

REPLACED SHEETS SG

- ☒ Description : paged to paged ...48.
☒ Claim(s) : paged ...49... to paged ...60.
☐ Drawing(s) : paged to paged
☒ Abstract : paged ^{last page} to paged

**SUBSTITUTED-1,3-OXATHIOLANES
WITH ANTIVIRAL PROPERTIES**

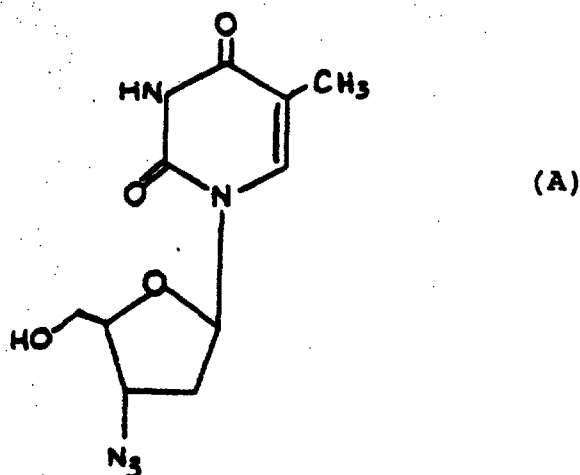
5 The present invention relates to novel
substituted 1,3-oxathiolane cyclic compounds having
pharmacological activity, to processes for and inter-
mediates of use in their preparation, to pharmaceutical
compositions containing them, and to the use of these
compounds in the antiviral treatment of mammals.

10 Retroviral infections are a serious cause of
disease, most notably, the acquired immunodeficiency
syndrome (AIDS). The human immunodeficiency virus (HIV)
has been recognized as the etiologic agent of AIDS and
compounds having an inhibitory effect against HIV
multiplication have been actively sought.

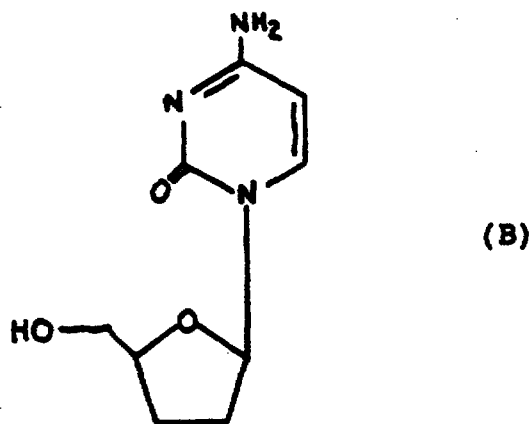
15 Mitsuya et al., "3'-Azido-3'-deoxythymidine
(BW A509U): An antiviral agent that inhibits the
infectivity and cytopathic effect of human T-lymphotropic
virus type III/lymphadenopathy-associated virus in
vitro", Proc. Natl. Acad. Sci. U.S.A., 82, pp. 7096-7100
20 (1985), refers to a compound of formula (A) (3'-azido-
2'3'-dideoxythymidine), commonly referred to as AZT.
This compound is said to be useful in providing some
protection for AIDS carriers against the cytopathogenic
effect of immunodeficiency virus (HIV).

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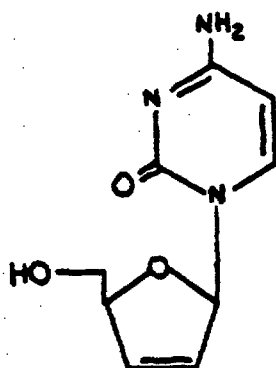


Mitsuya et al., "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides", Proc. Natl. Acad. Sci. U.S.A., 86, pp. 1911-15 (1986), have also referred to a group of 2',3'- dideoxynucleosides shown in formula (B) which are said to possess protective activity against HIV-induced cytopathogenicity.



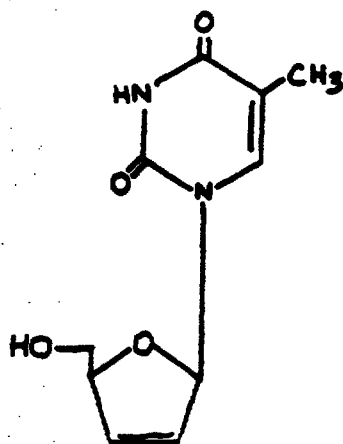
Balzarini et al., "Potent and selective anti-HTLV-III/LAV activity of 2',3'-dideoxycytidinene, the 2',3'-unsaturated derivative of 2',3'-dideoxycytidine", Biochem. Biophys. Res. Comm., 140, pp. 735-42 (1986), refer to an unsaturated analogue of these nucleosides-- 2',3'-dideoxy-cytidine, shown in formula (C)--as being characterized by antiretroviral activity.





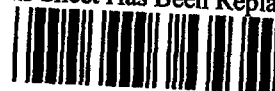
(C)

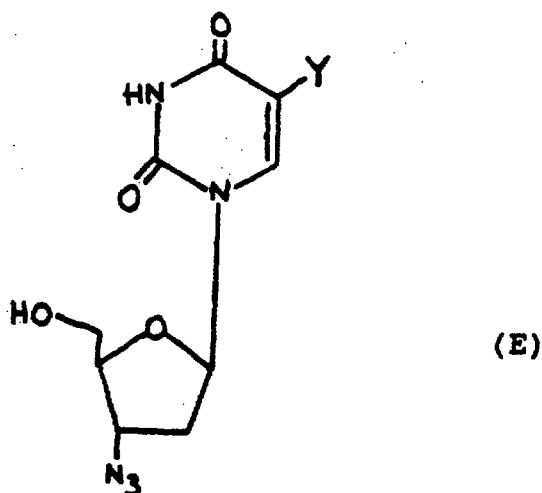
Baba et al., "Both 2',3'-dideoxythymidine and its 2',3'-unsaturated derivative (2',3'-dideoxythymidinene) are potent and selective inhibitors of human immunodeficiency virus replication in vitro", Biochem. Biophys. Res. Comm., 142, pp. 128-34 (1987), refer to the 2',3'-unsaturated analogue shown in formula (D) of 2',3'-dideoxythymidine. This analogue is purported to be a potent selective inhibitor of HIV replication.



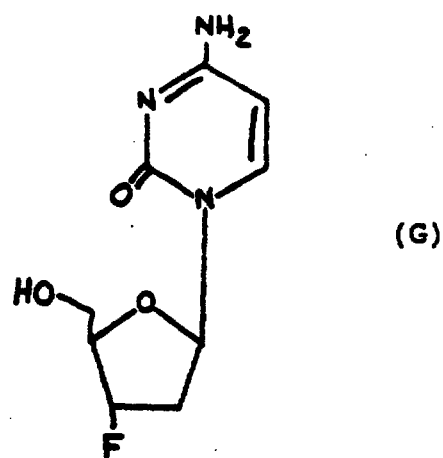
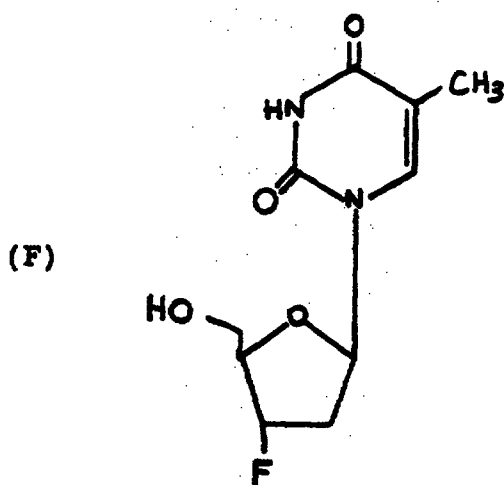
(D)

Analogues of AZT known as 3'-azido-2', 3'-dideoxyuridine shown in formula (E), where Y is bromine or iodine, have been said to have an inhibitory activity against Moloney murine leukemia in T.S. Lin et al., "Synthesis and antiviral activity of various 3'-azido, 3'-amino, 2',3'-unsaturated and 2',3'- dideoxy analogues of pyrimidine, deoxyribonucleosides against retroviruses", J. Med. Chem., 30, pp. 440-41 (1987).





Finally, the 3'-fluoro analogues of 2',3'-dideoxycytidine shown in formula (F) and of 2',3'-dideoxythymidine shown in formula (G) are referred to in Herdewijn et al., "3'-Substituted 2',3'-dideoxynucleoside analogues as potential anti- HIV(HTLV-III/LAV) agents", J. Med. Chem., 30, pp. 1270-78 (1987), as having potent antiretroviral activity.



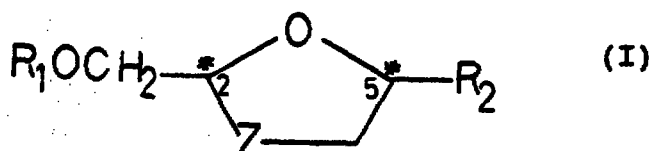
The most potent anti-HIV compounds thus far reported are 2',3'-dideoxynucleosides, more particularly, 2',3'-dideoxy cytidine (ddCyd) and 3'-azido-2',3'-dideoxythymidine (AzddThd or AZT). These compounds are also active against other kinds of retroviruses such as the Moloney murine leukemia virus. Because of the increasing incidence and the life-threatening characteristics of AIDS, efforts are being expended to discover and develop new non-toxic and potent inhibitors



of HIV and blockers of its infectivity. It is therefore an object of the present invention to provide effective anti-HIV compounds of low toxicity and a synthesis of such new compounds that is readily feasible.

5 A structurally distinct class of compounds known as 2-substituted-5-substituted-1,3-oxathiolanes has now been discovered and found to have antiretroviral activity. In particular, these compounds have been found to act as non-toxic inhibitors of the replication of HIV-
10 1 in T-lymphocytes over prolonged periods of time.

There is accordingly provided in a first aspect a compound of formula (I)



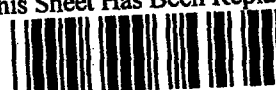
wherein R_1 is hydrogen;

15 R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

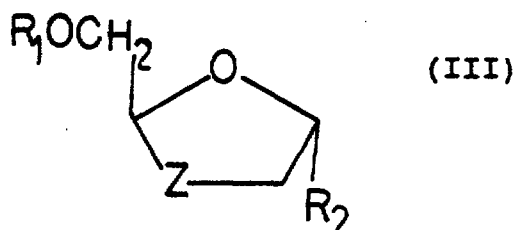
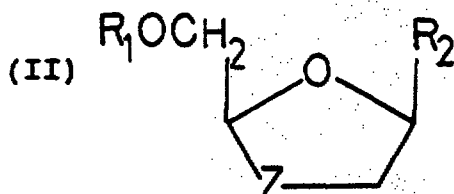
Z is S, S=O or SO_2 ; and

pharmaceutically acceptable derivatives thereof.

It will be appreciated by those skilled in the
20 art that the compounds of formula (I) contain at least two chiral centers (shown as * in formula (I)) and thus exist in the form of two pairs of optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures. Thus the compounds of formula (I) may be
25 either cis isomers, as represented by formula (II), or trans isomers, as represented by formula (III), or mixtures thereof. Each of the cis and trans isomers can exist as one of two enantiomers or as mixtures thereof including racemic mixtures. All such isomers and

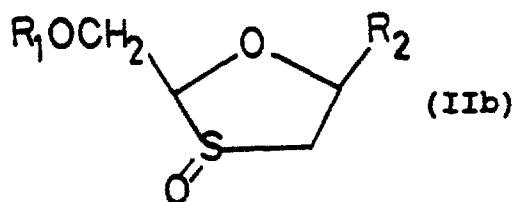
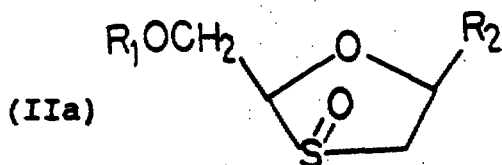


mixtures thereof including racemic mixtures are included within the scope of the invention.



The compounds of formula (I) are preferably in the form of their cis isomers.

It will also be appreciated that when Z is S=O the compounds exist in two additional isomeric forms as shown in formulas (IIa) and (IIb) which differ in the configuration of the oxide oxygen atom relative to the 2,5-substituents. The compounds of the invention additionally embrace such isomers and mixtures thereof.



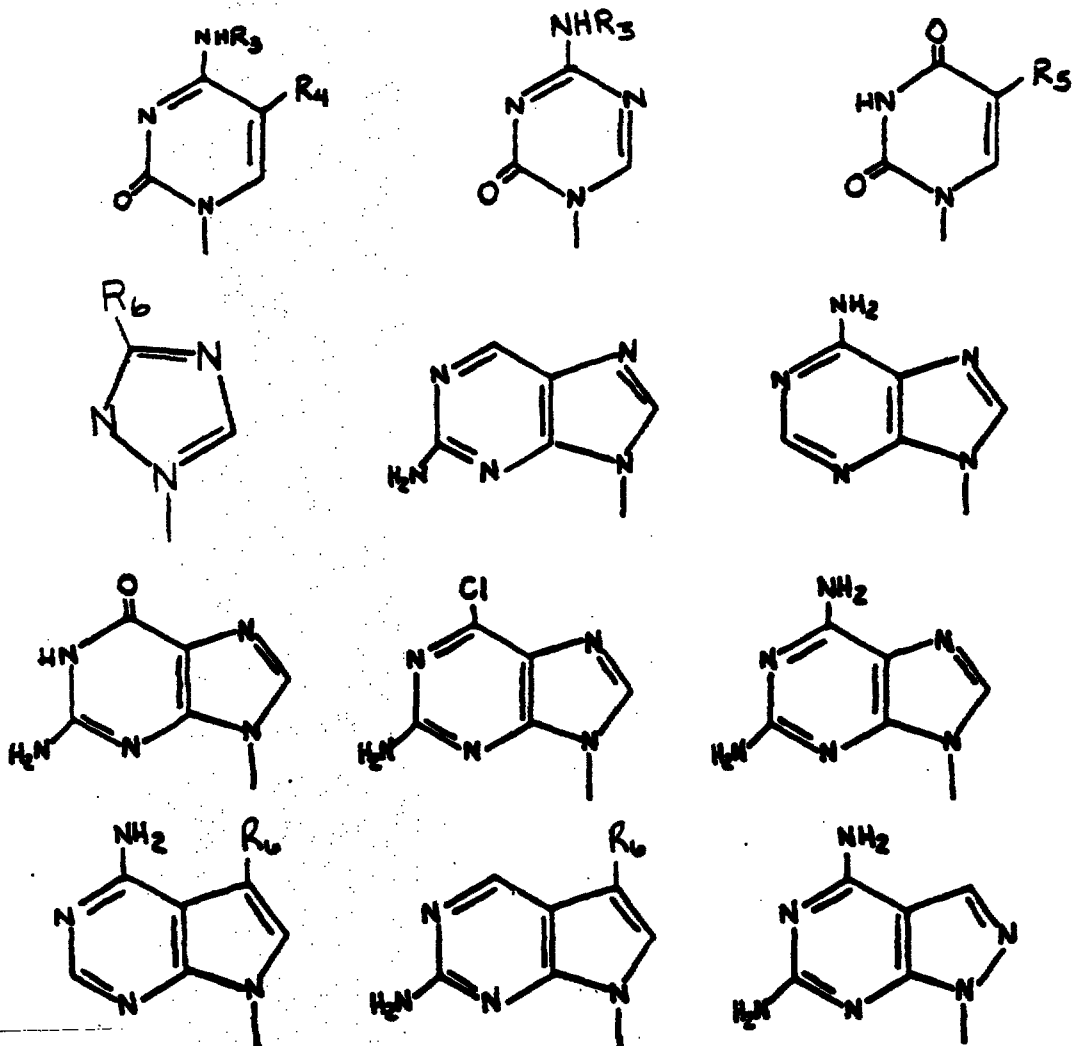
The purine or pyrimidine base or analog or derivative thereof R₂ will be linked at the 9- or 1-position respectively.

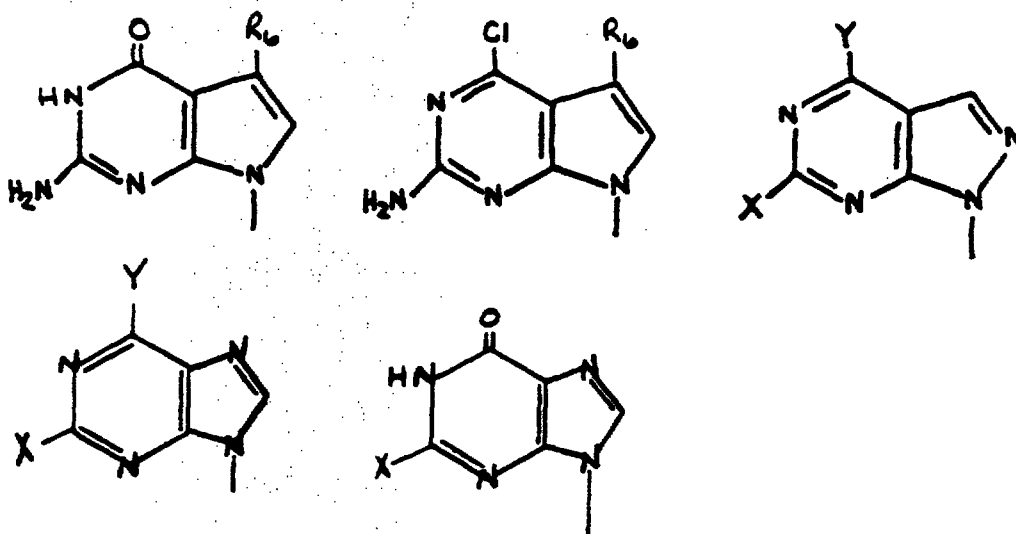
By purine or pyrimidine base or an analogue or derivative thereof is meant a purine or pyrimidine base found in native nucleosides or an analogue thereof which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the native



bases but may either possess additional or lack certain of the functional properties of the native bases. Such analogues include those derived by replacement of a CH_2 moiety by a nitrogen atom (for example, 5-azapyrimidines such as 5-azacytosine) or vice versa (for example 7-deazapurines, for example 7-deazadenosine or 7-deazaguanosine) or both (e.g., 7-deaza, 8-azapurines). By derivatives of such bases or analogues are meant those compounds wherein ring substituents are either incorporated, removed or modified by conventional substituents known in the art, e.g., halogen, hydroxyl, amino, C_{1-6} alkyl. Such purine or pyrimidine bases, analogues and derivatives will be well known to those skilled in the art.

Conveniently the group R_2 is selected from:





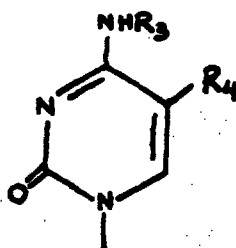
wherein R_1 is selected from the group of hydrogen, hydroxymethyl or saturated or unsaturated C_{1-6} alkyl groups;

5 R_2 and R_3 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;

R_4 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and

10 X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxy groups.

Preferably R_2 is



wherein R_2 and R_3 are as defined hereinabove.

15 Z is preferably -S-.

By "a pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any



other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an antivirally active metabolite or residue thereof.

5 It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof, at functional groups in both the base moiety, R_2 and at the hydroxymethyl group of the oxathiolane ring.

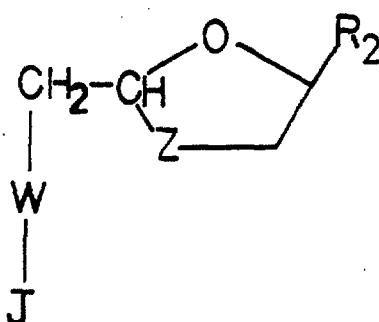
10 Modification at all such functional groups is included within the scope of the invention. However, of particular interest are pharmaceutically acceptable derivatives (e.g., esters) obtained by modification of the 2-hydroxymethyl group of the oxathiolane ring.

15 Preferred esters of the compounds of formula (I) include the compounds in which R_1 is replaced by a carboxyl function $R-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ in which the non-carbonyl moiety R of the ester grouping is selected from hydrogen, straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy); substituted dihydro pyridinyl (e.g., N-methyldihydro pyridinyl); sulphonate esters such as alkyl-
20 or aralkylsulphonyl (e.g., methanesulphonyl); sulfate esters; amino acid esters (e.g., L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters.

Also included within the scope of such esters are esters derived from polyfunctional acids such as
30 carboxylic acids containing more than one carboxyl group, for example, dicarboxylic acids $\text{HO}_2\text{C}(\text{CH}_2)_n\text{CO}_2\text{H}$ where n is an integer of 1 to 10 (for example, succinic acid) or phosphoric acids. Methods for preparing such esters are well known. See, for example, Hahn et al., "Nucleotide
35 Dimers as Anti Human Immunodeficiency Virus Agents", Nucleotide Analogues, pp. 156-159 (1989) and Busso et



al., "Nucleotide Dimers Suppress HIV Expression In Vitro", AIDS Research and Human Retroviruses, 4(6), pp. 449-455 (1988). Where esters are derived from such acids, each acidic group is preferably esterified by a compound of formula (I) or other nucleosides or analogues and derivatives thereof to provide esters of the formula (IV)



(IV)

where W is $-O-\overset{\overset{O}{\parallel}}{C}-(CH_2)_n-\overset{\overset{O}{\parallel}}{C}-O-$ and n is an integer of 1 to 10

or $-O-\overset{\overset{O}{\parallel}}{P}(O^-)-O-$ or $-O-\overset{\overset{S}{\parallel}}{P}(O^-)-O-$, J is any nucleoside or

nucleoside analog or derivative thereof and Z and R₂ are as defined above. Among the preferred nucleosides and nucleoside analogues are 3'-azido-2',3'-dideoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydro-thymidine, and 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin and those nucleosides whose bases are depicted on pages 7-8 of this specification. We most prefer a homodimer consisting of two nucleosides of formula (I).

With regard to the above described esters, unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, preferably 1 to 4 carbon atoms and could contain one or more double bonds. Any aryl moiety present in such esters advantageously comprises a phenyl group.



In particular the esters may be a C_{1-16} alkyl ester, an unsubstituted benzoyl ester or a benzoyl ester substituted by at least one halogen (bromine, chlorine, fluorine or iodine), saturated or unsaturated C_{1-6} alkyl, saturated or unsaturated C_{1-6} alkoxy, nitro or trifluoromethyl groups.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and NR_4^+ (where R is C_{1-4} alkyl) salts.

References hereinafter to a compound according to the invention includes both compounds of formula (I) and their pharmaceutically acceptable derivatives.

Specific compounds of formula (I) include:

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;



Cis-2-hydroxymethyl-5-(N,'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N,'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

5 Cis-2-benzoyloxymethyl-5-(N,'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N,'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;

10 Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;

Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;

15 Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;

20 Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;

25 Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;

30 in the form of a racemic mixture or a single enantiomer.

The compounds of the invention either themselves possess antiviral activity and/or are metabolizable to such compounds. In particular these compounds are effective in inhibiting the replication of
35 retroviruses, including human retroviruses such as human



immunodeficiency viruses (HIV's), the causative agents of AIDS.

There is thus provided as a further aspect of the invention a compound formula (I) or a
5 pharmaceutically acceptable derivative thereof for use as an active therapeutic agent in particular as an antiviral agent, for example in the treatment of retroviral infections.

In a further or alternative aspect there is
10 provided a method for the treatment of a viral infection, in particular an infection caused by a retrovirus such as HIV, in a mammal, including man, comprising administration of an effective amount of an antiviral compound of formula (I) or a pharmaceutically acceptable
15 derivative thereof.

There is also provided in a further or alternative aspect of this invention, use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament
20 for the treatment of a viral infection.

The compounds of the invention are also useful in the treatment of AIDS related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological
25 conditions (such as dementia), anti-HIV antibody positive and HIV- positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

The compounds of the invention are also useful in the prevention or progression to clinical
30 illness of individuals who are anti-HIV antibody or HIV-antigen positive and in prophylaxis following exposure to HIV.

The compounds of formula (I) or the pharmaceutically acceptable derivatives thereof, may also
35 be used for the prevention of viral contamination of biological fluids such as blood or semen in vitro.



Certain of the compounds of formula (I) are also useful as intermediates in the preparation of other compounds of the invention.

5 It will be appreciated by those skilled in the art that references herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

10 It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

15 In general however a suitable dose will be in the range from about 1 to about 750 mg/kg of bodyweight per day, such as 3 to about 120 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60

20 mg/kg/day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

25 The compound is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

30 Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 1 to 75 μ M, preferably about 2 to 50 μ M, most preferably about 3 to about 30 μ M. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active

35 ingredient, optionally in saline, or administered as a bolus containing about 0.1 to about 110 mg/kg of the



active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient therefor.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution; as a



suspension; or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils) or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more



emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

5 Formulations suitable for topical
administration in the mouth include lozenges comprising
active ingredient in a flavored based, usually sucrose
and acacia or tragacanth; pastilles comprising the active
ingredient in an inert base such as gelatin and glycerin
or sucrose and acacia; and mouthwashes comprising the
10 active ingredient in a suitable liquid carrier.

Pharmaceutically formulations suitable for
rectal administration wherein the carrier is a solid, are
most preferably represented as unit dose suppositories.
Suitable carriers include cocoa butter and other
15 materials commonly used in the art, and the suppositories
may be conveniently formed by admixture of the active
compound with the softened or melted carrier(s) followed
by chilling and shaping in molds.

Formulations suitable for vaginal
20 administration may be presented as pessaries, tampons,
creams, gels, pastes, foams or sprays containing in
addition to the active ingredient, such carriers as are
known in the art to be appropriate.

For intra-nasal administration the compounds
25 of the invention may be used as a liquid spray or
dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or
non-aqueous base also comprising one or more dispersing
agents, solubilizing agents or suspending agents. Liquid
30 sprays are conveniently delivered from pressurized packs.

For administration by inhalation, the
compounds according to the invention are conveniently
delivered from an insufflator, nebulizer or a pressurized
pack or other convenient means of delivering an aerosol
35 spray. Pressurized packs may comprise a suitable
propellant such as dichlorodifluoromethane,



trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

5 Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The
10 powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

 When desired, the above described
15 formulations adapted to give sustained release of the active ingredient, may be employed.

 The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

20 The compounds of the invention may also be used in combination with other therapeutic agents, for example, other antiinfective agents. In particular the compounds of the invention may be employed together with known antiviral agents.

25 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable derivative thereof together with another therapeutically active agent, in particular, an antiviral agent.

30 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier
35 therefor comprise a further aspect of the invention.



Suitable therapeutic agents for use in such combinations include acyclic nucleosides such as aciclovir, ganciclovir, interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as
5 probenicid; nucleoside transport inhibitors such as dipyridamole; nucleoside analogues such as 3'-azido-2',3'-dideoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydro-
10 thymidine, and 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as
15 2-deoxy-D-glucose, castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments and CD4-hybrid molecules.

The individual components of such combinations may be administered either sequentially or
20 simultaneously in separate or combined pharmaceutical formulations.

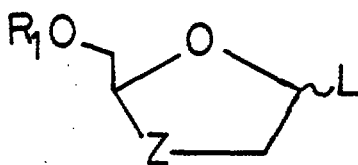
When the compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active
25 against the same virus, the dose of each compound may be either the same or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compounds of formula (I) and their
30 pharmaceutically acceptable derivatives may be prepared by any method known in the art for the preparation of compounds of analogous structure.

R_1 and R_2 as used hereunder have the same meaning as defined above unless otherwise stated.

35 In one such process (A) a 1,3-oxathiolane of formula (VIII)





(VIII)

wherein R_1 is hydrogen or hydroxyl protecting group as defined herein and the anomeric group L is a displaceable atom or group and is reacted with an appropriate base. Suitable groups L include alkoxy carbonyl groups such as ethoxy carbonyl or halogens, for example, iodine, bromine or chlorine or $-OR$ where R is a substituted or unsubstituted, saturated or unsaturated alkyl group, e.g., a C_{1-6} alkyl group such as methyl, or R is a substituted or unsubstituted aliphatic or aromatic acyl group, e.g., a C_{1-6} aliphatic acyl group such as acetyl and an aromatic acyl group such as benzoyl.

The compound of formula (VIII) is conveniently reacted with the appropriate purine or pyrimidine base R_2-H (previously silylated with a silyating agent such as hexamethyldisilazane) in a compatible solvent such as methylene chloride using a Lewis acid (such as titanium tetrachloride or stannic chloride) or trimethylsilyltriflate.

The 1,3-oxathiolanes of formula (VIII) may be prepared, for example, by reaction of an aldehyde of formula (VII) with a mercaptoacetal of formula (VI) in a compatible organic solvent, such as toluene, in the presence of an acid catalyst such as a para-toluene sulfonic acid or a Lewis acid, e.g., zinc chloride.



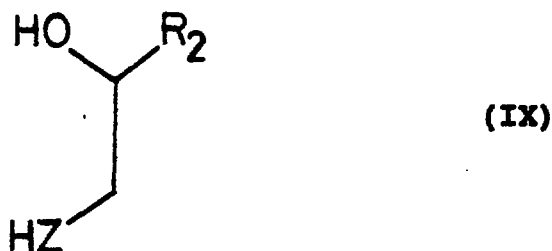
The mercaptoacetals of formula (VI) may be prepared by methods known in the art, for example, G. Hesse and I. Jorder, "Mercaptoacetaldehyde and dioxo-1, 4-dithiane", Chem. Ber., 85, pp. 924-932 (1952).

5 The aldehydes of formula (VII) may be prepared by methods known in the art, for example, E.G. Halloquist and H. Hibbert, "Studies on reactions relating to carbohydrates and polysaccharides.

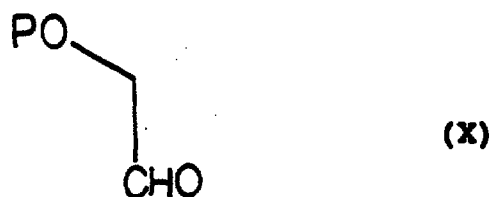
10 Part XLIV: Synthesis of isomeric bicyclic acetal ethers", Can. J. Research, 8, pp. 129-136 (1933).

In a second process (B) one compound of formula (I) is converted to another compound of formula (I) by base interconversion. Such interconversion may be effected either by simple chemical transformation (e.g.,
15 the conversion of uracil base to cytosine) or by an enzymatic conversion using, for example, a deoxyribosyl transferase. Such methods and conditions for base interconversions are well known in the art of nucleoside chemistry.

20 In a third process (C) the compounds of formula (I) may be prepared by the reaction of a compound of formula (IX)

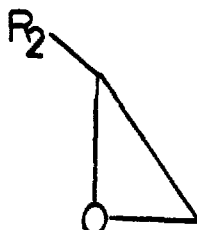


with a compound of formula (X)



where P is a protecting group, followed by removal of the protecting group.

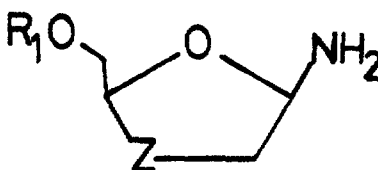
The compounds of formula (IX) may be prepared for reaction by a suitable epoxide (XI)



(XI)

with an appropriate sulphur-containing compound, e.g., sodium thioacetate. Compounds of formula (XI) are either known in the art or may be obtained by analogous processes.

In a fourth process (D) a compound of formula (XII)



(XII)

may be converted to a compound of formula (I) by conversion of the anomeric NH₂ group to the required base by methods well known in the art of nucleoside chemistry.

Many of the reactions described hereinabove have been extensively reported in the context of purine nucleoside synthesis, for example, in "Nucleoside Analogues - Chemistry, Biology and Medical Applications", R.T. Walker et al., Eds, Plenum Press, New York (1979) at pages 193-223, the text of which is incorporated by reference herein.

It will be appreciated that the above reactions may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be



required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g., benzyl), acyl or aryl (e.g., 2,4-dinitrophenyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g., methyl, t-butyl or methoxymethyl), aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl, (e.g., acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by treatment with BF₃/etherate and acetic anhydride followed by removal of acetate groups so formed at an appropriate stage in the synthesis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

In the above processes the compounds of formula (I) are generally obtained as a mixture of the cis and trans isomers.



These isomers may be separated, for example, by acetylation, e.g., with acetic anhydride followed by separation by physical means, e.g., chromatography on silica gel and deacetylation, e.g., with methanolic ammonia or by fractional crystallization.

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in United States Patent No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of a compound of formula (I), the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods. Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the free base with a suitable base such as an alkoxide (e.g., sodium methoxide) optionally in the presence of a solvent such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

A compound of formula (I) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as POCl_3 , or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of a compound of formula (I) may be converted to the parent compound, for example, by hydrolysis.

Where the compound of formula (I) is desired as a single isomer it may be obtained either by resolution of the final product or by stereospecific



synthesis from isomerically pure starting material or any convenient intermediate.

Resolution of the final product, or an intermediate or starting material therefore may be effected by any suitable method known in the art: see for example, Stereochemistry of Carbon Compounds, by E.L. Eliel (McGraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.

The invention will be further described by the following examples which are not intended to limit the invention in any way. All temperatures are in degrees celsius.

EXAMPLES

Example 1

2-thiobenzoyl acetaldehyde diethylacetal



To a solution of potassium t-butoxide (11.5 g. 0.11 mol) in DMF (100 ml) was added thiobenzoic acid (17 g. 0.11 mol) and the solution partially evaporated in vacuo, benzene added in two consecutive portions (2 x 30 ml) and evaporated in vacuo each time. To the residual DMF solution was added bromoacetaldehyde diethylacetal (20.3 g. 0.1 mol) and the mixture stirred at 120° for 15 h. After cooling, it was poured onto water (500 ml), the product extracted with ether (3 x 200 ml), the extract washed with aqueous NaHCO₃, followed by water, then dried and the solvent removed in vacuo. The residue was distilled in vacuo to give 17.2 g. of pure (V), b.p. 131-133°/0.07 mm. It was characterized by ¹H NMR δ(ppm in CDCl₃):

7.97 (d, 2H; aromatic)

7.47 (m, 3H; aromatic)



4.59 (t, 1H; $-\text{CH}(\text{OC}_2\text{H}_5)_2$)
 3.66 (m, 4H; $2 \times \text{OCH}_2\text{CH}_3$)
 3.30 (d, 2H; SCH_2-)
 1.23 (t, 6H; $2 \times \text{OCH}_2\text{CH}_3$)

5 Example 2

Mercaptoacetaldehyde diethylacetal



The preceding thiobenzoyl derivative (V)
 10 (17.2 g) was dissolved in 100 ml THF followed by the
 addition of 6 g NaOH in 20 ml H_2O . The mixture was
 refluxed under N_2 for 15 h, then cooled and diluted with
 water (200 ml) and the product extracted with ether (3 x
 200 ml). The extract was dried, the solvent removed in
 15 vacuo and the residue distilled in vacuo to yield 7.1 g
 of pure (VI), b.p. $60-62^\circ/18$ mm. It was characterized by
 ^1H NMR δ (ppm in CDCl_3):

4.51 (t, 1H; $\text{CH}(\text{OC}_2\text{H}_5)_2$)
 3.51 (m, 4H; $2 \times \text{OCH}_2\text{CH}_3$)
 20 2.65 (dd, 2H; $\text{HS}-\text{CH}_2$)
 1.54 (t, 1H; $\text{HS}-$)
 1.23 (t, 6H; $2 \times \text{OCH}_2\text{CH}_3$)

Example 3

Benzoyloxyacetaldehyde

25



This known intermediate was prepared by a
 previously unreported method from the known 1-benzoyl
 glycerol. Thus, 50 g of the latter in a mixture of
 30 500 ml of CH_2Cl_2 and 25 ml of H_2O was treated portionwise
 with 80 g of NaIO_4 under vigorous stirring at room
 temperature. After addition, stirring was continued for



2 h after which time 100 g of MgSO_4 was added and stirring continued for 30 min. The mixture was filtered, the filtrate evaporated in vacuo and the residue distilled in vacuo to yield 26 g of pure (VII) b.p. 92-94°/0.25 mm.

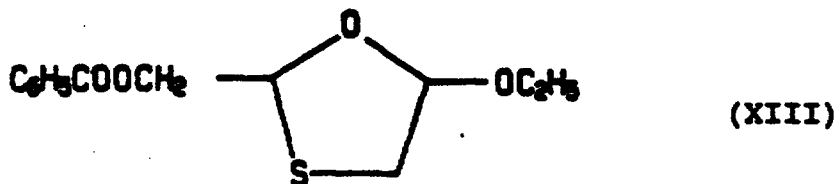
5 ^1H NMR (200 MHz ; TMS as internal reference)

δ (ppm in CDCl_3):

9.71 (s, 1H; -CHO)
 8.11 (d, 2H; aromatic)
 7.60 (m, 1H; aromatic)
 10 7.46 (m, 2H; aromatic)
 4.88 (s, 2H; $-\text{CH}_2\text{CHO}$)

Example 4

2-Benzoyloxymethyl-5-ethoxy-1,3-oxathiolane



15 The preceding mercaptoacetaldehyde acetal (VI)
 (7 g) was mixed in 100 ml of toluene with 7 g of the
 above benzoyloxyacetaldehyde (VII), a few crystals of
 para-toluene sulfonic acid added and the mixture placed
 in an oil-bath at 120° under N_2 . The formed ethanol was
 20 allowed to distill over, the mixture kept at 120° for an
 additional 30 minutes, then cooled and washed with
 aqueous NaHCO_3 , dried and evaporated in vacuo. The
 residue was distilled in vacuo to yield 9.8 g of pure
 (XIII) as a mixture of cis- and trans-isomers, b.p. 140-
 25 143°/0.1 mm; R_f 0.51 (hexane-EtOAc);

^1H NMR δ (ppm in CDCl_3):

8.05 (m, 2H; aromatic)
 7.57 (m, 1H; aromatic)
 7.43 (m, 2H; aromatic)



5

10

Cis- and trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-
oxathiolanes



15

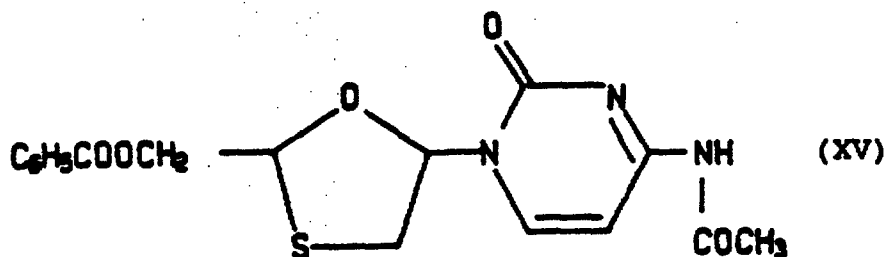
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25

mixture of cis- and trans-(XIV) in a 1:1 ratio as ascertained by ^1H NMR. These were separated as the N-acetyl derivatives as described in the following example.

Example 6

5 Cis- and trans-isomers of 2-benzoyloxymethyl-5-(N,'-acetyl-cytosin-1'-yl)-1,3-oxathiolane



The preceding mixture (XIV) (2.5 g) in 100 ml of dry pyridine containing 0.1 g of 4-dimethylamino-pyridine (DMAP) was treated with acetic anhydride (7 ml) at room temperature and after 16 hours, the mixture was poured onto cold water followed by extraction with CH_2Cl_2 (3 X 150 ml). The extract was washed with water, dried, and evaporated in vacuo. Toluene was added to the residue, then evaporated in vacuo and the residual oil purified by chromatography on silica gel using $\text{EtOAc}:\text{CH}_3\text{OH}$ 99:1 as the eluant to yield 1.35 g of pure trans-(XV) as the fast moving product and 1.20 g of pure cis-(XV) as the slow moving component. These were characterized by ^1H NMR spectroscopy.

trans-(XV): m.p. 158-160°; R_f : 0.48 $\text{EtOAc}:\text{CH}_3\text{OH}$ 95:5

U.V.: (CH_3OH) λ_{max} : 297 nm

^1H NMR δ (ppm in CDCl_3):

9.00 (b, 1H; C_4' -NH-Ac)
 8.06 (m, 2H; aromatic)
 7.74 (d, 1H; C_6' -H)
 7.56 (m, 1H; aromatic)



- 7.56 (m, 1H; aromatic)
 7.47 (d, 1H; C₅'-H)
 7.45 (m, 2H; aromatic)
 6.53 (dd, 1H; C₅-H)
 5
 5.89 (dd, 1H; C₂-H)
 4.46 (dd, 2H; C₂-CH₂OCOC₆H₅)
 3.66 (dd, 1H; C₄-H)
 3.32 (dd, 1H; C₄-H)
 2.25 (s, 3H; NH-COCH₃)

10 Cis-(XV): m.p. 150-152°; R_f: 0.40 EtOAc:MeOH 95:5)

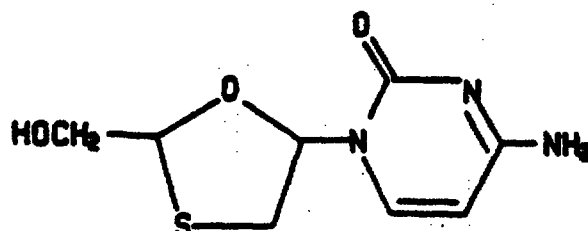
U.V.: (CH₃OH) Lambda max: 297 nm

¹H NMR δ(ppm in CDCl₃):

- 9.03 (b, 1H; NH-Ac)
 8.21 (d, 1H; C₆'-H)
 15 8.05 (m, 2H; aromatic)
 7.60 (m, 1H; aromatic)
 7.50 (m, 2H; aromatic)
 7.29 (d, 1H; C₅'-H)
 6.34 (dd, 1H; C₅-H)
 20 5.52 (dd, 1H; C₂-H)
 4.80 (dd, 2H; C₂-CH₂OCOC₆H₅)
 3.66 (dd, 1H; C₄-H)
 3.24 (dd, 1H; C₄-H)
 2.23 (s, 3H; NH-COCH₃)

25 Example 7

Cis- and trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolanes



(XVI)



a) Trans-(XVI): 375 mg of the preceding trans-(XV) was dissolved in 100 ml of methanolic ammonia at 24° and after stirring for 16 hours, the solvent was removed in vacuo and the residue crystallized with ether. It was recrystallized from ethanol-ether to yield 174 mg of pure product, m.p. >220° (dec). It was characterized by ¹H and ¹³C NMR.

¹H NMR δ(ppm in DMSO-d₆):

	7.57 (d, 1H; C ₆ '-H)
10	7.18 (d, 2H; C ₄ '-NH ₂)
	6.30 (dd, 1H; C ₅ -H)
	5.68 (d, 1H; C ₃ '-H)
	5.48 (t, 1H; C ₂ -H)
	5.18 (t, 1H; C ₂ -CH ₂ OH)
15	3.45 (m, 3H; C ₂ -CH ₂ OH + C ₄ H)
	3.06 (dd, 1H; C ₄ -H)

U.V.: (CH₃OH) Lambda max: 270 nm

¹³C NMR (DMSO-d₆, Varian XL-300); δ in ppm:

	C ₂ '	C ₄ '	C ₅ '	C ₆ '	C ₃	C ₄	C ₂	CH ₂ OH
20	154.71	165.70	93.47	140.95	87.77	36.14	86.80	64.71

b) Cis-(XVI): treating 375 mg of cis-(XV) by the same preceding procedure led to 165 mg of pure product after recrystallization from ethanol-ether, m.p. 171-173°. It was characterized by ¹H and ¹³C NMR.

¹H NMR: δ(ppm in DMSO-d₆):

	7.80 (d, 1H; C ₆ '-H)
	7.20 (d, 2H; C ₄ '-NH ₂)
	6.18 (t, 1H; C ₅ -H)
	5.70 (d, 1H; C ₃ '-H)
30	5.14 (t, 1H; C ₂ -CH ₂ OH)
	3.71 (m, 2H; C ₂ -CH ₂ OH)
	3.40 (dd, 1H; C ₄ -H)
	2.99 (dd, 1H; C ₄ -H).

U.V.: (CH₃OH) Lambda max: 270 nm

¹³C NMR δ(ppm in DMSO-d₆)

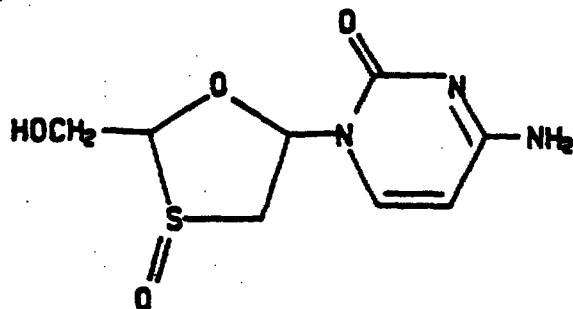
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C ₂ '	C ₄ '	C ₅ '	C ₆ '	C ₃	C ₄	C ₂	CH ₂ OH
154.63	165.59	93.86	140.91	86.47	36.22	85.75	62.79

Example 8Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane

5



(XVII)

The preceding cis-(XVI) (100 mg) in 30 ml of ice-cold methanol was treated with 93 mg of meta-chloro-perbenzoic acid and after stirring for 15 min a white solid separated which was collected and washed with 10 ml of methanol to give 45 mg of pure sulfoxide isomer a. The methanol filtrates were evaporated in vacuo and the solid residue washed with 15 ml of ethanolether (1:1) and then with 30 ml of ether to give 50 mg of pure sulfoxide isomer b. The isomers were characterized by ¹H NMR.

Isomer (XVII)a: m.p. >270° (dec); R_f: 0.30 (CH₂Cl₂-MeOH 3:1)U.V.: (CH₃OH) Lambda max: 270 nm¹H NMR δ (ppm in DMSO-d₆):

- 7.68 (d, 1H; C₆'-H)
- 7.36 (s, 2H; C₄'-NH₂)
- 6.69 (dd, 1H; C₅-H)
- 5.76 (d, 1H; C₅'-H)
- 5.47 (t, 1H; C₂-CH₂OH)
- 4.63 (dd 1H; C₂-H)
- 3.88 (m, 1H; C₂-CH-OH)
- 3.72 (m, 1H; C₂-CH-OH)

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3.36 (dd, 1H; C₄-H)

3.05 (dd, 1H; C₄-H)

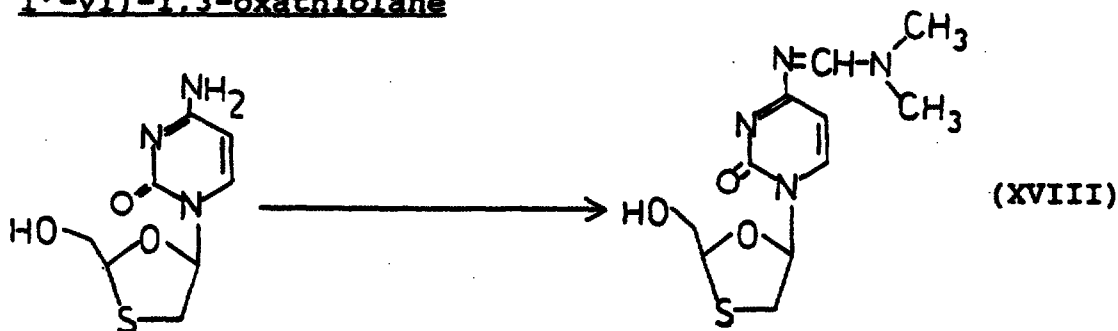
Isomer (XVII)b: m.p. >220° (dec); R_f: 0.32 CH₂Cl₂:MeOH 3:1

¹H NMR δ (ppm in DMSO-d₆):

- 5 7.76 (d, 1H; C₆'-H)
 7.28 (d, 2H; C₄'-NH₂)
 6.66 (dd, 1H; C₅-H)
 5.77 (d, 1H; C₅'-H)
 5.45 (t, 1H; C₂-CH₂OH)
 10 4.64 (t, 1H; C₂-H)
 3.77 (t, 2H; C₂-CH₂OH)
 3.65 (dd, 1H; C₄-H)
 3.17 (dd, 1H; C₄-H)

Example 9

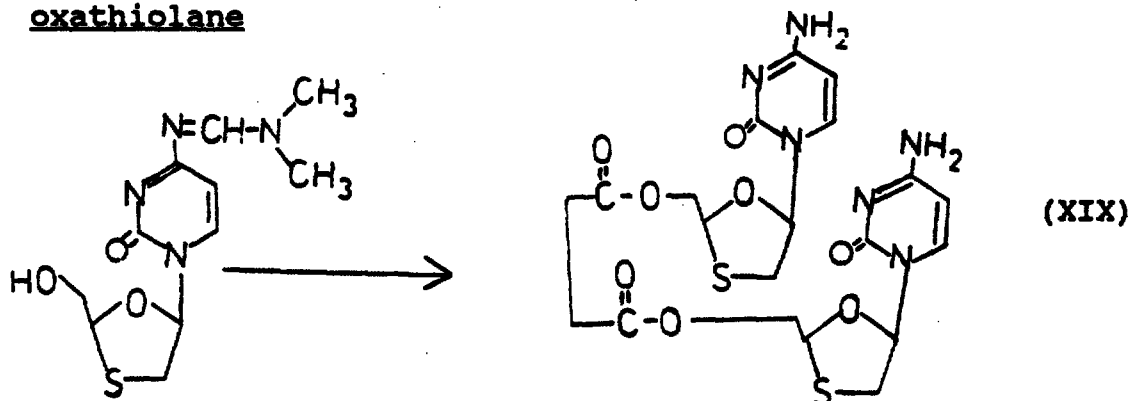
15 Cis-2-hydroxymethyl-5-(N-dimethylamino methylene cytosin-1'-yl)-1,3-oxathiolane



- 300 mg of cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane was suspended in 10 ml of N-dimethylformamide dimethyl acetal (DMF-dimethyl acetal). The mixture was stirred at room temperature overnight (18 hours). Volatile material was removed by evaporation under reduced pressure. The residue was crystallized in ethanol-ether. It yielded 345 mg (93%) of pure product.
- 25 m.p. 162-164°C; R_f: 0.56 in CH₂Cl₂:MeOH 4:1
 U.V.: Lambda max: 325 nm
 ¹H NMR δ (ppm in DMSO-d₆):
 8.64 (s, 1H, N=CH-N)



- 8.04 (d, 1H, C₆'-H, J = 7.2 Hz)
 6.22 (t, 1H, C₅-H, J = 4.9 Hz)
 5.97 (d, 1H, C₅'-H, J = 7.2 Hz)
 5.37 (t, 1H, -OH, J = 5.8 Hz, D₂O exchange)
 5.22 (t, 1H, C₂-H, J = 4.4 Hz)
 3.77 (t, 2H, C₂-CH₂OH, J = 4.9 Hz)
 3.50 (dd, 1H, C₄-H, J = 4.9 and 9.9 Hz)
 3.17 (s, 3H, -CH₃)
 3.12 (dd, 1H, C₄-H, J = 4.2 and 11.9 Hz)
 3.04 (s, 3H, -CH₃)

Example 10**Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane**

- 284 mg of cis-2-hydroxymethyl-5-(N, N-dimethylamino methylene cytosin-1'-yl)-1,3-oxathiolane was dissolved in 10 ml of dry pyridine and cooled at 0°C in an ice-bath. 60 μ l of succinyl chloride was added via a syringe. The mixture was stirred overnight (18 hours) and poured into 50 ml of saturated aqueous NaHCO₃ solution. The mixture was extracted with methylene chloride (3 x 50 ml). The combined CH₂Cl₂ solution was washed with water (2 x 50 ml) and dried over MgSO₄. After filtration, solvent was removed by evaporation under reduced pressure. The foam residue was dissolved in 10 ml of CH₂Cl₂ containing 5 ml of methanol. 2 ml of 80% aqueous acetic acid was added and the mixture was stirred



at room temperature overnight. The mixture was evaporated to dryness. The solid residue was purified on silica gel using CH_2Cl_2 : MeOH 4:1 as eluant. It yielded 145 mg (54%) of pure product.

5 m.p. Dec $>230^\circ\text{C}$; R_f : 0.23 (in CH_2Cl_2 :MeOH 4:1)

U.V.: (MeOH) Lambda max: 271 nm

$^1\text{H-NMR}$ δ (ppm in DMSO-d_6)

7.69 (d, 2H, 2 x $\text{C}_6'\text{-H}$, $J = 7.6$ Hz)

7.28 (d, 4H, 2 x NH_2 , $J = 24.9$ Hz, D_2O exchange)

10 6.24 (t, 2H, 2 x $\text{C}_5\text{-H}$, $J = 5.6$ Hz)

5.76 (d, 2H, 2 x $\text{C}_3'\text{-H}$; $J = 7.4$ Hz)

5.35 (t, 2H, 2 x $\text{C}_2\text{-H}$, $J = 4.5$ Hz)

4.37 (d, 4H, 2 x $\text{C}_2\text{-CH}_2\text{O-}$)

3.42 (dd, 2H, 2 x $\text{C}_4\text{-H}$, $J = 5.5$ and 10.9 Hz)

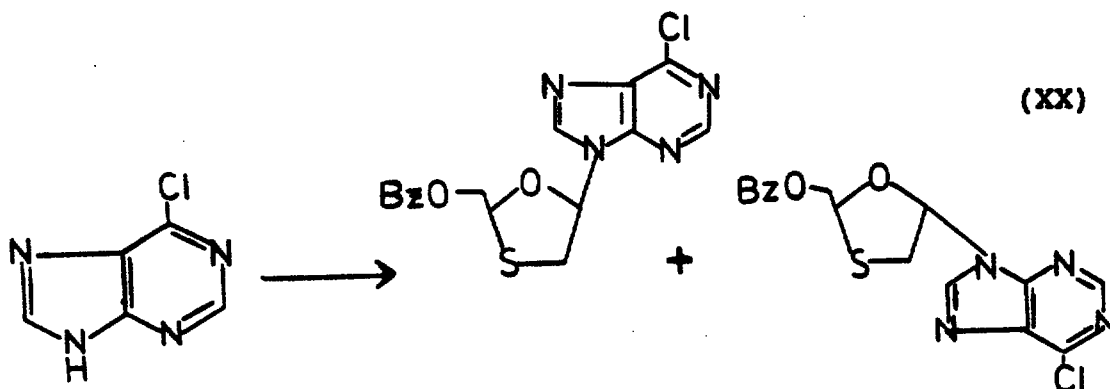
15 3.10 (dd, 2H, 2 x $\text{C}_4\text{-H}$, $J = 5.6$ and 11.7 Hz)

2.60 (s, 4H, 2 x $-\text{CH}_2\text{-C-O}$)

Example 11

Cis- and trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolanes

20



1.7 g of 6-chloropurine was heated at reflux in 50 ml of HMDS (hexamethyldisilazane) containing 50 mg of $(\text{NH}_4)_2\text{SO}_4$ (ammonium sulfate) until the solution became



clear (1 hour). Excess HMDS was removed under reduced pressure. The oily residue was dried under high vacuum for 1 hour and then dissolved in 100 ml of dry 1,2-dichloroethane.

5 2.7 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane (XIII) was dried in a 500 ml round bottom flask by evaporation twice with 50 ml of benzene and dissolved in 200 ml of dry 1,2-dichloroethane.

10 The solution of silylated 6-chloropurine was then transferred into the 1,3-oxathiolane solution through a canula under argon atmosphere. 11 ml of 1M TMS-triflate (trimethylsilyl trifluoromethane sulfonate) was added to the reaction flask. The mixture was heated at reflux for 5 hours, then cooled to room temperature.
15 The mixture was poured into 300 ml of saturated sodium bicarbonate solution (NaHCO₃ solution) while stirring. The organic layer was collected and the aqueous phase was extracted with CH₂Cl₂ (2 x 100 ml). The combined organic phase was washed with water, dried over MgSO₄, filtered
20 and evaporated under reduced pressure. The residue was purified and separated on silica gel using Hexane-ethyl acetate 7:3 as eluant. It yielded 1.05 g (28%) of the less polar product, which was identified as alpha- or trans- isomer as a foam, and 710 mg of lower product as beta- or cis-isomer. Total yield 46.1%; cis:trans ratio
25 1:1.4

trans-isomer (α -isomer): R_f: 0.43 in Hexane:EtOAc 1:1

U.V.: (MeOH) Lambda max: 264.7 nm

¹H-NMR δ (ppm in CDCl₃):

30 8.76 (s, 1H, C₈'-H)
 8.48 (s, 1H, C₂'-H)
 8.06 (m, 2H, aromatic)
 7.56 (m, 1H, aromatic)
 7.45 (m, 2H, aromatic)
35 6.90 (dd, 1H, C₅-H, J = 5.0 Hz)



5.78 (dd, 1H, C₂-H, J = 6.0 Hz)
 4.56 (m, 2H, C₂-CH₂OCOC₆H₅)
 3.74 (m, 2H, C₄-H)

cis-isomer (beta-isomer): R_f: 0:35 in Hexane:EtOAc: 1:1

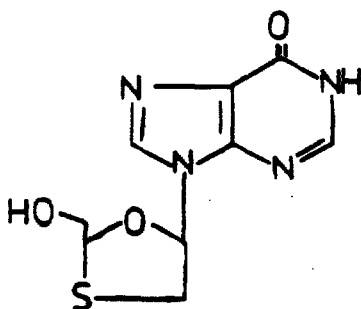
5 U.V.: (MeOH) Lambda max 264.7 nm

¹H-NMR δ(ppm in CDCl₃):

8.72 (s, 1H, C₈'-H)
 8.51 (s, 1H, C₂'-H)
 8.00 (m, 2H, aromatic)
 10 7.56 (m, 1H, aromatic)
 7.44 (m, 2H, aromatic)
 6.61 (t, 1H, C₅-H, J = 4.7 Hz)
 5.62 (t, 1H, C₂-H, J = 4.9 Hz)
 4.69 (m, 2H, C₂-CH₂OCOC₆H₅)
 15 3.66 (m, 2H, C₄-H)

Example 12

Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane (inosine derivative)



(XXI)

20 533 mg of cis-2-benzoyloxymethyl-5-(6-chloropurin-N-9'-yl)-1,3-oxathiolane was dissolved in 25 ml of methanol. 5 g of sodium hydroxide (NaOH) and 3 ml of water were added into the solution. The mixture was heated at reflux for 5 hours and cooled to room
 25 temperature. The solution was then diluted with 100 ml



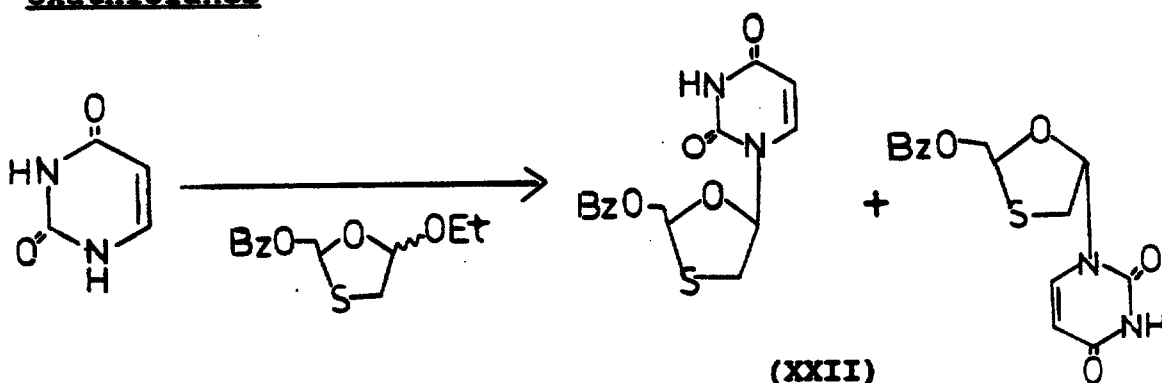
of water, neutralized with pyridinium resin and filtered. The resin residue was washed with 100 ml of methanol. The combined filtrate was evaporated under reduced pressure. The residue was purified on silica gel using $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 4:1 as eluant. It yielded 183 mg (51%) of pure product, which was identified as inosine derivative. m.p.: 208-210°C; R_f : 0.27 in $\text{EtOAc}:\text{MeOH}$ 4:1 U.V.: (MeOH) λ_{max} : 246 nm

$^1\text{H-NMR}$: δ (ppm in DMSO-d_6)

- 10 12.42 (s, 1H, -NH, D_2O exchange)
 8.36 (s, 1H, $\text{C}_8'\text{-H}$)
 8.07 (s, 1H, $\text{C}_2'\text{-H}$)
 6.37 (t, 1H, $\text{C}_5\text{-H}$, $J = 5.1$ Hz)
 5.29 (t, 1H, -OH, $J = 6.0$ Hz, D_2O exchange)
 15 5.24 (t, 1H, $\text{C}_2\text{-H}$, $J = 4.9$ Hz)
 3.63 (m, 4H, 2H from $\text{C}_4\text{-H}$ and 2H from $\text{CH}_2\text{-OH}$)

Example 13

Cis- and trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolanes



760 mg of uracil was heated at reflux in 30 ml of HMDS in the presence of 50 mg $(\text{NH}_4)_2\text{SO}_4$ until the solution became clear. The mixture was evaporated under reduced pressure. The residue was dried under high vacuum for 1 hour and dissolved in 100 ml of dry 1,2-dichloroethane.

25



1.5 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane was dried by evaporation twice with 50 ml of benzene in a 500 ml round bottom flask and dissolved in 150 ml of dry 1,2-dichloroethane.

5 The silylated uracil solution was transferred into the oxathiolane solution through a canula under argon atmosphere and 1.5 ml of TMS-Triflate in 20 ml of 1,2-dichloroethane was added. The reaction mixture was heated at reflux under argon atmosphere for 48 hours,
10 cooled to room temperature and poured into 300 ml of saturated aqueous NaHCO₃ solution. The organic layer was collected. The aqueous phase was extracted twice with CH₂Cl₂ (2 x 100 ml). The combined organic layer was washed with water (2 x 200 ml), once with NaCl solution
15 (1 X 150 ml) and dried over MgSO₄. After filtration, solvent was removed by evaporation in vacuum and the residue was purified on silica gel using Hexane:EtoAc 1:1 as eluant. It yielded 594 mg (32%) of pure product.

20 The product was shown as only one spot in the TLC. However the ¹H-NMR spectrum indicated the presence of two isomers cis:trans in a ratio of 1:1.2 and which were not separated at this stage.

R_f: 0.35 in Hexane:EtoAc 3:7

U.V.: (MeOH) Lambda max: 261 nm

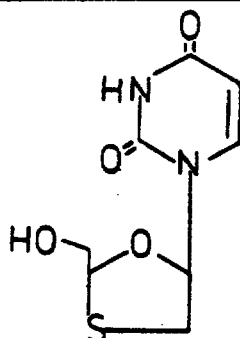
25 ¹H-NMR δ(ppm in CDCl₃)

- 8.88 (broad s, 1H, N₃'-H)
- 8.05 (m, 2H, aromatic)
- 7.71 (d, 1H, C₆'-H cis, J = 8.2 Hz)
- 7.57 (m, 1H, aromatic)
- 30 7.45 (m, 3H, aromatic and N₃'-H)
- 6.55 (dd, 1H, C₅-H trans, J = 2.4 and 5.4 Hz)
- 6.35 (dd, 1H, C₅-H cis, J = 4.1 and 5.6 Hz)
- 5.79 (t, 1H, C₂-H trans, J = 5.4 Hz)
- 5.73 (d, 1H, C₃'-H trans, J = 8.2 Hz)
- 35 5.57 (d, 1H, C₃'-H cis, J = 8.2 Hz)
- 5.46 (t, 1H, C₂-H cis, J = 3.9 Hz)



4.73 (d, 2H, $-\text{CH}_2\text{O}-\text{COC}_6\text{H}_5$)
 4.45 (t, 2H, $-\text{CH}_2\text{OCOC}_6\text{H}_5$)
 3.57 (m, 1H, $\text{C}_4\text{-H}$)
 3.17 (m, 1H, $\text{C}_4\text{-H}$)

5

Example 14**Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane**

(XXIII)

300 mg of a mixture cis- and trans-2-benzoyloxymethyl- 5-(uracil-N-1'-yl)-1,3-oxathiolanes was dissolved in 75 ml of methanolic ammonia. The mixture was stirred at room temperature overnight. The solution was evaporated by dryness. The residue was purified and the two isomers were separated on silica gel using EtOAc:MeOH 98:2 as eluant.

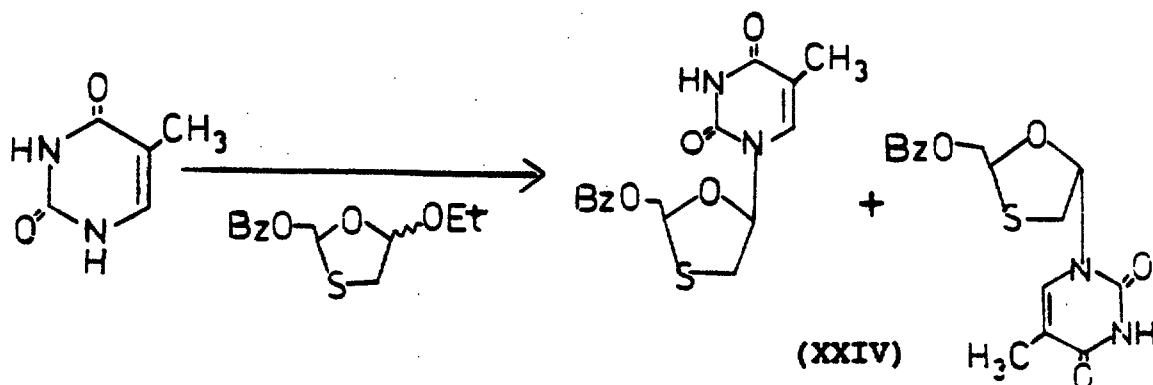
The top product was isolated as a solid product and was identified as cis-isomer.

Cis-isomer: m.p. 162-164°C; R_f : 0.57 in EtOAc:MeOH 95:5
 U.V.: (MeOH) λ_{max} : 261.4 nm

$^1\text{H-NMR}$ δ (ppm in DMSO- d_6):

20 11.36 (s, 1H, $\text{N}_3\text{'-H}$)
 7.88 (d, 1H, $\text{C}_6\text{'-H}$, $J = 8.1$ Hz)
 6.18 (t, 1H, $\text{C}_5\text{-H}$, $J = 4.8$ Hz)
 5.62 (d, 1H, $\text{C}_3\text{'-H}$, $J = 8.1$ Hz)
 5.33 (t, 1H, $\text{C}_2\text{-H}$, $J = 5.7$ Hz)
 25 5.17 (t, 1H, $-\text{OH}$, D_2O exchange)
 3.72 (t, 2H, $\text{C}_2\text{-CH}_2\text{OH}$, $J = 4.6$ Hz)
 3.41 (dd, 1H, $\text{C}_4\text{-H}$, $J = 5.7$ and 12 Hz)
 3.20 (dd, 1H, $\text{C}_4\text{-H}$, $J = 4.6$ and 9.9 Hz)



Example 15**Cis- and trans-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolanes**

5 1.7 g of thymine was heated at reflux in 50 ml of HMDS containing 50 mg of $(\text{NH}_4)_2\text{SO}_4$ until the solution became clear. The mixture was evaporated under reduced pressure. The residue was dried under high vacuum for 1 hour and dissolved in 150 ml of 1,2-dichloroethane.

10 3 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane was dried by evaporation twice with 75 ml of benzene and dissolved in 150 ml of dry 1,2-dichloroethane.

15 The silylated thymine solution was transferred into the oxathiolane through a canula under argon atmosphere. 3.3 ml of TMS-Triflate (trimethylsilyl-triflate) in 30 ml of dry 1,2-dichloroethane was introduced into the reaction mixture through a canula under argon atmosphere. The solution was heated at
20 reflux under argon atmosphere for 36 hours, cooled to room temperature and poured into 300 ml of saturated aqueous NaHCO_3 solution. The organic layer was collected and the aqueous phase was extracted twice with methylene chloride (2 X 100 ml). The combined organic phase was
25 washed twice with water (2 X 200 ml), once with NaCl solution (1 X 150 ml) and dried over MgSO_4 . The solution



was filtered. The filtrate was evaporated in vacuum. The residue was purified on silica gel using Hexane:EtOAc 1:1 as eluant. It yielded 1.3 g (35%) of pure product.

The product was shown as only one spot on TLC but the $^1\text{H-NMR}$ spectrum indicated the presence of the two isomers cis and trans in a ratio of 1:1.2.

R_f : 0.30 in Hexane:EtOAc 2:3

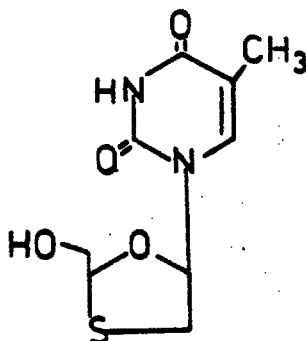
U.V.: (MeOH) λ_{max} : 266 nm

$^1\text{H-NMR}$ δ (ppm in CDCl_3):

10	8.60 (broad singlett, $\text{N}_3'\text{-H}$)
	8.06 (m, 2H, aromatic)
	7.59 (m, 1H, aromatic)
	7.49 (m, 2H, aromatic)
	7.38 (d, 1H, $\text{C}_6'\text{-H-cis}$, $J = 1.3$ Hz)
15	7.28 (d, 1H, $\text{C}_6'\text{-H-trans}$, $J = 1.3$ Hz)
	6.55 (dd, 1H, $\text{C}_5\text{-H-trans}$ isomer, $J = 3.1$ and 5.6 Hz)
	6.38 (t, 1H, $\text{C}_5\text{-H-cis}$ isomer, $J = 5.5$ Hz)
	5.78 (dd, 1H, $\text{C}_2\text{-H-trans}$, $J = 4.4$ and 6.4 Hz)
	5.46 (t, 1H, $\text{C}_2\text{-H-cis}$ -isomer, $J = 4.3$ Hz)
20	4.69 (d, 2H, $\text{C}_2\text{-CH}_2\text{OCOC}_6\text{H}_5$, $J = 4.2$ Hz)
	4.45 (m, 2H, $\text{C}_2\text{-CH}_2\text{OCOC}_6\text{H}_5$)
	3.58 (m, 1H, $\text{C}_4\text{-H}$)
	3.13 (m, 1H, $\text{C}_4\text{-H}$)
	1.93 (d, 1H, $\text{C}_3'\text{-CH}_3\text{-trans}$ isomer, $J = 1.2$ Hz)
25	1.78 (d, 1H, $\text{C}_3'\text{-CH}_3\text{-cis}$ isomers, $J = 1.2$ Hz)

Example 16

Cis-2-hydroxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolanes



(XXV)



500 mg of a mixture cis- and trans-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolanes (XXIV) was dissolved in 100 ml of saturated methanolic ammonia. The mixture was stirred at room temperature overnight (18 hours). The mixture was then evaporated to dryness under reduced pressure. The residue was separated on silica gel using EtOAc:MeOH 98:2 as eluant.

The less polar product was identified as cis-isomer mp: 167-168°C; R_f : 0.66 in EtOAc:MeOH 95:5

U.V.: (MeOH) λ_{max} : 266 nm

1H -NMR δ (ppm in DMSO- d_6)

- 11.38 (s, 1H, N_3' -H)
- 7.73 (d, 1H, C_6' -H, $J = 1.1$ Hz)
- 6.16 (t, 1H, C_5 -H, $J = 5.5$ Hz)
- 5.31 (t, 1H, C_2 -H, $J = 5.9$ Hz)
- 5.14 (t, 1H, OH, D_2O exchange)
- 3.70 (t, 2H, C_2 -CH₂OH, $J = 5.1$ Hz)
- 3.36 (dd, 1H, C_4 -H, $J = 5.7$ and 1.7 Hz)
- 3.16 (dd, 1H, C_4 -H, $J = 5.5$ and 11.7 Hz)
- 1.75 (d, 3H, C_3' -CH₃, $J = 1.7$ Hz)

Example 17

Tablet Formulations

A. The following formulation is prepared by wet granulation of the ingredients with a solution of povidone in water, drying and screening, followed by addition of magnesium stearate and compression.

	mg/tablet
(a) Active ingredient	250
(b) Lactose B.P.	210
(c) Povidone B.P.	15
(d) Sodium Starch Glycollate	20
(e) Magnesium Stearate	5
	500



B. The following formulation is prepared by direct compression; the lactose is of the direct compression type.

		<u>mg/tablet</u>
5	Active ingredient	250
	Lactose	145
	Avicel	100
	Magnesium Stearate	5
10		500

C. (Controlled Release Formulation) The formulation is prepared by wet granulation of the ingredients (below) with a solution of povidone in water, drying and screening followed by the addition of magnesium stearate and compression.

		<u>mg/tablet</u>
	(a) Active ingredient	500
	(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
20	(c) Lactose B.P.	53
	(d) Povidone B.P.	28
	(e) Magnesium Stearate	7
		700

25 Example 18

Capsule Formulation

A capsule formulation is prepared by admixing the ingredients below and filling into a two-part hard gelatin capsule.



		<u>mg/capsule</u>
	Active ingredient	125
	Lactose	72.5
	Avicel	50
5	Magnesium Stearate	2.5
		250

Example 19Injectable Formulation

- 10 Active ingredient 0.200 g
 Sodium hydroxide solution, 0.1M q.s. to a pH of about 11.
 Sterile water q.s. to 10 ml.

The active ingredient is suspended in some of the water (which may be warmed) and the pH adjusted to about 11 with a solution of sodium hydroxide. The batch is then made up to volume and filtered through a sterilizing grade membrane filter into a sterile 10 ml glass vial and sealed with sterile closures and overseas.

Example 2020 suppository

		<u>mg/suppository</u>
	Active ingredient	250
	Hard Fat, B.P.	1770
25		2020



One-fifth of the hard fat is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 μ m sieve and added to the molten base with mixing, using a high shear stirrer, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining hard fat is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 μ m stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.02 g of the mixture is filled into suitable, 2 ml plastic molds. The suppositories are allowed to cool to room temperature.

Example 21

Antiviral Activity

In vitro testing was conducted on several of the compounds of this invention to determine their inhibitory properties. The results are shown in Tables 1 and 2. The concentrations reported are μ g/ml in the incubation media which affect the susceptibility of a continuous line of T-cells developed at the Lady Davis Institute for Medical Research (Montreal) by Dr. Mark A. Wainberg toward infection by HIV-1 following a protocol similar to that of H. Mitsuya and S. Broder, "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2'3'-dideoxy-



nucleosides", Proc. Natl. Acad. Sci. USA, 83, pp. 1911-15 (1986). Protection of the cell line from infection was monitored by staining with monoclonal antibodies against viral proteins in the standard manner (Table 1). In all experiments, comparisons were made with the drug AZT as the control. In order to confirm the results, the drug effects were monitored by measuring reverse transcriptase (RT) activity in the U-937 line of human monocytic cells as assayed in the usual manner with tritiated thymidine triphosphate (TTP) (Table 2). Finally, the drug effects on cell viability as measured by the well-know cytolytic effects of HIV-1 on the MT-4 cell line was evaluated in the accepted manner (Table 1).

Toxicity

No toxic effects were observed in the above tests.

Table 1

Inhibition of HIV-1 product by compounds
of formula (I) in MT-4 cells

a) Viable cell counts (6 days in culture) using 2 µg/ml of compound

Compound	Cell Viability %
no drug	6.47
AZT	88.6
<u>cis</u> -XVI	87.4
<u>trans</u> -XVI	24
<u>cis</u> -XVII(b)	14
<u>cis</u> -XXV	11
<u>cis</u> -XXI	18
<u>cis</u> -XXIII	14



b) P-24 immunofluorescence

Time in Culture		% Immunofluorescent Cells		
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-XVI	
5	3	5.9	1.0	1.0
	6	99	1.0	7.6

c) Reverse transcriptase assay

Time in Culture		RT Activity (CPM X 1000)/ml		
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-XVI	
10	3	36.43	1.564	2.381
	6	339.0	1.748	2.301

Table 2

Inhibition of HIV-1 production by compounds of
formula (I) in H-9 cells

15

Reverse transcriptase assay

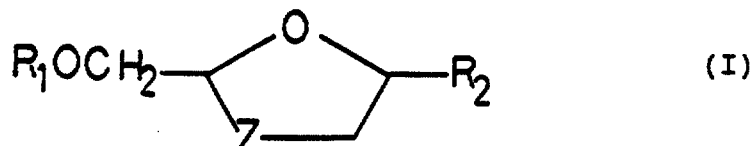
Time in Culture		RT Activity (CPM X 1000)/ml		
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-XVI	
20	5	9.117	3.346	3.077
	8	438.5	3.414	5.853
	11	2550	2.918	3.560
	14	2002	8.320	2.872
	17	584.5	2.997	2.399
	21	365.2	3.111	2.907
25	25	436.4	15.88	4.020
	29	92.38	32.08	3.756
	33	111.1	612.2	3.803
	37	32.28	878.2	4.193
30	41	384.4	994.0	4.515
	45	33.64	32.91	3.441





CLAIMS:

1. A 1,3-oxathiolane of formula (I), the
5 geometric and optical isomers thereof, and mixtures of
those isomers:



10 wherein:

R_1 is hydrogen;

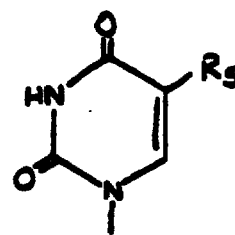
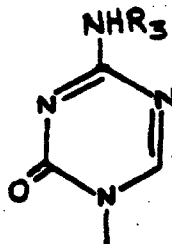
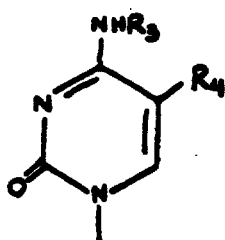
R_2 is a purine or pyrimidine base or an analogue
or derivative thereof;

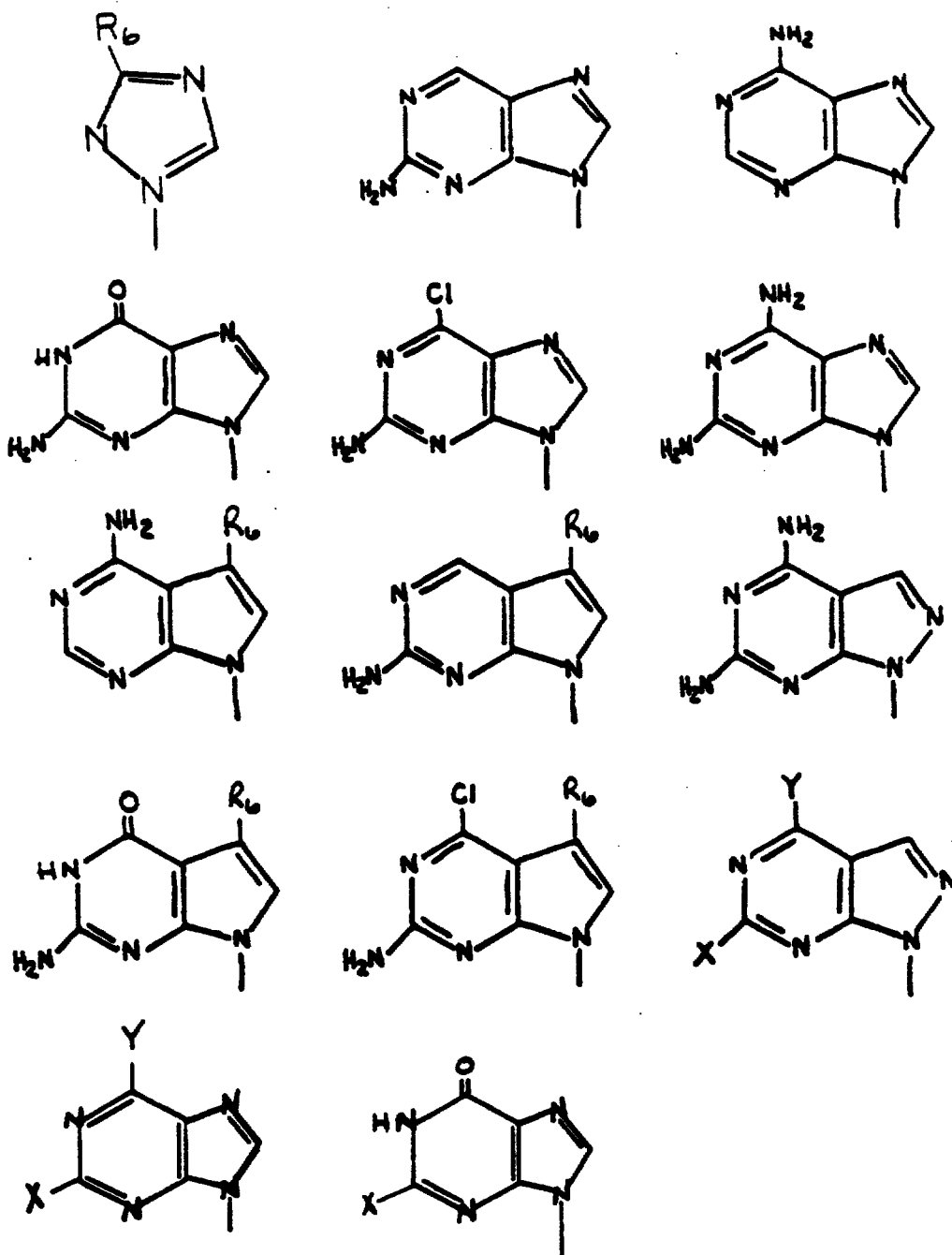
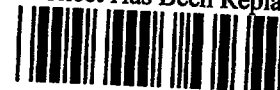
15 Z is selected from a group consisting of S, S=O
or SO₂; and
pharmaceutically acceptable derivatives thereof.

2. A compound of formula (I) as defined in
claim 1 in the form of its cis isomer.

20 3. A compound of formula (I) as defined in
claim 1 or claim 2 wherein Z is S.

4. A compound of formula (I) as defined in
any one of claims 1 to 3 wherein R_2 is selected from:





wherein:

R_1 is selected from the group of hydrogen or C_{1-6} alkyl groups;

5 R_2 and R_3 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;

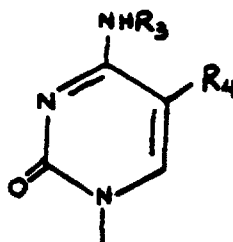
R_4 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and





X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.

- 5 5. A compound according to any one of claims 1 to 4 wherein R_2 is



10 wherein R_3 is selected from the group of hydrogen or C_{1-6} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine.

6. A compound selected from the group consisting of:

15 Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

20 Cis-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and

25

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;

Cis-2-hydroxymethyl-5-(N -dimethylamino-methylene





cytosin-1'-yl)-1,3-oxathiolane;

Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;

5 Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;

10 Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;

15 Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;

20 and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

7. Cis - 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

25 8. A compound according to any one of claims 1 to 7 in the form of a racemic mixture.

9. A compound according to any one of claims 1 to 7 substantially in the form of a single enantiomer.

30 10. A compound of formula (I) as defined in any one of claims 1 to 9 or a pharmaceutically acceptable





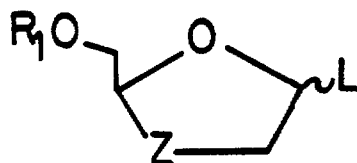
derivative thereof for use as an active therapeutic agent.

11. A compound of formula (I) as defined in any one of claims 1 to 9 or a pharmaceutically acceptable derivative thereof for use in the manufacture of a medicament for the treatment of a viral infection.

12. A pharmaceutical formulation comprising a compound of formula (I) as defined in any one of claims 1-9 or a pharmaceutically acceptable derivative thereof together with a pharmaceutically acceptable carrier therefor.

13. A pharmaceutical formulation according to claim 12 additionally comprising a further therapeutic agent.

14. A 1,3-oxathiolane of formula (VIII), the geometric and optical isomers thereof, and mixtures of those isomers:



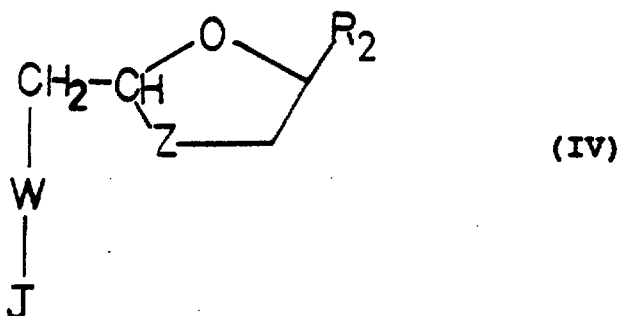
(VIII)

wherein:

R_1 is hydrogen or a hydroxyl protecting group; and
L is an alkoxy carbonyl group, iodine, bromine, chlorine or -OR where R is selected from the group consisting of a substituted or unsubstituted, saturated or unsaturated alkyl group and a substituted or unsubstituted, saturated or unsaturated aliphatic or aromatic acyl group.



15. The ester of formula (IV) the geometric and optical isomers thereof, and mixtures of those isomers:



5 wherein:

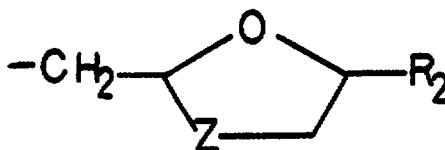
W is PO_4^- , SPO_3^- , or $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-(\text{CH}_2)_n-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-$ where n is an integer of 1 to 10;

J is any nucleoside or nucleoside analog or derivative thereof;

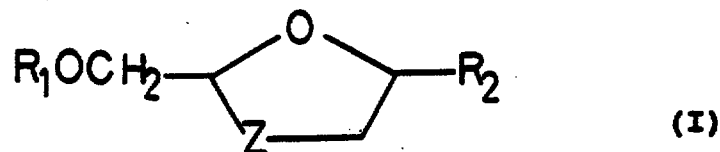
10 Z is S, S=O, or SO_2 ; and

R_2 is a purine or pyrimidine base or analogue or derivative thereof.

16. A compound according to claim 15 wherein J is:



17. A process for the preparation of a compound of formula (I)



wherein R_1 is hydrogen;



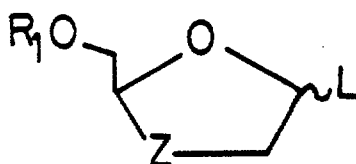
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

Z is S, S=O or SO_2 ; and

pharmaceutically acceptable derivatives thereof,

5 which comprises:

(a) reaction of a compound of formula (VIII)

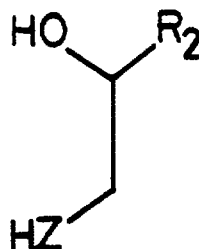


(VIII)

wherein R_1 is hydrogen or a hydroxyl protecting group and
 10 L is a displaceable atom or a group with a base R_2 -H group;

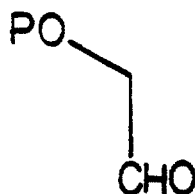
(b) base interconversion of one compound of formula (I) into another compound of formula (I);

(c) reaction of a compound of formula (IX)



(IX)

15 with a compound of formula (X)

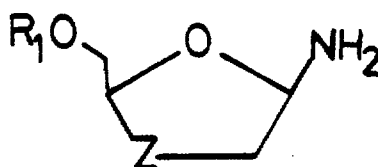


(X)

wherein P is a protecting group; or

(d) conversion of a compound of formula (XII)





(XII)

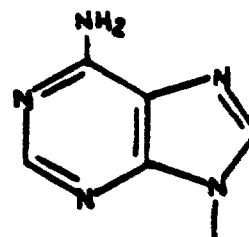
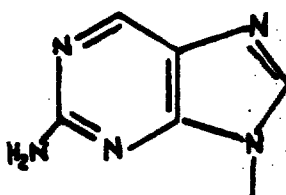
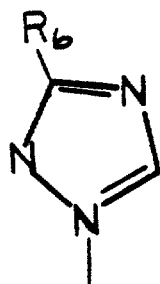
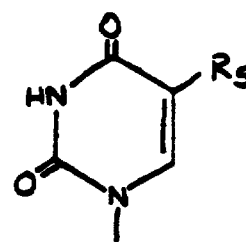
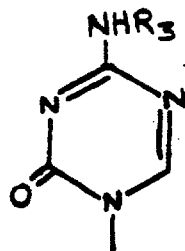
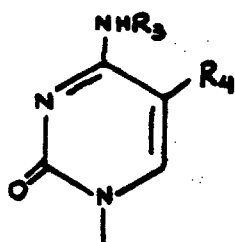
5 to a compound of formula (I)
and if necessary or desired subjecting the
compound resulting from any of steps (a) to (d) to one or
two further reactions comprising:

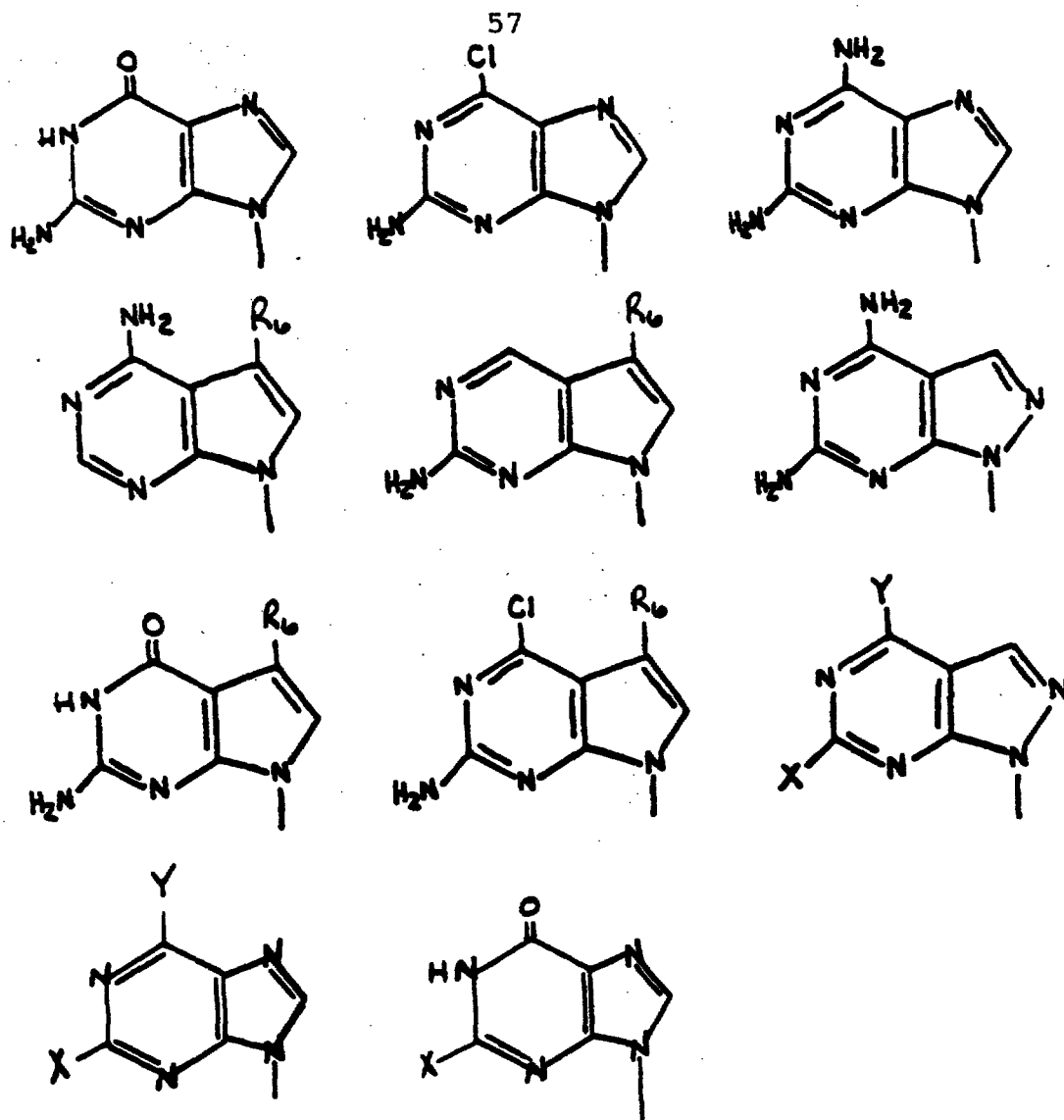
- 10 (i) removing any protecting groups;
(ii) converting a compound of formula (I) or a
salt thereof into a pharmaceutically acceptable salt
thereof.

15 18. A process as defined in claim 17
wherein the compound of formula (I) is obtained in the
form of its cis isomer.

19. A process according to claim 17 or
claim 18 wherein Z is S.

20 20. A process according to any one of
claims 17 to 19 wherein R₂ is:





5 wherein:

R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-6} alkyl groups;

10 R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;

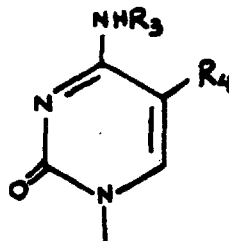
R_6 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and

15 X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.





21. A process according to any of claims 17 to 19 wherein R_2 is:



5 wherein R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-6} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or
10 unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine.

22. A process according to any one of claims 17 to 21 wherein the compound of formula (I) is selected from:

15 Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-
20 1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures
25 thereof; and

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;

30 Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;

Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;





Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;

5 Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;

Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

10 Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;

Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

15 Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;

and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

20 23. A process according to any one of claims 17 to 21 wherein the compound of formula (I) is Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

25 24. A process according to any one of claims 17 to 23 wherein the compound of formula (I) is obtained in the form of a racemic mixture.

30 25. A process according to any one of claims 1 to 7 wherein the compound of formula (I) is obtained substantially in the form of a single enantiomer.

35 26. A process according to any one of claims 17 to 25 wherein in step (a) the group L is selected from a group consisting of alkoxy carbonyl,

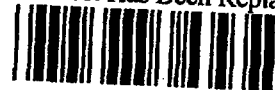


iodine, bromine, chlorine or -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl group or R is a substituted or unsubstituted aliphatic or aromatic acyl group.

5 27. A process according to any one of claims 17 to 26 wherein step (a) the compound of formula (VIII) is reacted with a silylated purine or pyrimidine base in a compatible solvent in the presence of a Lewis acid or trimethylsilyltriflate.

10 28. A method for the preparation of a pharmaceutical formulation comprising admixing a compound of formula (I) as defined in claim 17 or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier therefor.

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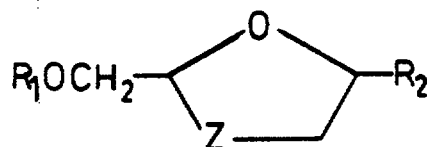


* C L N S *

5

ABSTRACT

Disclosed are compounds of the formula



10

wherein R_1 is hydrogen;

R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

Z is S, S=O or SO_2 ; and

pharmaceutically acceptable derivatives thereof.

15

Also described are use of the compounds as antiviral agents, pharmaceutical formulations, and methods for the preparation of the compounds.

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REPLACED SHEETS		SG
☒	Description	: paged 4 to paged 48
☒	Claim(s)	: paged 49 to paged 60
☐	Drawing(s)	: paged to paged
☒	Abstract	: paged 61 to paged

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REPLACEMENT SHEETS		SG
☒	Description	: paged 1 to paged 48
☒	Claim(s)	: paged 49 to paged 60
☐	Drawing(s)	: paged to paged
☒	Abstract	: paged 61 to paged
DATE OF RECEIPT 12-6-1996		

**SUBSTITUTED-1,3-OXATHIOLANES
WITH ANTIVIRAL PROPERTIES**

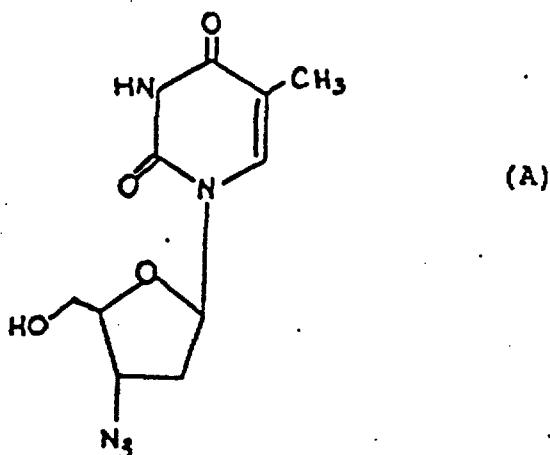
5 The present invention relates to novel substituted 1,3-oxathiolane cyclic compounds having pharmacological activity, to processes for and intermediates of use in their preparation, to pharmaceutical compositions containing them, and to the use of these compounds in the antiviral treatment of mammals.

10 Retroviral infections are a serious cause of disease, most notably, the acquired immunodeficiency syndrome (AIDS). The human immunodeficiency virus (HIV) has been recognized as the etiologic agent of AIDS and compounds having an inhibitory effect against HIV multiplication have been actively sought.

15 Mitsuya et al., "3'-Azido-3'-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro", Proc. Natl. Acad. Sci. U.S.A., 82, pp. 7096-7100
20 (1985), refers to a compound of formula (A) (3'-azido-2'3'-dideoxythymidine), commonly referred to as AZT. This compound is said to be useful in providing some protection for AIDS carriers against the cytopathogenic effect of immunodeficiency virus (HIV).

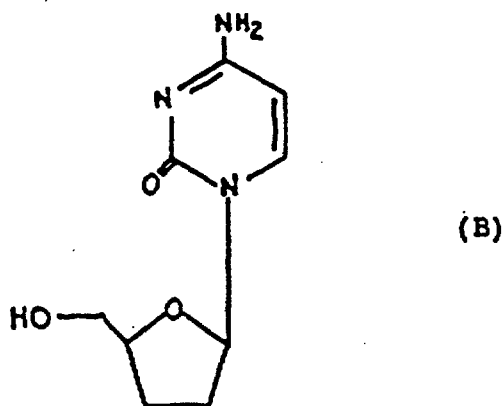
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Mitsuya et al., "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides", Proc. Natl. Acad. Sci. U.S.A., 86, pp. 1911-15 (1986), have also referred to a group of 2',3'- dideoxynucleosides shown in formula (B) which are said to possess protective activity against HIV-induced cytopathogenicity.

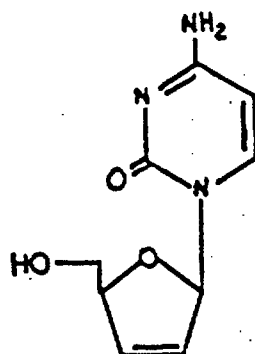
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Balzarini et al., "Potent and selective anti-HTLV-III/LAV activity of 2',3'-dideoxycytidinene, the 2',3'-unsaturated derivative of 2',3'-dideoxycytidine", Biochem. Biophys. Res. Comm., 140, pp. 735-42 (1986), refer to an unsaturated analogue of these nucleosides-- 2',3'-dideoxy-cytidine, shown in formula (C)--as being characterized by antiretroviral activity.

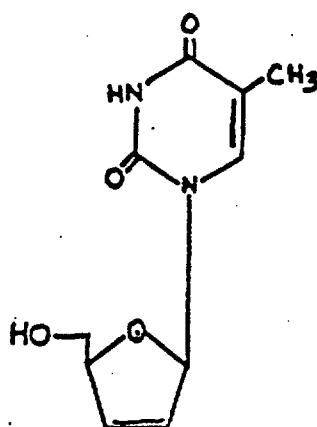
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(C)

Baba et al., "Both 2',3'-dideoxythymidine and its 2',3'-unsaturated derivative (2',3'-dideoxythymidinene) are potent and selective inhibitors of human immunodeficiency virus replication in vitro", Biochem. Biophys. Res. Comm., 142, pp. 128-34 (1987), refer to the 2',3'-unsaturated analogue shown in formula (D) of 2',3'-dideoxythymidine. This analogue is purported to be a potent selective inhibitor of HIV replication.

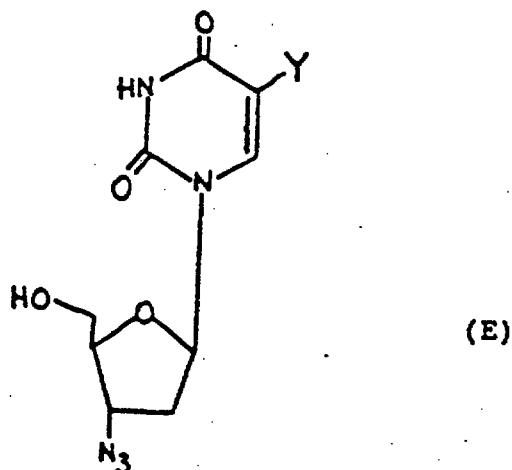


(D)

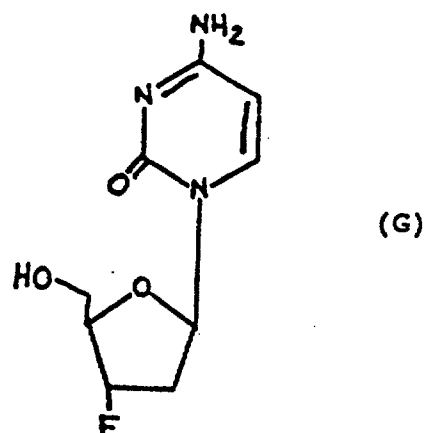
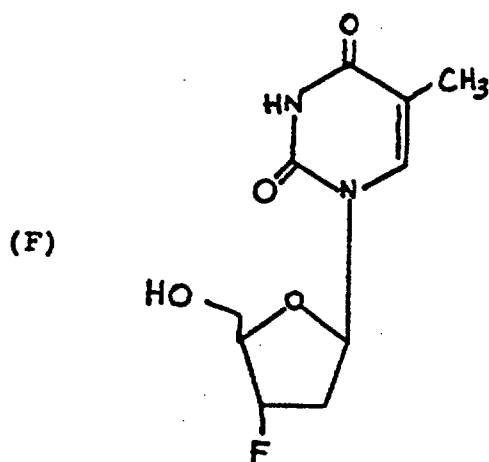
Analogues of AZT known as 3'-azido-2', 3'-dideoxyuridine shown in formula (E), where Y is bromine or iodine, have been said to have an inhibitory activity against Moloney murine leukemia in T.S. Lin et al., "Synthesis and antiviral activity of various 3'-azido, 3'-amino, 2',3'-unsaturated and 2',3'-dideoxy analogues of pyrimidine, deoxyribonucleosides against retroviruses", J. Med. Chem., 30, pp. 440-41 (1987).

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5 Finally, the 3'-fluoro analogues of 2',3'-dideoxycytidine shown in formula (F) and of 2',3'-dideoxythymidine shown in formula (G) are referred to in Herdewijn et al., "3'-Substituted 2',3'-dideoxynucleoside analogues as potential anti- HIV(HTLV-III/LAV) agents", J. Med. Chem., 30, pp. 1270-78 (1987), as having potent antiretroviral activity.



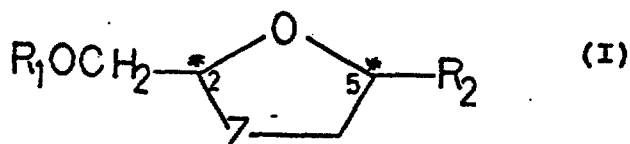
10 The most potent anti-HIV compounds thus far reported are 2',3'-dideoxynucleosides, more particularly, 2',3'-dideoxy cytidine (ddCyd) and 3'-azido-2',3'-
15 dideoxythymidine (AzddThd or AZT). These compounds are also active against other kinds of retroviruses such as the Moloney murine leukemia virus. Because of the increasing incidence and the life-threatening characteristics of AIDS, efforts are being expended to discover and develop new non-toxic and potent inhibitors



of HIV and blockers of its infectivity. It is therefore an object of the present invention to provide effective anti-HIV compounds of low toxicity and a synthesis of such new compounds that is readily feasible.

5 A structurally distinct class of compounds known as 2-substituted-5-substituted-1,3-oxathiolanes has now been discovered and found to have antiretroviral activity. In particular, these compounds have been found to act as non-toxic inhibitors of the replication of HIV-1 in T-lymphocytes over prolonged periods of time.

10 There is accordingly provided in a first aspect a compound of formula (I)



wherein R₁ is hydrogen;

15 R₂ is a purine or pyrimidine base or an analogue or derivative thereof;

Z is S, S=O or SO₂; and

pharmaceutically acceptable derivatives thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least two chiral centers (shown as * in formula (I)) and thus exist in the form of two pairs of optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures. Thus the compounds of formula (I) may be either cis isomers, as represented by formula (II), or trans isomers, as represented by formula (III), or mixtures thereof. Each of the cis and trans isomers can exist as one of two enantiomers or as mixtures thereof including racemic mixtures. All such isomers and

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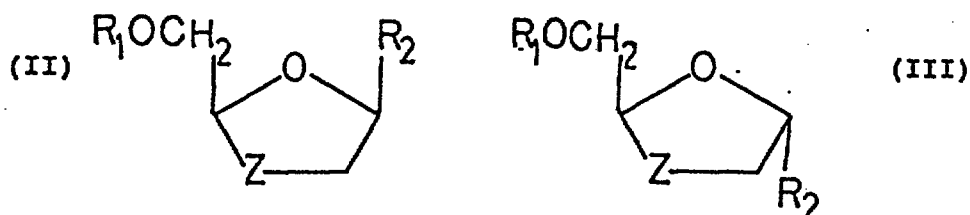
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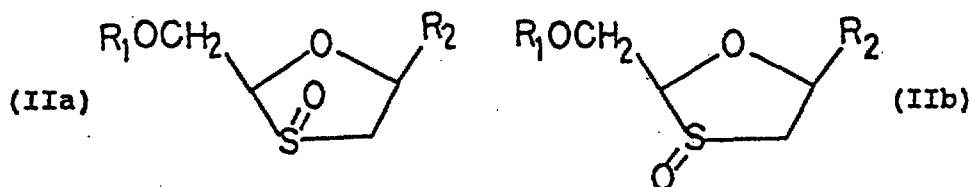
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mixtures thereof including racemic mixtures are included within the scope of the invention.



The compounds of formula (I) are preferably in the form of their cis isomers.

It will also be appreciated that when Z is S=O the compounds exist in two additional isomeric forms as shown in formulas (IIa) and (IIb) which differ in the configuration of the oxide oxygen atom relative to the 2,5-substituents. The compounds of the invention additionally embrace such isomers and mixtures thereof.



The purine or pyrimidine base or analog or derivative thereof R₂ will be linked at the 9- or 1-position respectively.

By purine or pyrimidine base or an analogue or derivative thereof is meant a purine or pyrimidine base found in native nucleosides or an analogue thereof which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the native

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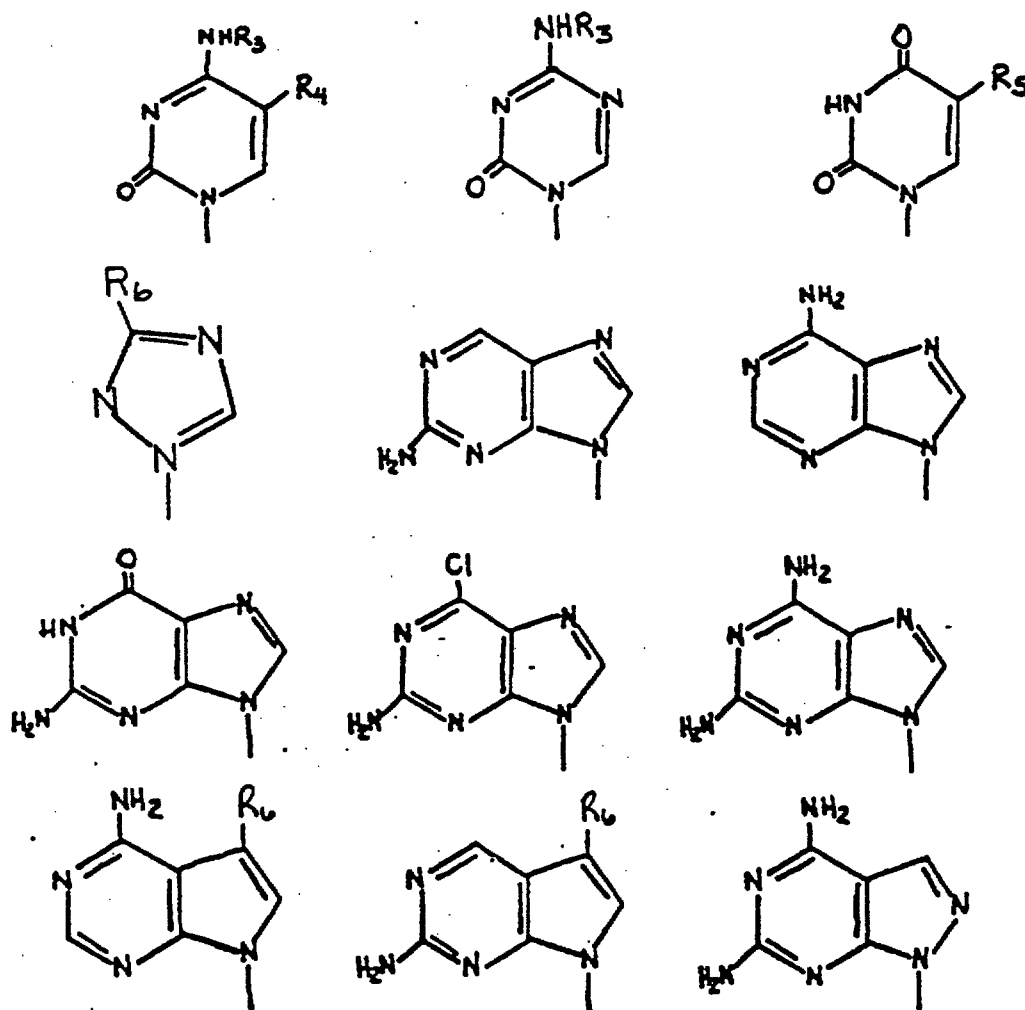


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bases but may either possess additional or lack certain of the functional properties of the native bases. Such analogues include those derived by replacement of a CH_2 moiety by a nitrogen atom (for example, 5-azapyrimidines such as 5-azacytosine) or vice versa (for example 7-deazapurines, for example 7-deazadenosine or 7-deazaguanosine) or both (e.g., 7-deaza, 8-azapurines). By derivatives of such bases or analogues are meant those compounds wherein ring substituents are either

incorporated, removed or modified by conventional substituents known in the art, e.g., halogen, hydroxyl, amino, C_{1-6} alkyl. Such purine or pyrimidine bases, analogues and derivatives will be well known to those skilled in the art.

Conveniently the group R_2 is selected from:

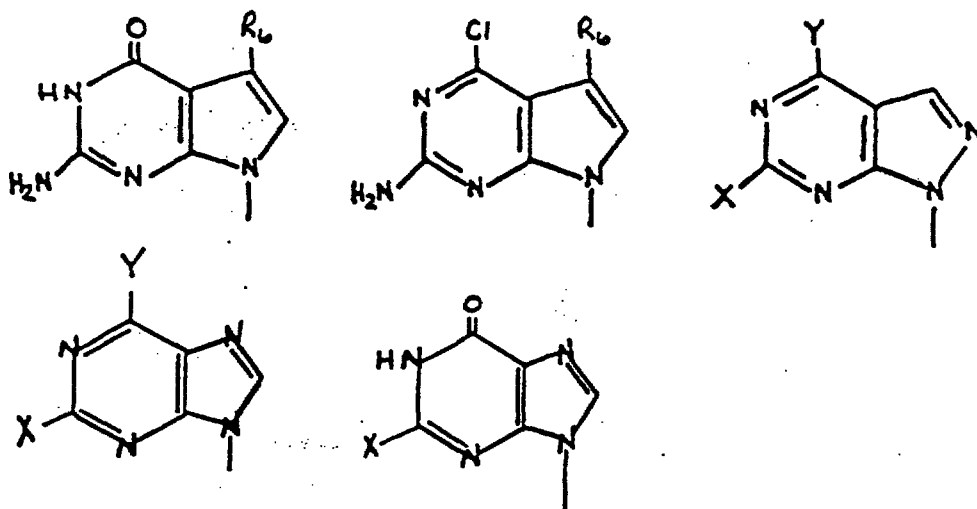


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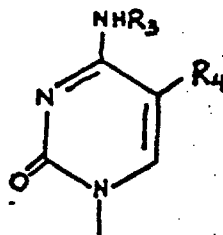
wherein R_3 is selected from the group of hydrogen, hydroxymethyl or saturated or unsaturated C_{1-6} alkyl groups;

5 R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;

R_6 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and

10 X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxy groups.

Preferably R_2 is



wherein R_3 and R_4 are as defined hereinabove.

15 Z is preferably -S-.

By "a pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any



other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an antivirally active metabolite or residue thereof.

5 It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof, at functional groups in both the base moiety, R_2 and at the hydroxymethyl group of the oxathiolane ring.

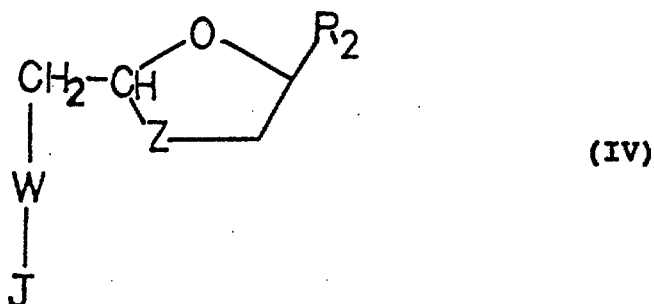
10 Modification at all such functional groups is included within the scope of the invention. However, of particular interest are pharmaceutically acceptable derivatives (e.g., esters) obtained by modification of the 2-hydroxymethyl group of the oxathiolane ring.

15 Preferred esters of the compounds of formula (I) include the compounds in which R_1 is replaced by a carboxyl function $R-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ in which the non-carbonyl moiety R of the ester grouping is selected from hydrogen, straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy); substituted dihydro pyridinyl (e.g., N-methyldihydro pyridinyl); sulphonate esters such as alkyl- or aralkylsulphonyl (e.g., methanesulphonyl); sulfate esters; amino acid esters (e.g., L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters.

Also included within the scope of such esters are esters derived from polyfunctional acids such as 30 carboxylic acids containing more than one carboxyl group, for example, dicarboxylic acids $\text{HO}_2\text{C}(\text{CH}_2)_n\text{CO}_2\text{H}$ where n is an integer of 1 to 10 (for example, succinic acid) or phosphoric acids. Methods for preparing such esters are well known. See, for example, Hahn et al., "Nucleotide Dimers as Anti Human Immunodeficiency Virus Agents", 35 Nucleotide Analogues, pp. 156-159 (1989) and Busso et



al., "Nucleotide Dimers Suppress HIV Expression In Vitro", AIDS Research and Human Retroviruses, 4(6), pp. 449-455 (1988). Where esters are derived from such acids, each acidic group is preferably esterified by a compound of formula (I) or other nucleosides or analogues and derivatives thereof to provide esters of the formula (IV)



where W is $-\text{O}-\overset{\text{O}}{\parallel}\text{C}-(\text{CH}_2)_n-\overset{\text{O}}{\parallel}\text{C}-\text{O}-$ and n is an integer of 1 to 10

or $-\text{O}-\overset{\text{O}}{\parallel}\text{P}(\text{O}^-)-\text{O}-$ or $-\text{O}-\overset{\text{S}}{\parallel}\text{P}(\text{O}^-)-\text{O}-$, J is any nucleoside or

nucleoside analog or derivative thereof and Z and R₂ are as defined above. Among the preferred nucleosides and nucleoside analogues are 3'-azido-2',3'-dideoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydro-thymidine, and 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin and those nucleosides whose bases are depicted on pages 7-8 of this specification. We most prefer a homodimer consisting of two nucleosides of formula (I).

With regard to the above described esters, unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, preferably 1 to 4 carbon atoms and could contain one or more double bonds. Any aryl moiety present in such esters advantageously comprises a phenyl group.

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In particular the esters may be a C₁₋₁₆ alkyl ester, an unsubstituted benzoyl ester or a benzoyl ester substituted by at least one halogen (bromine, chlorine, fluorine or iodine), saturated or unsaturated C₁₋₆ alkyl, saturated or unsaturated C₁₋₆ alkoxy, nitro or trifluoromethyl groups.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and NR₄⁺ (where R is C₁₋₄ alkyl) salts.

References hereinafter to a compound according to the invention includes both compounds of formula (I) and their pharmaceutically acceptable derivatives.

Specific compounds of formula (I) include: Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

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Cis-2-hydroxymethyl-5-(N₁'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N₁'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

5 Cis-2-benzoyloxymethyl-5-(N₁'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N₁'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;

10 Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;

Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;

15 Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;

20 Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;

25 Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;

30 in the form of a racemic mixture or a single enantiomer.

The compounds of the invention either themselves possess antiviral activity and/or are metabolizable to such compounds. In particular these compounds are effective in inhibiting the replication of
35 retroviruses, including human retroviruses such as human



immunodeficiency viruses (HIV's), the causative agents of AIDS.

There is thus provided as a further aspect of the invention a compound formula (I) or a
5 pharmaceutically acceptable derivative thereof for use as an active therapeutic agent in particular as an antiviral agent, for example in the treatment of retroviral infections.

In a further or alternative aspect there is
10 provided a method for the treatment of a viral infection, in particular an infection caused by a retrovirus such as HIV, in a mammal, including man, comprising administration of an effective amount of an antiviral compound of formula (I) or a pharmaceutically acceptable
15 derivative thereof.

There is also provided in a further or alternative aspect of this invention, use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament
20 for the treatment of a viral infection.

The compounds of the invention are also useful in the treatment of AIDS related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological
25 conditions (such as dementia), anti-HIV antibody positive and HIV- positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

The compounds of the invention are also useful in the prevention or progression to clinical
30 illness of individuals who are anti-HIV antibody or HIV-antigen positive and in prophylaxis following exposure to HIV.

The compounds of formula (I) or the pharmaceutically acceptable derivatives thereof, may also
35 be used for the prevention of viral contamination of biological fluids such as blood or semen in vitro.

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Certain of the compounds of formula (I) are also useful as intermediates in the preparation of other compounds of the invention.

5 It will be appreciated by those skilled in the art that references herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

10 It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

15 In general however a suitable dose will be in the range from about 1 to about 750 mg/kg of bodyweight per day, such as 3 to about 120 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

20

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

25 The compound is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

30 Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 1 to 75 μ M, preferably about 2 to 50 μ M, most preferably about 3 to about 30 μ M. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or administered as a bolus containing about 0.1 to about 110 mg/kg of the

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active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient therefor.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution; as a

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suspension; or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils) or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more

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emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical
5 administration in the mouth include lozenges comprising active ingredient in a flavored based, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the
10 active ingredient in a suitable liquid carrier.

Pharmaceutically formulations suitable for rectal administration wherein the carrier is a solid, are most preferably represented as unit dose suppositories. Suitable carriers include cocoa butter and other
15 materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for vaginal
20 administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient, such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds
25 of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid
30 sprays are conveniently delivered from pressurized packs.

For administration by inhalation, the compounds according to the invention are conveniently delivered from an insufflator, nebulizer or a pressurized
35 pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane,

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trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

5 Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The
10 powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

 When desired, the above described
15 formulations adapted to give sustained release of the active ingredient, may be employed.

 The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

20 The compounds of the invention may also be used in combination with other therapeutic agents, for example, other antiinfective agents. In particular the compounds of the invention may be employed together with known antiviral agents.

25 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable derivative thereof together with another therapeutically active agent, in particular, an antiviral agent.

30 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier
35 therefor comprise a further aspect of the invention.

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Suitable therapeutic agents for use in such combinations include acyclic nucleosides such as aciclovir, ganciclovir, interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole; nucleoside analogues such as 3'-azido-2',3'-dideoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydrothymidine, and 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments and CD4-hybrid molecules.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same virus, the dose of each compound may be either the same or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be prepared by any method known in the art for the preparation of compounds of analogous structure.

R_1 and R_2 as used hereunder have the same meaning as defined above unless otherwise stated.

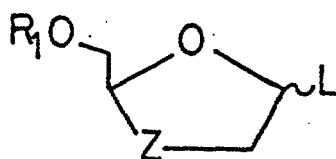
In one such process (A) a 1,3-oxathiolane of formula (VIII)

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(VIII)

wherein R_1 is hydrogen or hydroxyl protecting group as defined herein and the anomeric group L is a displaceable atom or group and is reacted with an appropriate base. Suitable groups L include alkoxy carbonyl groups such as ethoxy carbonyl or halogens, for example, iodine, bromine or chlorine or -OR where R is a substituted or unsubstituted, saturated or unsaturated alkyl group, e.g., a C_{1-6} alkyl group such as methyl, or R is a substituted or unsubstituted aliphatic or aromatic acyl group, e.g., a C_{1-6} aliphatic acyl group such as acetyl and an aromatic acyl group such as benzoyl.

The compound of formula (VIII) is conveniently reacted with the appropriate purine or pyrimidine base R_2-H (previously silylated with a silyating agent such as hexamethyldisilazane) in a compatible solvent such as methylene chloride using a Lewis acid (such as titanium tetrachloride or stannic chloride) or trimethylsilyltriflate.

The 1,3-oxathiolanes of formula (VIII) may be prepared, for example, by reaction of an aldehyde of formula (VII) with a mercaptoacetal of formula (VI) in a compatible organic solvent, such as toluene, in the presence of an acid catalyst such as a para-toluene sulfonic acid or a Lewis acid, e.g., zinc chloride.



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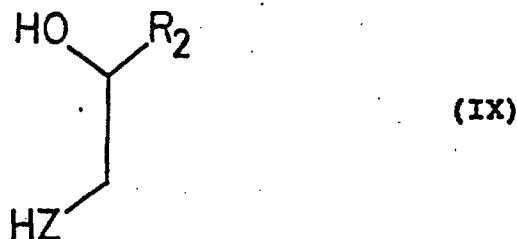
The mercaptoacetals of formula (VI) may be prepared by methods known in the art, for example, G. Hesse and I. Jorder, "Mercaptoacetaldehyde and dioxo-1, 4-dithiane", Chem. Ber., 85, pp. 924-932 (1952).

5 The aldehydes of formula (VII) may be prepared by methods known in the art, for example, E.G. Halloquist and H. Hibbert, "Studies on reactions relating to carbohydrates and polysaccharides.

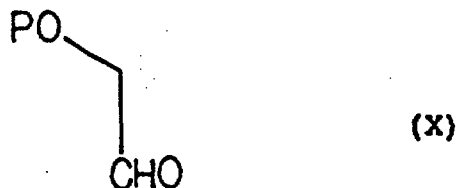
10 Part XLIV: Synthesis of isomeric bicyclic acetal ethers", Can. J. Research, 8, pp. 129-136 (1933).

In a second process (B) one compound of formula (I) is converted to another compound of formula (I) by base interconversion. Such interconversion may be effected either by simple chemical transformation (e.g.,
15 the conversion of uracil base to cytosine) or by an enzymatic conversion using, for example, a deoxyribosyl transferase. Such methods and conditions for base interconversions are well known in the art of nucleoside chemistry.

20 In a third process (C) the compounds of formula (I) may be prepared by the reaction of a compound of formula (IX)

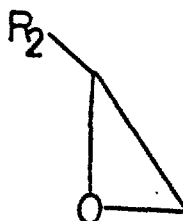


with a compound of formula (X)



where P is a protecting group, followed by removal of the protecting group.

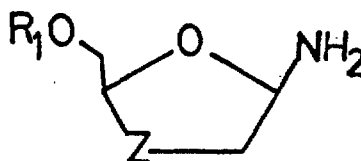
The compounds of formula (IX) may be prepared for reaction by a suitable epoxide (XI)



(XI)

with an appropriate sulphur-containing compound, e.g., sodium thioacetate. Compounds of formula (XI) are either known in the art or may be obtained by analogous processes.

In a fourth process (D) a compound of formula (XII)



(XII)

may be converted to a compound of formula (I) by conversion of the anomeric NH₂ group to the required base by methods well known in the art of nucleoside chemistry.

Many of the reactions described hereinabove have been extensively reported in the context of purine nucleoside synthesis, for example, in "Nucleoside Analogues - Chemistry, Biology and Medical Applications", R.T. Walker et al., Eds, Plenum Press, New York (1979) at pages 193-223, the text of which is incorporated by reference herein.

It will be appreciated that the above reactions may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be

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required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g., benzyl), acyl or aryl (e.g., 2,4-dinitrophenyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g., methyl, t-butyl or methoxymethyl), aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl, (e.g., acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by treatment with BF_3 /etherate and acetic anhydride followed by removal of acetate groups so formed at an appropriate stage in the synthesis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

In the above processes the compounds of formula (I) are generally obtained as a mixture of the cis and trans isomers.

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These isomers may be separated, for example, by acetylation, e.g., with acetic anhydride followed by separation by physical means, e.g., chromatography on silica gel and deacetylation, e.g., with methanolic ammonia or by fractional crystallization.

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in United States Patent No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of a compound of formula (I), the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods. Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the free base with a suitable base such as an alkoxide (e.g., sodium methoxide) optionally in the presence of a solvent such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

A compound of formula (I) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as POCl_3 , or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of a compound of formula (I) may be converted to the parent compound, for example, by hydrolysis.

Where the compound of formula (I) is desired as a single isomer it may be obtained either by resolution of the final product or by stereospecific



synthesis from isomerically pure starting material or any convenient intermediate.

Resolution of the final product, or an intermediate or starting material therefore may be effected by any suitable method known in the art: see for example, Stereochemistry of Carbon Compounds, by E.L. Eliel (McGraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.

The invention will be further described by the following examples which are not intended to limit the invention in any way. All temperatures are in degrees celsius.

EXAMPLES

Example 1

2-thiobenzoyl acetaldehyde diethylacetal



To a solution of potassium t-butoxide (11.5 g. 0.11 mol) in DMF (100 ml) was added thiobenzoic acid (17 g. 0.11 mol) and the solution partially evaporated in vacuo, benzene added in two consecutive portions (2 x 30 ml) and evaporated in vacuo each time. To the residual DMF solution was added bromoacetaldehyde diethylacetal (20.3 g. 0.1 mol) and the mixture stirred at 120° for 15 h. After cooling, it was poured onto water (500 ml), the product extracted with ether (3 x 200 ml), the extract washed with aqueous NaHCO₃, followed by water, then dried and the solvent removed in vacuo. The residue was distilled in vacuo to give 17.2 g. of pure (V), b.p. 131-133°/0.07 mm. It was characterized by ¹H NMR δ(ppm in CDCl₃):

7.97 (d, 2H; aromatic)

7.47 (m, 3H; aromatic)

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4.59 (t, 1H; $-\text{CH}(\text{OC}_2\text{H}_5)_2$)
 3.66 (m, 4H; $2 \times \text{OCH}_2\text{CH}_3$)
 3.30 (d, 2H; SCH_2-)
 1.23 (t, 6H; $2 \times \text{OCH}_2\text{CH}_3$)

5 Example 2

Mercaptoacetaldehyde diethylacetal



The preceding thiobenzoyl derivative (V)
 10 (17.2 g) was dissolved in 100 ml THF followed by the
 addition of 6 g NaOH in 20 ml H_2O . The mixture was
 refluxed under N_2 for 15 h, then cooled and diluted with
 water (200 ml) and the product extracted with ether (3 x
 200 ml). The extract was dried, the solvent removed in
 15 vacuo and the residue distilled in vacuo to yield 7.1 g
 of pure (VI), b.p. $60-62^\circ/18$ mm. It was characterized by
 ^1H NMR δ (ppm in CDCl_3):

4.51 (t, 1H; $\text{CH}(\text{OC}_2\text{H}_5)_2$)
 3.51 (m, 4H; $2 \times \text{OCH}_2\text{CH}_3$)
 20 2.65 (dd, 2H; $\text{HS}-\text{CH}_2$)
 1.54 (t, 1H; $\text{HS}-$)
 1.23 (t, 6H; $2 \times \text{OCH}_2\text{CH}_3$)

Example 3

Benzoyloxyacetaldehyde

25



This known intermediate was prepared by a
 previously unreported method from the known 1-benzoyl
 glycerol. Thus, 50 g of the latter in a mixture of
 30 500 ml of CH_2Cl_2 and 25 ml of H_2O was treated portionwise
 with 80 g of NaIO_4 under vigorous stirring at room
 temperature. After addition, stirring was continued for



2 h after which time 100 g of MgSO_4 was added and stirring continued for 30 min. The mixture was filtered, the filtrate evaporated in vacuo and the residue distilled in vacuo to yield 26 g of pure (VII) b.p. 92-94°/0.25 mm.

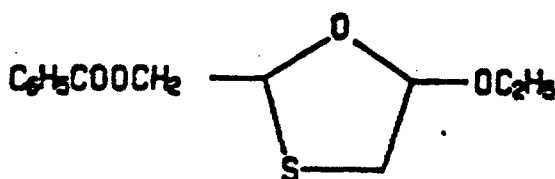
5 ^1H NMR (200 MHz ; TMS as internal reference)

δ (ppm in CDCl_3):

9.71 (s, 1H; $-\text{CHO}$)
 8.11 (d, 2H; aromatic)
 7.60 (m, 1H; aromatic)
 10 7.46 (m, 2H; aromatic)
 4.88 (s, 2H; $-\text{CH}_2\text{CHO}$)

Example 4

2-Benzoyloxymethyl-5-ethoxy-1,3-oxathiolane



(XIII)

15 The preceding mercaptoacetaldehyde acetal (VI) (7 g) was mixed in 100 ml of toluene with 7 g of the above benzoyloxyacetaldehyde (VII), a few crystals of para-toluene sulfonic acid added and the mixture placed in an oil-bath at 120° under N_2 . The formed ethanol was
 20 allowed to distill over, the mixture kept at 120° for an additional 30 minutes, then cooled and washed with aqueous NaHCO_3 , dried and evaporated in vacuo. The residue was distilled in vacuo to yield 9.8 g of pure
 25 (XIII) as a mixture of cis- and trans-isomers, b.p. 140-143°/0.1 mm; R_f 0.51 (hexane-EtOAc);

^1H NMR δ (ppm in CDCl_3):

8.05 (m, 2H; aromatic)
 7.57 (m, 1H; aromatic)
 7.43 (m, 2H; aromatic)

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5.55 (m, 2H; C₃-H, C₂-H)

4.55 (m, 2H; C₂-C₆H₅CO₂CH₂)

3.80 (m, 1H; C₂-C₆H₅CO₂CH₂)

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5 3.76 (m, 1H; C₃-OCHCH₃)

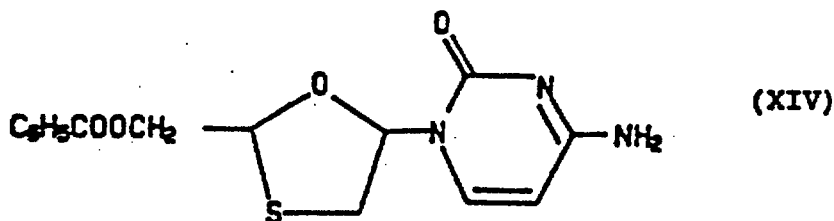
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3.17 (m, 2H; C₄-H₂)

1.21 (t, 3H; C₃-OCH₂CH₃)

Example 5

10 Cis- and trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolanes



15 A mixture of 2.7 g of cytosine, 30 ml of hexamethyldisilazane (HMDS) and 0.3 ml of trimethylsilyl chloride (TMSCl) was heated under reflux under dry N₂ until a clear solution resulted (3 hours) and the excess reagents evaporated in vacuo. The remaining volatiles were removed under high vacuum (15 min.), the solid residue taken up in 250 ml of 1, 2-dichloroethane and 5 g of the above key intermediate (XIII) in 50 ml of dichloroethane added under dry argon followed by 4.7 ml of trimethylsilyl triflate (TMST_f). After 3 days of heating under reflux under argon, it was cooled and poured onto 300 ml of saturated aqueous NaHCO₃. The organic layer was collected, the aqueous phase extracted with CH₂Cl₂ (2 X 100 ml) and the combined extracts washed with water, dried and evaporated in vacuo. The residue was purified by chromatography on silica gel using CH₂Cl₂:CH₃OH 9:1 as the eluant to give 2.5 g of a pure

20

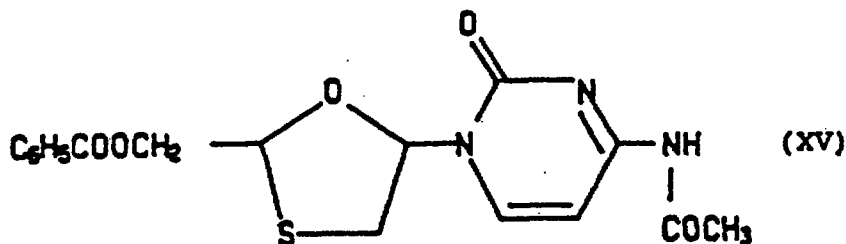
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mixture of cis- and trans-(XIV) in a 1:1 ratio as ascertained by ^1H NMR. These were separated as the N-acetyl derivatives as described in the following example.

Example 6

5 Cis- and trans-isomers of 2-benzoyloxymethyl-5-(N,'-acetyl-cytosin-1'-yl)-1,3-oxathiolane



The preceding mixture (XIV) (2.5 g) in 100 ml of dry pyridine containing 0.1 g of 4-dimethylamino-pyridine (DMAP) was treated with acetic anhydride (7 ml) at room temperature and after 16 hours, the mixture was poured onto cold water followed by extraction with CH_2Cl_2 (3 X 150 ml). The extract was washed with water, dried, and evaporated in vacuo. Toluene was added to the residue, then evaporated in vacuo and the residual oil purified by chromatography on silica gel using EtOAc: CH_3OH 99:1 as the eluant to yield 1.35 g of pure trans-(XV) as the fast moving product and 1.20 g of pure cis-(XV) as the slow moving component. These were characterized by ^1H NMR spectroscopy.

trans-(XV): m.p. 158-160°; R_f : 0.48 EtOAc: CH_3OH 95:5

U.V.: (CH_3OH) Lambda max: 297 nm

^1H NMR δ (ppm in CDCl_3):

9.00 (b, 1H; C_4' -NH-Ac)
 8.06 (m, 2H; aromatic)
 7.74 (d, 1H; C_6' -H)
 7.56 (m, 1H; aromatic)



- 7.56 (m, 1H; aromatic)
 7.47 (d, 1H; C₅'-H)
 7.45 (m, 2H; aromatic)
 6.53 (dd, 1H; C₃-H)
 5
 5.89 (dd, 1H; C₂-H)
 4.46 (dd, 2H; C₂-CH₂OCOC₆H₅)
 3.66 (dd, 1H; C₄-H)
 3.32 (dd, 1H; C₄-H)
 2.25 (s, 3H; NH-COCH₃)

10 Cis-(XV): m.p. 150-152°; R_f: 0.40 EtOAc:MeOH 95:5)

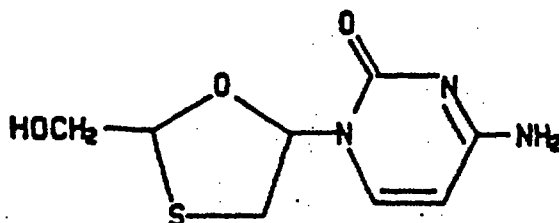
U.V.: (CH₃OH) Lambda max: 297 nm

¹H NMR δ(ppm in CDCl₃):

- 9.03 (b, 1H; NH-Ac)
 8.21 (d, 1H; C₆'-H)
 15
 8.05 (m, 2H; aromatic)
 7.60 (m, 1H; aromatic)
 7.50 (m, 2H; aromatic)
 7.29 (d, 1H; C₅'-H)
 6.34 (dd, 1H; C₃-H)
 20
 5.52 (dd, 1H; C₂-H)
 4.80 (dd, 2H; C₂-CH₂OCOC₆H₅)
 3.66 (dd, 1H; C₄-H)
 3.24 (dd, 1H; C₄-H)
 2.23 (s, 3H; NH-COCH₃)

25 Example 7

Cis- and trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolanes



(XVI)

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a) Trans-(XVI): 375 mg of the preceding trans-(XV) was dissolved in 100 ml of methanolic ammonia at 24° and after stirring for 16 hours, the solvent was removed in vacuo and the residue crystallized with ether. It was recrystallized from ethanol-ether to yield 174 mg of pure product, m.p. >220° (dec). It was characterized by ¹H and ¹³C NMR.

¹H NMR δ(ppm in DMSO-d₆):

	7.57 (d, 1H; C ₆ '-H)
10	7.18 (d, 2H; C ₄ '-NH ₂)
	6.30 (dd, 1H; C ₃ -H)
	5.68 (d, 1H; C ₃ '-H)
	5.48 (t, 1H; C ₂ -H)
	5.18 (t, 1H; C ₂ -CH ₂ OH)
15	3.45 (m, 3H; C ₂ -CH ₂ OH + C ₄ H)
	3.06 (dd, 1H; C ₄ -H)

U.V.: (CH₃OH) Lambda max: 270 nm

¹³C NMR (DMSO-d₆, Varian XL-300); δ in ppm:

	C ₂ '	C ₄ '	C ₃ '	C ₆ '	C ₃	C ₄	C ₂	CH ₂ OH
20	154.71	165.70	93.47	140.95	87.77	36.14	86.80	64.71

b) Cis-(XVI): treating 375 mg of cis-(XV) by the same preceding procedure led to 165 mg of pure product after recrystallization from ethanol-ether, m.p. 171-173°. It was characterized by ¹H and ¹³C NMR.

¹H NMR: δ(ppm in DMSO-d₆):

	7.80 (d, 1H; C ₆ '-H)
	7.20 (d, 2H; C ₄ '-NH ₂)
	6.18 (t, 1H; C ₃ -H)
	5.70 (d, 1H; C ₃ '-H)
30	5.14 (t, 1H; C ₂ -CH ₂ OH)
	3.71 (m, 2H; C ₂ -CH ₂ OH)
	3.40 (dd, 1H; C ₄ -H)
	2.99 (dd, 1H; C ₄ -H).

U.V.: (CH₃OH) Lambda max: 270 nm

¹³C NMR δ(ppm in DMSO-d₆)

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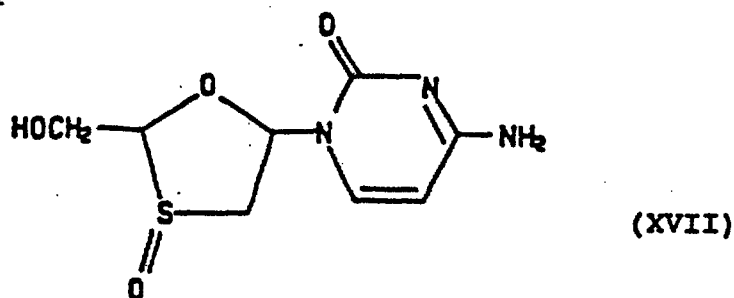


Date: 12 JUN 1996

C ₂ '	C ₄ '	C ₅ '	C ₆ '	C ₃	C ₄	C ₂	CH ₂ OH
154.63	165.59	93.86	140.91	86.47	36.22	85.75	62.79

Example 8Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane

5



The preceding cis-(XVII) (100 mg) in 30 ml of ice-cold methanol was treated with 93 mg of meta-chloro-perbenzoic acid and after stirring for 15 min a white solid separated which was collected and washed with 10 ml of methanol to give 45 mg of pure sulfoxide isomer a. The methanol filtrates were evaporated in vacuo and the solid residue washed with 15 ml of ethanolether (1:1) and then with 30 ml of ether to give 50 mg of pure sulfoxide isomer b. The isomers were characterized by ¹H NMR.

Isomer (XVII)a: m.p. >270° (dec); R_f: 0.30 (CH₂Cl₂-MeOH 3:1)

U.V.: (CH₃OH) Lambda max: 270 nm

¹H NMR δ (ppm in DMSO-d₆):

	7.68 (d, 1H; C ₆ '-H)
20	7.36 (s, 2H; C ₄ '-NH ₂)
	6.69 (dd, 1H; C ₅ -H)
	5.76 (d, 1H; C ₃ '-H)
	5.47 (t, 1H; C ₂ -CH ₂ OH)
	4.63 (dd 1H; C ₂ -H)
25	3.88 (m, 1H; C ₂ -CH-OH)
	H
	3.72 (m, 1H; C ₂ -CH-OH)
	H

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3.36 (dd, 1H; C₄-H)

3.05 (dd, 1H; C₄-H)

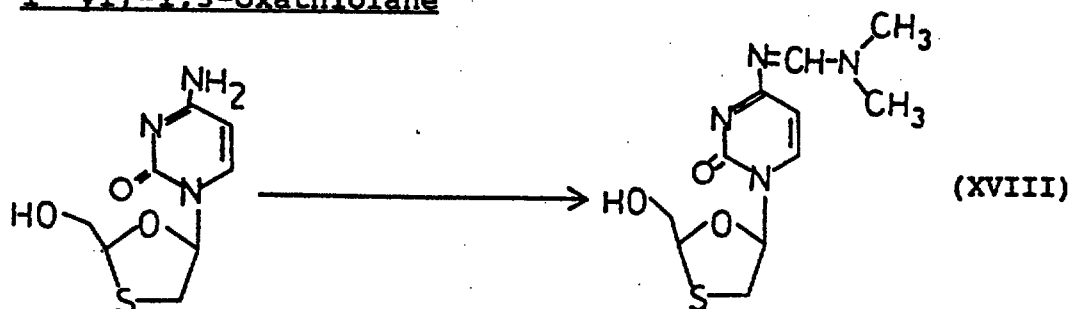
Isomer (XVII)b: m.p. >220° (dec); R_f: 0.32 CH₂Cl₂:MeOH 3:1

¹H NMR δ (ppm in DMSO-d₆):

- 5 7.76 (d, 1H; C₆'-H)
 7.28 (d, 2H; C₄'-NH₂)
 6.66 (dd, 1H; C₅-H)
 5.77 (d, 1H; C₅'-H)
 5.45 (t, 1H; C₂-CH₂OH)
 10 4.64 (t, 1H; C₂-H)
 3.77 (t, 2H; C₂-CH₂OH)
 3.65 (dd, 1H; C₄-H)
 3.17 (dd, 1H; C₄-H)

Example 9

15 Cis-2-hydroxymethyl-5-(N-dimethylamino methylene cytosin-1'-yl)-1,3-oxathiolane



300 mg of cis-2-hydroxymethyl-5-(cytosin-1'-yl)
 1,3-oxathiolane was suspended in 10 ml of N-
 20 dimethylformamide dimethyl acetal (DMF-dimethyl acetal).
 The mixture was stirred at room temperature overnight (18
 hours). Volatile material was removed by evaporation
 under reduced pressure. The residue was crystallized in
 ethanol-ether. It yielded 345 mg (93%) of pure product.
 25 m.p. 162-164°C; R_f: 0.56 in CH₂Cl₂:MeOH 4:1

U.V.: Lambda max: 325 nm

¹H NMR δ (ppm in DMSO-d₆):

8.64 (s, 1H, N=CH-N)

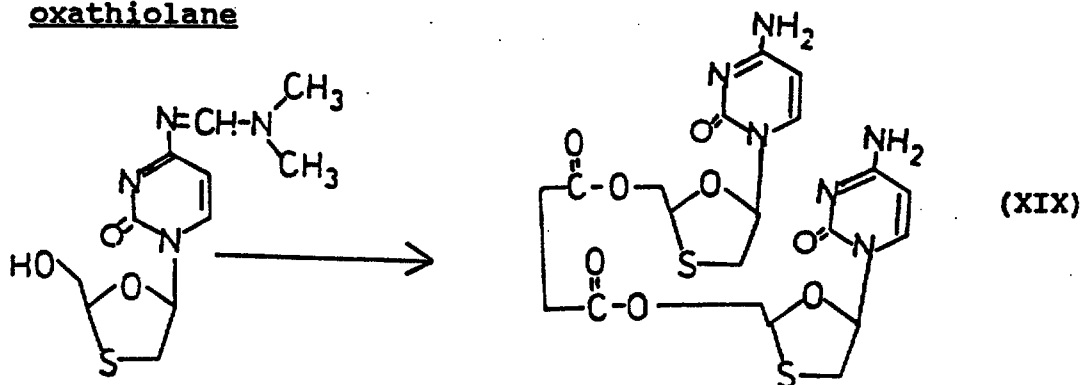
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- 8.04 (d, 1H, C₆'-H, J = 7.2 Hz)
 6.22 (t, 1H, C₅-H, J = 4.9 Hz)
 5.97 (d, 1H, C₃'-H, J = 7.2 Hz)
 5.37 (t, 1H, -OH, J = 5.8 Hz, D₂O exchange)
 5.22 (t, 1H, C₂-H, J = 4.4 Hz)
 3.77 (t, 2H, C₂-CH₂OH, J = 4.9 Hz)
 3.50 (dd, 1H, C₄-H, J = 4.9 and 9.9 Hz)
 3.17 (s, 3H, -CH₃)
 3.12 (dd, 1H, C₄-H, J = 4.2 and 11.9 Hz)
 3.04 (s, 3H, -CH₃)

Example 10**Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane**

- 284 mg of cis-2-hydroxymethyl-5-(N, N-dimethylamino methylene cytosin-1'-yl)-1,3-oxathiolane was dissolved in 10 ml of dry pyridine and cooled at 0°C in an ice-bath. 60 μ l of succinyl chloride was added via a syringe. The mixture was stirred overnight (18 hours) and poured into 50 ml of saturated aqueous NaHCO₃ solution. The mixture was extracted with methylene chloride (3 x 50 ml). The combined CH₂Cl₂ solution was washed with water (2 x 50 ml) and dried over MgSO₄. After filtration, solvent was removed by evaporation under reduced pressure. The foam residue was dissolved in 10 ml of CH₂Cl₂ containing 5 ml of methanol. 2 ml of 80% aqueous acetic acid was added and the mixture was stirred



at room temperature overnight. The mixture was evaporated to dryness. The solid residue was purified on silica gel using CH_2Cl_2 : MeOH 4:1 as eluant. It yielded 145 mg (54%) of pure product.

5 m.p. Dec $>230^\circ\text{C}$; R_f : 0.23 (in CH_2Cl_2 :MeOH 4:1)

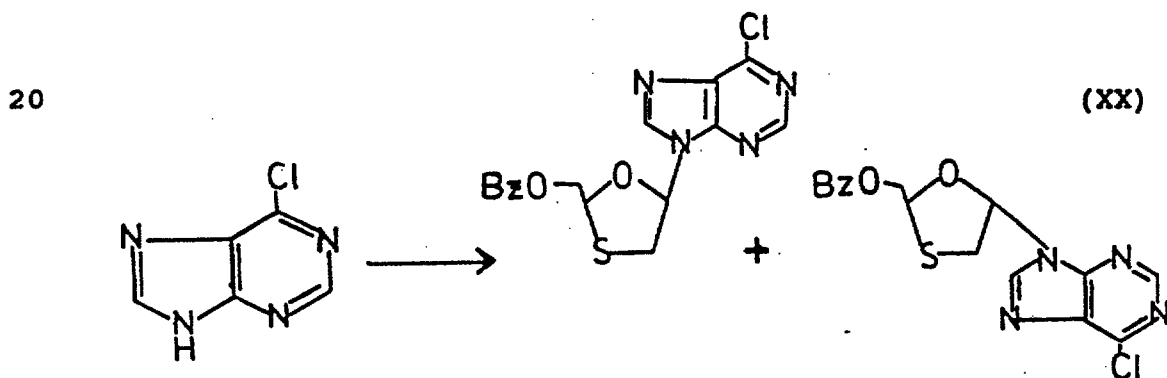
U.V.: (MeOH) Lambda max: 271 nm

$^1\text{H-NMR}$ δ (ppm in DMSO-d_6)

- 7.69 (d, 2H, 2 x $\text{C}_6'\text{-H}$, $J = 7.6$ Hz)
 7.28 (d, 4H, 2 x NH_2 , $J = 24.9$ Hz, D_2O exchange)
 10 6.24 (t, 2H, 2 x $\text{C}_5\text{-H}$, $J = 5.6$ Hz)
 5.76 (d, 2H, 2 x $\text{C}_3'\text{-H}$; $J = 7.4$ Hz)
 5.35 (t, 2H, 2 x $\text{C}_2\text{-H}$, $J = 4.5$ Hz)
 4.37 (d, 4H, 2 x $\text{C}_2\text{-CH}_2\text{O-}$)
 3.42 (dd, 2H, 2 x $\text{C}_4\text{-H}$, $J = 5.5$ and 10.9 Hz)
 15 3.10 (dd, 2H, 2 x $\text{C}_4\text{-H}$, $J = 5.6$ and 11.7 Hz)
 2.60 (s, 4H, 2 x $\text{-CH}_2\text{-C-O}$)

Example 11

Cis- and trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolanes



1.7 g of 6-chloropurine was heated at reflux in 50 ml of HMDS (hexamethyldisilazane) containing 50 mg of $(\text{NH}_4)_2\text{SO}_4$ (ammonium sulfate) until the solution became

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clear (1 hour). Excess HMDS was removed under reduced pressure. The oily residue was dried under high vacuum for 1 hour and then dissolved in 100 ml of dry 1,2-dichloroethane.

5 2.7 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane (XIII) was dried in a 500 ml round bottom flask by evaporation twice with 50 ml of benzene and dissolved in 200 ml of dry 1,2-dichloroethane.

10 The solution of silylated 6-chloropurine was then transferred into the 1,3-oxathiolane solution through a canula under argon atmosphere. 11 ml of 1M TMS-triflate (trimethylsilyl trifluoromethane sulfonate) was added to the reaction flask. The mixture was heated at reflux for 5 hours, then cooled to room temperature.

15 The mixture was poured into 300 ml of saturated sodium bicarbonate solution (NaHCO₃ solution) while stirring. The organic layer was collected and the aqueous phase was extracted with CH₂Cl₂ (2 x 100 ml). The combined organic phase was washed with water, dried over MgSO₄, filtered

20 and evaporated under reduced pressure. The residue was purified and separated on silica gel using Hexane-ethyl acetate 7:3 as eluant. It yielded 1.05 g (28%) of the less polar product, which was identified as alpha- or trans- isomer as a foam, and 710 mg of lower product as

25 beta- or cis-isomer. Total yield 46.1%; cis:trans ratio 1:1.4

trans-isomer (α -isomer): R_f: 0.43 in Hexane:EtOAc 1:1

U.V.: (MeOH) Lambda max: 264.7 nm

¹H-NMR δ (ppm in CDCl₃):

30 8.76 (s, 1H, C₈'-H)
 8.48 (s, 1H, C₂'-H)
 8.06 (m, 2H, aromatic)
 7.56 (m, 1H, aromatic)
 7.45 (m, 2H, aromatic)

35 6.90 (dd, 1H, C₅-H, J = 5.0 Hz)

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5.78 (dd, 1H, C₂-H, J = 6.0 Hz)

4.56 (m, 2H, C₂-CH₂OCOC₆H₅)

3.74 (m, 2H, C₄-H)

cis-isomer (beta-isomer): R_f: 0:35 in Hexane:EtoAc: 1:1

5 U.V.: (MeOH) Lambda max 264.7 nm

¹H-NMR δ (ppm in CDCl₃):

8.72 (s, 1H, C₈'-H)

8.51 (s, 1H, C₂'-H)

8.00 (m, 2H, aromatic)

10 7.56 (m, 1H, aromatic)

7.44 (m, 2H, aromatic)

6.61 (t, 1H, C₅-H, J = 4.7 Hz)

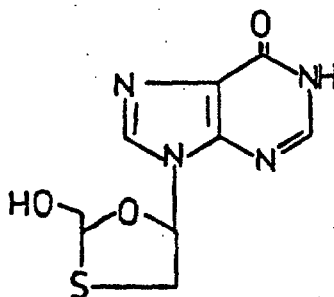
5.62 (t, 1H, C₂-H, J = 4.9 Hz)

4.69 (m, 2H, C₂-CH₂OCOC₆H₅)

15 3.66 (m, 2H, C₄-H)

Example 12

Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane (inosine derivative)



(XXI)

20 533 mg of cis-2-benzoyloxymethyl-5-(6-chloropurin-N-9'-yl)-1,3-oxathiolane was dissolved in 25 ml of methanol. 5 g of sodium hydroxide (NaOH) and 3 ml of water were added into the solution. The mixture was heated at reflux for 5 hours and cooled to room temperature. The solution was then diluted with 100 ml

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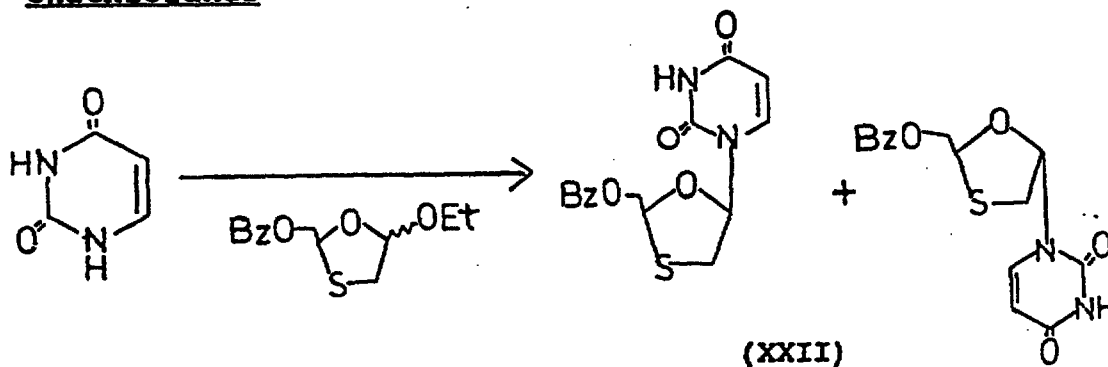
of water, neutralized with pyridinium resin and filtered. The resin residue was washed with 100 ml of methanol. The combined filtrate was evaporated under reduced pressure. The residue was purified on silica gel using $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 4:1 as eluant. It yielded 183 mg (51%) of pure product, which was identified as inosine derivative. m.p.: 208-210°C; R_f : 0.27 in EtOAc:MeOH 4:1 U.V.: (MeOH) Lambda max: 246 nm

$^1\text{H-NMR}$: δ (ppm in $\text{DMSO}-d_6$)

- 10 12.42 (s, 1H, -NH, D_2O exchange)
 8.36 (s, 1H, $\text{C}_8'\text{-H}$)
 8.07 (s, 1H, $\text{C}_2'\text{-H}$)
 6.37 (t, 1H, $\text{C}_5\text{-H}$, $J = 5.1$ Hz)
 5.29 (t, 1H, -OH, $J = 6.0$ Hz, D_2O exchange)
 15 5.24 (t, 1H, $\text{C}_2\text{-H}$, $J = 4.9$ Hz)
 3.63 (m, 4H, 2H from $\text{C}_4\text{-H}$ and 2H from $\text{CH}_2\text{-OH}$)

Example 13

Cis- and trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolanes



760 mg of uracil was heated at reflux in 30 ml of HMDS in the presence of 50 mg $(\text{NH}_4)_2\text{SO}_4$ until the solution became clear. The mixture was evaporated under reduced pressure. The residue was dried under high vacuum for 1 hour and dissolved in 100 ml of dry 1,2-dichloroethane.

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1.5 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane was dried by evaporation twice with 50 ml of benzene in a 500 ml round bottom flask and dissolved in 150 ml of dry 1,2-dichloroethane.

5 The silylated uracil solution was transferred into the oxathiolane solution through a canula under argon atmosphere and 1.5 ml of TMS-Triflate in 20 ml of 1,2-dichloroethane was added. The reaction mixture was heated at reflux under argon atmosphere for 48 hours,
10 cooled to room temperature and poured into 300 ml of saturated aqueous NaHCO₃ solution. The organic layer was collected. The aqueous phase was extracted twice with CH₂Cl₂ (2 x 100 ml). The combined organic layer was washed with water (2 x 200 ml), once with NaCl solution
15 (1 X 150 ml) and dried over MgSO₄. After filtration, solvent was removed by evaporation in vacuum and the residue was purified on silica gel using Hexane:EtOAc 1:1 as eluant. It yielded 594 mg (32%) of pure product.

20 The product was shown as only one spot in the TLC. However the ¹H-NMR spectrum indicated the presence of two isomers cis:trans in a ratio of 1:1.2 and which were not separated at this stage.

R_f: 0.35 in Hexane:EtOAc 3:7

U.V.: (MeOH) Lambda max: 261 nm

25 ¹H-NMR δ(ppm in CDCl₃)

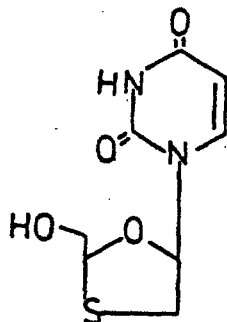
8.88 (broad s, 1H, N₃'-H)
8.05 (m, 2H, aromatic)
7.71 (d, 1H, C₆'-H cis, J = 8.2 Hz)
7.57 (m, 1H, aromatic)
30 7.45 (m, 3H, aromatic and N₃'-H)
6.55 (dd, 1H, C₃-H trans, J = 2.4 and 5.4 Hz)
6.35 (dd, 1H, C₃-H cis, J = 4.1 and 5.6 Hz)
5.79 (t, 1H, C₂-H trans, J = 5.4 Hz)
5.73 (d, 1H, C₅'-H trans, J = 8.2 Hz)
35 5.57 (d, 1H, C₅'-H cis, J = 8.2 Hz)
5.46 (t, 1H, C₂-H cis, J = 3.9 Hz)



4.73 (d, 2H, $-\text{CH}_2\text{O}-\text{COC}_6\text{H}_5$)
 4.45 (t, 2H, $-\text{CH}_2\text{OCOC}_6\text{H}_5$)
 3.57 (m, 1H, $\text{C}_4\text{-H}$)
 3.17 (m, 1H, $\text{C}_4\text{-H}$)

5 Example 14

Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane



(XXIII)

300 mg of a mixture cis- and trans-2-benzoyloxymethyl- 5-(uracil-N-1'-yl)-1,3-oxathiolanes was dissolved in 75 ml of methanolic ammonia. The mixture was stirred at room temperature overnight. The solution was evaporated by dryness. The residue was purified and the two isomers were separated on silica gel using EtOAc:MeOH 98:2 as eluant.

The top product was isolated as a solid product and was identified as cis-isomer.

Cis-isomer: m.p. 162-164°C; R_f : 0.57 in EtOAc:MeOH 95:5
 U.V.: (MeOH) λ_{max} : 261.4 nm

$^1\text{H-NMR}$ δ (ppm in DMSO- d_6):

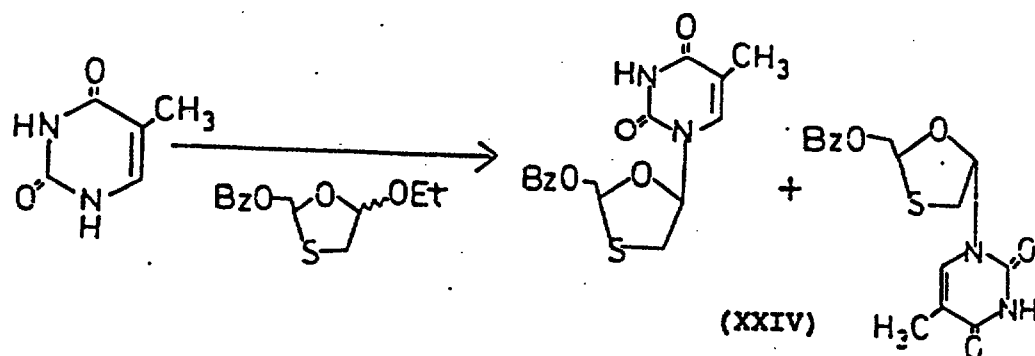
11.36 (s, 1H, $\text{N}_1\text{'-H}$)
 7.88 (d, 1H, $\text{C}_6\text{'-H}$, $J = 8.1$ Hz)
 6.18 (t, 1H, $\text{C}_5\text{-H}$, $J = 4.8$ Hz)
 5.62 (d, 1H, $\text{C}_3\text{'-H}$, $J = 8.1$ Hz)
 5.33 (t, 1H, $\text{C}_2\text{-H}$, $J = 5.7$ Hz)
 5.17 (t, 1H, $-\text{OH}$, D_2O exchange)
 3.72 (t, 2H, $\text{C}_2\text{-CH}_2\text{OH}$, $J = 4.6$ Hz)
 3.41 (dd, 1H, $\text{C}_4\text{-H}$, $J = 5.7$ and 12 Hz)
 3.20 (dd, 1H, $\text{C}_4\text{-H}$, $J = 4.6$ and 9.9 Hz)

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Example 15Cis- and trans-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolanes

5 1.7 g of thymine was heated at reflux in 50 ml of HMDS containing 50 mg of $(\text{NH}_4)_2\text{SO}_4$ until the solution became clear. The mixture was evaporated under reduced pressure. The residue was dried under high vacuum for 1

10 3 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane was dried by evaporation twice with 75 ml of benzene and dissolved in 150 ml of dry 1,2-dichloroethane.

15 The silylated thymine solution was transferred into the oxathiolane through a canula under argon atmosphere. 3.3 ml of TMS-Triflate (trimethylsilyl-triflate) in 30 ml of dry 1,2-dichloroethane was introduced into the reaction mixture through a canula under argon atmosphere. The solution was heated at

20 reflux under argon atmosphere for 36 hours, cooled to room temperature and poured into 300 ml of saturated aqueous NaHCO_3 solution. The organic layer was collected and the aqueous phase was extracted twice with methylene chloride (2 X 100 ml). The combined organic phase was

25 washed twice with water (2 X 200 ml), once with NaCl solution (1 X 150 ml) and dried over MgSO_4 . The solution



was filtered. The filtrate was evaporated in vacuum. The residue was purified on silica gel using Hexane:EtOAc 1:1 as eluant. It yielded 1.3 g (35%) of pure product.

The product was shown as only one spot on TLC but the ^1H -NMR spectrum indicated the presence of the two isomers cis and trans in a ratio of 1:1.2.

R_f : 0.30 in Hexane:EtOAc 2:3

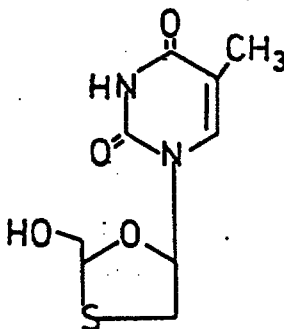
U.V.: (MeOH) Lambda max: 266 nm

^1H -NMR δ (ppm in CDCl_3):

10	8.60 (broad singlett, N_3' -H)
	8.06 (m, 2H, aromatic)
	7.59 (m, 1H, aromatic)
	7.49 (m, 2H, aromatic)
	7.38 (d, 1H, C_6' -H- <u>cis</u> , $J = 1.3$ Hz)
15	7.28 (d, 1H, C_6' -H- <u>trans</u> , $J = 1.3$ Hz)
	6.55 (dd, 1H, C_3 -H- <u>trans</u> isomer, $J = 3.1$ and 5.6 Hz)
	6.38 (t, 1H, C_3 -H- <u>cis</u> isomer, $J = 5.5$ Hz)
	5.78 (dd, 1H, C_2 -H- <u>trans</u> , $J = 4.4$ and 6.4 Hz)
	5.46 (t, 1H, C_2 -H- <u>cis</u> -isomer, $J = 4.3$ Hz)
20	4.69 (d, 2H, C_2 - $\text{CH}_2\text{OCOC}_6\text{H}_5$, $J = 4.2$ Hz)
	4.45 (m, 2H, C_2 - $\text{CH}_2\text{OCOC}_6\text{H}_5$)
	3.58 (m, 1H, C_4 -H)
	3.13 (m, 1H, C_4 -H)
	1.93 (d, 1H, C_3' - CH_3 - <u>trans</u> isomer, $J = 1.2$ Hz)
25	1.78 (d, 1H, C_3' - CH_2 - <u>cis</u> isomers, $J = 1.2$ Hz)

Example 16

Cis-2-hydroxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolanes



(XXV)



500 mg of a mixture cis- and trans-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolanes (XXIV) was dissolved in 100 ml of saturated methanolic ammonia. The mixture was stirred at room temperature overnight (18 hours). The mixture was then evaporated to dryness under reduced pressure. The residue was separated on silica gel using EtOAc:MeOH 98:2 as eluant.

The less polar product was identified as cis-isomer mp: 167-168°C; R_f : 0.66 in EtOAc:MeOH 95:5

U.V.: (MeOH) λ_{max} : 266 nm

1H -NMR δ (ppm in DMSO- d_6)

- 11.38 (s, 1H, N_1' -H)
- 7.73 (d, 1H, C_6' -H, J = 1.1 Hz)
- 6.16 (t, 1H, C_5 -H, J = 5.5 Hz)
- 5.31 (t, 1H, C_2 -H, J = 5.9 Hz)
- 5.14 (t, 1H, OH, D_2O exchange)
- 3.70 (t, 2H, C_2 -CH₂OH, J = 5.1 Hz)
- 3.36 (dd, 1H, C_4 -H, J = 5.7 and 1.7 Hz)
- 3.16 (dd, 1H, C_4 -H, J = 5.5 and 11.7 Hz)
- 1.75 (d, 3H, C_5' -CH₃, J = 1.7 Hz)

Example 17

Tablet Formulations

A. The following formulation is prepared by wet granulation of the ingredients with a solution of povidone in water, drying and screening, followed by addition of magnesium stearate and compression.

	<u>mg/tablet</u>
(a) Active ingredient	250
(b) Lactose B.P.	210
(c) Povidone B.P.	15
(d) Sodium Starch Glycollate	20
(e) Magnesium Stearate	5
	500

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B. The following formulation is prepared by direct compression; the lactose is of the direct compression type.

		<u>mg/tablet</u>
5	Active ingredient	250
	Lactose	145
	Avicel	100
	Magnesium Stearate	5
10		500

C. (Controlled Release Formulation) The formulation is prepared by wet granulation of the ingredients (below) with a solution of povidone in water, drying and screening followed by the addition of magnesium stearate and compression.

		<u>mg/tablet</u>
	(a) Active ingredient	500
	(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
20	(c) Lactose B.P.	53
	(d) Povidone B.P.	28
	(e) Magnesium Stearate	7
		700

25 Example 18

Capsule Formulation

A capsule formulation is prepared by admixing the ingredients below and filling into a two-part hard gelatin capsule.

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	<u>mg/capsule</u>
Active ingredient	125
Lactose	72.5
Avicel	50
5 Magnesium Stearate	2.5
	250

Example 19Injectable Formulation

- 10 Active ingredient 0.200 g
 Sodium hydroxide solution, 0.1M q.s. to a pH of about 11.
 Sterile water q.s. to 10 ml.

15 The active ingredient is suspended in some of
 the water (which may be warmed) and the pH adjusted to
 about 11 with a solution of sodium hydroxide. The batch
 is then made up to volume and filtered through a
 sterilizing grade membrane filter into a sterile 10 ml
 glass vial and sealed with sterile closures and overseas.

Example 2020 suppository

	<u>mg/suppository</u>
Active ingredient	250
Hard Fat, B.P.	1770
25	2020

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One-fifth of the hard fat is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 μ m sieve and added to the molten base with mixing, using a high shear stirrer, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining hard fat is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 μ m stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.02 g of the mixture is filled into suitable, 2 ml plastic molds. The suppositories are allowed to cool to room temperature.

Example 21

Antiviral Activity

In vitro testing was conducted on several of the compounds of this invention to determine their inhibitory properties. The results are shown in Tables 1 and 2. The concentrations reported are μ g/ml in the incubation media which affect the susceptibility of a continuous line of T-cells developed at the Lady Davis Institute for Medical Research (Montreal) by Dr. Mark A. Wainberg toward infection by HIV-1 following a protocol similar to that of H. Mitsuya and S. Broder, "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2'3'-dideoxy-

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nucleosides", Proc. Natl. Acad. Sci. USA, 83, pp. 1911-15 (1986). Protection of the cell line from infection was monitored by staining with monoclonal antibodies against viral proteins in the standard manner (Table 1). In all experiments, comparisons were made with the drug AZT as the control. In order to confirm the results, the drug effects were monitored by measuring reverse transcriptase (RT) activity in the U-937 line of human monocytic cells as assayed in the usual manner with tritiated thymidine triphosphate (TTP) (Table 2). Finally, the drug effects on cell viability as measured by the well-know cytolytic effects of HIV-1 on the MT-4 cell line was evaluated in the accepted manner (Table 1).

Toxicity

No toxic effects were observed in the above tests.

Table 1

Inhibition of HIV-1 product by compounds
of formula (I) in MT-4 cells

a) Viable cell counts (6 days in culture) using 2 μ g/ml of compound

Compound	Cell Viability %
no drug	6.47
AZT	88.6
<u>cis-XVI</u>	87.4
<u>trans-XVI</u>	24
<u>cis-XVII(b)</u>	14
<u>cis-XXV</u>	11
<u>cis-XXI</u>	18
<u>cis-XXIII</u>	14

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b) P-24 immunofluorescence

Time in Culture		% Immunofluorescent Cells		
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-XVI	
5	3	5.9	1.0	1.0
	6	99	1.0	7.6

c) Reverse transcriptase assay

Time in Culture		RT Activity (CPM X 1000)/ml		
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-XVI	
10	3	36.43	1.564	2.381
	6	339.0	1.748	2.301

Table 2

Inhibition of HIV-1 production by compounds of
formula (I) in H-9 cells

15

Reverse transcriptase assay

Time in Culture		RT Activity (CPM X 1000)/ml		
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-XVI	
20	5	9.117	3.346	3.077
	8	438.5	3.414	5.853
	11	2550	2.918	3.560
	14	2002	8.320	2.872
	17	584.5	2.997	2.399
	21	365.2	3.111	2.907
	25	436.4	15.88	4.020
25	29	92.38	32.08	3.756
	33	111.1	612.2	3.803
	37	32.28	878.2	4.193
	41	384.4	994.0	4.515
	45	33.64	32.91	3.441

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CLAIMS:

1. A 1,3-oxathiolane of formula (I), the
5 geometric and optical isomers thereof, and mixtures of
those isomers:



10 wherein:

R_1 is hydrogen;

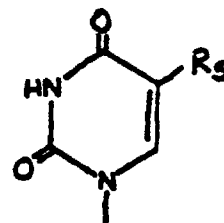
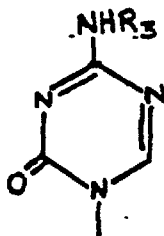
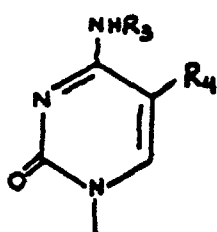
R_2 is a purine or pyrimidine base or an analogue
or derivative thereof;

15 Z is selected from a group consisting of S, S=O
or SO₂; and
pharmaceutically acceptable derivatives thereof.

2. A compound of formula (I) as defined in
claim 1 in the form of its cis isomer.

20 3. A compound of formula (I) as defined in
claim 1 or claim 2 wherein Z is S.

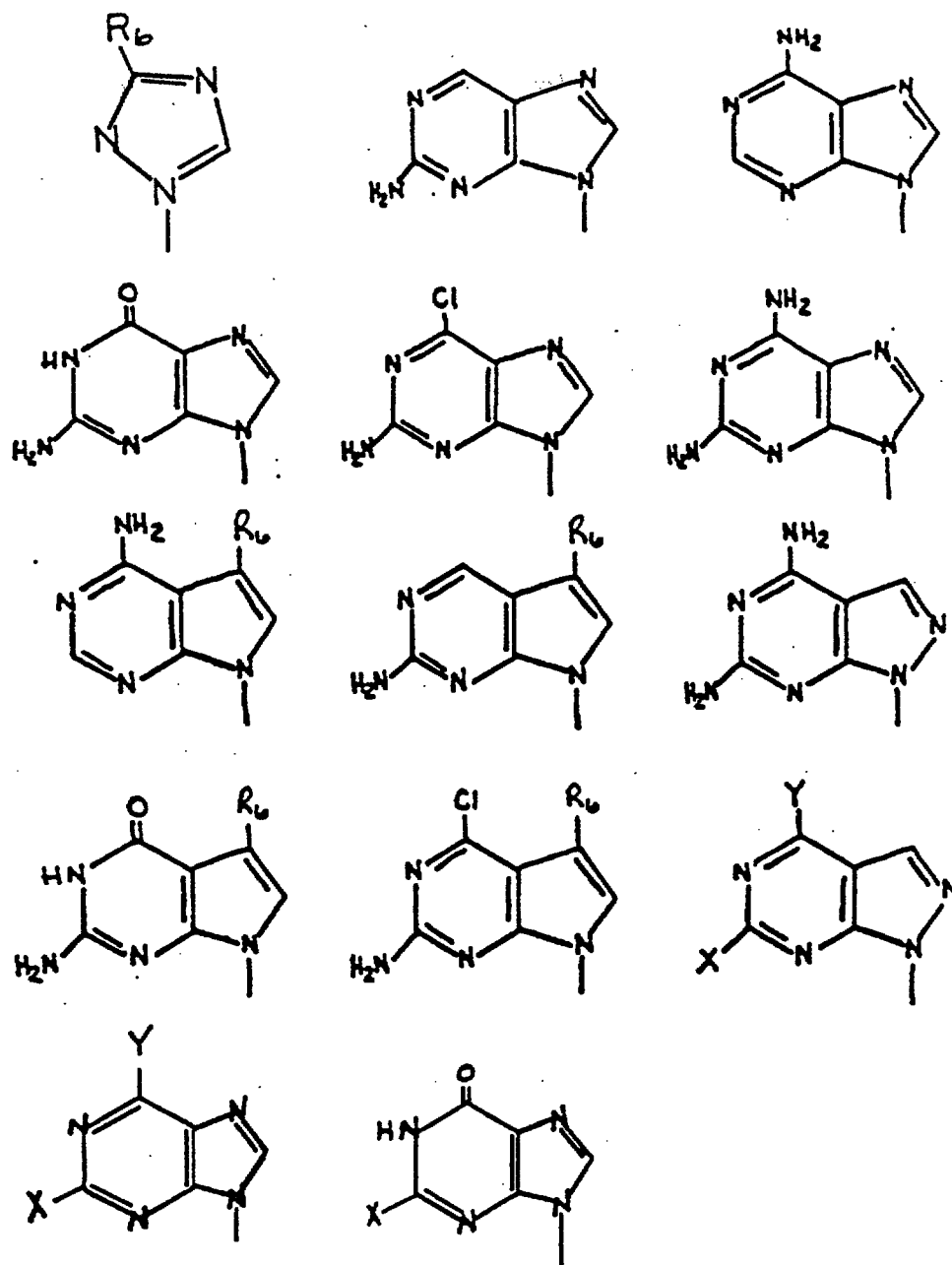
4. A compound of formula (I) as defined in
any one of claims 1 to 3 wherein R_2 is selected from:



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wherein:

R_1 is selected from the group of hydrogen or C_{1-6} alkyl groups;

5 R_2 and R_3 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;

R_4 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and

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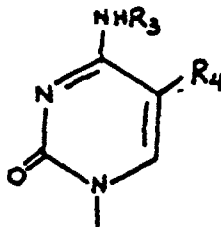


* C L M S *



X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.

5. A compound according to any one of claims 1 to 4 wherein R_2 is



wherein R_2 is selected from the group of hydrogen or C_{1-6} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine.

6. A compound selected from the group consisting of:

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;

Cis-2-hydroxymethyl-5-(N -dimethylamino-methylene

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* C L M S *

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cytosin-1'-yl)-1,3-oxathiolane;

Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;

5 Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;

10 Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;

15 Cis-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolane;

20 and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

 7. Cis - 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

25 8. A compound according to any one of claims 1 to 7 in the form of a racemic mixture.

 9. A compound according to any one of claims 1 to 7 substantially in the form of a single enantiomer.

30 10. A compound of formula (I) as defined in any one of claims 1 to 9 or a pharmaceutically acceptable

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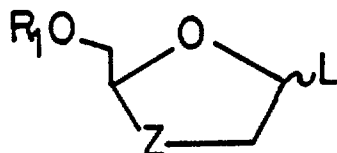
derivative thereof for use as an active therapeutic agent.

11. A compound of formula (I) as defined in any one of claims 1 to 9 or a pharmaceutically acceptable derivative thereof for use in the manufacture of a medicament for the treatment of a viral infection.

12. A pharmaceutical formulation comprising a compound of formula (I) as defined in any one of claims 1-9 or a pharmaceutically acceptable derivative thereof together with a pharmaceutically acceptable carrier therefor.

13. A pharmaceutical formulation according to claim 12 additionally comprising a further therapeutic agent.

14. A 1,3-oxathiolane of formula (VIII), the geometric and optical isomers thereof, and mixtures of those isomers:



(VIII)

wherein:

20 R_1 is hydrogen or a hydroxyl protecting group; and
 L is an alkoxy carbonyl group, iodine, bromine, chlorine or -OR where R is selected from the group consisting of a substituted or unsubstituted, saturated or unsaturated alkyl group and a substituted or
 25 unsubstituted, saturated or unsaturated aliphatic or aromatic acyl group.

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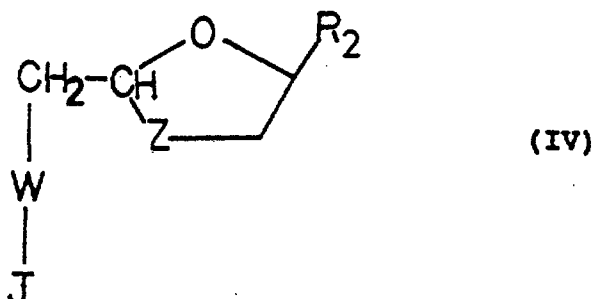
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* C L M S *

15. The ester of formula (IV) the geometric and optical isomers thereof, and mixtures of those isomers:



5 wherein:

W is PO_4^- , SPO_3^- , or $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-(\text{CH}_2)_n-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-$ where n is an integer of 1 to 10;

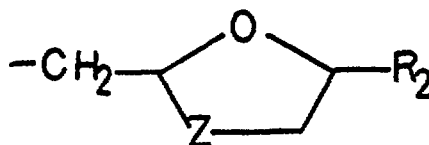
J is any nucleoside or nucleoside analog or derivative thereof;

10 Z is S, S=O, or SO_2 ; and

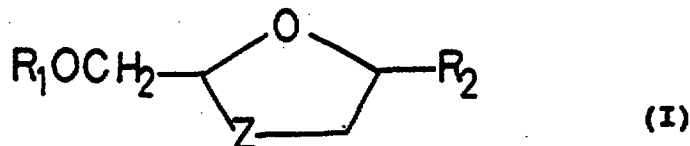
R_2 is a purine or pyrimidine base or analogue or derivative thereof.

16. A compound according to claim 15 wherein J is:

15



17. A process for the preparation of a compound of formula (I)



wherein R_1 is hydrogen;

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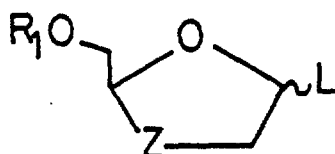
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

Z is S, S=O or SO_2 ; and

pharmaceutically acceptable derivatives thereof,

5 which comprises:

(a) reaction of a compound of formula (VIII)

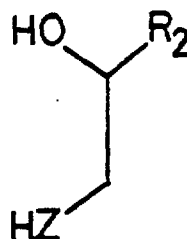


(VIII)

wherein R_1 is hydrogen or a hydroxyl protecting group and
 10 L is a displaceable atom or a group with a base R_2 -H group;

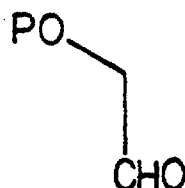
(b) base interconversion of one compound of formula (I) into another compound of formula (I);

(c) reaction of a compound of formula (IX)



(IX)

15 with a compound of formula (X)



(X)

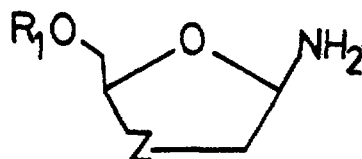
wherein P is a protecting group; or

(d) conversion of a compound of formula (XII)

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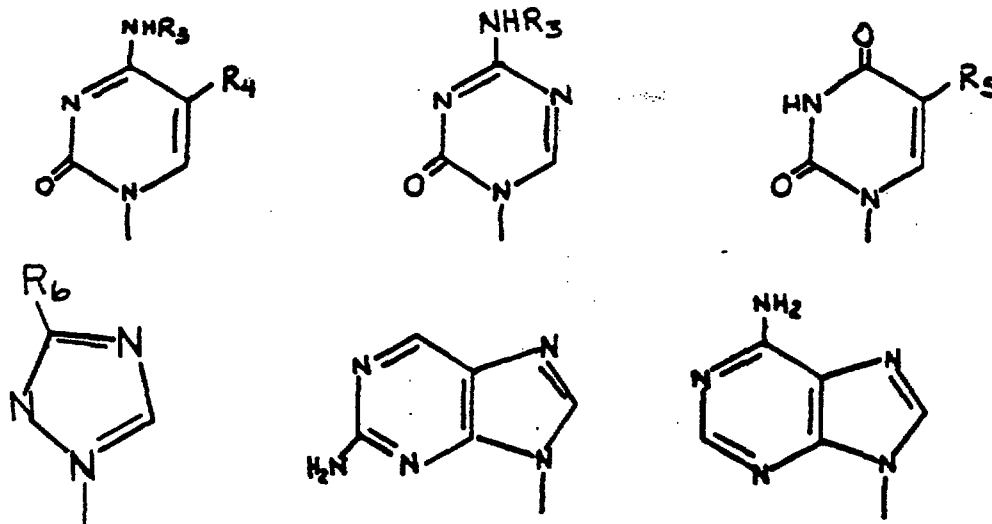
(XII)

- 5 to a compound of formula (I)
 and if necessary or desired subjecting the
 compound resulting from any of steps (a) to (d) to one or
 two further reactions comprising:
 (i) removing any protecting groups;
 10 (ii) converting a compound of formula (I) or a
 salt thereof into a pharmaceutically acceptable salt
 thereof.

- 15 18. A process as defined in claim 17
 wherein the compound of formula (I) is obtained in the
 form of its cis isomer.

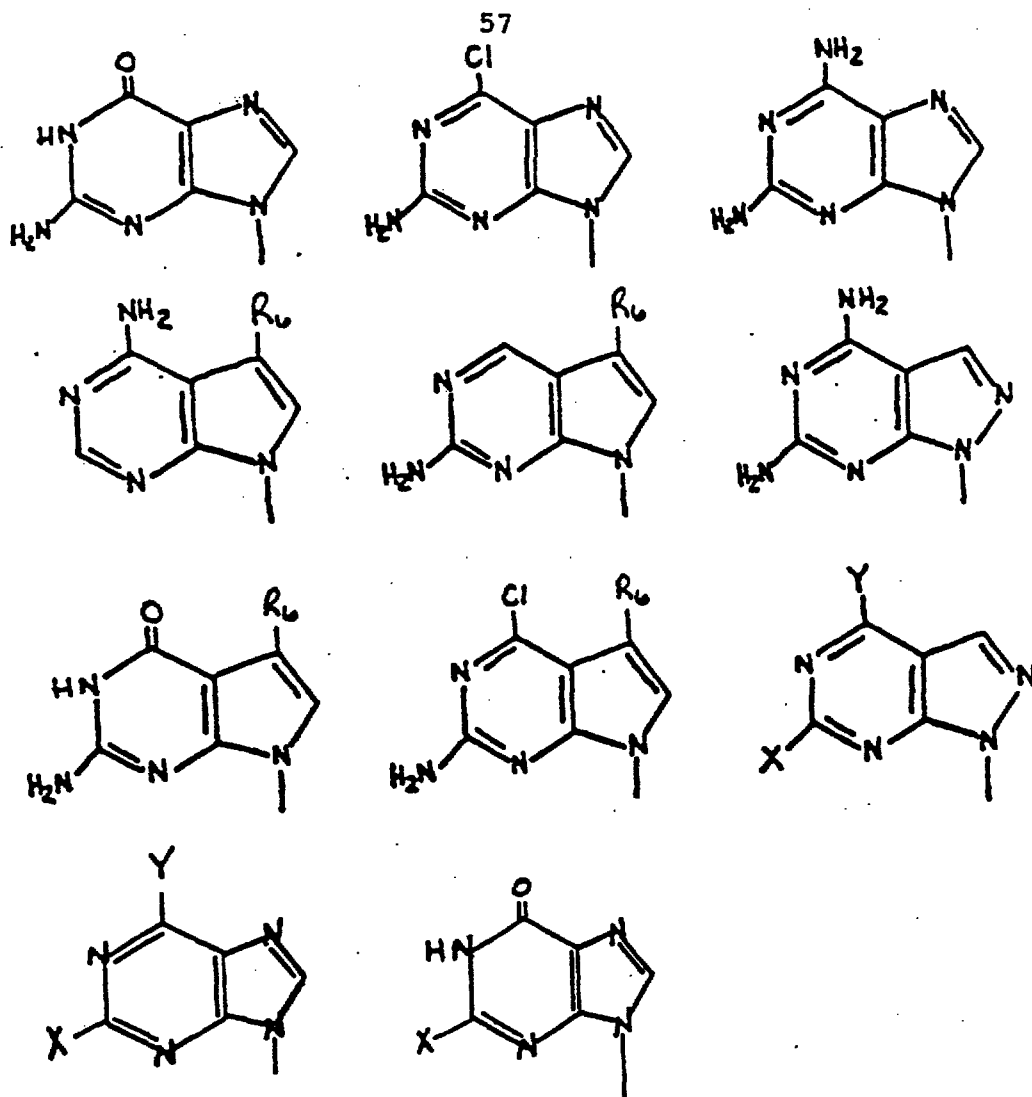
19. A process according to claim 17 or
 claim 18 wherein Z is S.

- 20 20. A process according to any one of
 claims 17 to 19 wherein R₂ is:



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5 wherein:

R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-6} alkyl groups;

10 R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;

R_6 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and

15 X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.

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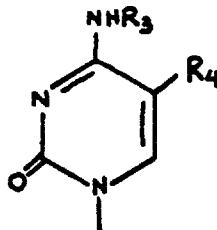


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21. A process according to any of claims 17 to 19 wherein R_2 is:



5 wherein R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-6} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or
10 unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine.

22. A process according to any one of claims 17 to 21 wherein the compound of formula (I) is selected from:

15 Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-
20 1,3-oxathiolane, and mixtures thereof;

Cis-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

25 Cis-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4' -acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;

30 Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;

Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;

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Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;

5 Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;

Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

10 Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;

Cis-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;

15 Cis-2-hydroxymethyl-5-(thymine-N-1'-yl)-1,3-oxathiolane;

and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

20 23. A process according to any one of claims 17 to 21 wherein the compound of formula (I) is Cis-2-hydroxymethyl-5-(cytosine-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

25 24. A process according to any one of claims 17 to 23 wherein the compound of formula (I) is obtained in the form of a racemic mixture.

30 25. A process according to any one of claims 1 to 7 wherein the compound of formula (I) is obtained substantially in the form of a single enantiomer.

35 26. A process according to any one of claims 17 to 25 wherein in step (a) the group L is selected from a group consisting of alkoxy carbonyl,

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iodine, bromine, chlorine or -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl group or R is a substituted or unsubstituted aliphatic or aromatic acyl group.

5

27. A process according to any one of claims 17 to 26 wherein step (a) the compound of formula (VIII) is reacted with a silylated purine or pyrimidine base in a compatible solvent in the presence of a Lewis acid or trimethylsilyltriflate.

10

28. A method for the preparation of a pharmaceutical formulation comprising admixing a compound of formula (I) as defined in claim 17 or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier therefor.

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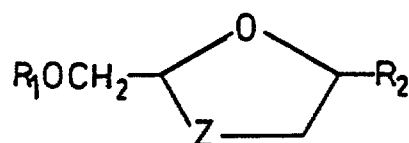
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ABSTRACT

Disclosed are compounds of the formula



10

wherein R_1 is hydrogen;

R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

Z is S, S=O or SO_2 ; and

pharmaceutically acceptable derivatives thereof.

15

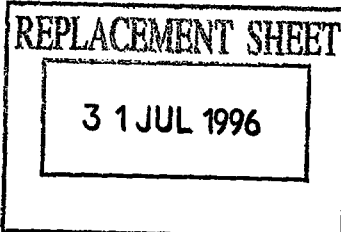
Also described are use of the compounds as antiviral agents, pharmaceutical formulations, and methods for the preparation of the compounds.

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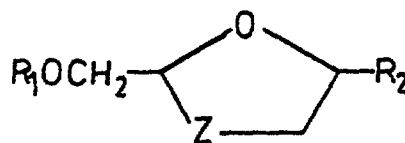


SUBSTITUTED-1, 3-OXATHIOLANES
WITH ANTIVIRAL PROPERTIES

5

ABSTRACT

Disclosed are compounds of the formula



10

wherein R₁ is hydrogen;

R₂ is a purine or pyrimidine base or an analogue or derivative thereof;

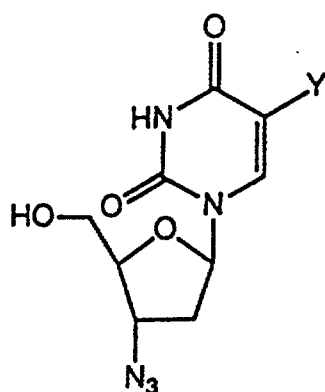
Z is S, S=O or SO₂; and

pharmaceutically acceptable derivatives thereof.

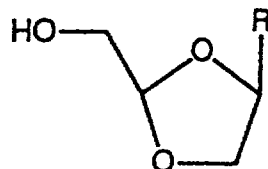
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Also described are use of the compounds as antiviral agents, pharmaceutical formulations, and methods for the preparation of the compounds.

REPLACEMENT SHEETS		SG
☒	Description	: paged 4 to paged 32
☒	Claim(s)	: paged 33 to paged 36
☐	Drawing(s)	: paged ... to paged ...
☐	Abstract	: paged ... to paged ...
DATE OF RECEIPT 3-12-1997		



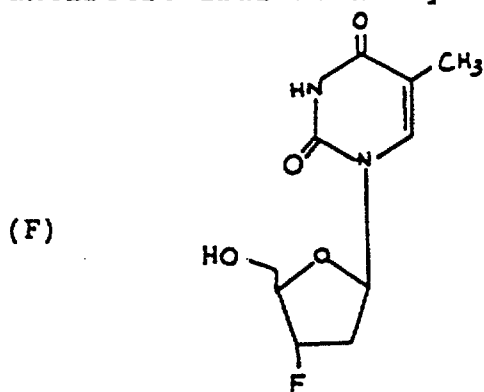
(E)



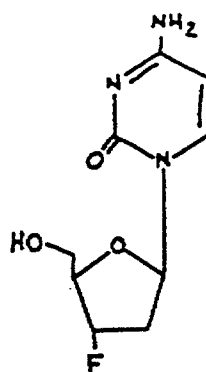
(E')

European publication EP A-337,713 is directed to 1,3-dioxolane nucleoside analogues of formula (E') with antiviral properties.

Finally, the 3'-fluoro analogues of 2',3'-dideoxycytidine shown in formula (F) and of 2',3'-dideoxythymidine shown in formula (G) are referred to in Herdewijn et al., "3'-Substituted 2',3'-dideoxynucleoside analogues as potential anti- HIV(HTLV-III/LAV) agents", J. Med. Chem., 30, pp. 1270-78 (1987), as having potent antiretroviral activity.



(F)



(G)

The most potent anti-HIV compounds thus far reported are 2',3'-dideoxynucleosides, more particularly, 2',3'-dideoxy cytidine (ddCyd) and 3'-azido-2',3'-dideoxythymidine (AzddThd or AZT). These compounds are also active against other kinds of retroviruses such as the Moloney murine leukemia virus. Because of the increasing incidence and the life-threatening characteristics of AIDS, efforts are being expended to discover and develop new non-toxic and potent inhibitors

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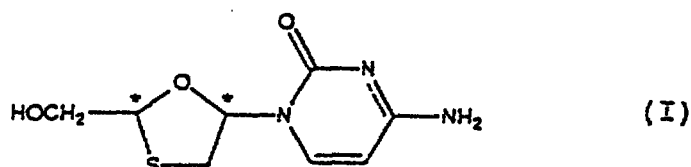
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of HIV and blockers of its infectivity. It is therefore an object of the present invention to provide effective anti-HIV compounds of low toxicity and a synthesis of such new compounds that is readily feasible.

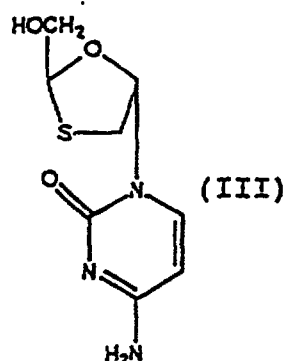
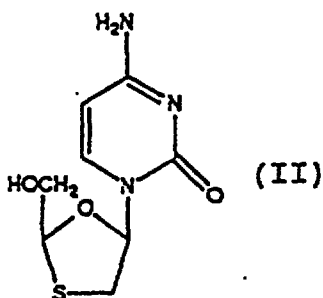
The present invention provides novel 2-substituted-5-substituted-1,3-oxathiolanes which have antiretroviral activity. In particular, these compounds have been found to act as non-toxic inhibitors of the replication of HIV-1 in T-lymphocytes over prolonged periods of time.

There is accordingly provided in a first aspect cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane may be represented by the formula



It will be appreciated by those skilled in the art that formula (I) contains two chiral centers (shown as * in formula (I)) and thus includes two pairs of optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures. Both cis-isomers and mixtures thereof, including racemic mixtures, are included within the scope of the invention. The cis-isomers may also be represented by formula (II), and similarly, the trans-isomers may be represented by formula (III)



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By "a pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt of a compound of formulae (I) or (II), and the following esters thereof: a C₁₋₁₆ alkanoyl ester, an unsubstituted benzoyl ester or a benzoyl ester substituted by at least one halogen (bromine, chlorine, fluorine or iodine), C₁₋₆ alkyl, C₁₋₆ alkoxy, nitro or trifluoromethyl groups.

It will be appreciated by those skilled in the art that the compounds of formulae (I) or (II) may be modified to provide pharmaceutically acceptable esters at the hydroxymethyl group of the oxathiolane ring.

Preferred esters of the compounds of formulae (I) or (II) include the compounds in which H is replaced by a carboxyl function R-C(=O) in which the non-carbonyl moiety R of the ester grouping is selected from hydrogen, straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, t-butyl, n-butyl), phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy.

Unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, preferably 1 to 4 carbon atoms.

Pharmaceutically acceptable salts of the compounds of formulae (I) or (II) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include

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hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and NR_4^+ (where R is C_{1-4} alkyl) salts.

References hereinafter to a compound according to the invention includes both compounds of formulae (I) or (II) and their pharmaceutically acceptable derivatives.

The compounds of the invention either themselves possess antiviral activity and/or are metabolizable to such compounds. In particular these compounds are effective in inhibiting the replication of retroviruses, including human retroviruses such as human

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immunodeficiency viruses (HIV's), the causative agents of AIDS.

There is thus provided as a further aspect of the invention a compound formula (I) or a pharmaceutically acceptable derivative thereof for use as an active therapeutic agent in particular as an antiviral agent, for example in the treatment of retroviral infections.

In a further or alternative aspect there is provided a method for the treatment of a viral infection, in particular an infection caused by a retrovirus such as HIV, in a mammal, including man, comprising administration of an effective amount of an antiviral compound of formula (I) or a pharmaceutically acceptable derivative thereof.

There is also provided in a further or alternative aspect of this invention, use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a viral infection.

The compounds of the invention are also useful in the treatment of AIDS related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological conditions (such as dementia), anti-HIV antibody positive and HIV- positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

The compounds of the invention are also useful in the prevention or progression to clinical illness of individuals who are anti-HIV antibody or HIV-antigen positive and in prophylaxis following exposure to HIV.

The compounds of formula (I) or the pharmaceutically acceptable derivatives thereof, may also be used for the prevention of viral contamination of biological fluids such as blood or semen in vitro.

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It will be appreciated by those skilled in the art that references herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range from about 1 to about 750 mg/kg of bodyweight per day, such as 3 to about 120 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 1 to 75 μM , preferably about 2 to 50 μM , most preferably about 3 to about 30 μM . This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or administered as a bolus containing about 0.1 to about 110 mg/kg of the

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active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient therefor.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution; as a

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suspension; or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils) or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more

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emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored based, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutically formulations suitable for rectal administration wherein the carrier is a solid, are most preferably represented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient, such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation, the compounds according to the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane,

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trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired, the above described formulations adapted to give sustained release of the active ingredient, may be employed.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compounds of the invention may also be used in combination with other therapeutic agents, for example, other antiinfective agents. In particular the compounds of the invention may be employed together with known antiviral agents.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable derivative thereof together with another therapeutically active agent, in particular, an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

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Suitable therapeutic agents for use in such combinations include acyclic nucleosides such as aciclovir, ganciclovir, interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as probenidicid; nucleoside transport inhibitors such as dipyridamole; nucleoside analogues such as 3'-azido-2',3'-dideoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydrothymidine, and 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments and CD4-hybrid molecules.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

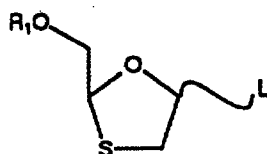
When the compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same virus, the dose of each compound may be either the same or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be prepared by any method known in the art for the preparation of compounds of analogous structure.

In one such process (A) a 1,3-oxathiolane of formula (VIII)

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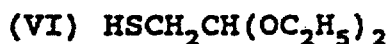


(VIII)

wherein R_1 is hydrogen or hydroxyl protecting group as defined herein and the anomeric group L is a displaceable atom or group, is reacted with an appropriate base. Suitable groups L include alkoxy carbonyl groups such as ethoxy carbonyl or halogens, for example, iodine, bromine or chlorine or -OR where R is a substituted or unsubstituted, saturated or unsaturated alkyl group, e.g., a C_{1-6} alkyl group such as methyl, or R is a substituted or unsubstituted aliphatic or aromatic acyl group, e.g., a C_{1-6} aliphatic acyl group such as acetyl and an aromatic acyl group such as benzoyl.

The compound of formula (VIII) is conveniently reacted with the appropriate purine or pyrimidine base R_2-H (previously silylated with a silylating agent such as hexamethyldisilazane) in a compatible solvent such as methylene chloride using a Lewis acid (such as titanium tetrachloride or stannic chloride) or trimethylsilyltriflate.

The 1,3-oxathiolanes of formula (VIII) may be prepared, for example, by reaction of an aldehyde of formula (VII) with a mercaptoacetal of formula (VI) in a compatible organic solvent, such as toluene, in the presence of an acid catalyst such as a para-toluene sulfonic acid or a Lewis acid, e.g., zinc chloride.



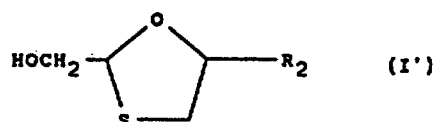
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The mercaptoacetals of formula (VI) may be prepared by methods known in the art, for example, G. Hesse and I. Jorder, "Mercaptoacetaldehyde and dioxy-1, 4-dithiane", Chem. Ber. 85, pp. 924-932 (1952).

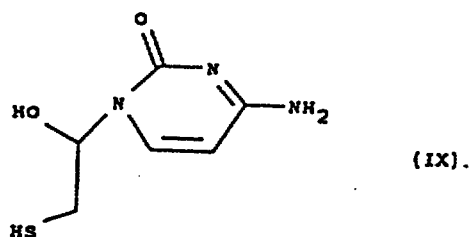
The aldehydes of formula (VII) may be prepared by methods known in the art, for example, E.G. Halloquist and H. Hibbert, "Studies on reactions relating to carbohydrates and polysaccharides. Part XLIV: Synthesis of isomeric bicyclic acetal ethers", Can. J. Research. 8, pp. 129-136 (1933).

In a second process (B) a compound of formula (I')

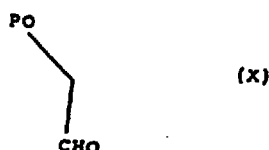


wherein R_2 is a purine or pyrimidine base other than cytosine is converted to a compound of formula (I) by base interconversion. Such interconversion may be effected either by simple chemical transformation (e.g., the conversion of uracil base to cytosine) or by an enzymatic conversion using, for example, a deoxyribosyl transferase. Such methods and conditions for base interconversions are well known in the art of nucleoside chemistry.

In a third process (C) the compounds of formula (I) may be prepared by the reaction of a compound of formula (IX)

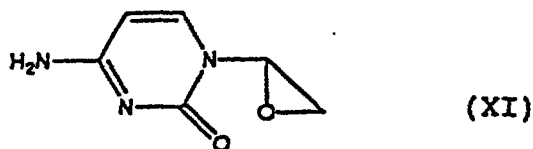


with a compound of formula (X)



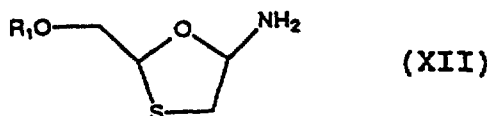
where P is a protecting group, followed by removal of the protecting group.

The compounds of formula (IX) may be prepared for reaction by a suitable epoxide (XI).



with an appropriate sulphur-containing compound, e.g., sodium thioacetate. Compounds of formula (XI) are either known in the art or may be obtained by analogous processes.

In a fourth process (D) a compound of formula (XII)



may be converted to a compound of formulae (I) or (II) by conversion of the anomeric NH₂ group to the required base by methods well known in the art of nucleoside chemistry.

Many of the reactions described hereinabove have been extensively reported in the context of purine nucleoside synthesis, for example, in "Nucleoside Analogues - Chemistry, Biology and Medical Applications", R.T. Walker et al., Eds, Plenum Press, New York (1979) at pages 193-223, the text of which is incorporated by reference herein.

It will be appreciated that the above reactions may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be

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required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g., benzyl), acyl or aryl (e.g., 2,4-dinitrophenyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g., methyl, t-butyl or methoxymethyl), aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl, (e.g., acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by treatment with BF₃/etherate and acetic anhydride followed by removal of acetate groups so formed at an appropriate stage in the synthesis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

In the above processes the compounds of formula (I) are generally obtained as a mixture of the cis and trans isomers.

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These isomers may be separated, for example, by acetylation, e.g., with acetic anhydride followed by separation by physical means, e.g., chromatography on silica gel and deacetylation, e.g., with methanolic ammonia or by fractional crystallization.

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in United States Patent No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of a compound of formula (I), the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods. Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the free base with a suitable base such as an alkoxide (e.g., sodium methoxide) optionally in the presence of a solvent such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

A compound of formula (I) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as POCl_3 , or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of a compound of formula (I) may be converted to the parent compound, for example, by hydrolysis.

Where the compound of formula (I) is desired as a single isomer it may be obtained either by resolution of the final product or by stereospecific

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synthesis from isomerically pure starting material or any convenient intermediate.

Resolution of the final product, or an intermediate or starting material therefore may be effected by any suitable method known in the art: see for example, Stereochemistry of Carbon Compounds, by E.L. Eliel (McGraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.

The invention will be further described by the following examples which are not intended to limit the invention in any way. All temperatures are in degrees celsius.

EXAMPLES

Example 1

2-(benzoylthio) acetaldehyde diethylacetal



To a solution of potassium t-butoxide (11.5 g. 0.11 mol) in DMF (100 ml) was added thiobenzoic acid (17 g. 0.11 mol) and the solution partially evaporated in vacuo, benzene added in two consecutive portions (2 x 30 ml) and evaporated in vacuo each time. To the residual DMF solution was added bromoacetaldehyde diethylacetal (20.3 g. 0.1 mol) and the mixture stirred at 120° for 15 h. After cooling, it was poured onto water (500 ml), the product extracted with ether (3 x 200 ml), the extract washed with aqueous NaHCO₃, followed by water, then dried and the solvent removed in vacuo. The residue was distilled in vacuo to give 17.2 g. of pure (V), b.p. 131-133°/0.07 mm. It was characterized by ¹H NMR δ(ppm in CDCl₃):

7.97 (d, 2H; aromatic)

7.47 (m, 3H; aromatic)

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- 4.59 (t, 1H; $-\underline{\text{CH}}(\text{OC}_2\text{H}_5)_2$)
 3.66 (m, 4H; 2 x OCH_2CH_3)
 3.30 (d, 2H; SCH_2-)
 1.23 (t, 6H; 2 x OCH_2CH_3)

Example 2Mercaptoacetaldehyde diethylacetal

The preceding benzoylthio derivative (V) (17.2 g) was dissolved in 100 ml THF followed by the addition of 6 g NaOH in 20 ml H_2O . The mixture was refluxed under N_2 for 15 h, then cooled and diluted with water (200 ml) and the product extracted with ether (3 x 200 ml). The extract was dried, the solvent removed in vacuo and the residue distilled in vacuo to yield 7.1 g of pure (VI), b.p. 60-62°/18 mm. It was characterized by ^1H NMR δ (ppm in CDCl_3):

- 4.51 (t, 1H; $\text{CH}(\text{OC}_2\text{H}_5)_2$)
 3.51 (m, 4H; 2 x OCH_2CH_3)
 2.65 (dd, 2H; $\text{HS}-\text{CH}_2$)
 1.54 (t, 1H; $\text{HS}-$)
 1.23 (t, 6H; 2 x OCH_2CH_3)

Example 3Benzoyloxyacetaldehyde

This known intermediate was prepared by a previously unreported method from the known 1-benzoyl glycerol. Thus, 50 g of the latter in a mixture of 500 ml of CH_2Cl_2 and 25 ml of H_2O was treated portionwise with 80 g of NaIO_4 under vigorous stirring at room temperature. After addition, stirring was continued for

2 h after which time 100 g of MgSO_4 was added and stirring continued for 30 min. The mixture was filtered, the filtrate evaporated in vacuo and the residue distilled in vacuo to yield 26 g of pure (VII) b.p. 92-94°/0.25 mm.

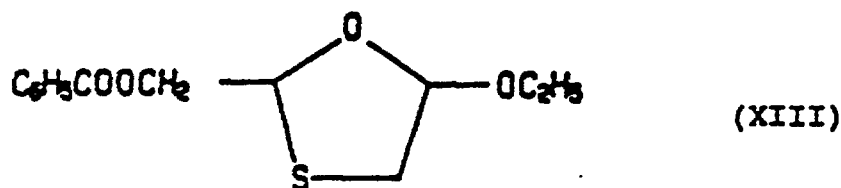
^1H NMR (200 MHz ; TMS as internal reference)

δ (ppm in CDCl_3):

- 9.71 (s, 1H; $-\text{CHO}$)
- 8.11 (d, 2H; aromatic)
- 7.60 (m, 1H; aromatic)
- 7.46 (m, 2H; aromatic)
- 4.88 (s, 2H; $-\text{CH}_2\text{CHO}$)

Example 4

2-Benzoyloxymethyl-5-ethoxy-1,3-oxathiolane



The preceding mercaptoacetaldehyde acetal (VI) (7 g) was mixed in 100 ml of toluene with 7 g of the above benzoyloxyacetaldehyde (VII), a few crystals of para-toluene sulfonic acid added and the mixture placed in an oil-bath at 120° under N_2 . The formed ethanol was allowed to distill over, the mixture kept at 120° for an additional 30 minutes, then cooled and washed with aqueous NaHCO_3 , dried and evaporated in vacuo. The residue was distilled in vacuo to yield 9.8 g of pure (XIII) as a mixture of cis- and trans-isomers, b.p. 140-143°/0.1 mm; R_f 0.51 (hexane-EtOAc);

^1H NMR δ (ppm in CDCl_3):

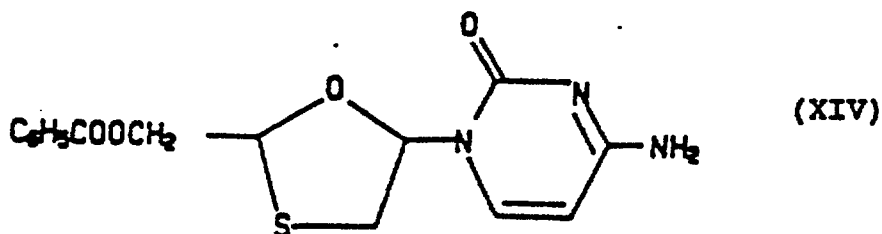
- 8.05 (m, 2H; aromatic)
- 7.57 (m, 1H; aromatic)
- 7.43 (m, 2H; aromatic)

5.55 (m, 2H; C₃-H, C₂-H)4.55 (m, 2H; C₂-C₆H₅CO₂CH₂)3.80 (m, 1H; C₂-C₆H₅CO₂CH₂)

H

3.76 (m, 1H; C₃-OCHCH₃)

H

3.17 (m, 2H; C₄-H₂)1.21 (t, 3H; C₃-OCH₂CH₃)Example 5Cis- and trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolanes

A mixture of 2.7 g of cytosine, 30 ml of hexamethyldisilazane (HMDS) and 0.3 ml of trimethylsilyl chloride (TMSCl) was heated under reflux under dry N₂ until a clear solution resulted (3 hours) and the excess reagents evaporated in vacuo. The remaining volatiles were removed under high vacuum (15 min.), the solid residue taken up in 250 ml of 1, 2-dichloroethane and 5 g of the above key intermediate (XIII) in 50 ml of dichloroethane added under dry argon followed by 4.7 ml of trimethylsilyl triflate (TMST_f). After 3 days of heating under reflux under argon, it was cooled and poured onto 300 ml of saturated aqueous NaHCO₃. The organic layer was collected, the aqueous phase extracted with CH₂Cl₂ (2 X 100 ml) and the combined extracts washed with water, dried and evaporated in vacuo. The residue was purified by chromatography on silica gel using CH₂Cl₂:CH₃OH 9:1 as the eluant to give 2.5 g of a pure

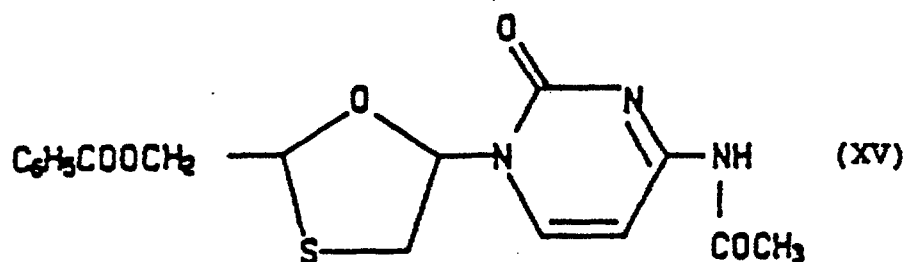
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mixture of cis- and trans-(XIV) in a 1:1 ratio as ascertained by ^1H NMR. These were separated as the N-acetyl derivatives as described in the following example.

Example 6

Cis- and trans-isomers of 2-benzoyloxymethyl-5-(N,'-acetyl-cytosin-1'-yl)-1,3-oxathiolane



The preceding mixture (XIV) (2.5 g) in 100 ml of dry pyridine containing 0.1 g of 4-dimethylamino-pyridine (DMAP) was treated with acetic anhydride (7 ml) at room temperature and after 16 hours, the mixture was poured onto cold water followed by extraction with CH_2Cl_2 (3 X 150 ml). The extract was washed with water, dried, and evaporated in vacuo. Toluene was added to the residue, then evaporated in vacuo and the residual oil purified by chromatography on silica gel using $\text{EtOAc}:\text{CH}_3\text{OH}$ 99:1 as the eluant to yield 1.35 g of pure trans-(XV) as the fast moving product and 1.20 g of pure cis-(XV) as the slow moving component. These were characterized by ^1H NMR spectroscopy.

trans-(XV): m.p. 158-160°; R_f : 0.48 $\text{EtOAc}:\text{CH}_3\text{OH}$ 95:5

U.V.: (CH_3OH) λ_{max} : 297 nm

^1H NMR δ (ppm in CDCl_3):

9.00 (b, 1H; C_4' -NH-Ac)

8.06 (m, 2H; aromatic)

7.74 (d, 1H; C_6' -H)

7.56 (m, 1H; aromatic)

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7.47 (d, 1H; C₅'-H)
 7.45 (m, 2H; aromatic)
 6.53 (dd, 1H; C₅-H)
 5.89 (dd, 1H; C₂-H)
 4.46 (dd, 2H; C₂-CH₂OCOC₆H₅)
 3.66 (dd, 1H; C₄-H)
 3.32 (dd, 1H; C₄-H)
 2.25 (s, 3H; NH-COCH₃)

Cis-(XV): m.p. 150-152°; R_f: 0.40 EtOAc:MeOH 95:5)

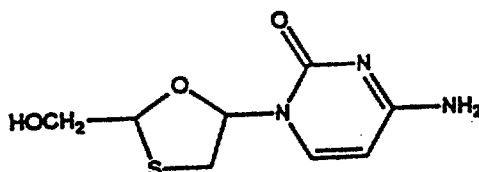
U.V.: (CH₃OH) Lambda max: 297 nm

¹H NMR δ (ppm in CDCl₃):

9.03 (b, 1H; NH-Ac)
 8.21 (d, 1H; C₆'-H)
 8.05 (m, 2H; aromatic)
 7.60 (m, 1H; aromatic)
 7.50 (m, 2H; aromatic)
 7.29 (d, 1H; C₅'-H)
 6.34 (dd, 1H; C₅-H)
 5.52 (dd, 1H; C₂-H)
 4.80 (dd, 2H; C₂-CH₂OCOC₆H₅)
 3.66 (dd, 1H; C₄-H)
 3.24 (dd, 1H; C₄-H)
 2.23 (s, 3H; NH-COCH₃)

Example 7

Cis- and trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolanes



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a) Trans-(III): 375 mg of the preceding trans-(XV) was dissolved in 100 ml of methanolic ammonia at 24° and after stirring for 16 hours, the solvent was removed in vacuo and the residue crystallized with ether. It was recrystallized from ethanol-ether to yield 174 mg of pure product, m.p. >220° (dec). It was characterized by ^1H and ^{13}C NMR.

^1H NMR δ (ppm in DMSO- d_6):

7.57 (d, 1H; $\text{C}_6'\text{-H}$)
 7.18 (d, 2H; $\text{C}_4'\text{-NH}_2$)
 6.30 (dd, 1H, $\text{C}_5\text{-H}$)
 5.68 (d, 1H; $\text{C}_5'\text{-H}$)
 5.48 (t, 1H; $\text{C}_2\text{-H}$)
 5.18 (t, 1H; $\text{C}_2\text{-CH}_2\text{OH}$)
 3.45 (m, 3H; $\text{C}_2\text{-CH}_2\text{OH} + \text{C}_4\text{H}$)
 3.06 (dd, 1H; $\text{C}_4\text{-H}$)

U.V.: (CH_3OH) Lambda max: 270 nm

^{13}C NMR (DMSO- d_6 , Varian XL-300); δ in ppm:

C_2'	C_4'	C_5'	C_6'	C_5	C_4	C_2	CH_2OH
154.71	165.70	93.47	140.95	87.77	36.14	86.80	64.71

b) Cis-(II): treating 375 mg of cis-(XV) by the same preceding procedure led to 165 mg of pure product after recrystallization from ethanol-ether, m.p. 171-173°. It was characterized by ^1H and ^{13}C NMR.

^1H NMR: δ (ppm in DMSO- d_6):

7.80 (d, 1H; $\text{C}_6'\text{-H}$)
 7.20 (d, 2H; $\text{C}_4'\text{-NH}_2$)
 6.18 (t, 1H; $\text{C}_5\text{-H}$)
 5.70 (d, 1H; $\text{C}_5'\text{-H}$)
 5.14 (t, 1H; $\text{C}_2\text{-CH}_2\text{OH}$)
 3.71 (m, 2H; $\text{C}_2\text{-CH}_2\text{OH}$)
 3.40 (dd, 1H; $\text{C}_4\text{-H}$)
 2.99 (dd, 1H; $\text{C}_4\text{-H}$)

U.V.: (CH_3OH) Lambda max: 270 nm

^{13}C NMR δ (ppm in DMSO- d_6)

C_2'	C_4'	C_5'	C_6'	C_5	C_4	C_2	CH_2OH
154.63	165.59	93.86	140.91	86.47	36.22	85.75	62.79

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Example 8Tablet Formulations

A. The following formulation is prepared by wet granulation of the ingredients with a solution of povidone in water, drying and screening, followed by addition of magnesium stearate and compression.

	<u>mg/tablet</u>
(a) Active ingredient	250
(b) Lactose B.P.	210
(c) Povidone B.P.	15
(d) Sodium Starch Glycolate	20
(e) Magnesium Stearate	5
	500

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B. The following formulation is prepared by direct compression; the lactose is of the direct compression type.

	<u>mg/tablet</u>
Active ingredient	250
Lactose	145
Avicel	100
Magnesium Stearate	5
	500

C. (Controlled Release Formulation) The formulation is prepared by wet granulation of the ingredients (below) with a solution of povidone in water, drying and screening followed by the addition of magnesium stearate and compression.

	<u>mg/tablet</u>
(a) Active ingredient	500
(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c) Lactose B.P.	53
(d) Povidone B.P.	28
(e) Magnesium Stearate	7
	700

Example 9

Capsule Formulation

A capsule formulation is prepared by admixing the ingredients below and filling into a two-part hard gelatin capsule.

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	<u>mg/capsule</u>
Active ingredient	125
Lactose	72.5
Avicel	50
Magnesium Stearate	2.5
	250

Example 10Injectable Formulation

Active ingredient 0.200 g

Sodium hydroxide solution, 0.1M q.s. to a pH of about 11.

Sterile water q.s. to 10 ml.

The active ingredient is suspended in some of the water (which may be warmed) and the pH adjusted to about 11 with a solution of sodium hydroxide. The batch is then made up to volume and filtered through a sterilizing grade membrane filter into a sterile 10 ml glass vial and sealed with sterile closures and overseas.

Example 11suppository

	<u>mg/suppository</u>
Active ingredient	250
Hard Fat, B.P.	1770
	2020

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One-fifth of the hard fat is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 μ m sieve and added to the molten base with mixing, using a high shear stirrer, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining hard fat is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 μ m stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.02 g of the mixture is filled into suitable, 2 ml plastic molds. The suppositories are allowed to cool to room temperature.

Example 12

Antiviral Activity

In vitro testing was conducted on the compound of this invention and AZT to determine their inhibitory properties. The results are shown in Tables 1 and 2. The concentrations reported are μ g/ml in the incubation media which affect the susceptibility of a continuous line of T-cells developed at the Lady Davis Institute for Medical Research (Montreal) by Dr. Mark A. Wainberg toward infection by HIV-1 following a protocol similar to that of H. Mitsuya and S. Broder, "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2'3'-dideoxy-

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nucleosides", Proc. Natl. Acad. Sci. USA, 83, pp. 1911-15 (1986). Protection of the cell line from infection was monitored by staining with monoclonal antibodies against viral proteins in the standard manner (Table 1). In all experiments, comparisons were made with the drug AZT as the control. In order to confirm the results, the drug effects were monitored by measuring reverse transcriptase (RT) activity in the U-937 line of human monocytic cells as assayed in the usual manner with tritiated thymidine triphosphate (TTP) (Table 2). Finally, the drug effects on cell viability as measured by the well-known cytolytic effects of HIV-1 on the MT-4 cell line was evaluated in the accepted manner (Table 1).

Toxicity

No toxic effects were observed in the above tests.

Table 1

Inhibition of HIV-1 production in MT-4 cells

a) Viable cell counts (6 days in culture) using 2 µg/ml of compound

Compound	Cell Viability
no drug	6.47
AZT	88.6
<u>cis-II</u>	87.4

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b) P-24 immunofluorescence

Time in Culture		% Immunofluorescent Cells	
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-II
3	5.9	1.0	1.0
6	99	1.0	7.6

c) Reverse transcriptase assay

Time in Culture		RT Activity (CPM X 1000)/ml	
(Days)	No Drug	2 μ g/ml AZT	2 μ g/ml cis-II
3	36.43	1.564	2.381
6	339.0	1.748	2.301

Table 2

Inhibition of HIV-1 production in H-9 cells

Reverse transcriptase assay

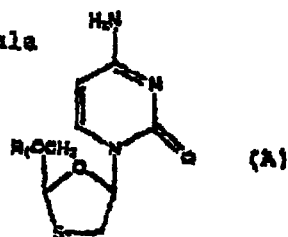
Time in Culture		RT Activity (CPM X 1000)/ml	
(Days)	No Drug	2 μ /ml AZT	2 μ g/ml cis-II
5	9.117	3.346	3.077
8	438.5	3.414	5.853
11	2550	2.918	3.560
14	2002	8.320	2.872
17	584.5	2.997	2.399
21	365.2	3.111	2.907
25	436.4	15.88	4.020
29	92.38	32.08	3.756
33	111.1	612.2	3.803
37	32.28	878.2	4.193
41	384.4	994.0	4.515
45	33.64	32.91	3.441

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CLAIMS

1. A cis-1,3-oxathiolane of formula



wherein R_1 represents hydrogen, a C_{1-16} alkanoyl group, a benzoyl group or a benzoyl group substituted by at least one halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or trifluoromethyl group, or a pharmaceutically acceptable salt thereof in the form of a single optical isomer or a mixture of optical isomers.

2. A compound according to claim 1 wherein the compound is cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane or a pharmaceutically acceptable salt thereof.
3. A compound according to claim 2 in the form of a racemic mixture.
4. A compound according to claim 2 substantially in the form of a single enantiomer.
5. A compound according to any of claims 2 to 4 wherein the compound is cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane.
6. A compound according to any preceding claim for use in the manufacture of a medicament for the treatment of a viral infection.



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7. A pharmaceutical formulation comprising a compound according to any of Claims 2 to 5 together with a pharmaceutically acceptable carrier therefor.
8. A pharmaceutical formulation according to Claim 7 additionally comprising a further therapeutic agent.
9. A process for the preparation of a compound as claimed in any of Claims 2 to 5 which comprises:
 - (a) reaction of a compound of formula (VIII)



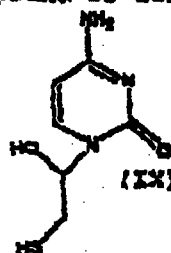
wherein R_1 is hydrogen or a hydroxyl protecting group and L is a displaceable atom or group with cytosine;

- (b) base interconversion of compound of formula (I')



wherein R_2 is a purine or pyrimidine base other than cytosine into sia-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;

- (c) reaction of a compound of formula (IX)

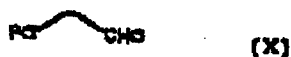


with a compound of formula (X)



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wherein P is a protecting group; or

(d) conversion of a compound of formula (XII)



(XII)

to *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane

and if necessary or desired subjecting the compound resulting from any of steps (a) to (d) to one or two further reactions comprising:

- (i) removing any protecting groups;
- (ii) converting *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane or a salt thereof into a pharmaceutically acceptable salt thereof.

- 10. A process according to Claim 9 wherein the obtained compound is in the form of a racemic mixture.
- 11. A process according to claim 9 wherein the obtained compound is substantially in the form of a single enantiomer.
- 12. A process according to any one of claims 9 to 11 wherein in step (a) the group L is selected from a group consisting of alkoxy carbonyl, iodine, bromine, chlorine or -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl



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group or R is a substituted or unsubstituted aliphatic or aromatic acyl group.

13. A process according to any one of Claims 9 to 12 wherein in step (a) the compound of formula (VIII) is reacted with a silylated cytosine in a compatible solvent in the presence of a Lewis acid or trimethylsilyltriflate.
14. A method for the preparation of a pharmaceutical formulation comprising admixing a compound as claimed in any of Claims 2 to 5 with a pharmaceutically acceptable carrier therefor.



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