

Pyrrolopyrimidine Nucleosides. 18.¹ Synthesis and Chemotherapeutic Activity of 4-Amino-7-(3-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide (3'-Deoxysangivamycin) and 4-Amino-7-(2-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide (2'-Deoxysangivamycin)

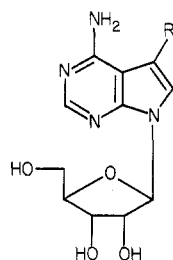
Tokumi Maruyama, Linda L. Wotring, and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, and Department of Medicinal Chemistry, University of Utah, Salt Lake City, Utah 84112.

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A multistep synthesis, using the nucleoside antibiotic toyocamycin as the starting material, has furnished 6,2'-S-cyclosangivamycin (6). Desulfurization of 6,2'-S-cyclosangivamycin (6) with Raney nickel has provided 2'-deoxysangivamycin (7). Treatment of sangivamycin (1c) with sodium iodide and α-acetoxyisobutyryl chloride has furnished 4-amino-7-[2-O-acetyl-3-deoxy-3-iodo-5-O-(2,5,5-trimethyl-4-oxo-1,3-dioxolan-2-yl)-β-D-xylofuranosyl]-pyrrolo[2,3-d]pyrimidine-5-carboxamide (8a). Dehalogenation of 8a with 10% palladium on charcoal was followed by a removal of the blocking groups with ammonium hydroxide to give 3'-deoxysangivamycin (9) in 49% overall yield. The reaction of sangivamycin (1c) with diphenyl disulfide and tributylphosphine gave 5'-(phenylthio)-5'-deoxysangivamycin (10). Treatment of 10 with Raney Nickel afforded 5'-deoxysangivamycin (11). Antitumor evaluation showed that 3'-deoxysangivamycin had significant activity against the murine leukemia L1210 both in vivo and in vitro, although it was less potent on a molar basis than the parent compound sangivamycin. The 2'- and 5'-deoxysangivamycins did not show significant antitumor activity.

The isolation, characterization, and chemical synthesis²⁻⁴ of the pyrrolo[2,3-d]pyrimidine nucleoside antibiotics tubercidin (1a), toyocamycin (1b), and sangivamycin (1c), as well as their biological and chemotherapeutic activity,²⁻⁵ created considerable interest in the synthesis of compounds related to this class of adenosine analogues.



1a, R = H (tubercidin)
b, R = CN (toyocamycin)
c, R = CONH₂ (sangivamycin)

Although the synthesis of base-modified analogues of tubercidin, toyocamycin, and sangivamycin has been described in some detail,⁶ there has been a paucity of research reported on sugar-modified analogues of tubercidin⁷ and

essentially nothing related to the most clinically promising⁸ pyrrolopyrimidine nucleoside antibiotic sangivamycin. The synthesis of a number of analogues of 2'-deoxyadenosine by an enzymatic procedure has been reported recently.⁹ However, this approach did not appear to be applicable to the pyrrolo[2,3-d]pyrimidine adenosine analogues, since the authors were unsuccessful in their attempt to synthesize 2'-deoxytubercidin. We now report the chemical synthesis and biological activities of the 2'-, 3'-, and 5'-deoxysangivamycins.

Chemistry. Although there have been tremendous advances made in the condensation methods¹⁰ used for the synthesis of nucleosides, the problem of obtaining an anomeric mixture still remains when preparing 2'-deoxy-ribofuranosides by a condensation procedure. However, 8,2'-S-cyclopurine nucleosides, have proven to be useful intermediates for the preparation of anomerically pure 2'-deoxypurine nucleosides.¹¹ The reactions of 2',3'-O-dibutylstannylene complexes of ribonucleosides with electrophiles have also been reported¹² to yield 8,2'-O-cyclopurine nucleosides. We elected to investigate the use of this method for the synthesis of 2'-deoxysangivamycin (7) (Scheme I).

6-Bromo-2',3'-O-(dibutylstannylene)toyocamycin (3a) was obtained from the reaction of 6-bromotoyocamycin¹³

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Table I. In Vitro Cytotoxicity and in Vivo Antitumor Testing against Murine Leukemia L1210

no.	R	in vitro: ID ₅₀ , ^a M	in vivo ^b		
			dose per injn, ^c mg/kg	ILS, ^d % of control	host toxicity at higher doses ^e
1c		3.4×10^{-9}	0.25	37	y
7		1.3×10^{-5}	160	4	nt
9		6×10^{-7}	128	48	nt
11		7×10^{-5}	100	5	y

^a ID₅₀ is the concentration required to reduce the growth rate of L1210 cells in culture to half of the control rate. ^b Data are presented for the dose that gave optimal activity or for inactive compounds (ILS < 25%), the highest nontoxic dose tested. Data for compound 1c is the average of seven experiments; others are from single experiments. ^c Administered ip to L1210-bearing mice once daily on days 1-9 after inoculation of the animals with 10⁵ tumor cells. ^d ILS is the increase in life span for drug-treated animals as compared to control, untreated tumor-bearing animals, expressed as a percentage of the life span of the untreated tumor-bearing animals. ^e Occurrence of drug-induced shortening of life span resulting from treatment with higher doses: y = yes; nt = no higher dose tested.

The route we envisaged for the preparation of the remaining deoxysangivamycin derivative (5'-deoxysangivamycin) was based on the fact that sulfur-containing compounds are good intermediates for 5'-deoxynucleoside synthesis. Sangivamycin (1c) was treated with diphenyl disulfide and tri-*n*-butylphosphine in pyridine¹⁸ to give 5'-(phenylthio)-5'-deoxysangivamycin (10) in 80% yield (Scheme III). A downfield shift of the peak assigned to the 5' protons and a disappearance of the signal for the 5'-hydroxy group indicated that a selective substitution had occurred at the 5' carbon. Desulfurization of compound 10 with Raney nickel gave a white solid, which was assigned the structure 4-amino-7-(5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (11, 5'-deoxysangivamycin). Additional confirmation for the proof of structure for 11 was determined by ¹H NMR, UV, and mass spectroscopy, as well as elemental analysis.

All of the monodeoxy derivatives of the nucleoside antibiotic sangivamycin have been synthesized, *vide supra*, and an evaluation of their anticancer activity is described in the following section.

Antitumor Results and Discussion

Sangivamycin (1c) and its three deoxy derivatives, 7, 9, and 11, were evaluated for their activity against murine leukemia L1210 in vitro and in vivo (Table I). The parent compound 1c was the most effective, and the 3'-deoxy derivative (9) also had significant antitumor activity both in vitro and in vivo. Using high-pressure liquid chromatographic methods (to be published elsewhere¹⁹), we checked the samples of compounds 7, 9, and 11 that were

used for cytotoxicity testing for possible contamination with sangivamycin (1c). Compound 7 was found to contain 0.05% 1c, but 1c was not detectable in 9 or 11 (detection limit = 0.01%). Thus, the slight cytotoxic effects of 7 and 11 could have been due to contamination with trace amounts of 1c, since 0.03% 1c in 7 and 0.005% 1c (less than the detection limit) in 11 would have been sufficient to produce the observed growth inhibition. However, the cytotoxic activity of 3'-deoxysangivamycin (9) was two orders of magnitude greater than could be accounted for by an undetectable amount of 1c; i.e., the ID₅₀ is two orders of magnitude lower than would result from the presence of 0.01% 1c in the sample of 9. Therefore, we have concluded that the activity observed for 9 was due to 3'-deoxysangivamycin, *per se*. This compound (9) also showed in vivo antitumor activity against murine leukemia L1210. The ILS produced by the optimal (highest tested) dose of 9 compared favorably with that obtained at the optimal dose of sangivamycin (1c) (Table I). In contrast, compounds 7 and 11 were inactive in the in vivo antitumor testing.

The 2'- and 3'-deoxy derivatives of another pyrrolo[2,3-*d*]pyrimidine antibiotic, tubercidin (1a), were recently reported²⁰ to be virtually ineffective in inhibiting the growth of L1210 cells in vitro. On the other hand, 3'-deoxyadenosine, in the presence of the adenosine deaminase inhibitor 2'-deoxycoformycin, caused a 50% decrease in the growth rate at about 5×10^{-7} M,²⁰ a value comparable to the ID₅₀ reported here for 3'-deoxysangivamycin (9), *per se* (Table I). Since sangivamycin resists deamination, it appears that 3'-deoxysangivamycin may be viewed as a deamination-resistant analogue of 3'-

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deoxyadenosine, which has been reported to have *in vivo* as well as *in vitro* antitumor activity when administered in combination with 2'-deoxycoformycin.⁵ 3'-Deoxytubercidin should also resist deamination, since the parent compound tubercidin is not deaminated.⁵ The observation²⁰ that 3'-deoxytubercidin was, nevertheless, ineffective as an antitumor agent *in vitro* further suggests that the antitumor activity of 3'-deoxysangivamycin cannot be totally accounted for by its resistance to deamination.

Thus, 3'-deoxysangivamycin (9) will be further investigated as an antitumor agent. As compared with sangivamycin (1c), its lesser potency on a molar basis may provide a wider therapeutic dosage range without host toxicity. The major clinical toxicities of sangivamycin were hypotension and flushing, which could be minimized if the drug was infused slowly.²¹ These side effects indicated that sangivamycin had a vasodilator effect such as has been observed for adenosine.²² Studies on the structure-activity requirements for coronary vasodilation showed that 3'-deoxyadenosine was only 6% as effective as adenosine, on a molar basis.²³ If a similar difference in vasodilating potency applied to sangivamycin (1c) and 3'-deoxysangivamycin (9), it would at least partially offset the requirement for higher doses of 9 to achieve a therapeutic effect comparable to 1c (see Table I). This prediction was supported by the observations that 9 was nontoxic to the host at 128 mg/kg, the highest dose tested, while 1c caused drug-induced shortening of the host life span when the dose exceeded 0.25 mg/kg.

The biochemical mechanism of action for 3'-deoxysangivamycin is unknown, but the most likely hypothesis would be that its effects would resemble those of sangivamycin and/or cordycepin (3'-deoxyadenosine), which interfere with various aspects of RNA transcription and posttranscriptional modifications.^{5,24}

Experimental Section

Proton magnetic resonance (¹H NMR) spectra were obtained with JEOL C60H, Varian A56/60, and Varian EM-390 spectrometers (solution in dimethyl-*d*₆ sulfoxide or chloroform-*d*) with chemical-shift values reported in δ (parts per million) relative to an internal standard (sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane). Ultraviolet spectra were recorded on a Beckman Acta CIII spectrophotometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Preparative thin-layer chromatography was performed on glass plates coated with silica gel (1.50 mm, SilicAR 7GF, Mallinckrodt). Compounds of interest were detected by either ultraviolet lamp (Mineralight, 254 nm) or treatment with sulfuric acid, followed by charring. Open-bed column chromatography was carried out on SilicAR CC7 (Mallinckrodt) using gravity flow. The columns were packed as slurries with the elution solvent. All solvent proportions are given by volume. Evaporations were performed in a rotary evaporator under reduced pressure (water aspirator) or *in vacuo* at 40 °C unless otherwise stated. All compounds were dried *in vacuo* at 80 °C for 10 to 15 h before submission for elemental analysis. Elemental analyses were performed by M-H-W Laboratories,

Phoenix, AZ. The presence of water of crystallization in the elemental analyses was verified by ¹H NMR.

4-Amino-6-bromo-5-cyano-7-[2,3-*O*-(dibutylstannylene)- β -D-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine [6-Bromo-2',3'-*O*-(dibutylstannylene)toyocamycin, 3a]. A mixture of 6-bromotoyocamycin (2a; 577 mg, 1.56 mmol) and di-*n*-butyltin oxide (390 mg, 1 equiv) in methanol (50 mL) was heated at reflux for 3 h to produce an amorphous solid. This solid was collected by filtration to give 841 mg (92%, 1.43 mmol) of a white solid. A sample was recrystallized from ethanol-acetone to yield colorless prisms of 2a, mp 206–208 °C. Anal. (C₁₉H₂₈H₅O₄BrSn) C, H, N.

4-Amino-6-bromo-7-[2,3-*O*-(dibutylstannylene)- β -D-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine-5-carboxamide [6-Bromo-2',3'-*O*-(dibutylstannylene)sangivamycin, 3b]. 4-Amino-6-bromo-7- β -D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxamide (2b; 2.60 g, 6.70 mmol) and di-*n*-butyltin oxide (1.733 g, 6.93 mmol) were dissolved in methanol (150 mL), and the mixture was heated at reflux for 2.5 h. The reaction mixture was allowed to stand at 5 °C for 12 h, and the crystalline precipitate was collected by filtration to yield 3.71 g (91%) of 3b, mp 215–217 °C. Anal. (C₁₉H₃₀BrN₅O₅Sn) C, H, N.

4-Amino-6-bromo-5-cyano-7-(2-*O*-*p*-toluenesulfonyl- β -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (6-Bromo-2'-*O*-tosyltoyocamycin, 4a). 6-Bromo-2',3'-*O*-(butylstannylene)toyocamycin (3a, 841 mg) was dissolved in 50 mL of methanol. Tosyl chloride (4.1 g, 15 equiv) and triethylamine (3.0 mL, 15 equiv) were then added, and the solution was stirred for 3 h at room temperature. The white crystals that had formed were collected by filtration to yield 480 mg (64%) of 4a: mp 188–191 °C; IR (KBr) 2240 (CN), 1180 (covalent tosylate) cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 8.14 (s, 1 H, H-2), 7.39 (d, 2 H, Ts H_a), 7.10 (d, 2 H, Ts H_b), 6.15 (d, 1 H, H-1', *J*_{1',2'} = 6.5 Hz), 2.36 (s, 3 H, Ts CH₃). Anal. (C₁₈H₁₆N₅O₆SBr) C, H, N.

Large-Scale Synthesis of 6-Bromo-2'-tosylsangivamycin (4b). 6-Bromotoyocamycin (2a; 7.77 g, 20 mmol) and di-*n*-butyltin oxide (5.27 g, 1 equiv) were added to 1 L of methanol, and the reaction mixture was heated at reflux for 1.5 h. The reaction mixture was cooled to room temperature, with tosyl chloride (59.2 g, 15 equiv) and triethylamine (43.5 mL) then being added while cooling the solution in an ice bath. The reaction mixture was stirred at room temperature for 3 h, during which time white crystals precipitated from the solution. The moist crystals were then suspended and stirred in a mixture of 30% hydrogen peroxide (34 mL), concentrated ammonia solution (68 mL), and methanol (270 mL) at room temperature for 4 h. Concentration of the solvent yielded 4-amino-6-bromo-7-(2-*O*-*p*-toluenesulfonyl- β -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (4b; 6.93 g, 13.1 mmol, 66% from 6-bromotoyocamycin).

4-Amino-6-bromo-7-(2-*O*-*p*-toluenesulfonyl- β -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (2'-*O*-Tosylsangivamycin, 4b). **Method 1.** 2',3'-*O*-(Dibutylstannylene)-6-bromosangivamycin (3b; 3.68 g, 6.06 mmol) was dissolved in methanol, with triethylamine (12.7 mL, 15 equiv) and tosyl chloride (17.3 g, 15 equiv) then being added. The mixture was allowed to stir at room temperature for 1 h, and the solvent was then evaporated *in vacuo*. Water (120 mL) was added to the residue, and the solution was extracted with ether (50 mL). The aqueous layer was separated and washed with ether (50 mL \times 3). The aqueous layer was then concentrated to 100 mL *in vacuo* and allowed to stand at 5 °C for 18 h to yield 4b (2.28 g, 71%): mp 191–193.5 °C; ¹H NMR (Me₂SO-*d*₆) δ 8.0 (br, 2, 5-CONH₂), 7.96 (s, 1 H, H-2), 7.76 (br, 2 H, 4-NH₂), 7.47 (d, 2 H, Ts H_a), 7.01 (d, 2 H, Ts H_b), 6.15 (m, 2 H, H-1' and 3'-OH), 5.86 (t, 1 H, H-2'), 5.73 (br, 1 H, 5'-OH), 4.42 (m, 1 H, H3'), 4.08 (m, 1 H, H-4'), 3.63 (m, 2 H, H-5'), 2.26 (s, 3 H, Ts CH₃); IR (KBr) 1180 (covalent tosylate) cm⁻¹. Anal. (C₁₉H₂₁N₅O₇Br \cdot 0.5 H₂O) C, H, N.

Method 2. 6-Bromo-2'-tosyltoyocamycin (4a; 153 mg) was stirred in a mixture of 30% hydrogen peroxide (0.5 mL), concentrated ammonia solution (1 mL), and methanol (4 mL) at room temperature. After 2 h, the solution became a clear, yellow color, and then a solid began to separate from the solution. After 5.5 h, the solvent was removed *in vacuo*, and water (5 mL) was then added to the residue. The mixture was allowed to stand at 5 °C for 18 h to yield 4b (104 mg, 0.19 mmol, 66%), identical in all respects with the product obtained by method 1.

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6,2'-Cyclo-4-amino-6-mercapto-7- β -D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxamide Hydrobromide (6,2'-S-Cyclosangivamycin Hydrobromide, 5). 6-Bromo-2'-tosylsangivamycin (4b, 6.93 g, 13.1 mmol) was dissolved in 1-propanol (400 mL) and then saturated with argon gas. Thiourea (2.55 g, 3 equiv) was added to the solution, and the solution was heated at reflux for 3 h. More thiourea (2.55 g) was then added, and heating at reflux was continued for an additional 3.5 h. The reaction mixture was allowed to stand for 19 h at room temperature. The solid was removed by filtration and then recrystallized from an ethanol-water mixture to give 5 (2.96 g, 56%): mp 267–269 °C dec; ¹H NMR (Me₂SO-*d*₆) δ 9.24 and 7.44 (2 br s, 4 H, 4-NH₂, 5-CONH₂), 8.47 (s, 1 H, H-2), 6.52 (d, 1 H, H-1', *J*_{1',2'} = 6.5 Hz), 6.0 (br, OH), 4.99 (d, 1 H, H-2'), 4.46 (m, 1 H, H-3'), 4.08 (q, 1 H, H-4'), 3.45 (m, 2 H, H-5'). Anal. (C₁₂H₁₃N₅O₄S·HBr) C, H, N.

6,2'-Cyclo-4-amino-6-mercapto-7- β -D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxamide (6). 6,2'-S-Cyclosangivamycin hydrobromide (5; 20 mg, 0.05 mmol) was dissolved with heating in 10 mL of water. The solution was cooled to room temperature, 0.5 mL of triethylamine was added, and the solution was then concentrated to \approx 5 mL to yield 6 (0.33 mmol, 66%). The product was recrystallized from an ethanol-water mixture to afford an analytical sample, mp 290 °C. Anal. (C₁₂H₁₃N₅O₄S) C, H, N.

4-Amino-7-(2-deoxy- β -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (2'-Deoxysangivamycin, 7). 6,2'-S-Cyclosangivamycin hydrobromide (5; 1.0 g) was dissolved in a mixture of water (70 mL) and dioxane (10 mL) with heating and then neutralized with concentrated ammonia solution. A solid began to separate but was redissolved by the addition of dioxane. The mixture was then heated at reflux with the addition of Raney nickel (4 mL) for 45 min. An additional 3.3 mL of Raney nickel was then added, and the mixture was heated at reflux for another 1.5 h. The Raney nickel was removed by filtration, and the solvent was evaporated to dryness in vacuo. The resulting solid was crystallized from methanol to yield 340 mg (1.16 mmol, 47%) of 7: mp 258 °C; mass spectrum, *m/z* 581 (M + 4-Me₃Si); ¹H NMR (Me₂SO-*d*₆) δ 8.12 and 8.15 (2 s, 2 H, H-2 and H-6), 7.8 and 7.4 (2 br s, 4 H, 4-NH₂ and 5-CONH₂), 6.52 (t, 1 H, H-1', *J*_{1',2'} = 7 Hz), 5.30 (d, 1 H, H-3' OH), 4.96 (t, 1 H, H-5' OH), 4.39 (m, 1 H, H-3'), 3.86 (m, 1 H, H-4'), 3.58 (m, 2 H, H-5'), 2.3 (m, 2 H, H-2'). Anal. (C₁₂H₁₅N₅O₄·0.5H₂O) C, H, N.

4-Amino-7-[2-*O*-acetyl-3-deoxy-3-iodo-5-*O*-(2,5,5-trimethyl-4-oxo-1,3-dioxolan-2-yl)- β -D-xylofuranosyl]pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (8a) and 4-Amino-7-(2,5-di-*O*-acetyl-3-deoxy-3-iodo- β -D-xylofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (8b). To a vigorously stirred solution of dried sodium iodide (12.1 g) in 80 mL of anhydrous acetonitrile was added 4.64 g of α -acetoxyisobutryl chloride, followed immediately by 2.45 g of previously dried sangivamycin (1c). The brown reaction mixture was stirred for 1 h at room temperature while being protected from moisture. The mixture was then poured into a stirred solution of 192 mL of saturated aqueous NaHCO₃ and 125 mL of saturated Na₂S₂O₃ solution. A 100-mL portion of CHCl₃ was added, and the layers were separated. The aqueous layer was extracted with CHCl₃ (2 \times 30 mL), and the combined organic extractions were washed with water and dried over Mg₂SO₄; the Mg₂SO₄ was collected by filtration, and the filtrate was then concentrated to 20 mL. The solution was applied to and isolated from a column of silica gel using CHCl₃-EtOH. Compounds 8a and 8b were obtained in 56 and 20% yields, respectively, from the evaporation of the appropriate middle fraction (s).

4-Amino-7-(3-deoxy- β -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (3'-Deoxysangivamycin, 9). Compound 8a (2.6 g) and 280 mg of sodium acetate were dissolved in a mixture of 50 mL of EtOH and 8 mL of water. This solution was hydrogenated for 18 h at 40 psi of hydrogen in the presence of 0.4 g of 10% Pd/C catalyst. The mixture was partitioned between CHCl₃ and water; the organic phase was separated and then washed again with water, dried over Mg₂SO₄, and filtered, and the filtrate was evaporated to dryness in vacuo. The resulting solid was dissolved in 15 mL of methanol, and this solution was then saturated with NH₃ at 0 °C and allowed to stand at room temperature for 20 h. The solution was evaporated to dryness

in vacuo, and the resulting solid was crystallized from an EtOH-H₂O mixture to yield 196 mg of compound 9.

The water layer was treated with 10 mL of 60% ammonium hydroxide at 4 °C for 16 h to yield an additional 430 mg of 9: total yield 626 mg (2.17 mmol, 49%); mp 280–281 °C; ¹H NMR (Me₂SO-*d*₆) δ 8.19 and 8.13 (2 s, 2 H and H₈), 8.00 and 7.43 (2 br s, 4 H, 5-CONH₂ and 4-NH₂), 6.13 (d, 1 H, *J*_{1',2'} = 1 Hz), 5.69 (d, 1 H, H-2' OH), 5.00 (br, 1 H, H-5' OH), 4.46 (m, 2 H, H-2', H-4'), 3.67 (m, 2 H, H-5'), 2.10 (m, 2 H, H-3'). Anal. (C₁₂H₁₅N₅O₄) C, H, N.

4-Amino-7-[5-(phenylthio)-5-deoxy- β -D-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine-5-carboxamide [5'-Deoxy-5'-(phenylthio)sangivamycin, 10]. Sangivamycin (1c; 0.87 g, 2.82 mmol) and diphenyl disulfide (1.41 g, 6.27 mmol) were dissolved in 2.8 mL of pyridine, followed by the addition of tributylphosphine (2.25 mL, 9.02 mmol). The mixture was stirred at room temperature for 20 h and then poured into a mixture of water (50 mL) and ether (50 mL). The resulting solid was dissolved in a small amount of ethanol and allowed to stand at 5 °C for 24 h. The solid was recrystallized from a water-ether mixture to give a white solid (770 mg, 68%): mp 106–109 °C; ¹H NMR (Me₂SO-*d*₆) δ 8.02 and 7.99 (2 s, 2 H, H-2, H-6), 7.4–8.3 (br, 4 H, 4-NH₂ and 5-CONH₂), 7.1–7.4 (m, 5 H, phenyl), 6.01 (d, 1 H, H-1', *J*_{1',2'} = 5 Hz), 5.41 and 5.24 (2 d, 2 H, H-2' OH and H-3' OH), 4.31 (q, 1 H, H-2'), 3.8–4.2 (m, 2 H, H-3' and H-4'), 3.30 (m, 2 H, H-5'). Anal. (C₁₈H₂₀N₅O₄S) C, H, N.

4-Amino-7-(5-deoxy- β -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (5'-Deoxysangivamycin, 11). 5'-Deoxy-5'-(phenylthio)sangivamycin (10; 0.4 g, 1 mmol) was added to a mixture of 30 mL of dioxane and 20 mL of water. The mixture was heated at reflux with Raney nickel (3 mL) for 45 min. An additional 3 mL of Raney nickel was added, and heating at reflux was continued for 45 min. Raney nickel was removed by filtration, the filtrate was evaporated, and the resulting solid was crystallized from methanol to yield 118 mg (0.40 mmol, 41%) of 11: mp 262–264 °C; ¹H NMR (Me₂SO-*d*₆) δ 8.12 (s, 2 H, H-2 and H-6), 7.9 and 7.3 (2 br s, 4 H, 5-CONH₂ and 4-NH₂), 6.08 (d, 1 H, H-1', *J*_{1',2'} = 4 Hz), 5.43 and 5.13 (2 d, 2 H, H-2' OH and H-3' OH), 4.24 (q, 1 H, H-2'), 4.1–3.7 (m, 2 H, H-3' and H-4'), 1.35 (d, 3 H, H-5', *J*_{4',5'} = 6 Hz). Anal. (C₁₂H₁₅N₅O₄) C, H, N.

Antitumor Studies. The *in vitro* cytotoxicity against L1210 was evaluated as described previously.²⁵ L1210 cells were grown in static suspension culture using Fischer's medium for leukemic cells of mice, and the growth rate over a 3-day period was determined in the presence of various concentrations of the test compound. The ID₅₀ was defined as the concentration required to reduce the growth rate to 50% of the control.

The *in vivo* antitumor data were furnished by the Division of Cancer Treatment using standard National Cancer Institute protocols for evaluation of compounds against the murine leukemia L1210.²⁶

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