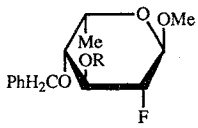
SYNTHESES AND ANTITUMOR ACTIVITIES OF 7-*O*-(3-AMINO-2,3,6-TRIDEOXY-2-FLUORO-α-L-TALOPYRANOSYL)DAUNOMYCINONE AND -ADRIAMYCINONE

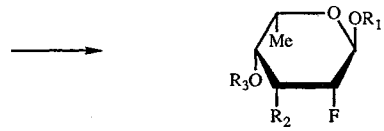
Sir:

Daunorubicin (daunomycin; DNR) and doxorubicin (adriamycin; DOX) are clinically important anthracycline antitumor antibiotics but their use is restricted by their cardiotoxic character and other undesirable side-toxicities, as well as by the occurrence of resistance in the tumor cells after repeated medication. Recently we reported the synthesis of a new fluorine-containing anthracycline glycoside, 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone (**7**)[1,2] and its 14-*O*-acyl derivatives[3]; all of them showed strong antitumor activity with broad effective dose ranges and weak toxicity. Recently 2′-fluoro analogs of DNR have gained attention in several groups[4,5]. As our compounds (**7** and its derivatives) have a 2′-(*R*)-fluoro atom and a 3′-hydroxyl group instead of the 2′-deoxy and 3′-amino groups in usual anthracycline antibiotics, synthesis and evaluation of the biological activities of analogs with 2′-fluoro and 3′-amino substituents were prompted. In this paper we describe the synthesis and biological activities of (*R*)-2′-fluorodaunorubicin (**10**), (*R*)-2′-fluorodoxorubicin (**11**) and its 3′-morpholino derivative (**12**).

1,4-Di-*O*-acetyl-2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-α-L-talopyranose (**6**) has been prepared from methyl 4-*O*-benzyl-2,6-dideoxy-2-fluoro-α-L-idopyranoside (**1**)[1,2] *via* 5 steps. Compound **1** was converted (with $(CF_3SO_2)_2O$ in pyridine - CH_2Cl_2) to the 3-triflate (**2**, syrup, 96%), which, on S_N2 displacement with LiN_3 (in DMF, 90°C) afforded 3-azido derivative (**3**, 78%) with L-*talo* configuration: $[\alpha]_D^{23}$ −18° ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.88 (1H, dd, 1-H), 4.68 (1H, dddd, 2-H), 3.33 (1H, dt, 3-H); $J_{1\text{-}H,F}$=9 Hz, $J_{2\text{-}H,F}$=49 Hz and $J_{3\text{-}H,F}$=34 Hz. Simultaneous debenzylation and reduction of the azido group by catalytic hydrogenation (H_2 - Pd black, in 1,4-dioxane - AcOH - H_2O, 5 : 1 : 1) gave methyl (*R*)-2-fluoro-α-L-daunosaminide (**4**, 62% as hydrochloride): $[\alpha]_D^{23}$ −105° (MeOH). After the amino group of **4** was protected with ethyl trifluoroacetate[6] (in DMF in the presence of Na_2CO_3), the *N*-trifluoroacetate (**5**, 91%: MP 117~118.5°C (prisms); $[\alpha]_D^{23}$ −77° ($CHCl_3$)) was acetylated (Ac_2O - H_2SO_4, 1 : 0.003, in $MeNO_2$) to give the 1,4-diacetate (**6**, 91%): MP 149~150°C; $[\alpha]_D^{23}$ −120° ($CHCl_3$); ^1H NMR ($CDCl_3$, ^{19}F broad band decoupled) δ 6.33 (1H, d, 1-H), 4.58 (1H, dt, 3-H), 4.52 (1H, m, 2-H), 2.19 and 2.16 (each s, Ac); $J_{1,2}$=~1.5 Hz, $J_{2,3}$=$J_{3,4}$=3.5 Hz and $J_{3,NH}$=8.5 Hz.

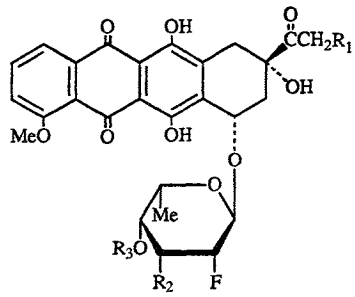
Coupling of **6** with daunomycinone was carried out basically under the condition reported by KIMURA *et al.*[7] (trimethylsilyl triflate and Molecular Sieves 4A in CH_2Cl_2 - Et_2O, reflux) to give the α-L-isomer (**8**, 36%), a red solid: $[\alpha]_D^{23}$ +212° (*c* 0.05, acetone). Mild alkaline hydrolysis of





1 R=H
2 R=SO_2CF_3

3 R_1=Me R_2=N_3 R_3=CH_2Ph
4 R_1=Me R_2=NH_2 R_3=H
5 R_1=Me R_2=$NHCOCF_3$ R_3=H
6 R_1=Ac R_2=$NHCOCF_3$ R_3=Ac



7 R_1 = R_2 = OH R_3 = H
8 R_1 = H R_2 = $NHCOCF_3$ R_3 = Ac
9 R_1 = R_3 = H R_2 = $NHCOCF_3$
10 R_1 = R_3 = H R_2 = NH_2
11 R_1 = OH R_2 = NH_2 R_3 = H
12 R_1 = OH R_2 =  R_3 = H

Table 1. Antitumor activities (T/C, %) of **10**, **11** and **12** in comparison with DNR and DOX on L1210.

Compound[a]	T/C (%)										
	Dose (μg/mouse/day)										
	100	50	25	12.5	6.25	3.13	1.56	1.00	0.50	0.25	0.125
10	174*	200*	222	140	133	117					
11	97*	187*	168*	203	135	123					
12		22*	25*	33*	33*	49*	53*	73*	144	124	115
DNR	117*	151*	193	166	133	130					
DOX	177*	273*	330	208	132	140					

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.

* Toxic.

[a] Hydrochloride.

Table 2. Growth inhibitory effect of **11** and **12** in comparison with DOX on P388/S and P388/ADM cells *in vitro*[a].

Compound	IC_{50} (ng/ml)		RF[b]
	P388/S	P388/ADM	
11	3.4	113	33
12	1.8	2.2	1.2
DOX	15.7	1,406	90

[a] IC_{50} values were determined on day-3 culture.

[b] Resistant factor (RF): IC_{50} for resistant subline/IC_{50} for sensitive subline.

8 (0.05 N NaOH in aq MeOH, 1:1, 3°C) gave the *N*-trifluoroacetyl derivative (**9**, 52%): $[\alpha]_D^{23}$ +222° (*c* 0.1, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ (downfield from internal $CFCl_3$) −76.4 (s, $COCF_3$), −197.3 (ddd, F-2′, J=10, 33.5 and 49 Hz); hydrolysis with 0.1 N NaOH in aq MeOH, 1:1, at 16°C afforded fully deprotected (*R*)-2′-fluorodaunorubicin (**10**, 52% as hydrochloride) as a red solid: $[\alpha]_D^{22}$ +192° (*c* 0.05, MeOH); ^1H NMR (10 mg in CD_3OD (0.5 ml); chemical shifts were considerably influenced by concentration of the solution) δ 5.51 (1H, br d, 1′-H), 4.67 (1H, br d, 2′-H), 3.63 (1H, dt, 3′-H), 2.37 (3H, s, 14-CH_3); $J_{1'\text{-H,F}}$=10 Hz, $J_{2'\text{-H,F}}$=49 Hz and $J_{3'\text{-H,F}}$=33 Hz. Transformation of 14-CH_3 of **10** into hydroxymethyl group by a 3 step reaction sequence ((i) Br_2, $HC(OMe)_3$ in CH_2Cl_2 - MeOH - 1,4-dioxane, 0°C to room temperature; (ii) acetone; (iii) HCOONa in aq acetone) according, basically, to ARCAMONE *et al.*[8] gave (*R*)-2′-fluorodoxorubicin (**11**, 54% as hydrochloride), a red solid: $[\alpha]_D^{22}$ +193° (*c* 0.05, MeOH); ^1H NMR (5 mg in CD_3OD (0.5 ml)) δ 5.54 (1H, br d, 1′-H), 4.73, center of an ABq (2H, CH_2OH), 4.66 (1H, br d, 2′-H). The morpholino derivative (**12**, 54%) was obtained by treatment of **11** with $(ICH_2CH_2)_2O$ and Et_3N in DMF[9], a red solid: $[\alpha]_D^{22}$ +188° (*c* 0.1, $CHCl_3$); ^1H NMR (6.5 mg in $CDCl_3$ (0.5 ml)) δ 5.62 (1H, br d, 1′-H), 4.75 (2H, s, CH_2OH), 4.68 (1H, br d, 2′-H), 3.7~3.8 (5H, m, morpholino $CH_2\times2$ and 4′-H), 2.5~2.7 (4H, m, morpholino $CH_2\times2$), 2.23 (1H, dt, 3′-H).

As shown in Table 1, **10** and **11** exhibited similar antitumor activities to those of DNR and DOX against murine L1210 leukemia, the toxicity of **11** being slightly higher than that of DOX. Compound **12**, like 3′-deamino-3′-morpholinoadriamycin[9], had a strong toxicity and its effective dose range was very narrow. Compound **9** was inactive at doses up to 100 μg/mouse/day. Growth inhibitory effects of **11** and **12** on P388/S and P388/ADM *in vitro* are shown in Table 2. It is noteworthy that **12** was not cross-resistant with DOX in P388/ADM subline.

These results, together with those of other workers[4,5,10~14], indicate that, in 2′-fluorodaunorubicin and -doxorubicin analogs, compounds with an α-side 2′-fluoro atom and an α-side 3′-hydroxyl group will exhibit most satisfactory activities.

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