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Synthesis and Antitumor Activity of Novel 4-Demethoxyanthracyclines

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A versatile and efficient synthetic route to 4-demethoxyanthracyclinones has been utilized in the preparation of a number of aglycons having 9-alkyl, 9-(hydroxylalkyl), or 9-carbamoyl substituents. Silver trifluoromethanesulfonate catalyzed coupling of these aglycons with various daunosamine derivatives has yielded a series of novel anthracyclines which have been evaluated as antitumor agents. 9-Alkylanthracyclines 22, 23, 33, and 34 have higher efficacy vs L-1210 leukemia than the parent 4-demethoxydaunorubicin (21), or the natural anthracyclines daunorubicin (1) and doxorubicin (2). 9-(Hydroxyalkyl) derivatives have in most cases high efficacy but are slightly less potent than 21. 9-Methyl analogue 22 has higher efficacy vs P388 leukemia than other anthracyclines tested, while 9-(hydroxymethyl) derivative 37 retains similar efficacy to anthracyclines 1, 2, and 21 but is considerably more potent. The N-substituted 9-carbamoylanthracyclines are devoid of antitumor activity.

The anthracyclines daunorubicin (daunomycin, 1; Chart I) and, particularly, doxorubicin (adriamycin, 2) are widely used for the treatment of human tumors.¹⁻³ However, the clinical use of these agents is hampered by a number of undesirable side effects, particularly a dose-related and irreversible cardiotoxicity. Consequently a major goal for anthracycline research is the identification of new analogues with reduced toxicity, as well as a broader spectrum of antitumor activity, and this objective has stimulated considerable research activity in various industrial and academic laboratories.⁴ Some structure-activity relationships have been established for the anthracyclines, but these are largely derived from the investigation of analogues obtained through chemical modification of fermentation-derived products.⁵ This has limited the range of new structures since the natural products have labile functions at positions 7 and 9 which are essential for good biological activity. We have therefore undertaken to extend the understanding of structure-activity relationships by utilizing a new method of total synthesis which facilitates the preparation of the substantial quantities of novel anthracylinones necessary for subsequent glycosidation and biological evaluation.^{6,7} We have selected as targets for synthesis a number of novel 4-demethoxyanthracyclines because 4-demethoxydaunorubicin (21) and 4-demethoxydoxorubicin are claimed to be more potent and less toxic than the parent compounds⁸ and are effective in human therapy.^{9,10} The choice of position 9 substituents is supported by various observations. Some natural products such as aclacinomycin A,B¹¹ and cinerubin A¹² which lack a C-13 oxo function show interesting antitumor activities. Besides being a potent antitumor agent, aclacinomycin A is claimed to be considerably less cardiotoxic than doxorubicin, while cinerubin A shows low but reproducible activity against a doxorubicin-resistant strain of P-388 leukemia.¹³ In addition, both daunorubicin (1) and doxorubicin (2) have been converted to 13-deoxy derivatives with retention of considerable antitumor activity.¹⁴ As one of the principal metabolic reactions of the anthracyclines 1 and 2 in man¹⁵ and in animal tissues¹⁶⁻¹⁹



involves reduction of the C-13 oxo function to give 13dihydroanthracyclines, analogues which lack this function

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might show markedly different biological properties. The finding that the 13-dihydroanthracyclines themselves possess significant antitumor activity^{20,21} has stimulated considerable interest in their preparation. Reduction of the parent anthracyclines has been carried out by microbial^{22,23} and by chemical methods,²⁴ but the configuration at C-13 has not been established in these studies. Recently Cassinelli et al. reported the microbial reduction of 4-demethoxydaunorubicin (21) to a 13-dihydro derivative,²⁵ which was shown to be identical with the major metabolite obtained from the urine of patients treated with 21, and formulated this as the (13R)-dihydro derivative.²⁵ By means of total synthesis of both the (13R)- and (13S)dihydroanthracyclines 24 and 25, we have now established that the mammalian and microbial metabolites possess the 13S configuration²⁶ and this has recently been confirmed by Penco et al.²⁷ In view of the fact that 13S dihydro

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metabolite 25 may be partly responsible for the clinical activity of 21, we have synthesized other hydroxyalkyl analogues. Following the observation that a 9-carbamoyl anthracycline obtained through side-chain degradation of doxorubicin shows good activity against solid tumors in mice²⁸ we have prepared a number of N-substituted 9-carbamoyl analogues of 4-demethoxydaunorubicin.

Finally, as it has been shown that modification of anthracyclines 1 and 2 in the sugar residue at the 4'-position may confer advantageous biological properties,²⁹ a number of novel 4'-modified analogues have been synthesized.

Chemistry

The synthesis of aglycons 7-13 has been described previously.³⁰ Aglycons 14-18 were prepared through treatment of acid chloride 20 (derived from the corresponding methyl ester 19^{30}) with the appropriate amine or hydroxylamine followed by removal of the benzeneboronate protecting group. Chloro sugars 3-6 were synthesized by published procedures.^{29,31} Coupling to aglycons 7-18 was catalyzed by silver triflate to give high yields of the desired α -glycosides as shown by the presence of a narrow multiplet in the region δ 5.3–5.4 in the ¹H NMR spectrum for the anomeric proton. In no case was an appreciable amount of the β -glycoside obtained. Stepwise deprotection of the resulting glycosides through treatment with a trace of base in methanol to remove the *p*-nitrobenzoyl residue, followed by hydrolysis of the N-trifluoroacetyl group and simultaneously, the side-chain O-acetate residue, if present, gave the desired anthracyclines 22-41 which were isolated as hydrochlorides.

Results and Discussion

Biological activity of the new 4-demethoxyanthracyclines against L-1210 leukemia in mice is shown in Table I. The compounds possessing an amide side chain at C-9 (27-30 and hydroxamate 31) were devoid of antitumor activity. These results were unexpected in view of the reported activity of a doxorubicin analogue with a primary amide side chain²⁸ and the significant antitumor activity of analogues with large acyl groups at C-9.^{32,33} In contrast the compounds with simple alkyl or hydroxylalkyl side chains had potent activity. 9-Methyl and 9-ethyl analogues 22, 33 and 23, 34 were highly efficacious, giving survival times markedly better than those of 21, daunorubicin (1), and doxorubicin (2). Compounds with hydroxyalkyl side chains were in most cases highly potent but with slightly reduced efficacy. Results for selected compounds tested against p-388 leukemia by using the stringent q4d 5,9, 13-test regimen³⁴ are shown in Table II. The best efficacy was obtained with 22 (T/C = 1.92) while 37 retained the antitumor activity of doxorubicin (2) (T/C = 1.74) but with much greater potency. Interestingly, in this test 37 was considerably more potent than the parent 4-methoxy-

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daunorubicin (21) while retaining similar efficacy.

Whether any of the new anthracyclines offer real advantages over compounds currently in the clinic will require further careful evaluation. However, preliminary in vitro investigations indicate that 22 may have useful activity against some doxorubicin resistant cell lines.³⁵⁻³⁷

Further studies on the antitumor activity of 22 and other analogues are in progress and will be reported in due course.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian XL 100 spectrometer for $(CD_3)_2SO$ solutions unless otherwise stated. Optical rotations were determined on a Perkin-Elmer 141 MC polarimeter and microanalyses were carried out with a Perkin-Elmer elemental analyzer. Silica gel used for column chromatography was Kieselgel 60 (70–230 mesh, Merck).

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9methyl-5,12-naphthacenedione Hydrochloride (22). (i). A solution of naphthacenedione 8 (1.0 g, 2.94 mmol) in dry tetrahydrofuran (100 mL) was cooled to -5 °C with stirring under nitrogen and a solution of the chloro sugar 3 [prepared³¹ from 2,3,6-trideoxy-1,4-di-O-p-nitrobenzoyl-3-(trifluoroacetamido)-Llyxohexopyranose (1.0 g, 1.84 mmol)] in dry tetrahydrofuran (15 mL) was added. A solution of silver trifluoromethanesulfonate (0.5 g, 1.85 mmol) in anhydrous diethyl ether (15 mL) was added during 20 min, and the mixture was stirred at -5 °C for 2 h. Additional chloro sugar (1.84 mmol) in tetrahydrofuran (15 mL) was added, followed by a solution of silver trifluoromethanesulfonate (0.5 g) in diethyl ether (15 mL) and the mixture was stirred at -5 °C for a further 1.5 h. The reaction mixture was poured into a mixture of 10% aqueous sodium hydrogen carbonate (300 mL) and dichloromethane (100 mL) and filtered. The organic layer was separated and the aqueous layer was extracted with three additional portions of dichloromethane (100 mL). The combined dichloromethane extracts were washed with water $(2 \times 200 \text{ mL})$, dried, and evaporated. The residue was chromatographed on a column of silica gel (200 g), using hexane-ethyl acetate (1:1 v/v)as eluent to give glycoside 42 (1.12 g, 53%) as a bright red, crystalline solid: mp 225-6 °C; $[\alpha]_{D}^{20}$ -94° (c 0.1% in CHCl₃).

(ii). Glycoside 42 (1.12 g) was dissolved in a mixture of dichloromethane (100 mL) and methanol (250 mL), and the solution was cooled to 0 °C with stirring in a nitrogen atmosphere. A 0.1 M aqueous sodium hydroxide solution (20 mL) was added and the purple solution was stirred at 0 °C for 30 min. Glacial acetic acid was added until the solution became bright orange and the mixture was poured into water (1 L) and extracted with dichloromethane (3 × 300 mL). The combined dichloromethane extracts were dried and evaporated, and the residue was triturated with ether to give glycoside 43 (0.8 g, 88%) as a bright red, crystalline solid: mp 253-4 °C; $[\alpha]^{20}_{D} + 181^{\circ}$ (c 0.1% in CHCl₃).

(iii). A solution of glycoside 43 (0.565 g) in tetrahydrofuran (20 mL) was added to 0.1 M aqueous sodium hydroxide (90 mL) and the solution stirred in a nitrogen atmosphere for 1 h. The solution was then adjusted to pH 8 with 5 M hydrochloric acid and extracted with 5% ethanol in dichloromethane (5 × 80 mL). The combined extracts were washed with water (200 mL), dried, and evaporated. The residue was dissolved in a mixture of dichloromethane (12 mL) and methanol (3 mL) and filtered, and the filtrate was treated with 0.25 M methanolic hydrogen chloride (4 mL). The solution was concentrated to ca. 5 mL and anhydrous diethyl ether (50 mL) was added with swirling to precipitate the hydrochloride of glycoside 22 (0.47 g, 93%) as a bright orange solid: mp 174-6 °C; $[\alpha]^{20}_{D} + 160^{\circ}$ (c 0.05% in MeOH); NMR δ 1.20 (d, 3, 6'-H₃), 1.26 (s, 3, 13-H₃), 1.55-2.22 (m, 4, 2'-H₂ and 8-H₂), 2.58 (d, 1, 10-H), 2.94 (d, 1, 10-H), 3.20-3.50 (m, H₂O and 3'-H),

 $3.64 \ (m, \ 1, \ 4'-H), \ 4.17 \ (q, \ 1, \ 5'-H), \ 4.46 \ (s, \ 1, \ exch \ D_2O, \ 9-OH), \\ 4.88 \ (br \ s, \ 1, \ 7-H), \ 5.36 \ (br \ s, \ 1, \ 1'-H), \ 5.44 \ (d, \ 1, \ exch \ D_2O, \ 4'-OH), \\ 7.88-8.07 \ (m, \ 2, \ 2-H \ and \ 3-H), \ 8.18-8.35 \ (m, \ 2, \ 1-H \ and \ 4-H). \ Anal. \\ (C_{25}H_{27}NO_8 \cdot HCl\cdot 2.25H_{2}O) \ C, \ H, \ N, \ Cl.$

Similar procedures were employed in the synthesis of the following compounds.

(7S, 9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-9-ethyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (23) was obtained in a yield of 38% over three steps from 9 and 3: mp 174-6 °C; $[\alpha]^{20}_{D}$ +176° (c 0.1% in MeOH); NMR δ 0.96 (t, 3, 14-H₃), 1.17 (d, 3, 6'-H₃), 1.4-2.25 (m, 6, 2'-H₂, 8-H₂ and 13-H₂), 2.54 (d, 1, 10-H), 2.92 (d, 1, 10-H), 3.2-3.45 (m, H₂O and 3'-H), 3.62 (m, 1, 4'-H), 4.16 (q, 1, 5'-H), 4.16 (s, 1, exch D₂O, 9-OH), 4.88 (br s, 1, 7-H), 5.31 (br s, 1, 1'-H), 5.41 (d, 1, exch D₂O, 4'-OH), 7.90-8.06 (m, 2, 2-H and 3-H), 8.20-8.36 (m, 2, 1-H and 4-H). Anal. (C₂₈H₂₉NO₈HCl-1.2H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(*R*)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (24) was obtained in 50% yield over three steps from 10 and 3: mp 180-2 °C; [α]²⁰_D +142° (c 0.05% in MeOH); NMR (300 MHz) δ 1.16 (d, 3, H₃), 1.17 (d, 3, H₃), 1.65-2.1 (m, 4, 2'-H₂ and 8-H₂), 2.61 (d, 1, 10-H), 2.93 (d, 1, 10-H), 3.3-3.45 (m, H₂O and 3'-H), 3.53 (m, 1, 13-H), 3.60 (m, 1, 4'-H), 4.10 (s, 1, exch D₂O, 9-OH), 4.21 (q, 1, 5'-H), 4.81 (d, 1, exch D₂O, OH), 4.92 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.48 (d, 1, exch D₂O, OH), 7.92-7.98 (m, 2, 2-H and 3-H), 8.22-8.28 (m, 2, 1-H and 4-H). Anal. (C₂₆H₂₉N-O₉·HCl·1.2H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(S)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (25) was obtained in 45% yield over three steps from 11 and 3: mp 174-5 °C; [α]²⁰_D+141° (c 0.05% in MeOH); NMR (300 MHz) δ 1.15 (d, 3, H₃), 1.17 (d, 3, H₃), 1.65–1.96 (m, 3, 2'-H₂ and 8-H), 2.23 (d, 1, 8-H), 2.74 (d, 1, 10-H), 2.83 (d, 1, 10-H), 3.27–3.44 (m, H₂O and 3'-H), 3.55 (m, 1, 13-H), 3.60 (m, 1, 4'-H), 4.06 (s, 1, exch D₂O, 9-OH), 4.23 (q, 1, 5'-H), 4.82 (d, 1, exch D₂O, OH), 4.92 (br s, 1, 7-H), 5.27 (br s, 1, 1'-H), 5.48 (d, 1, exch D₂O, OH), 7.93–8.00 (m, 2, 2-H and 3-H), 8.22–8.29 (m, 2, 1-H and 4-H). Anal. (C₂₈H₂₉NO₉·HCl·1.5H₂O) C, H, N, Cl.

(7S, 9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxymethyl)-5,12-naphthacenedione hydrochloride (26) was obtained in 31% yield over three steps from 12 and 3: mp 183-6 °C; [α]²⁰_D +153° (c 0.05% in MeOH); NMR δ 1.16 (d, 3, 6'-H₃), 1.55-2.28 (m, 4, 2'-H₂ and 8-H₂), 2.81 (m, 2, 10-H₂), 3.22-3.45 (m, H₂O, 3'-H and 13-H₂), 3.62 (m, 1, 4'-H), 4.22 (q, 1, 5'-H), 4.28 (s, 1, exch D₂O, 9-OH), 4.85 (t, 1, exch D₂O, 13-OH), 4.94 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.38 (d, 1, exch D₂O, 4'-OH), 7.95-8.06 (m, 2, 2-H and 3-H), 8.20-8.38 (m, 2, 1-H and 4-H). Anal. (C₂₈H₂₇NO₉·HCl·1.75H₂O) C, H, N, Cl.

(75,95)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-(Nphenylcarbamoyl)-5,12-naphthacenedione (14). A suspension of methyl ester 19 (2.0 g, 4.25 mmol) in tetrahydrofuran (40 mL) was treated with 0.1 M aqueous sodium hydroxide (140 mL) and the resulting dark purple solution was stirred at ambient temperature for 5.5 h. The solution was then acidified by dropwise addition of concentrated hydrochloric acid and the majority of the tetrahydrofuran was removed by evaporation. The precipitate was filtered off and dried in vacuo over P2O5 to give a red solid (1.6 g) which was finely powdered and suspended in dry dichloromethane (400 mL) and treated with oxalyl chloride (1.6 g) and 2 drops of dimethylformamide. The mixture was stirred at ambient temperature for 2.5 h to give a clear orange solution which was evaporated to remove solvent and excess oxalyl chloride to give acid chloride 20 as a red gum. This material was dissolved in dichloromethane (20 mL), the solution was cooled to 0 °C, and a solution of aniline (0.4 g, 4.3 mmol) in dichloromethane (10 mL) was added dropwise with stirring during 10 min. After a further 10 min the solution was washed with 2 M hydrochloric acid (100 mL) and water (100 mL), dried, and evaporated to give a red gum which was dissolved in a mixture of dichloromethane (60 mL), 2-methyl-pentane-2,4-diol (10 mL), and acetic acid (1 mL). The mixture was warmed at 60 °C for 15 min and then allowed to stand at room temperature for 2 days. Chloroform (400 mL) and

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Table I. Activity vs L-1210 Leukemia^a



compd	R1	R²	R ³	optimal dose, mg/kg ip	% T/C
21	Ac	Н	OH	0.05	230
22	Me	Н	OH	0.5	400
23	Et	Н	OH	0.5	420 (1)
24	(R)-CH(OH)CH ₃	н	OH	0.125	250
25	(S)-CH(OH)CH ₃	н	OH	0.125	220
26	CH ₂ OH	Н	OH	0.1	230
27	CONHC ₆ H ₅	н	OH	16	120
28	$CON(CH_3)C_6H_5$	Η	OH	16	120
29	CONHCH ₂ C ₆ H ₅	Н	OH	4	130
30	CONHCH ₂ CH ₂ CH ₃	Н	OH	2	120
31	CONHOCH ₂ C ₆ H ₅	н	OH	8	100
32	Ac	OH	Н	0.5	240
33	Me	OH	Н	2	470 (2)
34	Et	OH	Н	0.5	460 (3)
35	(R)-CH(OH)CH ₃	OH	Н	0.125	270
36	(S)-CH(OH)CH ₃	OH	Н	0.125	360
37	CH ₂ OH	OH	Н	0.125	340 (1)
38	CH ₂ CH ₂ OH	OH	н	0.25	450
39	Ac	н	OMe	0.25	230
40	CH₂OH	Н	OMe	0.125	350
41	CH₂OH	Н	Н	0.125	280
1	-			0.5	290 (1)
2				2	330 (3)

^aAqueous solutions of test compounds were administered ip daily, five times a week for 4 weeks or until death. Groups of five female BDF_1 mice were used for each dose. Efficacy is expressed as the ratio T/C of mean survival time of treated animals to that of untreated controls, and the optimal dose is that which gave the highest T/C value. Animals surviving for 4 weeks are deemed long-term survivors. Where long-term survivors occurred, their number is shown in parentheses. Evidence of leucopenia was observed at the doses indicated for 23, 29, 32, daunorubicin (1), and doxorubicin (2).

Table II. Activity vs P388 Leukemia³⁴

compd	optimal dose, ^a mg/kg ip	% T/C ^b	ref	
22	6.25	192		
23	3.0	155		
34	4.0	184		
37	0.38	174		
1	8.0	143	3 9	
2	8.0	174	39	
21	2.4	174	39	

^a Dose giving the highest value of T/C. ^b Ratio of mean survival time of treated animals to untreated controls.

methanol (50 mL) were then added, and the mixture was warmed to dissolve the precipitated solid. After cooling, the solution was washed with water (2 × 200 mL), dried, and evaporated. Trituration of the residue with ethyl acetate gave naphthacenedione 14 (1.48 g, 78%) as orange-red crystals: mp 228-30 °C; $[\alpha]^{20}$ D +157° (c 0.05% in dioxane); NMR (CDCl₃) δ 2.48 (m, 2, 8-H₂) 3.36 (m, 3, part. exch D₂O, 10-H₂ and 7-OH), 5.13 (s, 1, exch D₂O, 9-OH), 5.43 (m, 1, 7-H), 7.14-7.73 (m, 5, ArH) 7.79-7.91 (m, 2, 2-H and 3-H), 8.30-8.45 (m, 2, 1-H and 4-H), 9.13 (br s, 1, NH), 13.24 (s, 1, exch D₂O, OH), 13.60 (s, 1, exch D₂O, OH). Anal. (C₂₅H₁₉NO₇·0.2H₂O) C, H, N.

Similar procedures were employed in the synthesis of the following naphthacenediones.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-(*N*-methyl-*N*-phenylcarbamoyl)-5,12-naphthacenedione (15) was obtained in 76% yield over four steps from 19 and *N*-methyl-

aniline: mp 245–7 °C; $[\alpha]^{20}_{D}$ +204° (c 0.05% in CHCl₃); NMR (CDCl₃ + DMSO) δ 2.04 (dd, 1, 10-H), 2.45 (dt, 1, 10-H), 3.07 (d, 1, 8-H), 3.36 (dd, 1, 8-H), 3.42 (s, 3, 15-H₃), 4.52 (d, 1, exch D₂O, 7-OH), 5.04 (s, 1, exch D₂O, 9-OH), 5.08 (m, 1, 7-H), 7.26–7.56 (m, 5, ArH), 7.78–7.92 (m, 2, 2-H and 3-H), 8.28–8.42 (m, 2, 1-H and 4-H), 13.36 (br s, 1, OH), 13.56 (br s, 1, OH). Anal. (C₂₆-H₂₁NO₇-1.1H₂O) C, H, N.

 $(7S, 9S) - 9 - (N - \text{Benzylcarbamoyl}) - 7,8,9,10 - \text{tetrahydro-} 6,7,9,11 - \text{tetrahydroxy-} 5,12 - naphthacenedione (16) was obtained in 76% yield over four steps from 19 and benzylamine: mp 257-8 °C; <math>[\alpha]^{20}_{D} + 87.5^{\circ}$ (c 0.05% in dioxane); NMR δ 2.18 (m, 2, 8-H₂), 3.10 (br s, 2, 10-H₂), 4.37 (m, 2, 15-H₂), 5.13 (m, 1, 7-H), 7.30 (s, 5, ArH), 7.90-8.06 (m, 2, 2-H and 3-H), 8.39-8.49 (m, 2, 1-H and 4-H), 8.56 (br s, 1, NH). Anal. (C₂₆H₂₁NO₇) C, H, N.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-(*N*-propylcarbamoyl)-5,12-naphthacenedione (17) was obtained in 65% yield over four steps from 19 and *n*-propylamine: mp 253-6 °C; $[\alpha]^{20}_{D}$ +157° (c 0.05% in dioxane); NMR δ 0.88 (t, 3, 17-H₃), 1.53 (m, 2, 16-H₂), 2.14 (m, 2, 8-H₂), 2.99-3.20 (m, 4, 10-H₂ and 15-H₂), 5.12 (m, 1, 7-H), 5.66 (br s, 1, exch D₂O, 7-OH), 6.01 (s, 1, exch D₂O, 9-OH), 7.88-8.08 (m, 2, 2-H and 3-H), 8.22-8.38 (m, 2, 1-H and 4-H), 13.37 (br s, 2, exch D₂O, OH). Anal. (C₂₂H₂₁NO₇·0.2H₂O) C, H, N.

(7S, 9S)-9-[N-(Benzyloxy)carbamoyl]-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-5,12-naphthacenedione (18) was obtained in 75% yield over four steps from 19 and O-benzylhydroxylamine: mp 233-4 °C; $[\alpha]^{20}_{D}$ +59° (c 0.05% in dioxane); NMR δ 2.14 (m, 2, 8-H₂), 3.07 (s, 2, 10-H₂), 4.87 (s, 2, 16-H₂), 5.13 (m, 1, 7-H), 5.97 (br s, 1, exch D₂O), 7.41 (m, 5, ArH), 7.92-8.08 (m, 2, 2-H and 3-H), 8.24-8.38 (m, 2, 1-H and 4-H). Anal. (C₂₆H₂₁NO₈) C, H, N.

(7 \vec{S} ,9 \vec{S})-7-[(3'-Amino-2',3',6'-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(Nphenylcarbamoyl)-5,12-naphthacenedione Hydrochloride (27). Silver triflate catalyzed coupling of chloro sugar 3 with aglycon 14 followed by stepwise deprotection gave 27 (54% over three steps): mp 180-1 °C; [α]²⁰_D +158° (c 0.05% in MeOH); NMR (300 MHz) δ 1.17 (d, 3, 6'-H₃), 1.74 (dd, 1, 2'-H), 1.93 (dt, 1, 2'-H), 2.24 (dd, 1, 8-H), 2.45 (dd, 1, 8-H), 3.14 (m, 2, 10-H₂), 3.30-3.47 (m, H₂O and 3'-H), 3.64 (m, 1, 4'-H), 4.29 (q, 1, 5'-H), 5.00 (br s, 1, 7-H), 5.37 (br s, 1, 1'-H), 5.48 (d, 1, exch D₂O, 4'-OH), 5.91 (s, 1, exch D₂O, 9-OH), 7.08 (t, 1, ArH), 7.32 (t, 2, ArH), 7.79 (d, 2, ArH), 7.98 (m, 2, 2-H and 3-H), 8.27 (m, 2, 1-H and 4-H), 10.00 (s, 1, NH). Anal. (C₃₁H₃₀N₂O₉·HCl·2.0H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(*N*methyl-*N*-phenylcarbamoyl)-5,12-naphthacenedione hydrochloride (28) was obtained in 50% yield over three steps from 15 and 3: mp 170-2 °C; [α]²⁰_D +134° (c 0.05% in MeOH); NMR δ 1.19 (d, 3, 6'-H₃), 1.70-2.27 (m, 4, 2'-H₂ and 8-H₂), 2.68 (d, 1, 10-H), 2.94 (d, 1, 10-H), 3.17-3.68 (m, H₂O, 3'-H and 15-H₃), 3.96 (q, 1, 5'-H), 5.04 (br s, 1, 7-H), 5.28 (m, 2, part exch D₂O, 4'-OH and 1'-H), 5.54 (s, 1, exch D₂O, 9-OH), 7.33 (m, 5, ArH), 7.93-8.08 (m, 2, 2-H and 3-H), 8.20-8.37 (m, 2, 1-H and 4-H). Anal. (C₃₂H₃₂N₂O₉-HCl-2H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-9-(*N*-benzylcarbamoyl)-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (29) was obtained in 18% yield over three steps from 16 and 3: mp 174-6 °C; $[\alpha]^{20}_{D}$ +127° (C 0.05% in MeOH); NMR δ 1.15 (d, 3, 6'-H₃), 1.56-2.33 (m, 4, 2'-H₂ and 8'-H₂), 2.95-3.72 (m, H₂O, 3'-H and 10-H₂), 4.12-4.44 (m, 3, 5'-H and 15-H₂), 4.94 (br s, 1, 7-H), 5.32 (br s, 1, 1'-H), 5.54 (d, 1 exch D₂O, 4'-OH), 5.60 (s, 1, exch D₂O, 9-OH), 7.32 (m, 5, ArH), 7.84-8.05 (m, 2, 2-H and 3-H), 8.16-8.32 (m, 2, 1-H and 4-H), 8.52 (br t, 1, NH), 13.42 (br s, 2, exch D₂O, OH). Anal. (C₃₂H₃₂N₂O₉·HCl-1.5H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(*N*propylcarbamoyl)-5,12-naphthacenedione hydrochloride (30) was obtained in 22% yield over three steps from 17 and 3: mp 168-70 °C; [α]²⁰_D +148° (c 0.05% in MeOH); NMR δ 0.78 (t, 3, 17-H₃), 1.15 (d, 3, 6'-H₃), 1.50 (m, 2, 16-H₂), 1.54-2.34 (m, 4, 2'-H₂ and 8-H₂), 2.90-3.76 (m, H₂O, 3'-H, 10-H₂ and 15-H₂), 4.22 (q, 1, 5'-H), 4.96 (br s, 1, 7-H), 5.27-5.48 (m, 3, part. exch D₂O, 1'-H, 4'-OH and 9-OH), 7.90-8.14 (m, 3, NH, 2-H and 3-H), 8.18-8.38 (m, 2, 1-H and 4-H), 13.30 (br s, 1, exch D_2O , OH), 13.57 (br s, 1 exch D_2O , OH). Anal. ($C_{28}H_{32}N_2O_9$ -HCl-1.6H₂O) C, H, N, Cl.

(7 S, 9 S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-9-[*N*-(benzyloxy)carbamoyl]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (31) was obtained in 25% yield over three steps from 18 and 3: mp 173-5 °C; $[\alpha]^{20}_{D}$ +147° (c 0.05% in MeOH); NMR δ 1.16 (d, 3, 6'-H₃), 1.56-2.34 (m, 4, 2'-H₂ and 8-H₂), 2.96-3.70 (m, H₂O, 3'-H and 10-H₂), 4.20 (q, 1, 5'-H), 4.86 (s, 2, 16-H₂), 4.96 (br s, 1, 7-H), 5.36 (m, 2, part. exch D₂O, 4'-OH and 1'-H), 5.54 (s, 1, exch D₂O, 9-OH), 7.38 (m, 5, ArH), 7.88-8.08 (m, 3, NH, 2-H and 3-H), 8.20-8.36 (m, 2, 1-H and 4-H), 13.48 (br s, 2, exch D₂O, OH). Anal. (C₃₂H₃₂N₂O₁₀·HCl-2.3H₂O) C, H, N, Cl.

OH). Anal. $(C_{32}H_{32}N_2O_{10}\cdot HCl\cdot 2.3H_2O)$ C, H, N, Cl. (7S,9S)-9-Acetyl-7-[(3'-Amino-2',3',6'-trideoxy- α -Larabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione Hydrochloride (32). Silver triflate catalyzed coupling of chloro sugar 4 with 4-demethoxydaunomycinone (7) followed by stepwise deprotection gave 32 (25% over three steps): mp 173-5 °C; $[\alpha]^{20}_{D} + 200^{\circ}$ (0.05% in MeOH); NMR (300 MHz) δ 1.24 (d, 3, 6'-H₃), 1.75-2.3 (m, 4, 2'-H₂ and 8-H₂), 2.27 (s, 3, 14-H₃), 3.0 (m, 2, 10-H₂), 3.1-3.4 (m, H₂O and 3'-H and 4'-H), 4.0 (m, 1, 5'-H), 4.98 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.60 (s, 1, exch D₂O, OH), 5.78 (s, 1, exch D₂O, OH), 7.94-8.02 (m, 2, 2-H and 3-H), 8.24-8.32 (m, 2, 1-H and 4-H), 13.33 (s, 1, exch D₂O, OH), 13.56 (s, 1, exch D₂O, OH). Anal. (C₂₆-H₂₇NO₈+Hcl·1.5H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy-α-L-arabinohexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9methyl-5,12-naphthacenedione hydrochloride (33) was obtained in 30% yield over three steps from 8 and 4: mp 181–3 °C; $[\alpha]^{20}_{D} + 243^{\circ}$ (c 0.05% in MeOH); NMR δ 1.24 (m, 6, 6'-H₃ and 13-H₃), 1.70–2.20 (m, 4, 2'-H₂ and 8-H₂), 2.36 (d, 1, 10-H), 2.76 (d, 1, 10-H), 2.94–3.40 (m, H₂O and 3'-H and 4'-H), 3.96 (m, 1, 5'-H), 4.44 (d, 1, exch D₂O, OH), 4.90 (br s, 1, 7-H), 5.34 (br s, 1, 1'-H), 5.64 (br s, 1, exch D₂O, OH), 7.86–8.02 (m, 2, 2-H and 3-H), 8.15–8.32 (m, 2, 1-H and 4-H), 13.30 (br s, 1, exch D₂O, OH), 13.60 (br s, 1, exch D₂O, OH). Anal. (C₂₅H₂₇NO₈·HCl-1.8H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-arabinohexopyranosyl)oxy]-9-ethyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (34) was obtained in 44% yield over three steps from 9 and 4: mp 186-7 °C; $[\alpha]^{20}_{D} + 240^{\circ}$ (c 0.01% in MeOH); NMR [(CD₃)₂SO-CDCl₃] δ 1.00 (t, 3, 14-H₃), 1.23 (d, 3, 6'-H₃), 1.55-2.40 (m, 6, 2'-H₂, 8-H₂, and 13-H₂), 2.60 (d, 1, 10-H), 3.14 (d, 1, 10-H), 3.3-3.7 (m, H₂O and 3'-H and 4'-H), 3.9 (m, 1, 5'-H), 4.85 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 7.58-7.78 (m, 2, 2-H and 3-H), 7.96-8.16 (m, 2, 1-H and 4-H). Anal. (C₂₆H₃₀NO₈·HCl·1.8H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(*R*)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (35) was obtained in 40% yield over three steps from 10 and 4: mp 187-9 °C; $[\alpha]^{20}_{D}$ +213° (c 0.1% in MeOH); NMR (300 MHz) δ 1.17 (d, 3, H₃), 1.21 (d, 3, H₃), 1.75-2.2 (m, 4, 2'-H₂ and 8-H₂), 2.65 (d, 1, 10-H), 2.93 (d, 1, 10-H), 3.03-3.17 (m, 2, 3'-H and 4'-H), 3.52 (m, 1, 13-H), 3.95 (m, 1, 5'-H), 4.10 (s, 1, 9-OH), 4.80 (br s, 1, exch D₂O, OH), 4.94 (br s, 1, 7-H), 5.29 (br s, 1, 1'-H), 5.73 (d, 1, exch D₂O, OH), 7.95-8.01 (m, 2, 2-H and 3-H), 8.22-8.08 (m, 2, 1-H and 4-H). Anal. (C₂₆H₂₉NO₉·HCl·H₂O) C, H, N, Cl.

(75,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(S)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (36) was obtained in 49% yield over three steps from 11 and 4: mp 185-7 °C; $[\alpha]^{20}_{D}$ +192° (c 0.05% in MeOH); NMR δ 1.23 (m, 6, 6'-H₃ and 13-H₃), 1.67-2.45 (m, 4, 2'-H₂ and 8-H₂), 2.83 (m, 2, 10-H₂), 3.05-3.53 (m, 3'-H, 4'-H, and H₂O), 3.93 (s, 1, 9-OH), 3.96 (m, 1, 5'-H), 4.76 (br s, 1, exch D₂O, OH), 5.02 (br s, 1, 7-H), 5.33 (br s, 1, 1'-H), 5.67 (d, 1, exch D₂O, OH), 7.92-8.12 (m, 2, 2-H and 3-H), 8.24-8.43 (m, 2, 1-H and 4-H). Anal. (C₂₆H₂₉NO₉·HCl-1.2H₂O) C, H, N, Cl.

 $(7\overline{S},9S)$ -7-[(3'-Amino-2',3',6'-trideoxy- α -L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxymethyl)-5,12-naphthacenedione hydrochloride (37) was obtained in 50% yield over three steps from 12 and 4: mp 189–3 °C; $[\alpha]^{20}_{D}$ +216° (c 0.05% in MeOH); NMR δ 1.23 (d, 3, 6'-H₃), 1.60–2.22 (m, 4, 2'-H₂ and 8-H₂), 2.79 (m, 2, 10-H₂), 3.03–3.44 (m, $\begin{array}{l} H_2O, 3'-H, 4'-H, \mbox{ and } 13\text{-}H_2), \ 3.98 \ (m, 1, 5'-H), \ 4.22 \ (s, 1, \mbox{ exch } D_2O, \\ 9\text{-}OH), \ 4.82 \ (br \ s, 1, \mbox{ exch } D_2O, \ OH), \ 4.96 \ (br \ s, 1, 7\text{-}H), \ 5.32 \ (br \ s, 1, 1'-H), \ 5.64 \ (br \ m, 1, \mbox{ exch } D_2O, \ OH), \ 7.89\text{-}8.04 \ (m, 2, 2\text{-}H \ \mbox{ and } 3\text{-}H), \ 8.17\text{-}8.36 \ (m, 2, 1\text{-}H \ \mbox{ and } 4\text{-}H), \ 13.36 \ (br \ s, 1, \ OH), \ 13.58 \ (br \ s, 1, \ OH). \ \ Anal. \ \ (C_{25}H_{27}NO_{9}\text{-}HCl\text{-}1.5H_2O) \ C, \ H, \ N, \ Cl. \end{array}$

 $\begin{array}{l} (7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy-\alpha-L-arabinohexo-pyranosyl)oxy]-9-(2-hydroxyethyl)-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (38) was obtained in 5% yield over three steps from 13 and 4: mp 176-8 °C; [\alpha]^{20}_D+172° (0.05% in MeOH); NMR (300 MHz) <math display="inline">\delta$ 1.22 (d, 3, 6'-H_3), 1.65-2.20 (m, 6, 2'-H_2, 8-H_2, and 13-H_2), 2.75 (d, 1, 10-H), 2.91 (d, 1, 10-H), 3.03-3.15 (m, 2, 3'-H and 4'-H), 3.65 (m, 2, 14-H_2), 3.87 (m, 1, 5'-H), 4.42 (s, 1, exch D_2O, 9-OH), 4.46 (d, 1, exch D_2O, OH), 4.92 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.71 (d, 1, exch D_2O, OH), 7.97-8.03 (m, 2, 2-H and 3-H), 8.28-8.33 (m, 2, 1-H and 4-H). Anal. (C₂₆H₂₉NO₃·HCl·2H₂O) C, H, N, Cl.

(7S, 9S)-9-Acetyl-7-[(3'-amino-2',3',6'-trideoxy-4'-Omethyl- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione Hydrochloride (39). Coupling of 4-demethoxydaunomycinone (7) with sugar 5 followed by treatment with 0.1 M NaOH gave product 39 (39% over two steps): mp 195-6 °C (lit.³⁸ mp 189-90 °C); $[\alpha]^{20}_{D}$ +223° (0.05% in MeOH); NMR (300 MHz) δ 1.24 (d, 3, 6'-H₃), 1.68-2.2 (m, 4, 2'-H₂ and 8-H₂), 2.28 (s, 3, 14-H₃), 2.95 (br s, 2, 10-H₂), 3.3-3.5 (m, H₂O and 3'-H and 4'-H), 3.50 (s, 3, 4'-OMe), 4.25 (m, 1, 5'-H), 4.92 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.57 (s, 1, exch D₂O, 9-OH) 7.96-8.03 (m, 2, 2-H and 3-H), 8.25-8.32 (m, 1, 1-H and 4-H). Anal. (C₂₇H₂₉NO₉·HCl·1.5H₂O) C, H, N, Cl.

(75,95)-7-[(3'-Amino-2',3',6'-trideoxy-4'-O-methyl-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-tri-hydroxy-9-(hydroxymethyl)-5,12-naphthacenedione hydrochloride (40) was obtained in 20% yield over three steps from 12 and 5: mp 190–5 °C; $[\alpha]^{20}_{D}$ +132° (c 0.05% in MeOH); NMR δ 1.25 (d, 3, 6'-H₃), 1.62–2.18 (m, 4, 2'-H₂ and 8-H₂), 2.76 (m, 2, 10-H₂), 3.12–3.50 (m, H₂O and 3'-H and 4'-H), 3.54 (s, 3, 4'-OMe), 4.28 (m, 1, 5'-H), 4.92 (br s, 1, 7-H), 5.33 (br s, 1, 1'-H), 7.86–8.08 (m, 2, 2-H and 3-H), 8.11–8.38 (m, 5, part. exch D₂O, 1-H and 4-H and 3'-NH₃), 13.29 (br s, 1, OH), 13.55 (br s, 1, OH). Anal. (C₂₆H₂₉NO₉·HCl·2.1H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',4',6'-tetradeoxy- α -L-threohexopyranosoyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxymethyl)-5,12-naphthacenedione Hydrochloride (41). Silver triflate catalyzed coupling of chloro sugar 6 with aglycon 12 followed by treatment with 0.1 M NaOH gave product 41 (32% over three steps): mp 179–81 °C; [α]²⁰_D +200° (c 0.05% in MeOH); NMR δ 1.19 (d, 3, 6'-H₃), 1.13–2.16 (m, 6, 2'-H₂, 4'-H₂, and 8-H₂), 2.78 (m, 2, 10-H₂), 3.14–3.49 (m, H₂O, 3'-H), 4.20 (m, 1, 5'-H), 4.29 (s, 1, exch D₂O, 9-OH), 4.90 (m, 2, part. exch D₂O, 7-H and OH), 5.40 (br s, 1, 1'-H), 7.92–8.08 (m, 2, 2-H and 3-H), 8.18–8.36 (m, 2, 1-H and 4-H). Anal. (C₂₅H₂₇NO₈·HCl·0.7H₂O) C, H, N, Cl.

Biological Evaluation. For determination of antitumor activity against L-1210 leukemia BDF_1 mice were injected intraperitoneally with 10⁵ viable L-1210 ascites tumor cells, and intraperitoneal administration of aqueous solutions of test compounds started on the same day. Test compounds were administered daily, five times a week for 4 weeks or until death. Groups of five female mice were used for each dose. Efficacy is expressed as the ratio T/C of mean survival time of treated animals to that of untreated controls. Animals surviving for 4 weeks were deemed long-term survivors. At the doses reported, apart from evidence of leucopenia with some compounds, no specific toxic effects were observed.

Selected compounds were evaluated against P-388 leukemia at the NCI by using the q4d 5,9,13-test regimen.³⁴

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