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(71) Applicant: SOUTHERN RESEARCH INSTITUTE [US/US]; 2000 Ninth Avenue South, Birmingham, AL 35255-5305 (US).

(72) Inventors: MONTGOMERY, John, A. ; 3596 Springhill Road, Birmingham, AL 35233 (US). SECRIST, John, A., III ; 5564 Surrey Lane, Birmingham, AL 35242 (US).

(74) Agent: BERDO, Robert, H.; Roylance, Abrams, Berdo & Goodman, 1225 Connecticut Avenue, N.W., Washington, DC 20036 (US).

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(54) Title: 2′-DEOXY-4′-THIORIBONUCLEOSIDES AS ANTIVIRAL AND ANTICANCER AGENTS

(57) Abstract

2′-Deoxy-4′-thio-ribonucleosides, intermediates in their production, and their use as antiviral and anticancer agents are disclosed.

* See back of page

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2'-DEOXY-4'-THIORIBONUCLEOSIDES AS ANTIVIRAL AND ANTICANCER AGENTS

Background of the Invention

1. Field of the Invention

This invention relates to 2'-deoxy-4'-thioribonucleosides and intermediates useful in their production, and to the use of 2'-deoxy-4'-thioribonucleosides as antiviral and anticancer agents.

A nucleoside is a molecule comprised of a pentose sugar in a furanose ring joined to a nitrogenous heterocyclic base that is a derivative of either purine or pyrimidine. A 4'-thionucleoside is a nucleoside wherein the furanose ring

oxygen has been replaced by sulfur. A 2'-deoxy-4'-thioribonucleoside is a 4'-thionucleoside wherein the pentose sugar is 2'-deoxy-D-ribose.

As used herein, the terms "nucleoside", "4'-thionucleoside" and "2'-deoxy-4'-thioribonucleoside" shall also include compounds wherein the nitrogenous heterocyclic base is a base related to the purine and pyrimidine bases, but with a ring alteration, such nitrogenous heterocyclic bases including 3-deazapurines, 7-deazapurines, 8-azapurines, 2-azapurines, 5-azapyrimidines, 6-azapyrimidines, and 3-deazapyrimidines and shall also include compounds having acyl protecting groups at the 3' position, or the 5' position, or both, of the 2'-deoxy-D-ribose.

2. Description of the Related Art

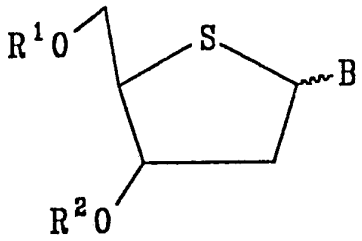
Several 4'-thionucleosides have been reported in the literature. Reist, et al, J. Am. Chem. Soc., 86, 5658 (1964) disclose L and D forms of 4'-thioriboadenosine. Biological effects of 4'-thioriboadenosine are described in Miura, et al in Purine and Pyrimidine Metabolism in Man, V, Part B, (Plenum Publishing Corp., 1986) p. 667. Richie, et al, Can. J. Chem., 56, 794 (1977) disclose the synthesis of 9-(3-deoxy-4-thio-β-D-erythro-pentofuranosyl)adenine (4'-thiocordycepin). Reist, et al, J. Org. Chem., 33, 189 (1968) describe the synthesis of adenine nucleosides of 4-thio-D-xylose and 4-thio-D-arabinose. Ototani, et al. J. Med. Chem., 17, 535 (1974) disclose the preparation and antitumor activity of 4'-thio-1-β-D-arabinofuranosylcytosine and 2,2'-anhydro-4'-thio-1-β-D-arabinofuranosylcytosine hydrochloride.

The description, preparation and use of specific 2'-deoxy-4'-thioribonucleosides is not found in the literature. Fu, et al, J. Org. Chem., 41, 3831 (1976) disclose a method for the preparation of anomeric methyl-2-deoxy-4-thio-D-erythro-pentofuranosides and suggest

that the furanosides could be used as precursors for the synthesis of 2'-deoxy-4'-thionucleosides.

Summary of the Invention

It has now been found that certain 2'-deoxy-4'-thioribonucleosides have useful antiviral and anticancer activities. Thus, in accordance with this invention, there are provided novel 2'-deoxy-4'-thioribonucleosides represented by the formula



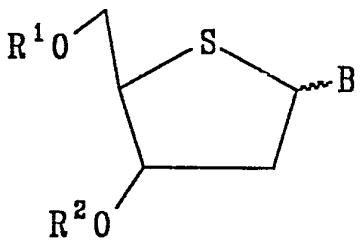
wherein:

~B indicates that B can be either alpha or beta, and

B is a nitrogenous heterocyclic base selected from the group consisting of pyrimidine, 5-azapyrimidine, 6-azapyrimidine, 3-deazapyrimidine purine, 3-deazapurine, 7-deazapurine, 8-azapurine, and 2-azapurine bases. By the term "pyrimidine base" is meant any pyrimidine derivative including, but not limited to, uracil (2,4-dioxopyrimidine), thymine (5-methyl-2,4-dioxopyrimidine), cytosine (4-amino-2-oxopyrimidine), and 5-methylcytosine (4-amino-5-methyl-2-oxopyrimidine), and derivatives having a halogen attached to the C^5 heterocyclic carbon. By the term "5-azapyrimidine base" is meant any 5-azapyrimidine derivative including, but not limited to, 5-aza-2,4-dioxopyrimidine and 4-amino-5-aza-2-oxopyrimidine. By the term "6-azapyrimidine base" is meant any 6-azapyrimidine derivative including, but not limited to, 6-aza-2,4-dioxopyrimidine, 4-amino-6-aza-2-oxopyrimidine, and derivatives having a methyl group or

halogen attached to the C^5 heterocyclic carbon. By the term "3-deazapyrimidine base" is meant any 3-deazapyrimidine derivative including, but not limited to, 3-deaza-2,4-dioxopyrimidine, 4-amino-3-deaza-2-oxopyrimidine, and derivatives having a methyl group or halogen attached to the C^5 heterocyclic carbon. By the term "purine base" is meant any purine derivative including, but not limited to, adenine (6-aminopurine), guanine (2-amino-6-oxopurine), 2,6-diaminopurine, 1-6-dihydro-6-oxopurine, and derivatives having a halogen attached to the C^2 heterocyclic carbon. By the term "3-deazapurine base" is meant any 3-deazapurine derivative including, but not limited to, 6-amino-3-deazapurine, 3-deaza-6-oxopurine, and derivatives having an amino group or halogen attached to the C^2 heterocyclic carbon. By the term "7-deazapurine base" is meant any 7-deazapurine derivative including, but not limited to, 6-amino-7-deazapurine, 7-deaza-6-oxopurine, and derivatives having an amino group or a halogen attached to the C^2 heterocyclic carbon. By the term "8-azapurine base" is meant any 8-azapurine derivative including, but not limited to, 6-amino-8-azapurine, 8-aza-6-oxopurine, and derivatives having a halogen attached to the C^2 heterocyclic carbon. By the term "2-azapurine base" is meant any 2-azapurine derivative including, but not limited to, 6-amino-2-azapurine and 2-aza-6-oxopurine. R^1 and R^2 in the above diagram may be the same or different and may be hydrogens or conventional acyl protecting groups.

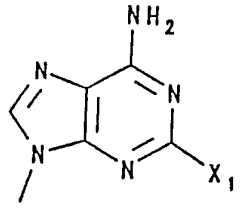
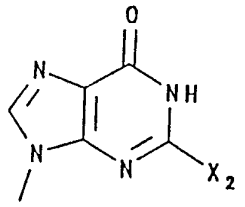
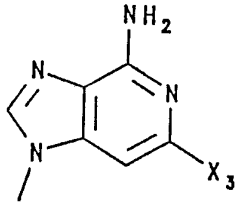
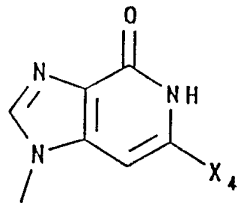
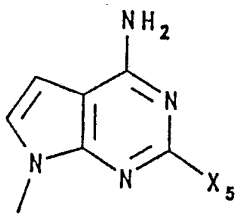
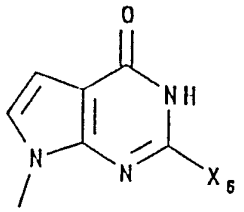
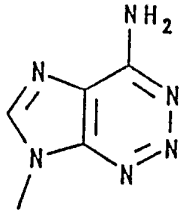
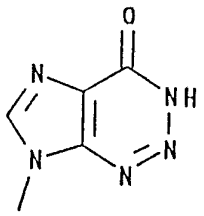
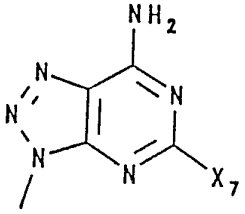
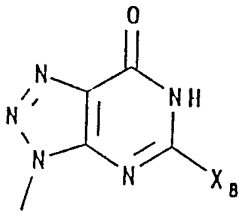
The invention may be illustrated by the following, wherein the compounds encompassed by the invention are represented by the formula



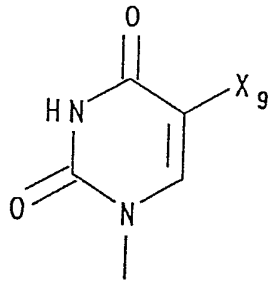
wherein:

~B indicates that B can be either alpha or beta, and

B is a member selected from the group consisting of the following nitrogenous heterocyclic bases:

where $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8$ = H, NH_2 or halogen,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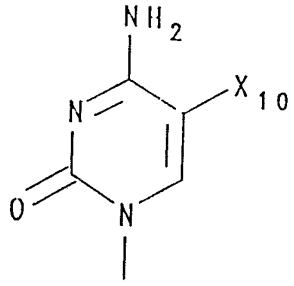
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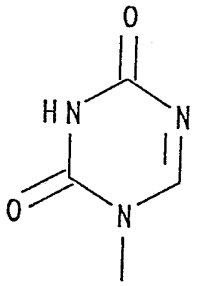
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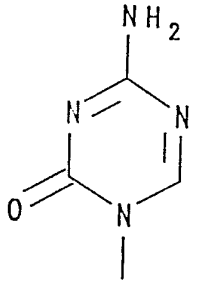
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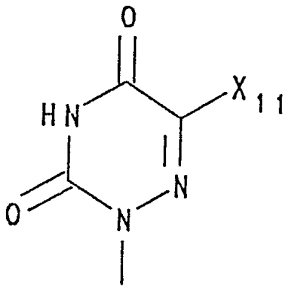
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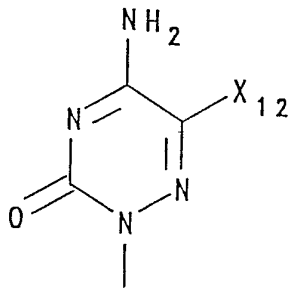
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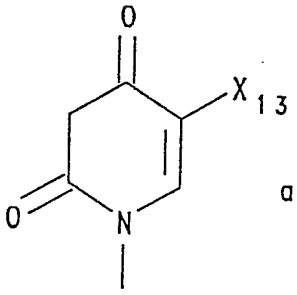
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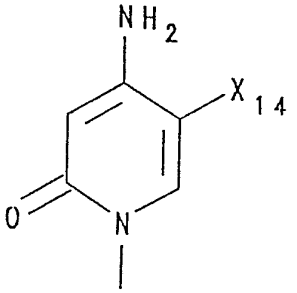
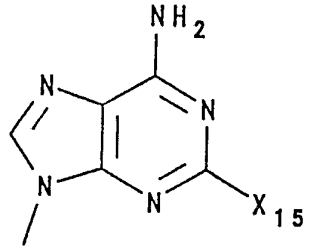

,

where X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14} = H, CH_3, or halogen and R^1 and R^2 can be the same or different and may be hydrogen or acyl protecting groups.

Preferably, the nitrogenous heterocyclic base is selected from the group consisting of the following purine and pyrimidine bases:



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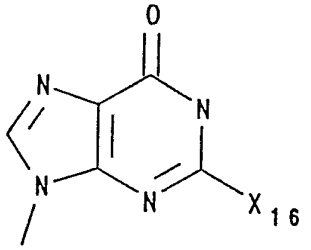

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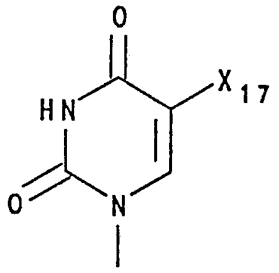
where X_{15}, X_{16} = H, NH_2 or halogen, and



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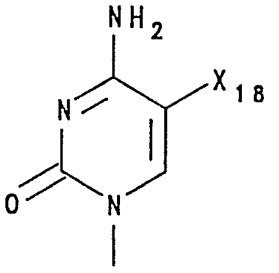

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where X_{17}, X_{18} = H, CH_3 or halogen.

According to another aspect of this invention, there is administered to a host animal, including man, afflicted with a viral infection, e.g., an infection caused by herpes simplex virus types 1 or 2, a therapeutically effective amount of a 2'-deoxy-4'-thioribonucleoside as previously defined.

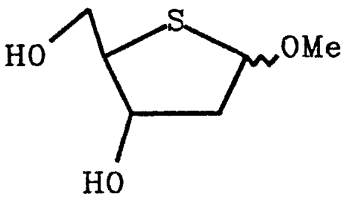
According to another aspect of this invention, there is administered to a host animal, including man, afflicted with cancer, a therapeutically effective amount of a 2'-deoxy-4'-thioribonucleoside as previously defined. By the term "cancer" is meant any new and abnormal cell growth, specifically a new growth of tissue which is uncontrolled

and progressive. Compounds of this invention may be used, for example, in the treatment of leukemias, epidermoid carcinoma, lymphomas, choriocarcinoma, Wilm's tumor, neuroblastoma, rhabdomyosarcoma, carcinoma of the testis, and breast and lung tumors.

In accordance with still another aspect of this invention, there are provided novel intermediates useful in the preparation of certain 2'-deoxy-4'-thioribonucleosides.

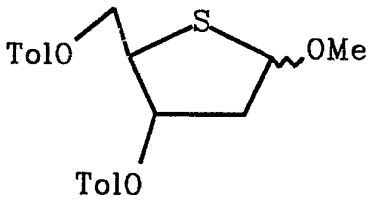
Detailed Description of the Invention

The synthesis of the 2'-deoxy-4'-thioribonucleosides may be carried out by beginning with 1-O-methyl 2-deoxy-4-thio-α,β-D-ribofuranose of formula 1



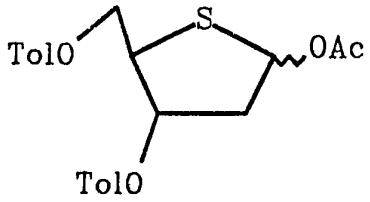
1

the preparation of which is described in Fu, et al, J. Org. Chem., 41, 3831 (1976), the disclosure of which is incorporated herein by reference. The compound of formula 1 is reacted with p-toluoyl chloride to give the compound of formula 2



2

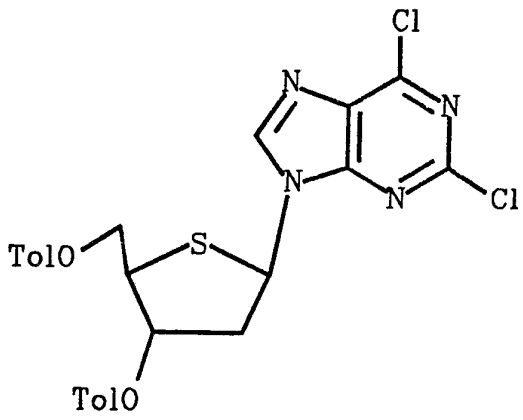
The methyl group is then replaced by an acetyl group to give the compound of formula 3



3

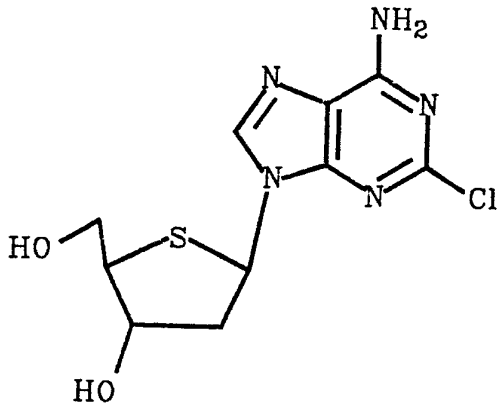
The 2'-deoxy-4'-thioribonucleosides are prepared by coupling compound 3 with nitrogenous heterocyclic bases and then removing the toluoyl protecting groups. Compound 3 is coupled with a purine in the presence of tin(IV) chloride. (See Saneyoshi, et al, Chem. Pharm. Bull., 27, 2518 (1979)). Compound 3 is coupled with a 3-deazapurine, 7-deazapurine, 8-azapurine or 2-azapurine in a similar manner. Compound 3 is coupled with a pyrimidine using the catalysts hexamethyldisilazane, trimethylchlorosilane, and trimethylsilyl trifluoromethanesulfonate (see Vorbruggen, et al, Chem. Ber., 114, 1234 (1981)). Compound 3 is coupled with a 5-azapyrimidine, 6-azapyrimidine and 3-deazapyrimidine in a similar manner. The coupling reaction provides both α and β nucleosides in most cases. Anomers may be separated by conventional methods.

As examples of the preparation of purine compounds of this invention, compound 3 can be reacted with 2,6 dichloropurine in the presence of tin(IV) chloride to give the compound of formula 4



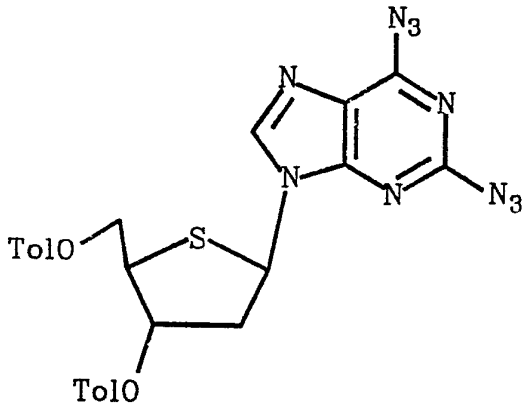
4

Compound 4 can be reacted with saturated ethanolic NH_3 to give the compound of formula 5



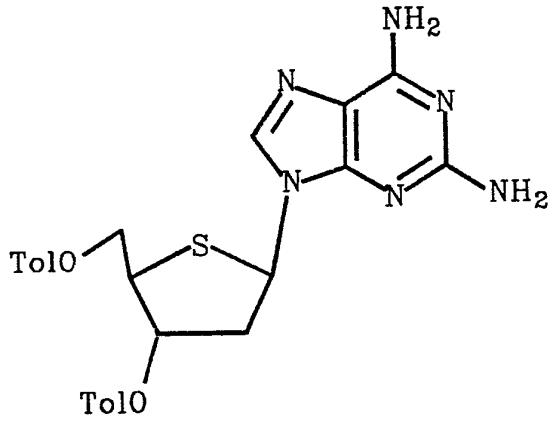
5

Compound 4 can also be reacted with sodium azide to give the compound



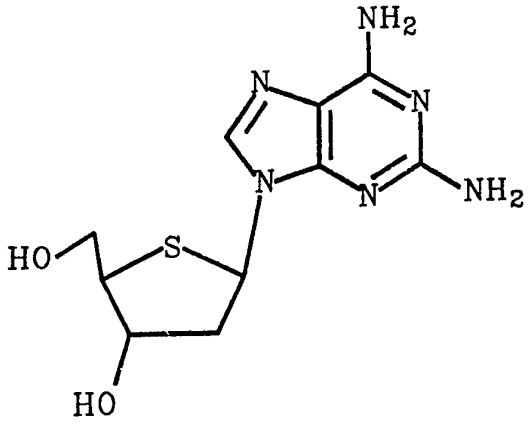
6

which can be reduced to the compound of formula 7:



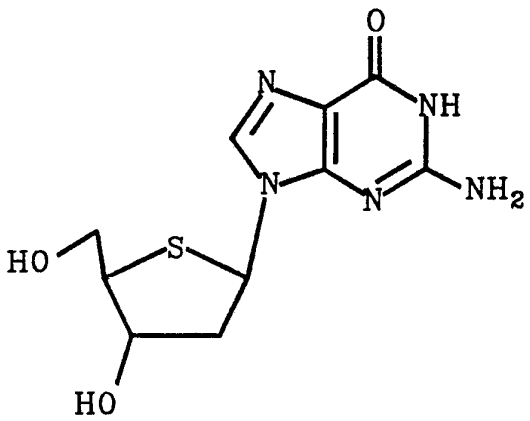
7

Deprotection of compound 7 gives the compound of formula 8



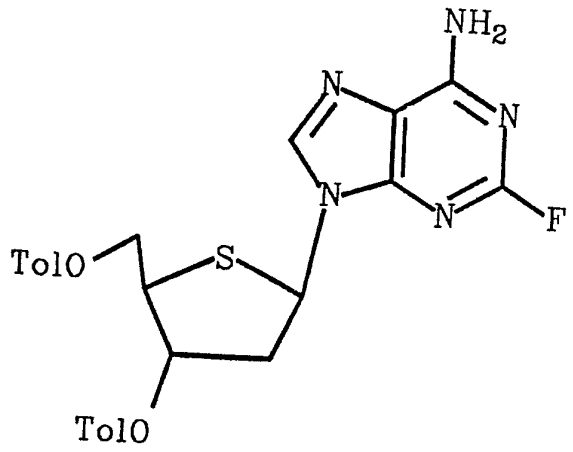
8

Compound 8 can be reduced to the compound of formula 9



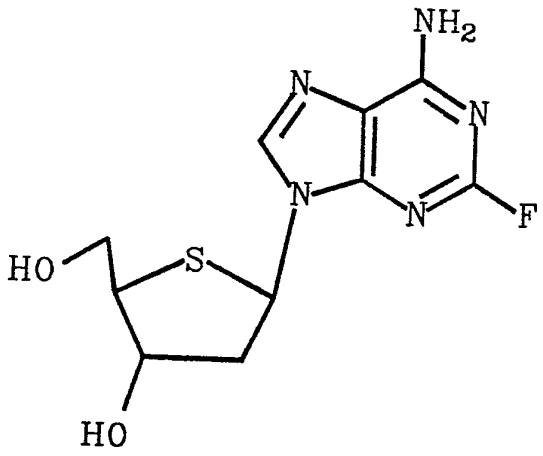
9

Compound 3 can also be reacted with 2-fluoroadenine in the presence of tin(IV) chloride to give the compound of formula 10



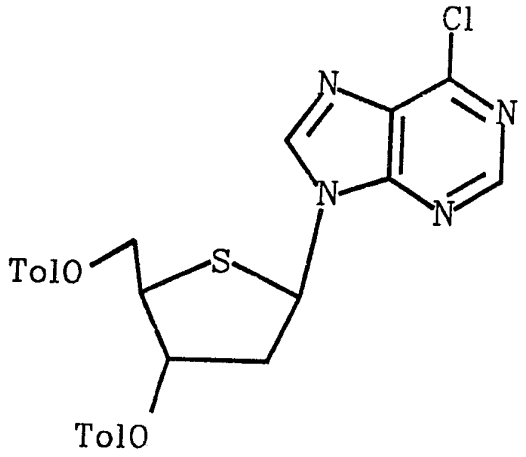
10

Removal of the toluoyl protecting groups gives the compound of formula 11



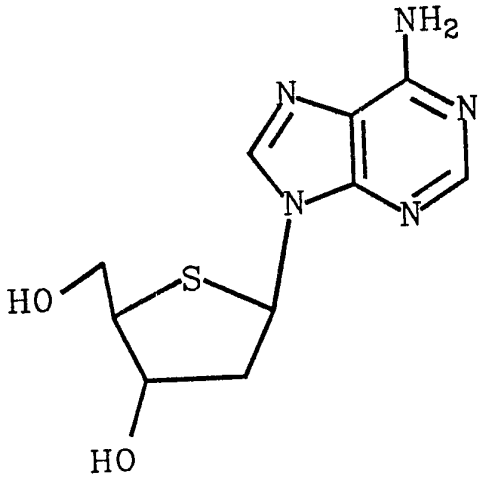
11

Compound 3 can also be reacted with 6-chloropurine in the presence of tin(IV) chloride to give the compound of formula 12



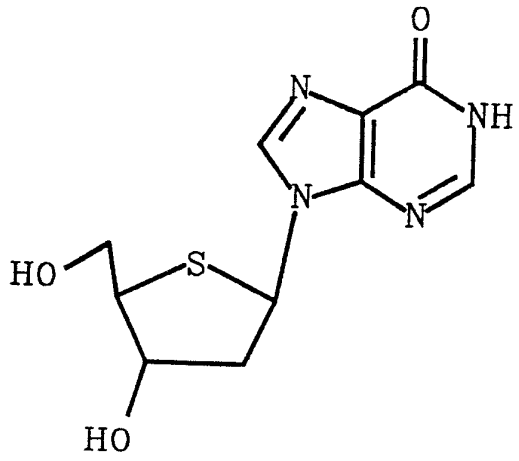
12

Reaction with saturated ethanolic NH_3 gives the compound of formula 13



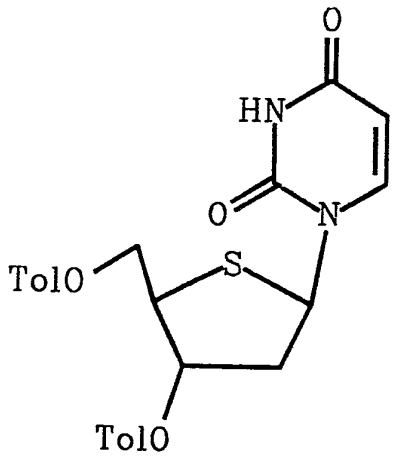
13

Compound 13 can be reduced to the compound of formula 14



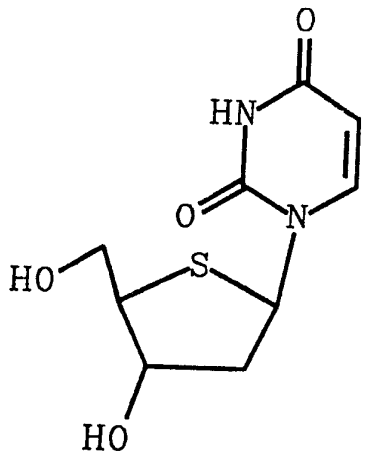
14

As examples of the preparation of pyrimidine compounds of this invention, the compound of formula 3 can be combined with uracil to give the compound of formula 15



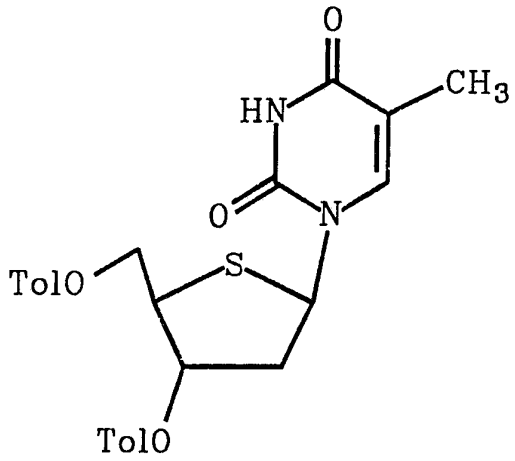
15

Removal of the toluoyl protecting groups gives the compound of the formula 16



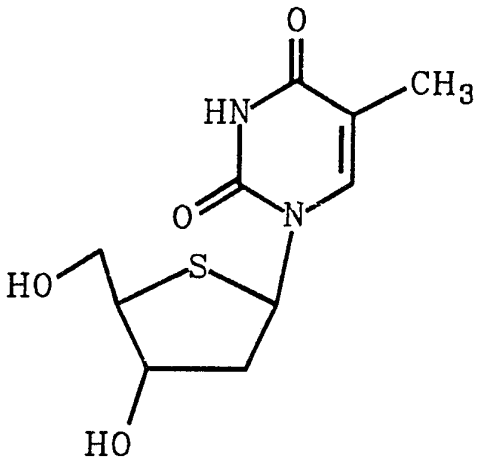
16

The compound of formula 3 can also be combined with thymine to give the compound of formula 17



17

Removal of the toluoyl protecting groups gives the compound of formula 18



18

In carrying out the synthesis of 2'-deoxy-4'-thioribonucleosides of this invention, other acyl protecting groups besides the toluoyl protecting group may be used. Further, conventional acyl protecting groups may be substituted or added, using conventional methods, to the 3' position or 5' position, or both, of the 2'-deoxy-4'-thioribonucleosides.

The following examples illustrate the preparation of the compounds described above. In these examples, MeOH is methyl alcohol, EtOH is ethyl alcohol, and Me_2SO-d_6 is deuterated dimethyl sulfoxide $(CD_3)_2SO$.

EXAMPLE 1

1-O-Acetyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose (formula 3). To a solution of 1-O-methyl-2-deoxy-4-thio-α,β-D-ribofuranose (formula 1) (10 g, 60.97 mmol) in 250 mL of sieve-dried pyridine was added p-toluoyl chloride (23.57 g, 152.5 mmol) dropwise at 0-5°C. The cooling bath was removed. After the reaction stirred for 10 hours, the reaction was essentially complete as indicated by TLC (cyclohexane-ethylacetate 5:1). The reaction mixture was poured into an ice-water mixture, stirred for 1 hour, and then diluted with 500 mL of $CHCl_3$ to give a total volume of 1000 mL. The aqueous layer was extracted with $CHCl_3$ (2 x 100 mL). The combined organic extracts were washed with dilute sulfuric acid (200 mL), aqueous saturated sodium bicarbonate (2 x 200 mL) and water until neutral, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in $CHCl_3$ (200 mL) and filtered through a 9.0 cm in diameter and 4 cm thick bed of silica gel, washed with $CHCl_3$ (2 x 100 mL) and filtrate was evaporated to dryness to afford crude

1-O-methyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose (formula 2) as a dark brown solid (24 g) which was dissolved in a acetolysis mixture containing acetic anhydride (200 mL), glacial acetic acid (200 mL), p-toluene sulfonic acid monohydrate (2.4 g) and conc. sulfuric acid (10 mL) and warmed to 40°C for 1 hour, then was decomposed by the addition of anhydrous sodium acetate. The resulting mixture was evaporated to dryness in vacuo at a temperature below 30°C. The residue was partitioned between 500 mL of water and 300 mL of $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (2 x 100 mL). The combined $CHCl_3$ layers were evaporated to dryness in vacuo, then several portions of methanol were added and removed in vacuo to eliminate the last traces of acetic anhydride. The residue was purified by a flash column containing 100 g of silica gel and eluted with 6:1 cyclohexane-ethylacetate and appropriate fractions were combined and evaporated to give a white solid, which was crystallized by 95% ethanol to give 1-O-acetyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose, yield 18.26 g (70% from 1-O-methyl-2-deoxy-4-thio-α,β-D-ribofuranose) as a α,β mixture; MS z/e 429 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (s, 3, CH_3CO), 2.04 (s, 3, CH_3CO), 2.34 (s, 6, CH_3 of toluoyl), 2.36 (s, 6, CH_3 of toluoyl), 2.52-2.74 (m, 4, H-2), 3.92-4.06 (m, 2, H-4), 4.28-4.52 (m, 4, CH_2), 5.64-5.74 (m, 2, H-3), 6.12 (dd, 1, H-1 of β, J = 3 and 6 Hz), 6.2 (d, 1, H-1 of α, J = 5.5 Hz), 7.24-7.36 (m, 4, meta CH's of toluoyl), 7.8-7.92 (m, 4, ortho CH's of toluoyl). Anal. ($C_{23}H_{24}O_6S$), C, H, S.

EXAMPLE 2

9-(2-Deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-dichloropurine (formula 4). To a solution of 1-O-acetyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose (formula 3) (411 mg, 0.96 mmol) and

2,6-dichloropurine (181.5 mg, 0.96 mmol) in CH_3CN (30 mL) was added Tin(IV) chloride (0.499 mg, 1.92 mmol) at 0°C. After the mixture was stirred for 1.5 hours, the reaction was essentially complete as indicated by TLC (cyclohexane-ethylacetate 3:1). The reaction mixture was concentrated to a small volume (about 5 mL), sodium bicarbonate (500 mg) and distilled water (2 mL) were added. When the vigorous evolution of carbon dioxide had ceased, the mixture was evaporated down under reduced pressure. The residue was dissolved in $CHCl_3$ (25 mL) and washed with water (2 x 15 mL), dried ($MgSO_4$), and evaporated to dryness. The residue contained one major and one minor component on TLC, and applied to a flash column containing 75 g of silica gel with cyclohexane- ethylacetate 5:1 to afford 9-(2'-deoxy-4'-thio-3',5'-di-O-toluoyl-β-D-ribofuranosyl)-2,6-dichloropurine (382 mg, 71%), mp 70-71°C, TLC 3:1 cyclohexane-ethylacetate, R_f 0.48; MS z/e 558 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3, CH_3), 2.42 (s, 3, CH_3), 3.0 (br d, 2, H-2'), 4.38 (m, 1, H-4'), 4.52 (m, 2, 2 x H-5'), 5.86 (s, 1, H-3'), 6.42 (t, 1, H-1', J = 3 Hz), 7.22 (d, 2, H's of toluoyl, J = 8 Hz), 7.28 (d, 2, H's of toluoyl, J = 8 Hz), 7.56 (d, 2, H's of toluoyl, J = 8 Hz), 7.98 (d, 2, H's of toluoyl, J = 8 Hz), 8.26 (s, 1, H-8); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.68, 21.71 (CH_3's of toluoyl), 42.28 (C-2'), 54.66 (C-4'), 62.01 (C-1'), 64.82 (C-5'), 78.53 (C-3'), 125.71, 126.49, 129.26, 129.36, 129.42, 129.74 (toluoyl ring carbon), 131.49 (C-5), 144.25, 144.74 (toluoyl ring carbon), 145.58 (C-8), 151.71 (C-6), 152.57 (C-4), 152.89 (C-2), 165.37, 166.07 (carbonyl carbon of toluoyl).

EXAMPLE 3

9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine (formula 5). A mixture of 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-dichloropurine (formula 4) (300 mg, 0.54 mmol) and saturated ethanolic NH_3

(50 mL) was heated at 50°C in a glass lined stainless steel pressure vessel for 48 hours. The reaction mixture was evaporated to dryness to afford a syrup which was purified on two silica gel thick plates (Analtech, GF, 1000 μM) that were developed in 4:1 $CHCl_3$-MeOH. The product was eluted with hot EtOH and evaporated. The residue was crystallized from 45 mL of boiling EtOH to give pure 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine: yield 122 mg 75%; mp 204-205°C; TLC 4:1 $CHCl_3$-MeOH, R_f 0.45; MS z/e 302 $(M + 1)^+$; UV λ_{max} pH 1 267 (11.7), pH 7 266 (12.7), pH 13 265 (12.7); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.38-2.48 (m, 1, H-2'), 2.60-2.68 (m, 1, H-2'), 3.36-3.56 (m, 2, H-5'), 3.62-3.70 (m, 1, H-4'), 4.40-4.46 (m, 1, H-3'), 5.06 (t, 1, 5'-OH, J= 5 Hz), 5.52 (d, 1, 3'-OH, J = 4 Hz), 6.12 (dd, 1, H-1', J = 4 and 8 Hz), 7.78 (br s, 2, NH_2), 8.50 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 42.39 (C-2'), 58.33 (C-1', J = 160.5 Hz), 59.91 (C-4'), 63.54 (C-5'), 74.35 (C-3'), 117.55 (C-5), 140.79 (C-8), 150.02 (C-4), 152.65 (C-2), 156.52 (C-6). Anal. ($C_{10}H_{12}ClN_5O_2S$) C, H, N, S.

EXAMPLE 4

9-(2-Deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-diazidopurine (formula 6). To a solution of 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-dichloropurine (formula 4) (200 mg, 0.36 mmol) in 25 mL of EtOH was added a solution of sodium azide (46.8 mg, 0.72 mmol) in distilled water (10 mL) and the mixture was refluxed. A TLC aliquot at 2 hours showed complete reaction. The solution was evaporated, and the residue was dissolved in $CHCl_3$ (25 mL) and washed with water (20 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized from MeOH to give 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-diazidopurine (199 mg, 97%); mp 88-90°C; TLC 3:1 cyclohexane-ethylacetate; R_f 0.45; MS

z/e 571 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3, CH_3 of toluoyl), 2.42 (s, 3, CH_3 of toluoyl), 2.98 (br d, 2, H-2'), 4.34-4.38 (m, 1, H-4'), 4.44-4.56 (m, 2, 2 H-5'), 5.84 (br d, 1, H-4'), 6.36 (t, 1, H-1', J = 3 Hz), 7.20 (d, 2, H's of toluoyl, J = 8 Hz), 7.28 (d, 2, H's of toluoyl, J = 8 Hz), 7.62 (d, 2, H's of toluoyl, J = 8 Hz), 7.98 (d, 2, H's of toluoyl, J = 8 Hz), 8.52 (s, 1, H-8); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.67, 21.70 (CH_3's of toluoyl), 42.12 (C-2'), 54.40 (C-4'), 61.19 (C-1'), 64.89 (C-5'), 78.45 (C-3'), 121.96 (C-5), 125.90, 126.57, 129.24, 129.32, 129.53, 129.75 (toluoyl ring carbon), 143.20 (C-8), 144.18, 144.57 (toluoyl ring carbon), 153.46 (C-4), 153.70, 155.90 (C-2, C-6), 165.47, 166.10 (carbonyl carbon of toluoyl).

EXAMPLE 5

9-(2-Deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-diaminopurine (formula 7). To a solution of 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-diazidopurine (formula 6) (175 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) was added MeOH (20 mL) and Tin(II) chloride (188.6 mg, 1 mmol) and the mixture was stirred at 25°C. A TLC aliquot at 1.5 hours showed complete reaction. The solution was evaporated to dryness, the residue was dissolved in $CHCl_3$ (50 mL) and washed with water (20 mL), and aqueous sodium bicarbonate (20 mL), dried ($MgSO_4$) evaporated to dryness. The residue was purified by 35 g of silica gel with $CHCl_3$-MeOH 95:5 to afford 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-aminopurine (146 mg, 92%), mp 118-121°C; TLC 93:7 $CHCl_3$-MeOH; R_f 0.48; MS z/e 519 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.34 (s, 3, CH_3), 2.36 (s, 3, CH_3), 2.0-3.06 (m, 2, H-2'), 4.34-4.52 (m, 3, H-4', 2 x H-5'), 5.75 (br d, 1, H-3'), 5.90 (s, 2, C-2, NH_2), 6.18 (dd, 1, H-1', J = 3 and 7 Hz), 7.26 (d, 2, H's of toluoyl, J = 8 Hz), 7.32 (d, 2, H's of toluoyl, J = 8 Hz), 7.70 (d, 2,

H's of toluoyl, J = 8 Hz), 7.90 (d, 2, H's of toluoyl, J = 8 Hz), 8.08 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 21.08, 21.10 (CH_3's of toluoyl), 40.17 (C-2'), 52.69 (C-4'), 58.53 (C-1'), 64.90 (C-5'), 77.94 (C-3'), 113.40 (C-5), 126.35, 126.51 (toluoyl ring carbon), 129.07, 129.19, 129.26 (toluoyl ring carbon), 135.66 (C-8), 143.71, 143.74 (toluoyl ring carbon), 151.46 (C-4), 156.08 (C-6), 160.12 (C-2), 164.88, 165.24 (carbonyl carbon of toluoyl).

EXAMPLE 6

9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2,6-diaminopurine (formula 8). A solution of 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-diaminopurine (formula 7) (125 mg, 0.24 mmol) in anhydrous MeOH (25 mL) was stirred at room temperature with a freshly prepared solution of sodium methoxide (26 mg, 0.48 mmol) in MeOH (5 mL). A TLC aliquot at 1 hour showed complete reaction. The solution was rendered neutral with Dowex 50W-X8 (H^+) ion-exchange resin, the suspension was filtered, and the resin was washed with MeOH. The filtrates were combined and evaporated to dryness, and methyl p-toluate was removed at 50°C/0.01 torr. Crystallization of the residue from absolute EtOH gave pure 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2,6-diaminopurine, yield 63 mg (93%); mp 186-188°C; TLC 4:1 $CHCl_3$-MeOH, R_f 0.30; MS z/e 283 $(M + 1)^+$; UV λ_{max} pH 1 292 (10.10), pH 7 280 (10.61), pH 13 280 (10.41); ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 2.30-2.40 (m, 1, H-2'), 2.54-2.68 (m, 1, H-2'), 3.34-3.40 (m, 1, H-5'), 3.52-3.60 (m, 1, H-5'), 3.68-3.74 (m, 1, H-4'), 4.48 (br t, 1, H-3'), 5.02 (t, 1, 5'-OH, J = 6 Hz), 5.62 (d, 1, 3'-OH, J = 4 Hz), 5.78 (s, 2, NH_2), 6.02 (dd, 1, H-1', J = 3.0 and 8 Hz), 6.68 (s, 1, NH_2), 8.10 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 42.56 (C-2'), 57.10 (C-1'),

59.65 (C-4'), 63.67 (C-5'), 74.38 (C-3'), 112.80 (C-5), 136.65 (C-8), 151.18 (C-4), 155.91 (C-2), 159.91 (C-6). Anal. ($C_{10}H_{14}N_6O_2S$) C, H, N, S.

EXAMPLE 7

9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2-amino-1,6-dihydro-6-oxopurine (formula 9). To a solution of 9-(2-deoxy-4-thio- β-D-ribofuranosyl)-2,6-diaminopurine (formula 8) (30 mg, 0.11 mmol) in distilled H_2O (10 mL) was added a suspension of adenosine deaminase in 3.2 M $(NH_4)_2SO_4$ (0.1 mL) and reaction mixture was kept at room temperature. A 12-day TLC aliquot showed complete reaction. The solution was evaporated to dryness, the residue was crystallized from EtOH to give 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-amino-1,6-dihydro-6-oxopurine (28 mg, 93%); mp 257-260°C; TLC 3:1 $CHCl_3$, MeOH, R_f 0.55; MS z/e 284 $(M + 1)^+$, UV λ_{max} pH 1 254 (11.15), pH 7 254 (12.51), pH 13 267 (11.09); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.30-2.40 (m, 1, H-2'), 2.52-2.62 (m, 1, H-2'), 3.30-3.40 (m, 1, H-5'), 3.46-3.58 (m, 1, H-5'), 3.60-3.66 (m, 1, H-4'), 4.46 (br t, 1, H-3'), 5.04 (br t, 1, 5'-OH), 5.50 (d, 1, 3'-OH, J = 4 Hz), 5.94 (dd, 1, H-1', J = 4 and 8 Hz), 6.50 (s, 2, NH_2), 8.08 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 42.57 (C-2'), 57.32 (C-1'), 59.63 (C-4'), 63.58 (C-5'), 74.34 (C-3'), 116.09 (C-5), 136.53 (C-8), 150.63 (C-4), 153.41 (C-2), 156.54 (C-6). Anal. ($C_{10}H_{13}N_5O_3S$) C, H, N, S.

EXAMPLE 8

9-(2-Deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2-fluoro-6-aminopurine (formula 10). To a solution of 1-O-acetyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose (formula 3) (214 mg, 0.5 mmol) and

2-fluoroadenine (76.5 mg, 0.5 mmol) in CH_3CN (25 mL) was added Tin(IV) chloride (260 mg, 1.0 mmol) at 0°C. After the mixture was stirred for 1 hour, the reaction was almost complete as indicated by TLC ($CHCl_3$-MeOH 95:5). The reaction mixture was concentrated to a small volume (about 5 mL), sodium bicarbonate (300 mg) and distilled water (2 mL) were added. When the vigorous evolution of carbon dioxide had ceased, the mixture was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (25 mL) and washed with water (2 x 10 mL), dried ($MgSO_4$), and evaporated to dryness. The residue contained one major and one minor component on TLC, and applied to a flash column containing 60 g of silica gel with $CHCl_3$-MeOH 98:2, to afford 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2-fluoro-6-aminopurine (200 mg, 76%); TLC $CHCl_3$-MeOH 95:5; R_f 0.45; MS z/e 522 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3, CH_3 of toluoyl), 2.52 (s, 3, CH_3 of toluoyl), 2.98-3.0 (m, 2, H-2'), 4.34-4.40 (m, 1, H-4'), 4.45-4.58 (m, 2, H-5'), 5.82 (br s, 1, H-3'), 6.34 (dd, 1, H-1', J = 3 and 5 Hz), 6.42 (br s, 2, NH_2), 7.16 (d, 2, H's of toluoyl, J = 8 Hz), 7.26 (d, 2, H's of toluoyl, J = 8 Hz), 7.60 (d, 2, H's of toluoyl), 7.96 (d, 2, H's of toluoyl), 8.38 (s, 1, H-8); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.66, 21.70 (CH_3's of toluoyl), 42.28 (C-2'), 54.38 (C-4'), 61.08 (C-1'), 64.97 (C-5'), 78.57 (C-3'), 118.30 (C-5, $J_{C-5,2-F}$ = 3.9 Hz), 126.09, 126.63, 129.23, 129.59, 129.76 (toluoyl ring carbon), 140.41 (C-8), 144.13, 144.43 (toluoyl ring carbon), 151.2 (C-4, $J_{C-4,2-F}$ = 19.7 Hz), 157.0 (C-6, $J_{C-6,2-F}$ = 20 Hz), 159 (C-2, $J_{C-2,2-F}$ = 211.3 Hz), 165.46, 166.11 (carbonyl carbon of toluoyl).

EXAMPLE 9

9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine (formula 11). A mixture of 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2-fluoro-6-

aminopurine (formula 10) (175 mg, 0.33 mmol), and saturated ethanolic NH_3 (50 mL) was heated at 50°C in a glass lined stainless steel pressure vessel for 48 hours. The reaction mixture was evaporated to dryness to afford a syrup which was purified on a silica gel thick plate (Analtech GF, 1000 μM) that were developed in 4:1 $CHCl_3$-MeOH. The product was eluted with hot EtOH and evaporated. The residue was crystallized from boiling EtOH to give pure 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine (77.5 mg, 81%); mp 248-250°C; TLC 4:1 $CHCl_3$-MeOH, R_f 0.48; MS z/e 286 $(M + 1)^+$, UV λ_{max} pH 1 265 (11.7), pH 7 262 (13.5), pH 13 262 (13.5); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.40-2.48 (m, 1, H-2'), 2.56-2.68 (m, 1, H-2'), 3.38-3.46 (m, 1, H-5'), 3.48-3.58 (m, 1, H-5'), 3.62-3.70 (m, 1, H-4'), 4.42 (br t, 1, H-3', J = 4 Hz), 5.06 (t, 1, 5'-OH, J = 6 Hz), 5.52 (d, 1, 3'-OH, J = 4 Hz), 6.08 (dd, 1, H-1', J = 4 and 8 Hz), 7.70 (br s, 2, NH_2), 8.46 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 42.35 (C-2'), 58.23 (C-2'), 59.82 (C-4'), 63.54 (C-5'), 74.37 (C-3'), 116.9 (C-5, $J_{C-5,2-F}$ = 4.2 Hz), 140.6 (C-8, $J_{C-8,2-F}$ = 2.0 Hz), 150.3 (C-4, $J_{C-4,2-F}$ = 20.3 Hz), 157.36 (C-6, $J_{C-6,2-F}$ = 21.2 Hz), 158.33 (C-2, $J_{C-2,2-F}$ = 203.5 Hz). Anal. ($C_{10}H_{12}FN_5O_2S$) C, H, N, S.

EXAMPLE 10

9-(2-Deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-6-chloropurine (formula 12). To a solution of 1-O-acetyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose (formula 3) (428 mg, 1.0 mmol) and 6-chloropurine (154.5 mg, 1.0 mmol) in CH_3CN (40 mL) was added Tin(IV) chloride (0.521 mg, 2 mmol) at 0°C. After the mixture was stirred for 2 hours, the reaction was essentially complete as indicated by TLC ($CHCl_3$-MeOH 98:2). The reaction mixture was concentrated to a small volume (about 5 mL), sodium bicarbonate (500 mg), and distilled

water (2 mL) were added. When the vigorous evolution of carbon dioxide had ceased, the mixture was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (30 mL) and washed with water (2 x 20 mL), dried ($MgSO_4$), and evaporated to dryness. The residue contained one major and one minor component on TLC, and applied to a flash column containing 75 g of silica gel with $CHCl_3$-MeOH 99:1 to afford pure 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-6-chloropurine (365.5 mg, 70%); TLC 97:3 $CHCl_3$-MeOH, R_f 0.60; MS z/e 523 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.92-3.02 (m, 1, H-2'), 3.04-3.12 (m, 1, H-2'), 4.36-4.54 (m, 1, H-4'), 4.50-4.58 (m, 2, H-5'), 5.85 (br t, 1, H-3', J = 3.0 Hz), 6.48 (dd, 1, H-1', J = 2 and 5.0 Hz), 7.20 (d, 2, H's of toluoyl, J = 8 Hz), 7.26 (d, 2, H's of toluoyl, J = 8 Hz), 7.56 (d, 2, H's of toluoyl, J = 8 Hz), 7.98 (d, 2, H's of toluoyl, J = 8 Hz), 8.76 (s, 1, H-2 or H-8), 8.78 (s, 1, H-2 or H-8); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.68, 21.71 (CH_3's of toluoyl), 42.04 (C-2'), 54.58 (C-4'), 61.71 (C-1'), 64.87 (C-3'), 78.43 (C-5'), 125.76, 126.54, 129.25, 129.34, 129.76, 129.44 (toluoyl ring carbon), 132.43 (C-5), 146.20, 144.66 (toluoyl ring carbon), 144.83 (C-8, $^1J_{C-8,H-8}$ = 215 Hz, $^3J_{C-8,H-1'}$ = 3.6 Hz), 151.04 (C-6, $^3J_{C_6H_2}$ = 13.7 Hz), 151.36 (C-4, $^3J_{C-4,H_8}$ = 12.1 Hz, $^3J_{C_4,H-4'}$ = 4.5 Hz), 151.84 (C-2, $^1J_{C-2,H-2}$ = 209.6 Hz), 165.43, 166.09 (carbonyl carbon of toluoyl).

EXAMPLE 11

9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine (formula 13). A mixture of 9-(2'-deoxy-4'-thio-3',5'-di-O-toluoyl-β-D-ribofuranosyl)-6-chloropurine (formula 12) (340 mg, 0.65 mmol) and saturated ethanolic NH_3 (50 mL) was heated at 50°C in a glass-lined stainless steel pressure vessel for 3 days. The reaction mixture was evaporated to dryness to afford a syrup which was purified on three silica

gel thick plates (Analtech, GF, 1000 μM), that were developed in 4:1 $CHCl_3$-MeOH. The product was eluted with hot EtOH and evaporated. The residue was crystallized from boiling EtOH to give pure 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine (148 mg, 85%); mp 218-220°C; TLC 4:1 $CHCl_3$-MeOH, R_f 0.30; MS z/e 268 $(M + 1)^+$, UV λ_{max} pH 1 260 (14.7), pH 7 261 (15.2), pH 13 261 (15.3); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.40-2.52 (m, 1, H-2'), 2.60-2.70 (m, 1, H-2'), 3.36-3.44 (m, 1, H-5'), 3.50-3.58 (m, 1, H-5'), 3.64-3.70 (m, 1, H-4'), 4.38-4.46 (m, 1, H-3'), 5.06 (t, 1, 5'-OH, J = 4.5 Hz), 5.64 (d, 1, 3'-OH, J = 4 Hz), 6.20 (dd, 1, H-1', J = 4 and 7.5 Hz), 7.26 (s, 2, NH_2), 8.15 (s, 1, H-2), 8.50 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 42.42 (C-2'), 58.03 (C-1'), 59.85 (C-4'), 63.60 (C-5'), 74.47 (C-3'), 118.59 (C-5), 140.20 (C-8), 148.96 (C-4), 152.14 (C-2), 155.78 (C-6). Anal. ($C_{10}H_{13}N_5O_2S$) C, H, N, S.

EXAMPLE 12

9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-1,6-dihydro-6-oxopurine (formula 14). To a solution of 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine (formula 13) (50 mg, 0.18 mmol) in distilled H_2O (10 mL) was added a suspension of adenosine deaminase in 3.2 M $(NH_4)_2SO_4$ (0.2 mL) and the reaction mixture was kept at room temperature. A TLC aliquot at 18 hours showed complete reaction. The solution was evaporated to dryness. The residue was crystallized from hot EtOH to give 9-(2'-deoxy-4'-thio-β-D-ribofuranosyl)-1,6-dihydro-6-oxopurine (40 mg, 80%); mp 198-200°C; TLC 3:1 $CHCl_3$-MeOH, R_f 0.50; MS z/e 269 $(M + 1)^+$; UV λ_{max} pH 1 251 (11.76), pH 7 251 (12.45), pH 13 255 (13.68); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.41-2.50 (m, 1, H-2'), 2.60-2.70 (m, 1, H-2'), 3.46-3.44 (m, 1, H-5'), 3.48-3.58 (m, 1, H-5'), 3.64-3.72 (m, 1, H-4'), 4.44 (dd, 1, H-3', J = 2 and 7 Hz), 6.18 (dd, 1, H-1', J = 3 and 8 Hz), 8.06 (s, 1, H-8), 8.66 (s, 1, H-2); ^{13}C NMR (Me_2SO-d_6, 300

MHz) δ 42.53 (C-2'), 58.44 (C-1', $J_{C,H}$ = 160.59 Hz), 59.87 (C-4, $J_{C,H}$ = 161.26 Hz), 63.42 (C-5), 74.40 (C-3'), 123.78 (C-5), 139.58 (C-8, J_{C_8,H_8} = 215.3 Hz, $J_{C_8,H\text{-}1'}$ = 4.7 Hz), 145.68 (C-2, $J_{C,H}$ = 205.5 Hz), 167.81 (C-6), 156.50 (C-4).

EXAMPLE 13

1-(2-Deoxy-4-thio-3,5-di-O-toluoyl-D-ribofuranosyl)uracil (formula 15). To a suspension of 1-O-acetyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose (formula 3) (428 mg, 1.0 mmol) and uracil(2,4-dioxopyrimidine) (112.1 mg, 1.0 mmol) in anhydrous 1,2-dichloroethane (30 mL) were added consecutively hexamethyldisilazane (HMDS, 161.5 mg, 1.0 mmol) and trimethylchlorosilane (TMSCl, 108.6 mg, 1.0 mmol) and the mixture was stirred at room temperature. After 0.5 hours, the resulting solution was cooled to -78°C and trimethylsilyl trifluoromethanesulfonate (266.7 mg, 1.2 mmol) was added to it and stirred at the same temperature for another 1 hour, after which time the reaction was essentially complete. The reaction mixture was warmed to room temperature and concentrated to a small volume (5 mL), diluted with methylene chloride (about 50 mL), then washed with water (15 mL) followed by saturated sodium bicarbonate and finally with water. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by 50 g of silica gel with $CHCl_3$-MeOH 98:2 to afford a solid, which was crystallized from EtOH-dioxane to give pure 1-(2-deoxy-4-thio-3,5-di-O-toluoyl-D-ribofuranosyl)uracil (192 mg, 40%); mp 118-120°C; TLC 98:2 $CHCl_3$-MeOH; R_f 0.35; MS z/e 481 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 6, CH_3 of toluoyl), 2.54-2.60 (m, 1, H-2'), 2.86-2.96 (m, 1, H-2'), 4.20-4.26 (m, 1, H-4'), 4.36-4.52 (m, 2, H-5'), 5.68-5.72 (m, 2, H-3', H-5), 6.44 (br d, 1, H-6, J = 6 Hz), 7.26 (d, 2, H's of toluoyl, J = 8 Hz), 7.30 (d, 2, H's of

toluoyl, J = 8 Hz), 7.96 (d, 2, H's of toluoyl, J = 8 Hz), 8.14 (d, 2, H's of toluoyl, J = 8 Hz), 9.48 (s, 1, H-3); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 42.148 (C-2'), 56.46 (C-4'), 63.55 (C-1'), 64.96 (C-5'), 78.21 (C-3'), 101.94 (C-5), 126.03, 126.55, 129.23, 129.27, 129.783, 129.63 (toluoyl ring carbon), 141.74 (C-6), 144.14, 144.73 (toluoyl ring carbon), 150.71 (C-2), 163.05 (C-4), 165.36, 166.07 (carbonyl carbon of toluoyl).

EXAMPLE 14

1-(2-Deoxy-4-thio-D-ribofuranosyl)uracil (formula 16). A solution of 1-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)uracil (formula 15) (175 mg, 0.36 mmol) in anhydrous MeOH (30 mL) was stirred at room temperature with a freshly prepared solution of sodium methoxide (39 mg, 0.72 mmol) in MeOH (7.5 mL). A TLC aliquot at 2.5 hours showed complete reaction. The solution was rendered neutral with Dowex 50W-X8 (H^+) ion-exchange resin, the suspension filtered, and the resin was washed with MeOH. The filtrate was combined and evaporated to dryness, and methyl p-toluate was removed at 50°C/0.01 torr. Crystallization of the residue from absolute EtOH gave pure 1-(2-deoxy-4-thio-D-ribofuranosyl)uracil (75 mg, 85%), mp 190-192°C; TLC 9:1 $CHCl_3$-MeOH, R_f 0.30; MS z/e 245 $(M + 1)^+$, UV λ_{max} pH 1 266 (9.24), pH 7 266 (9.52), pH 13 265 (8.72); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.0-2.28 (m, 1, H-2'), 2.44-2.54 (m, 1, H-2'), 3.30-3.38 (m, 1, H-5'), 3.40-3.48 (m, 1, H-5'), 3.50-3.58 (m, 1, H-4'), 4.32 (br dd, 1, H-3', J = 2 and 8 Hz), 5.66 (d, 1, H-6, J = 8 Hz), 6.14 (dd, 1, H-1', J = 3 and 7.5 Hz), 8.26 (d, 1, H-5, J = 8 Hz); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 42.16 (C-2), 60.01 (C-4'), 60.95 (C-1'), 63.57 (C-5'), 74.14 (C-3'), 101.16 (C-5, $J_{C,H}$ = 175.24 Hz), 142.92 (C-6, $J_{C,H}$ = 181.88 Hz), 150.69 (C-2), 162.97 (C-4). Anal. ($C_9H_{12}N_4O_2S$) C, H, N, S.

EXAMPLE 15

1-(2-Deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)thymine (formula 17). To a suspension of 1-O-acetyl-2-deoxy-4-thio-3,5-di-O-p-toluoyl-α,β-D-ribofuranose (formula 3) (428 mg, 1.0 mmol), and thymine(5-methyl-2,4-dioxopyrimidine) (126 mg, 1.0 mmol) in anhydrous 1,2-dichloroethane (30 mL) were added consecutively hexamethyldisilazane (HMDS, 161.5 mg, 1.0 mmol), and trimethylchlorosilane (TMSCl, 108.6 mg, 1.0 mmol), and the mixture was stirred at room temperature after 0.5 hours. The resulting solution was cooled to -78°C and trimethylsilyl trifluoromethanesulfonate (266.7 mg, 1.2 mmol) was added to it and stirred at the same temperature for another 1.5 hours, after which time the reaction was essentially complete. The reaction mixture was warmed to room temperature and concentrated to a small volume (5 mL), diluted with methylene chloride (about 50 mL), then washed with water (15 mL) followed by saturated sodium bicarbonate and finally with water. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by 50 g of silica gel with $CHCl_3$-MeOH 99:1 to afford a solid which was crystallized from EtOH-$CHCl_3$ to give pure 1-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)thymine (173 mg, 35%); mp 178-182°C; TLC 98:2 $CHCl_3$-MeOH, R_f 0.55; MS z/e 495 $(M + 1)^+$; ^1H NMR (CDCl, 300 MHz) δ 1.78 (s, 3, C-5, CH_3), 2.42 (s, 3, CH_3 of toluoyl), 2.43 (s, 3, CH_3 of toluoyl), 2.36-2.44 (m, 1, H-2'), 3.98-4.04 (m, 1, H-4'), 4.12 (d, 2, H-5', J = 6 Hz), 5.76 (br t, 1, H-3'), 6.66 (dd, 1, H-1', J = 6 and 9 Hz), 7.26 (d, 4, H's of toluoyl, J = 8 Hz), 7.56 (s, 1, H-6), 7.94 (d, 2, H's of toluoyl, J = 8 Hz), 7.96 (d, 2, H's of toluoyl, J = 8 Hz), 8.58 (s, 1, H-3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 12.41 (C-5, CH_3), 21.69, 21.72 (CH_3's of toluoyl), 39.98 (C-2'), 53.13 (C-4', $J_{C,H}$ = 148.1 Hz), 61.27 (C-1', $J_{C,H}$ = 163.3 Hz), 65.14 (C-5'),

77.13 (C-3'), 112.28 (C-5), 126.41, 126.58 (toluoyl ring carbon), 129.25, 129.35, 129.76, 129.87 (toluoyl ring carbon), 135.46 (C-6, $J_{C,H}$ = 176.46 Hz), 144.38, 144.47 (toluoyl ring carbon), 150.45 (C-2), 162.90 (C-4), 165.61, 166.17 (carbonyl carbon of toluoyl).

EXAMPLE 16

1-(2'-Deoxy-4'-thio-β-D-ribofuranosyl)thymine (formula 18). A solution of 1-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)thymine (formula 17) (150 mg, 0.30 mmol) in anhydrous MeOH (30 mL) was stirred at room temperature with a freshly prepared solution of sodium methoxide (32.5 mg, 0.60 mmol) in MeOH (7.5 mL). A TLC aliquot at 3 hours showed complete reaction. The solution was rendered neutral with Dowex 50W-X8 (H^+) ion-exchange resin, the suspension was filtered, and the resin was washed with MeOH. The filtrate was combined and evaporated to dryness, and methyl p-toluate was removed at 50°C/0.01 torr. Crystallization of the residue from absolute EtOH gave pure 1-(2'-deoxy-4'-thio-β-D-ribofuranosyl)thymine (61 mg, 78%), mp 213-215°C; TLC 9:1 $CHCl_3$-MeOH, R_f 0.40; MS z/e 258 $(M + 1)^+$, UV λ_{max} pH 1 272 (10.3), pH 7 272 (10.2), pH 13 271 (10.3); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 1.80 (C-5, CH_3), 2.10-2.24 (m, 2, H-2'), 3.24-3.32 (m, 1, H-4'), 3.50-3.66 (m, 2 H, H-5'), 4.38 (br s, 1, H-3'), 5.16 (br t, 1, 5'-OH), 5.24 (d, 1, 3'-OH, J = 4 Hz), 6.30 (dd, 1, H-1', J = 6.5 and 8 Hz), 7.32 (s, 1, H-6), 11.32 (br s, 1, H-3); ^{13}C NMR (Me_2SO-d_6, 300 MHz) δ 12.16 (C-5, CH_3), 40.97 (C-2', $J_{C,H}$ = 132.33 Hz), 59.01 (C-4', $J_{C,H}$ = 143.4 Hz), 59.93 (C-1', $J_{C,H}$ = 167.74), 63.51 (C-5'), 73.40 (C-3'), 109.82 (C-5), 136.70 (C-6, $J_{C,H}$ = 179 Hz), 150.59 (C-4), 163.37 (C-2). Anal. ($C_{10}H_{13}N_2O_6S$) C, H, N, S.

EXAMPLE 17

Antiviral activity of 2'-deoxy-4'-thioribonucleosides.

2'-Deoxy-4'-thioribonucleosides were tested for antiviral activity against viruses that replicate in mammalian cells growing in cell culture. The results of these tests against herpes simplex virus, Type 1 and Type 2, are summarized in Table 1. The Virus Rating (VR) is a standard weighted measurement of antiviral activity which takes into account the degree of inhibition of virus-induced cytopathogenic effects (CPE) and the degree of cytotoxicity produced by the test compound, determined by a modification of the method of Ehrlich et al, Ann. N.Y. Acad. Sci. 130, 5-16 (1965).

The CPE-inhibition assays were designed to test seven 0.5 $\log_{10}$ concentrations of each compound, beginning with 320 µg/mL, against HSV in triplicate 24-hour Vero cell monolayers in 96-well tissue culture plates. To each of the replicate cell cultures were dispensed 0.1 mL of the test compound solution (or suspension) and 0.1 mL of HSV suspension (diluted in medium to yield 32 $CCID_{50}$ units per 0.1 mL). Cell controls, untreated virus-infected controls and drug cytotoxicity controls were included in each assay. The plates were incubated at 37°C in a humidified atmosphere containing 2% CO_2 until 100% CPE were observed in the untreated virus control cultures. The cell monolayers were examined microscopically for drug cytotoxicity and for CPE which was graded on a scale of 0-4 (0-100% CPE).

The VR was calculated as 0.1 of the sum of the numerical differences between the recorded CPE grade of each test well and that of the corresponding virus control in the culture plate. Numerical differences between the scores of test wells containing a drug concentration which is partially cytotoxic and their corresponding virus controls were halved.

In tests carried out by this method, a greater value of VR indicates greater antiviral activity. A compound with a VR of 1.0 or greater is considered to have significant antiviral activity with a high degree of reproducibility in confirmatory in vitro tests. A compound with a VR of 0.5-0.9 is considered to have possible or marginal activity; a compound with a VR of less than 0.5 is considered to be inactive.

The MIC_{50} (minimum inhibitory concentration, 50%) is the concentration of a test compound required for 50% inhibition of virus-induced cytopathogenic effect calculated by using a regression analysis program for semilog curve fitting. MTC (minimum toxic concentration) is the minimum drug concentration (μg/ml) causing any cytotoxicity. TI is the therapeutic index, calculated by dividing the minimum cytotoxic drug concentration (MTC) by the minimum inhibitory concentration, 50% (MIC_{50}). The results were compared with two commercial antiviral agents, acyclovir and 9-β-D-arabinofuranosyladenine (Ara-A). The tests summarized in Table I show that definite antiviral activity against herpes simplex Type 1 is exhibited by two of the invention compounds, 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine and 1-(2-deoxy-4-thio-α-D-ribofuranosyl)thymine.

TABLE 1

Compound	Virus	VR	MIC_{50}	MTC	TI
9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine	HSV-1[a/]	0			
	HSV-2[b/]	0			
9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine	HSV-1	0			
	HSV-2	0			
9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine	HSV-1	0			
	HSV-2	0			
1-(2-Deoxy-4-thio-α-D-ribofuranosyl)-thymine	HSV-1	1.4	110.1	>257.2	2.3
	HSV-2	0.3	-	>257.3	-
1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-thymine	HSV-1	1.3	0.8	2.6	3.2
	HSV-2	0.1	-	2.6	-
9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2,6-diaminopurine	HSV-1	0			
	HSV-2	0			
Controls					
Acyclovir	HSV-1	6.7	0.5	>225.2	>441
	HSV-2	4.8	3.6	>225.2	63.2
Ara-A	HSV-1	1.8	15.2	84.8	5.6
	HSV-2	1.1	39.3	84.8	2.2

a/ HSV-1 (E377)
b/ HSV-2 (MS)

EXAMPLE 18

2'-Deoxy-4'-thioribonucleosides were tested for antitumor activity against leukemia L1210 ("L1210") cells and human epidermoid carcinoma No. 2 ("H.Ep.-2") cells.

Table 2 sets forth the results of cytotoxicity tests. For L1210 cells the IC_{50} is the concentration required to decrease cellular proliferation by 50% as compared to untreated controls. The cells were grown in suspension cultures and the number of cells present was determined at 24 and 48 hours. The values shown in Table 2 are 48 hour values.

For H.Ep.-2 cells, the IC_{50} is the concentration required to reduce colony formation by 50% as compared to controls. One hundred cells in 10 mL of medium were placed in prescription bottles, and after 10 days incubation, the medium was decanted and the colonies were stained and counted.

In the cytotoxicity tests, the lower the IC_{50} value, the greater the antitumor activity. An IC_{50} value of less than 40 µg/mL indicates a compound of interest, and an IC_{50} value of less than 1 indicates a compound that is extremely effective. As shown in Table 2 below, all the compounds tested show an IC_{50} value of less than 40 µg/mL with respect to either H.Ep.-2 or L1210 cells, or both. One compound, 1-(2-Deoxy-4-thio-β-D-ribofuranosyl)thymine shows an IC_{50} value of mucn less than 1 µg/mL.

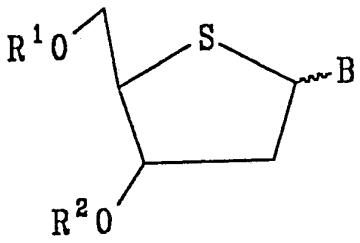
TABLE 2

Compound	IC_{50} (µg/mL) H.Ep.-2	L1210
1-(2-Deoxy-4-thio-β-D-ribofuranosyl)thymine	0.075	0.025
1-(2-Deoxy-4-thio-α-D-ribofuranosyl)thymine	2.7	20
9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine	20	>40
9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine	30	>40
9-(2-Deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine	>40	30

Although the invention has been described in considerable detail with specific reference to certain advantageous embodiments thereof, variations and modifications can be made without departing from the scope of the invention as described in the specification and defined in the appended claims.

WE CLAIM:

1. A compound represented by the formula:

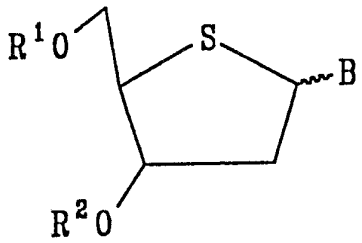


wherein:

~B indicates that B can be either alpha or beta, and

B is a member selected from the group consisting of pyrimidine, 5-azapyrimidine, 6-azapyrimidine, 3-deazapyrimidine, purine, 3-deazapurine, 7-deazapurine, 8-azapurine, and 2-azapurine bases and R^1 and R^2 may be the same or different and may be hydrogens or acyl protecting groups.

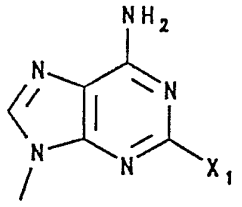
2. A compound represented by the formula:



wherein:

~B indicates that B can be either alpha or beta, and

B is a member selected from the group consisting of the following nitrogenous heterocyclic bases:



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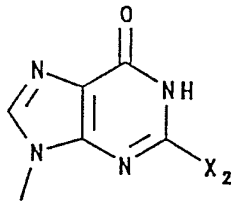

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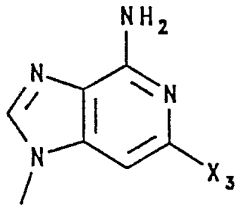

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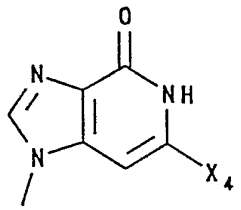

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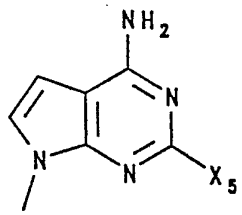

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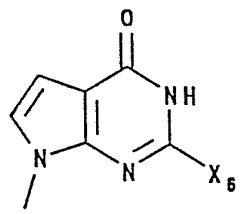

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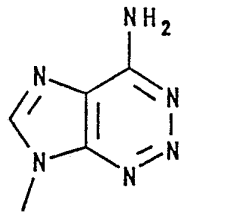

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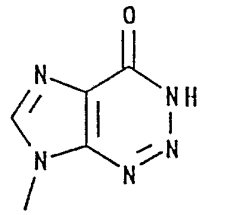

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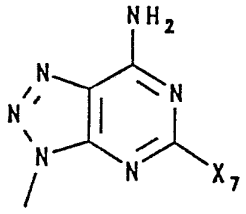

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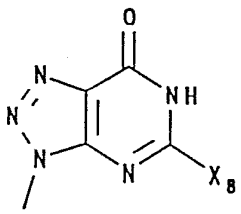
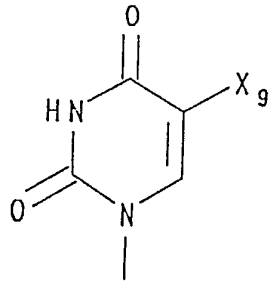


,

where $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8$ = H, NH_2 or halogen,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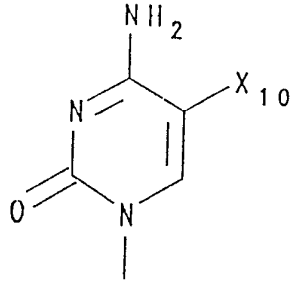
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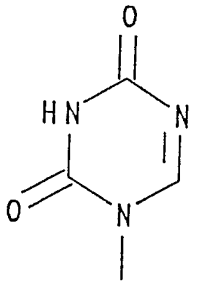
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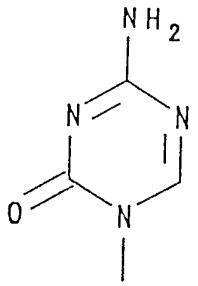
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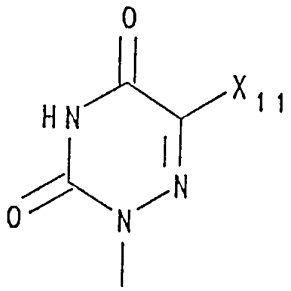
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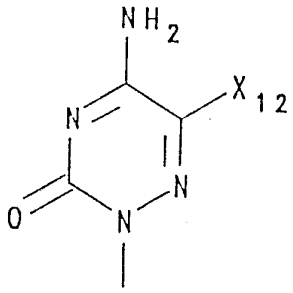
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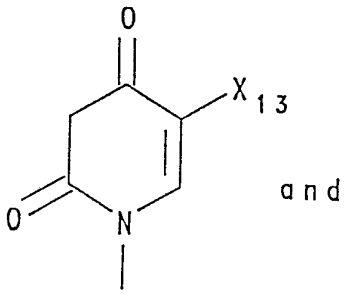
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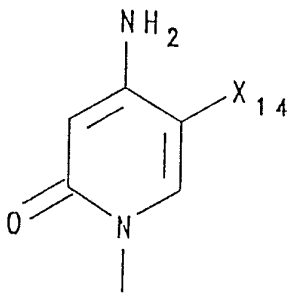
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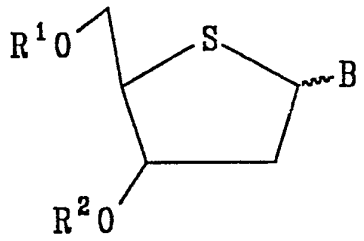
where X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14} = H, CH_3, or halogen and R^1 and R^2 can be the same or different and may be hydrogen or acyl protecting groups.

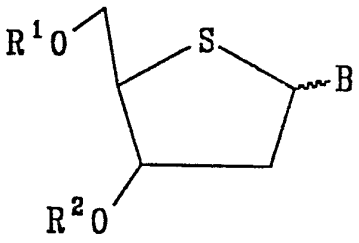
3. A 2'-deoxy-4'-thioribonucleoside represented by the formula:



wherein:

~B indicates that B can be either alpha or beta, and B is a member selected from the group consisting of pyrimidine and purine bases and R^1 and R^2 may be the same or different and may be hydrogens or acyl protecting groups.

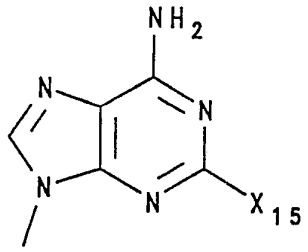
4. A 2'-deoxy-4'-thioribonucleoside represented by the formula:



wherein:

~B indicates that B can be either alpha or beta, and

B is a member selected from the group consisting of the following purine and pyrimidine bases:



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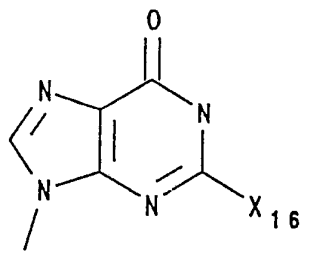
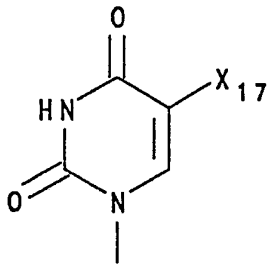
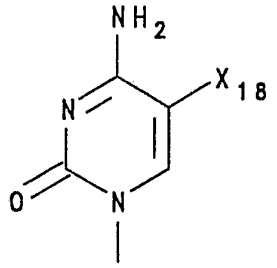


,

where X_{15}, X_{16} = H, NH_2 or halogen, and



and



,

where X_{17}, X_{18} = H, CH_3 or halogen and R^1 and R^2 may be the same or different and may be hydrogens or acyl protecting groups.

5. The compound of claim 1 wherein each of R^1 and R^2 is hydrogen.

6. The compound of claim 2 wherein each of R^1 and R^2 is hydrogen.

7. The 2'-deoxy-4'-thioribonucleoside of claim 3 wherein each of R^1 and R^2 is hydrogen.

8. The 2'-deoxy-4'-thioribonucleoside of claim 4 wherein each of R^1 and R^2 is hydrogen.

9. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine.

10. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2,6-diaminopurine.

11. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-amino-1,6-dihydro-6-oxopurine.

12. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine.

13. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine.

14. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-1,6-dihydro-6-oxopurine.

15. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 1-(2-deoxy-4-thio-β-D-ribofuranosyl)uracil.

16. A 2'-deoxy-4'-thioribonucleoside as defined by claim 8 which is 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine.

17. A 2'-deoxy-4'-thioribonucleoside as defined by claim 3 which is 1-(2-deoxy-4-thio-α-D-ribofuranosyl)thymine.

18. An intermediate useful in the production of 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine as defined by claim 9 which is 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-dichloropurine.

19. An intermediate useful in the production of 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2,6-diaminopurine as defined by claim 10 which is 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2,6-diaminopurine.

20. An intermediate useful in the production of 9-(2'-deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine as defined by claim 12 which is 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-2-fluoro-6-aminopurine.

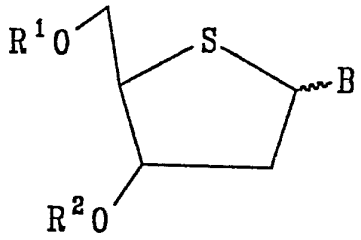
21. An intermediate useful in the production of 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine as defined by claim 13 which is 9-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)-6-chloropurine.

22. An intermediate useful in the production of 1-(2-deoxy-4-thio-β-D-ribofuranosyl)uracil as defined in claim 15 which is 1-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)uracil.

23. An intermediate useful in the production of 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine as defined in claim 16 which is 1-(2-deoxy-4-thio-3,5-di-O-toluoyl-β-D-ribofuranosyl)thymine.

24. A process for the treatment of a host animal having a viral infection which comprises administering to

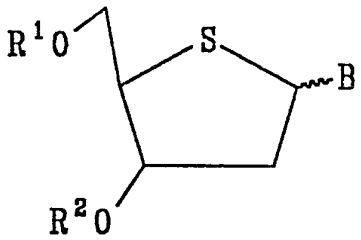
said host animal a therapeutically effective amount of a compound represented by the formula:



wherein:

~B indicates that B can be either alpha or beta, and B is a member selected from the group consisting of pyrimidine, 5-azapyrimidine, 6-azapyrimidine, 3-deazapyrimidine, purine, 3-deazapurine, 7-deazapurine, 8-azapurine, and 2-azapurine bases and R^1 and R^2 may be the same or different and may be hydrogens or acyl protecting groups.

25. A process for the treatment of a host animal having a viral infection which comprises administering to said host animal a therapeutically effective amount of a 2'-deoxy-4'-thioribonucleoside represented by the formula:



wherein:

~B indicates that B can be either alpha or beta, and

B is a member selected from the group consisting of pyrimidine and purine bases and R^1 and R^2 may be the same or different and may be hydrogens or acyl protecting groups.

26. The process as defined in claim 24 wherein each of R^1 and R^2 is hydrogen.

27. The process as defined in claim 25 wherein each of R^1 and R^2 is hydrogen.

28. A process as defined in claim 27 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine.

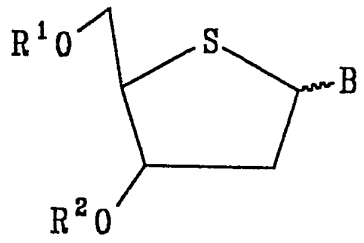
29. A process as defined in claim 27 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-α-D-ribofuranosyl)thymine.

30. A process as defined in claim 27 wherein said virus infection is a herpes simplex virus infection.

31. A process as defined in claim 30 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine.

32. A process as defined in claim 30 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-α-D-ribofuranosyl)thymine.

33. A process for the treatment of an animal afflicted with cancer comprising administering to said animal an antineoplastically effective amount of compound represented by the formula:

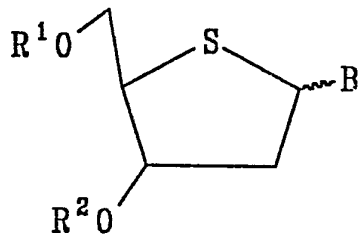


wherein:

~B indicates that B can be either alpha or beta, and

B is a member selected from the group consisting of pyrimidine, 5-azapyrimidine, 6-azapyrimidine, 3-deazapyrimidine, purine, 3-deazapurine, 7-deazapurine, 8-azapurine, and 2-azapurine bases and R^1 and R^2 may be the same or different and may be hydrogens or acyl protecting groups.

34. A process for the treatment of an animal afflicted with cancer comprising administering to said animal an antineoplastically effective amount of 2'-deoxy-4'-thioribonucleoside represented by the formula:



wherein:

~B indicates that B can be either alpha or beta, and

B is a member selected from the group consisting of pyrimidine and purine bases and R^1 and R^2 may be the same or different and may be hydrogens or acyl protecting groups.

35. The process of claim 33 where each of R^1 and R^2 is hydrogen.

36. The process of claim 34 where each of R^1 and R^2 is hydrogen.

37. The process as defined in claim 36 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine.

38. The process as defined in claim 36 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-α-D-ribofuranosyl)thymine.

39. The process as defined in claim 36 wherein said 2'-deoxy-4'-thioribonucleoside is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine.

40. The process as defined in claim 36 wherein said 2'-deoxy-4'-thioribonucleoside is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine.

41. The process as defined in claim 36 wherein said 2'-deoxy-4'-thioribonucleoside is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine.

42. The process as defined in claim 36 wherein said cancer is L1210 leukemia.

43. A process as defined in claim 42 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine.

44. A process as defined in claim 42 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-α-D-ribofuranosyl)thymine.

45. The process as defined in claim 42 wherein said 2'-deoxy-4'-thioribonucleoside is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-fluoro-6-aminopurine.

46. The process as defined in claim 36 wherein said cancer is human epidermoid carcinoma No. 2.

47. A process as defined in claim 46 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-β-D-ribofuranosyl)thymine.

48. A process as defined in claim 46 wherein said 2'-deoxy-4'-thioribonucleoside is 1-(2-deoxy-4-thio-α-D-ribofuranosyl)thymine.

49. The process as defined in claim 46 wherein said 2'-deoxy-4'-thioribonucleoside is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-6-aminopurine.

50. The process as defined in claim 46 wherein said 2'-deoxy-4'-thioribonucleoside is 9-(2-deoxy-4-thio-β-D-ribofuranosyl)-2-chloro-6-aminopurine.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 90/05252

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5th Ed.): A 61 K 31/70; C 07 H 5/08, 5/10

US Cl.: 514/258; 514/274; 544/242; 544/314; 514/24

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
US Cl.:	544/242; 544/314; 514/258; 514/274; 514/24

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Computer Structure Search - no hits.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	J. Am. Chem. Soc., 86, Issued 20 December 1964, (Am. Chem. Soc.) Easton, PA, Reist et al., "Synthesis of 4-Thio-D-and L-ribofuranose and the Corresponding Adenine Nucleosides," see whole document., pages 5658-5663.	1-17, 24-32
A	Purine and Pyrimidine Metabolism in Man, Volume V,.Part B, Nyhan et al. eds., Issued 1986, (Plenum Publishing Corporation) New York, Miura et al., "4'-thioadenosine as a Novel Inhibitor of S-Adenosylhomocysteine Hydrolase and an Inducer for the Differentiation of HL-60 Human Leukemia Cells," see whole document.	1-17, 24-32

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 December 1990	17 JAN 1991
International Searching Authority	**Signature of Authorized Officer**
IPEA/US	Eric Crane

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	J. Organic Chemistry, Vol. 33(1), Issued January 1968, (Am. Chem. Soc.) Easton, PA, Reist et al., "Thio Sugars. Synthesis of Adenine Nucleosides of 4-Thio-D-xylose and 4-Thio-D-arabinose," see whole document., page 189-190.	1-17, 24-32
A	J. Medicinal Chem., Vol. 17(5), Issued 1974, (Am. Chem. Soc.) Easton, PA, Ototani et al., "Preparation and Antitumor Activity of 4'-Thio Analogs of 2,2'-Anhydro-1-β-D-arabinofuranosylcytosine," see whole document., page 535-537.	1-17, 24-32
A	Canadian J. Chem., Volume 56, Issued 1977, Canada, Richie et al., "Addition of Pseudohalogens to Unsaturated Carbohydrates. VI. Synthesis of 4'-thiocordycepin," see whole document, pp. 794-802.	1-17, 24-32

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	J., Organic Chem., Vol. 41(24), Issued 1976, (Am. Chem. Soc.) Easton, PA, Fu et al., "An Alternative Synthesis of Anomeric Methyl 2-Deoxy-4-thio-D-*erythro*-pentofuranosides," see whole document, pages 3831-3834.	1-17, 24-32
A	J. Organic Chem., Vol. 35(2), Issued February 1970, (Am. Chem. Soc.) Easton, PA, Whistler et al., "Anomeric Methyl 4-thio-D-arabinofuranosides," see whole document., pages 519-521.	1-17, 24-32

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.