,4′-*O*-isopropylidene-14-hemipimelate, 72 mg (65% based on **9**), $[\alpha]_D^{25}$ +64° (*c* 0.13, $CHCl_3$), *m/z* 745 $(M+1)^+$. A solution of the product (60 mg) in AcOH - water (4 : 1, 6 ml)



1 R=H
3 R=SO_3Na
4 R=$CO(CH_2)_2COOH$
5 R=$CO(CH_2)_3COOH$
6 R=$CO(CH_2)_4COOH$
7 R=$CO(CH_2)_5COOH$
8 R=$CO(CH_2)_6COOH$



2

† A part of this was read by H. UMEZAWA at the 14th Maxwell Finland Lecture at Harvard Medical School in Boston, Massachusetts, Apr. 16, 1986 (Reviews of Infectous Deseases, Vol. 9, No. 1 pp. 147~164, 1987) and also at the 54th National Meeting of the Chemical Society of Japan, Tokyo, Apr. 4, 1987 (Abstract 4III L17 by Y. TAKAGI, H. KAMINAGA, T. TSUCHIYA, S. UMEZAWA and H. UMEZAWA).

†† TSUCHIYA, T.; Y. TAKAGI, N. KOBAYASHI and S. UMEZAWA: Details will be published elsewhere.

Table 1. Antitumor activities (T/C, %; 60 days survivor numbers/treated numbers of mice) of 14-*O*-acyl (14-*O*-COR) derivatives of 7-*O*-(2,6-dideoxy-2-fluoro-*α*-L-talopyranosyl)adriamycinone in comparison with doxorubicin (DOX) on L1210.

Compound	R		Dose (μg/mouse)								
			2,560	1,280	640	320	160	80	40	20	10
5	$(CH_2)_3COOH$	T/C	>706*	>612	>571	>344	176	129	150	115	
		Survivor	4/4	3/4	3/4	1/4	0/4	0/4	0/4	0/4	
6	$(CH_2)_4COOH$	T/C	>706	>706	>706	>706	>535	129	135	118	
		Survivor	4/4	4/4	4/4	4/4	2/4	0/4	0/4	0/4	
4	$(CH_2)_2COOH$	T/C	>632*	>632*	>632	>632	>463	182	126	118	
		Survivor	4/4	4/4	4/4	4/4	1/4	0/4	0/4	0/4	
8	$(CH_2)_6COOH$	T/C	>221*	>495*	>632*	229	179	182	121	113	
		Survivor	1/4	3/4	4/4	0/4	0/4	0/4	0/4	0/4	
7	$(CH_2)_5COOH$	T/C	>581	>686	>686	>587	>375	187	142	123	117
		Survivor	4/5	5/5	5/5	4/5	2/5	0/5	0/5	0/5	0/5
DOX·HCl		T/C			89*	>418*	>311	>359	297	118	
		Survivor			0/5	2/5	1/5	1/5	0/5	0/5	

Leukemia L1210 cells (10^5) were inoculated into CDF_1 mice (20±1 g) intraperitoneally. Drugs were administered day 1 only, 24 hours after inoculation, intraperitoneally. DOX was dissolved in saline and other compounds were dissolved in 0.05 M KH_2PO_4 - NaOH (pH 7.4).

* Toxic.

Table 2. Antitumor activities (T/C, %; 60 days survivor numbers/treated numbers of mice) of **7** and doxorubicin (DOX) on L1210.

Injection (route)	Compound		Dose (μg/mouse/day)									
			2,560	1,280	640	320	160	80	40	20	10	5
Once (iv)[b]	**7**	T/C	>676[a]	>539	>450	306	169	117	110	114	123	
		Survivor	5/5	3/5	2/5	0/5	0/5	0/5	0/5	0/5	0/5	
	DOX·HCl	T/C			>569[a]	>341	146	114	110	110		
		Survivor			4/5	1/5	0/5	0/5	0/5	0/5		
3 times (ip)[c]	**7**	T/C			>657	>657	>563	>432	245	114	116	103
		Survivor			5/5	5/5	4/5	1/5	0/5	0/5	0/5	0/5
	DOX·HCl	T/C				112[a]	254[a]	>462	261	193	140	
		Survivor				0/5	0/5	3/5	0/5	0/5	0/5	
3 times (iv)[c]	**7**	T/C			>657	>548	230	138	101	101	99	96
		Survivor			5/5	3/5	0/5	0/5	0/5	0/5	0/5	0/5
	DOX·HCl	T/C				153[a]	283	142	110	103	101	
		Survivor				0/5	0/5	0/5	0/5	0/5	0/5	

Leukemia L1210 cells (10^5) were inoculated into CDF_1 mice (20 ± 1 g) intraperitoneally. DOX was dissolved in saline and **7** was dissolved in 0.05 M KH_2PO_4 - NaOH (pH 7.4).

[a] Toxic.

[b] Drugs were administered once, 24 hours after the inoculation of cells.

[c] Drugs were administered 3 times on day 1 (after 24 hours), 5, and 9.

was heated at 70°C for 40 minutes (to remove the isopropylidene group). After evaporation, the residue was chromatographed on a column of silica gel with $CHCl_3$ - MeOH (10:1) to give red crystals of **7**, 46 mg (81%): MP 201~203°C; $[\alpha]_D^{25}$ +161° (*c* 0.056, $CHCl_3$ - MeOH, 1:1); MS *m/z* 704 (M^+). Other compounds were prepared similarly. Compound **4**: Yield 51% based on **9**; $[\alpha]_D^{25}$ +121° (*c* 0.062); MS *m/z* 662 (M^+), **5**: 46%; $[\alpha]_D^{25}$ +139° (*c* 0.035); MS *m/z* 676 (M^+), **6**: 54%; $[\alpha]_D^{25}$ +135° (*c* 0.069); MS *m/z* 691 $(M+1)^+$, **8**: 56%; $[\alpha]_D^{25}$ +121° (*c* 0.12); MS *m/z* 718 (M^+). Optical rotations were all measured in $CHCl_3$ - MeOH (1:1). Except for **7**, the products were not crystallized.

All compounds (**4**, **5**, **6**, **7** and **8**) showed good solubility in water (25~33 mg/ml in 0.05 M KH_2PO_4 - NaOH at pH 7.4 at room temp; **1**: less than 1 mg/ml). Their antitumor activities are shown in Tables 1 and 2. All compounds showed excellent activities against murine L1210 leukemia with lower toxicities than those of doxorubicin. Importantly, compound **7** proved effective in L1210 by the intravenous route of administration, being at least as effective as doxorubicin over 5 very broad effective range.

Acknowledgments

The present work was supported in part by the Grant-in-Aid for Cancer Research No. 62015093 from the Ministry of Education, Science and Culture, Japan, and that for Cancer Research (61-21) from the Ministry of Health and Welfare.

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(Received January 22, 1988)

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† Deceased.