SYNTHESES AND ANTITUMOR ACTIVITIES OF 7-*O*-(2,6-DIDEOXY-2-FLUORO-α-L-TALOPYRANOSYL)-DAUNOMYCINONE AND -ADRIAMYCINONE

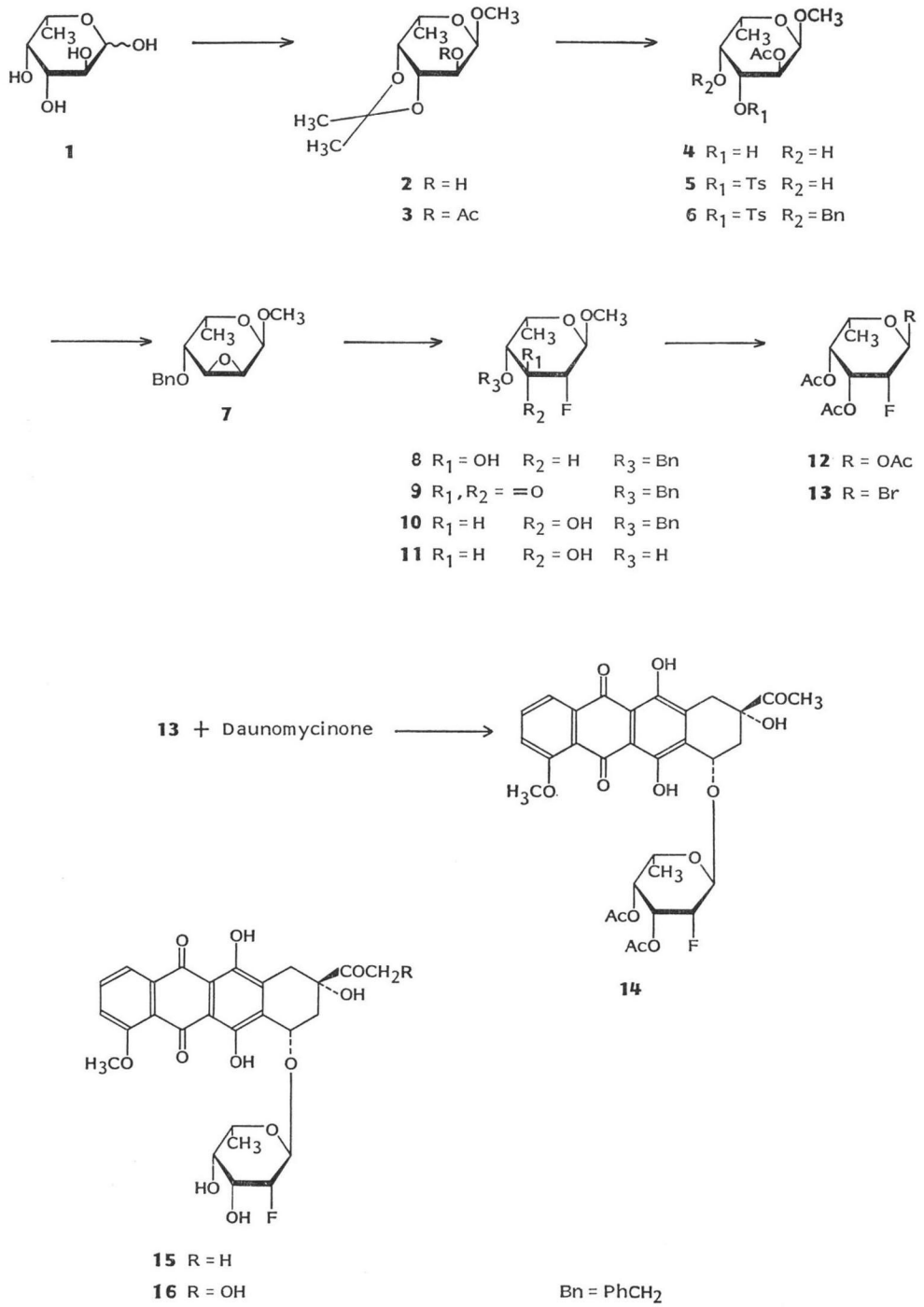
Sir:

Daunorubicin (daunomycin) and doxorubicin (adriamycin) are clinically important anthracycline antitumor antibiotics but their use is restricted by their cardiotoxic and other undesirable side-effects. In 1975 we reported[1] on the aclacinomycins obtained by fermentation consisting of aklavinone and a chain of three sugars which showed considerable antitumor activity, and in 1979, on the semi-synthetic 4′-(*O*-tetrahydropyranyl)daunorubicins and -doxorubicins, which were highly active with low toxicity.[2] 4-Demethoxy-11-deoxy analogs of daunorubicin and doxorubicin were also prepared.[3] In this paper we report on fluorine-containing analogs of daunorubicin and doxorubicin.

Since aglycones of anthracycline antibiotics which are produced as metabolites during medical treatment have no antitumor activity, strengthening of the glycosidic linkage to make it more resistant to hydrolysis is anticipated to be important in creating highly effective drugs. 2-Fluoroglycosides, on the other hand, are known to resist chemical hydrolysis on account of the strongly electron-attracting property of the fluorine atom at C-2. We therefore undertook to prepare anthracycline derivatives having a fluorine atom at the C-2′. HORTON *et al.*[4~6] reported that the replacement of the 3′-amino group of daunorubicin and doxorubicin with a hydroxyl group gave, unexpectedly, derivatives having strong antitumor activity with weak cardiotoxicity; this led us to prepare daunorubicin and doxorubicin analogs having a 2-fluorinated neutral sugar, 2,6-dideoxy-2-fluoro-α-L-talopyranose. During our synthesis, HORTON *et al.*[7,8] reported a stimulating study along the same lines, the preparation of anthracycline derivatives having 2-iodo neutral sugars.

2,6-Dideoxy-2-fluoro-L-talopyranose derivative (**13**) has been prepared from L-fucose (**1**) *via* 13 steps. Treatment of **1** with 1% HCl - MeOH (reflux, 8 hours) gave a mixture of methyl glycosides, which, on acetonation (2,2-dimethoxypropane, TsOH, in DMF) gave, after chromatography, the α-L-isomer (**2**, 59%), $[\alpha]_D^{26}$ −147° ($CHCl_3$). After acetylation (Ac_2O - pyridine), the 2-*O*-acetyl derivative (**3**) [mp 101~102°C, ^1H NMR ($CDCl_3$) δ 2.14 (s, Ac)] was deacetonated, and the diol (**4**) was selectively tosylated to give the 3-*O*-tosyl derivative (**5**, 76% from **2**), mp 118~120°C, ^1H NMR ($CDCl_3$) δ 1.79 (s, Ac), 2.45 (s, Ts). After benzylation of **5** with $Cl_3CC(=NH)OCH_2Ph$[9] (in cyclohexane - CH_2Cl_2 in the presence of CF_3SO_3H), the 4-*O*-benzyl derivative (**6**, 83%) was converted (with MeONa - MeOH) to 2,3-anhydro derivative (**7**, 62%). Ring opening of **7** with KHF_2 (180°C, 3 hours, in ethyleneglycol) gave the 2-fluoro derivative (**8**, 44%). $[\alpha]_D^{26}$ −62° ($CHCl_3$), ^1H NMR ($CDCl_3$) δ 4.80 (1H, dd, H-1), 4.32 (1H, dddd, H-2); $J_{H-1,F}$ 9, $J_{H-2,F}$ 48, and $J_{H-3,F}$ 11 Hz. Oxidation of **8** (DMSO - C_6H_6 - pyridine, dicyclohexylcarbodiimide, in the presence of pyridinium trifluoroacetate) gave the 3-oxo derivative (**9**, 79%), mp 63~64°C (needles), which, on reduction with $LiAlH_4$ (in oxolane, −30°~0°C), led to the corresponding α-L-talopyranoside (**10**, syrup, 82%), ^1H NMR ($CDCl_3$) δ 4.90 (1H, dd, H-1), 4.45 (1H, dddd, H-2); $J_{H-1,F}$ 9, $J_{H-2,F}$ 49.5, and $J_{H-3,F}$ 31.5 Hz. Catalytic debenzylation (H_2-Pd black, in 1,4-dioxane - AcOH - H_2O, 10: 1: 1, to give **11**) followed by acetylation (Ac_2O - H_2SO_4, 1: 0.03 in CH_3NO_2, room temp) gave 1,3,4-tri-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranose (**12**, 84%), mp 102~103°C, ^1H NMR ($CDCl_3$) δ 6.33 (1H, dd, H-1), 4.55 (1H, dddd, H-2), 2.10, 2.14, and 2.18 (each s, Ac); $J_{H-1,F}$ 8, $J_{H-2,F}$ 48.5, $J_{H-3,F}$ 32 Hz. Finally bromination of **12** ($TiBr_4$, in CH_2Cl_2 - EtOAc, 10: 1, room temp) gave the 1-bromide (**13**, syrup, 94%).

Coupling of **13** with daunomycinone was carried out by the KOENIGS-KNORR reaction [HgO(yellow) - $HgBr_2$, in CH_2Cl_2] to give **14** as a red solid (82%), mp 144~146°C, $[\alpha]_D^{26}$ +211° (*c* 0.036, $CHCl_3$). Deprotection of **14** (0.2 N aq NaOH, 0°C, 30 minutes) gave 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**15**) as a powder (72%), $[\alpha]_D^{25}$ +197° (*c* 0.02, $CHCl_3$ - MeOH, 1: 1), ^1H NMR (pyridine-d_5) δ 6.02 (1H, br d, H-1′), 5.16 (1H, br d, H-2′), 4.26 (1H, dt, H-3′), 2.57 (3H, s, H-14); $J_{H-1',F}$ 10, $J_{H-2',F}$ 50, and $J_{H-3',F}$ 34.5 Hz. Finally bromination of **15** at C-14 according basically to ARCAMONE[10] (to **15** in MeOH - 1,4-dioxane, 1: 1.5 was added Br_2 in CH_2Cl_2 in the presence of methyl orthoformate, 0°C to room temp, 1.5 hours) followed by substitution of the



bromine with a hydroxyl group (HCOONa in aq acetone) gave **16** as a red powder (56%), $[\alpha]_D^{25}$ +194° (*c* 0.01, $CHCl_3$ - MeOH, 1:1), ^1H NMR ($CDCl_3$ - CD_3OD, 1:1) δ 5.56 (1H, br d, H-1′), 4.75 (2H, s, CH_2OH), 4.55 (1H, br d, H-2′), 3.72 (1H, dt, H-3′); $J_{H-1',F}$ 10, $J_{H-2',F}$ 49, and $J_{H-3',F}$ 34 Hz. As shown in Table 1, **16** showed strong antitumor activity and decreased toxicity in comparison to doxorubicin. Further study on its usefulness in cancer treatment is

Table 1. Antitumor activities (T/C, %) of **15** and **16** in comparison with daunorubicin (DM) and doxorubicin (ADM) on L1210.

Compound	Dose (μg/mouse/day)					
	100	50	25	12.5	6.25	3.13
DM·HCl	138*	171*	158	145	112	132
15	184	217	171	125	105	105
ADM·HCl	191*	228	222	142	136	123
16	>740	>352	275	185	182	127

Leukemia L1210 cells (10^5) were inoculated into CDF_1 mice (20 ± 1 g) intraperitoneally. Drugs were administered daily, starting 24 hours after inoculation, from day 1 to 9, intraperitoneally. Survival studies were continued up to 60 days.

* Toxic.

now underway.

Stability against acid hydrolysis of **15** was examined: **15** resisted to 1 N HCl in CH_3CN - H_2O (4: 1) at 60°C for 8 hours, whereas daunorubicin was completely hydrolyzed in weaker conditions (0.2 N HCl in CH_3CN - H_2O, 4: 1, 60°C, 30 minutes). Clarification of the relationship between chemical stability and antitumor activity (and toxicity) will be the subject of future studies.

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