

Anthracycline Glycosides

The invention relates to anthracycline glycosides, to
5 processes for their preparation and to pharmaceutical
compositions containing them.

The invention provides 4'-deoxy-4'-iodo-daunorubicin,
4'-deoxy-4'-iodo-doxorubicin, and pharmaceutically
acceptable salts of either thereof. The glycosides
10 according to the invention have been found to be endowed
with outstanding antitumoural activity.

The starting material for their preparation is 4'-deoxy-
-4'-iodo-N-trifluoroacetyl-daunorubicin, an intermediate
compound already described in our European Patent Specification
15 No. 81107618.1 (0048967). Mild alkaline hydrolysis
of said intermediate, suitably with an aqueous solution
of 0.1 N sodium hydroxide, provides 4'-deoxy-4'-iodo-
-daunorubicin. The doxorubicin analogue may be prepared
from 4'-deoxy-4'-iodo-daunorubicin by bromination at
20 C-14 followed by treatment with aqueous sodium formate.
Details of this conversion method are given in United
States Patent Specification No. 3803124. These processes
are within the scope of the invention.

The new anthracycline glycosides of the invention display
25 antitumour activity. Particularly, 4'-deoxy-4'-iodo-

doxorubicin displays remarkable activity on experimental tumours in mice.

Accordingly, the invention further provides a pharmaceutical composition comprising a pharmaceutically effective amount of 4'-deoxy-4'-iodo-daunorubicin or 4'-deoxy-4'-iodo-doxorubicin or a pharmaceutically acceptable salt of either thereof in admixture with a pharmaceutically acceptable diluent or carrier.

The invention is illustrated by the following Examples.

Example 1

10 4'-deoxy-4'-iodo-daunorubicin (XOO-0138)

A solution of 2.0 g of 4'-deoxy-4'-iodo-N-trifluoroacetyl-daunorubicin in 10 ml of acetone was treated with 80 ml of a 0.1 N aqueous solution of sodium hydroxide. After 3 hours at 0°C, the solution was adjusted to pH 4.5 with 0.1 N aqueous hydrochloric acid and extracted with chloroform in order to eliminate the aglycones. The aqueous solution was then adjusted to pH 8.6 and extracted with chloroform. The combined extracts were dried over anhydrous sodium sulphate, concentrated to a small volume and acidified to pH 4.5 with 0.1 N methanolic hydrogen chloride to allow crystallization of the title compound as its hydrochloride. Yield 1.5 g; m.p. 157° (with decomposition); FD-MS: 637 (M⁺)

TLC on Kieselgel plates F₂₅₄ (Merck) Using chloroform: methanol:water:acetic acid (80:20:7:3) by volume: Rf = 0.72 'E.Merck' is a Trade Mark.

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Example 2
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4'-deoxy-4'-iodo-doxorubicin (XOO-0163)

A solution of 4'-deoxy-4'-iodo-daunorubicin in a mixture of methanol and dioxan was treated, in accordance with the method described in United States Patent Specification No. 3803124, with bromine to form the 14-bromo derivative, which by treatment with an aqueous solution of sodium formate gave 4'-deoxy-4'-iodo-doxorubicin, which was isolated as hydrochloride. m.p. 230°C (with decomposition);

FD-MS: 653 (M^+)

TLC on Kieselgel plates F₂₅₄ (Merck) using chloroform: methanol:water:acetic acid (80:20:7:3 by volume): R_f=0.5.

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Biological Activity of compounds XOO-0138 and XOO-0163
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The compounds have been tested in comparison with daunorubicin (DNR) and doxorubicin (DX) against HeLa cells in vitro. Data reported in Table 1 show that XOO-0138 was less cytotoxic than DNR, while XOO-0163 was more cytotoxic than DX.

The antitumour activity was assessed in vivo in mice bearing P388 ascitic leukemia. Results are reported in Table 2. Both the new derivatives are active against P388 leukemia. Of particular interest is the result obtained by treatment of the tumoured mice with compound XOO-0163: at the optimal, non-toxic dose of 15 mg/kg, XOO-0163 cured more than 50% of the mice (6/10), and at the dose of 10 mg/kg cured 3/10 mice and produced a

remarkably high increase of life span in comparison with controls (205%). Therefore, the antitumour activity of X00-0163 is definitely superior to that of DX, which, at the optimal non-toxic dose of 10 mg/kg, cures only occasionally the tumoured mice.

Compound X00-0138 was also tested against Gross leukemia (treatment on Day 1 after tumour inoculum). Data reported in Table 3 show that, at the optimal non-toxic dose of 11.8 mg/kg, X00-0138 showed an antitumour activity superior to that of DNR, and similar to that of DX.

Table 1. Effect on HeLa cells cloning efficiency^a

Compound	Dose (ng/ml)	%	ID ₅₀ (ng/ml)
Daunorubicin	12.5	7	7
	6.25	53	
	3.1	110	
X00-0138	100	0	15
	25	5	
	6.2	109	
Doxorubicin	25	0	8
	12.5	16	
	6.2	70	
X00-0163	25	0	5.5
	6.2	16	
	1.5	91	
	0.39	104	

^aTreatment for 24 hours

Table 2. Effect against P 388 ascitic leukemia^a

Compound	Dose ^b (mg/kg)	T/C ^c %	LTS ^d	Toxic ^e deaths
Daunorubicin	2.9	160, 165	0/10, 0/10	0/10, 0/10
	4.4	160, 185	0/10, 0/10	1/10, 0/10
	6.6	175, 135	0/10, 0/10	7/10, 7/10
XOO-0138	4.4	140	0/10	0/10
	6.6	155	1/10	0/10
	10	185, 75	0/10, 0/10	0/10, 6/10
	15	70	0/10	8/10
	22.5	60	0/10	10/10
Doxorubicin	4.4	210	0/10	0/10
	6.6	260	0/10	0/10
	10	265	1/10	0/10
XOO-0163	6.6	240	0/10	0/10
	10	305	3/10	0/10
	15	620	6/10	0/10
	22.5	390	3/10	1/10

^aExperiments were performed in BDF1 or CDF1 mice, inoculated with 10^6 leukemia cells i.p.

^bTreatment i.p. on Day 1 after tumour inoculum

^cMedian survival time of treated mice/median survival time of controls x 100

^dLong term survivors (>60 days)

^eEvaluated on the basis of autoptic findings.

Table 3. Effect against Gross leukemia^a

Compound.....	Dose ^b (mg/kg)	T/C % ^c	LTS ^d	Toxic ^e deaths
Daunorubicin	15	191	0/8	0/8
	22.5	158	0/8	4/8
Doxorubicin	7.7	150	0/10	0/10
	10	175	0/10	0/10
	13	200	0/10	0/10
	16.9	233	0/10	0/10
	22	266	0/10	1/10
X00-0138	11.8	208	0/10	0/10
	15.4	208	0/10	2/10
4'iodo-dauno- rubicin	20	175, 117	0/8, 0/10	4/8, 6/10
	30	100	0/8	8/8
	40	92	0/8	8/8

^aC3H mice were injected i.v. with 2×10^6 leukemia cells

^bTreatment i.v. on Day 1 after tumour inoculum

^{c, d, e}see Table 2.



CLAIMS:

1. 4'-Deoxy-4'-iodo-daunorubicin or a pharmaceutically acceptable salt thereof.

2. 4'-Deoxy-4'-iodo-doxorubicin or a pharmaceutically acceptable salt thereof.

3. A method for the preparation of 4'-deoxy-4'-iodo-daunorubicin, the method comprising mild alkaline hydrolysis of 4'-deoxy-4'-iodo-N-trifluoroacetyl-daunorubicin.

4. A method for the preparation of 4'-deoxy-4'-iodo-doxorubicin, the method comprising bromination of 4'-deoxy-4'-iodo-daunorubicin at C-14 followed by treatment with aqueous sodium formate.

5. A method for the preparation of 4'-deoxy-4'-iodo-daunorubicin, the method being substantially as described herein with reference to Example 1.

6. A method for the preparation of 4'-deoxy-4'-iodo-doxorubicin, the method being substantially as described herein with reference to Example 2.

7. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 1 or



claim 2 or a compound prepared according to any of
claims 3 to 6 in admixture with a pharmaceutically
acceptable diluent or carrier.
