Description

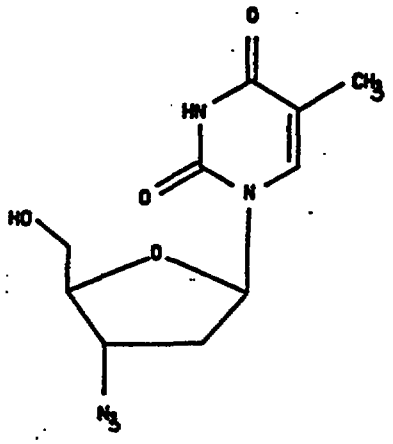
FIELD OF THE INVENTION

The present invention relates to novel 2-substituted-4-substituted-1,3 dioxolanes which are useful as antiviral agents.

PRIOR ART

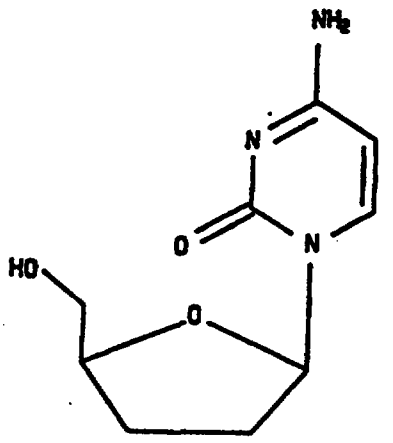
Retroviral infections are a serious cause of disease and among others the acquired immunodeficiency syndrome (AIDS) is an immunosuppressive disease associated with life-threatening opportunistic infections and high susceptibility to unusual neoplasms (Kaposi sarcoma for instance). The human immunodeficiency virus (HIV) has been recognized as the etiologic agent of AIDS and compounds having an inhibitory effect against HIV multiplication have been actively sought.

One product which has been proposed for the treatment of AIDS is the 3'-azido-2',3'-dideoxythymidine commonly referred to as AZT. The activity of this compound was disclosed by MITSUYA et al. in Proc. Natl. Acad. Sci., U.S.A. 1985, 82, 7096. The compound has the structure:

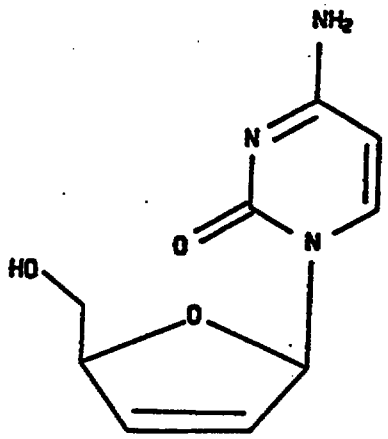


This compound is useful in protecting AIDS carriers against the cytopathogenic effect of the human immunodeficiency virus (HIV) which is the etiologic agent of AIDS.

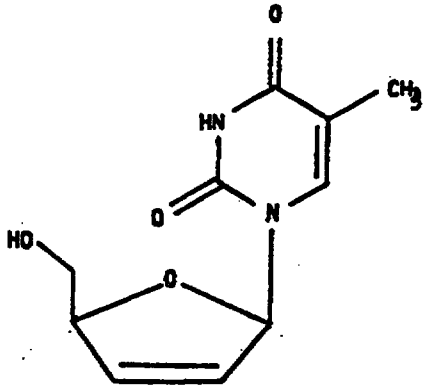
Mitsuya et al. have also disclosed in Proc. Natl. Acad. Sci., U.S.A. 1986, 86, 1911 a group of 2',3'-dideoxynucleosides which appear to possess potent protective activity against HIV-induced cytopathogenicity. A typical such compound is the 2',3'-dideoxycytidine of the formula:



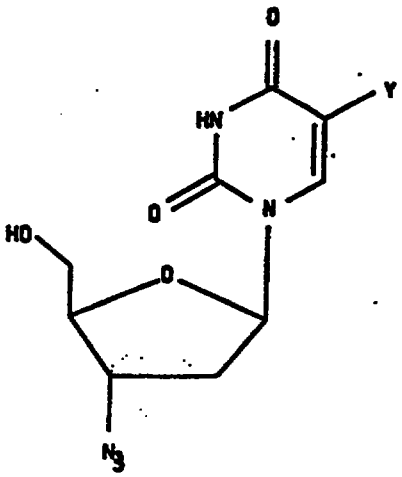
Balzarini et al. in Biochem. Biophys. Res. Comm. 1986, 140, 735 disclose that the unsaturated analog of the 2',3'-dideoxycytidine also possesses antiretroviral effectiveness. This unsaturated analog has the formula:



Baba et al. in Biochem. Biophys. Res. Comm. 1987, 142, 128 have described the 2',3'-unsaturatedanalog of the 2',3'-dideoxythymidine which is a potent selective inhibitor of HIV replication and which corresponds to the formula:

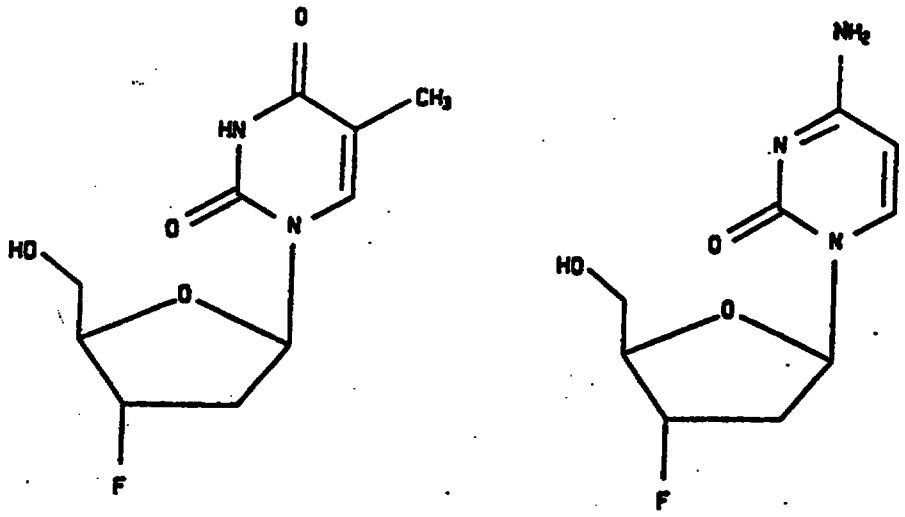


Analogues of the 3'-azido-2',3'-dideoxythymidine are the 3'-azido-2',3'-dideoxyuridine of the formula:



where y is bromine or iodine. These have been disclosed as having an inhibitory activity against Moloney murine leukemia by T.S. Lin et al., in J. Med. Chem. 1987, 30, 440.

Finally, the 3'fluoro analogues of the 2',3'-dideoxycytidine and of the 2',3'-dideoxythymidine have been disclosed by Herdewijn et al. in J. Med. Chem. 1987, 30, 1270 as having potent antiretroviral activity (anti-HIV). These analogues correspond to the formulae:



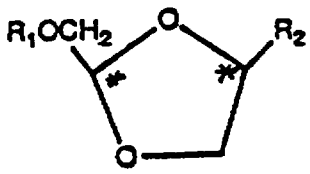
The most potent anti-HIV compounds thus far reported are 2',3'-dideoxynucleosides, more particularly, 2',3'-dideoxycytidine (ddCyd) and 3'-azido-2',3'-dideoxythymidine (AzddThd or AZT). These compounds are also active against other kinds of retroviruses (such as the Moloney murine leukemia virus). It is because of the increasing incidence and the life-threatening characteristics of AIDS that 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.

SUMMARY OF THE INVENTION

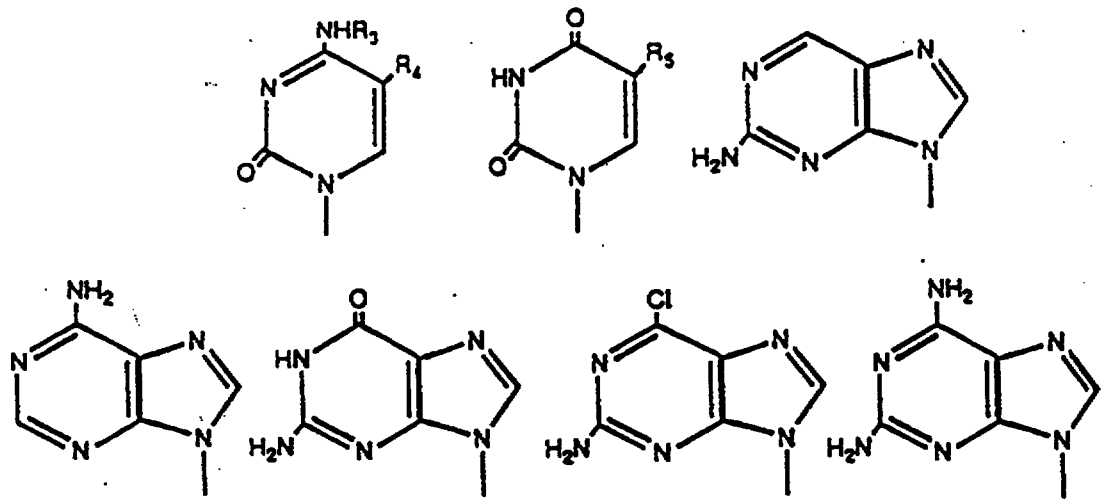
In accordance with the present invention there are provided novel 2-substituted-4-substituted-1,3-dioxolanes which are particularly useful as antiviral agents.

More specifically, the novel 2-substituted- 4-substituted-1,3-dioxolane derivatives of the present invention correspond to the following formula (L):



(L)

wherein R_1 is selected from the group consisting of hydrogen, an acyl group having 1 to 16 carbon atoms, benzoyl and a benzoyl substituted in any position by at least one halogen, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, nitro and trifluromethyl groups; R_2 is a heterocyclic radical selected from:



wherein R_3 and R_4 are independently selected from the group consisting of hydrogen and C_1 - C_3 alkyl and R_5 is selected from the group consisting of C_1 - C_3 alkyl and halogen.

Also within the scope of the present invention are the 2,4-disubstituted-1,3-dioxolanes of Formula (L) wherein R_2 could be any nucleoside base analog, those base analogs being known by those of skill in the art of nucleoside chemistry.

There are two asymmetric carbons (asterisks) in the disubstituted 1,3-dioxolane molecule which provide for two racemic forms (±) and therefore four optical isomers. These racemates differ in the relative configurations of the 2- and 4-substituents which can either assume the cis- and trans-configurations. The use of a graphic representation of the 2,4-disubstituted-1,3-dioxolanes of Formula (L) is meant to include the dl racemic mixture as well as the separate d and l isomers thereof.

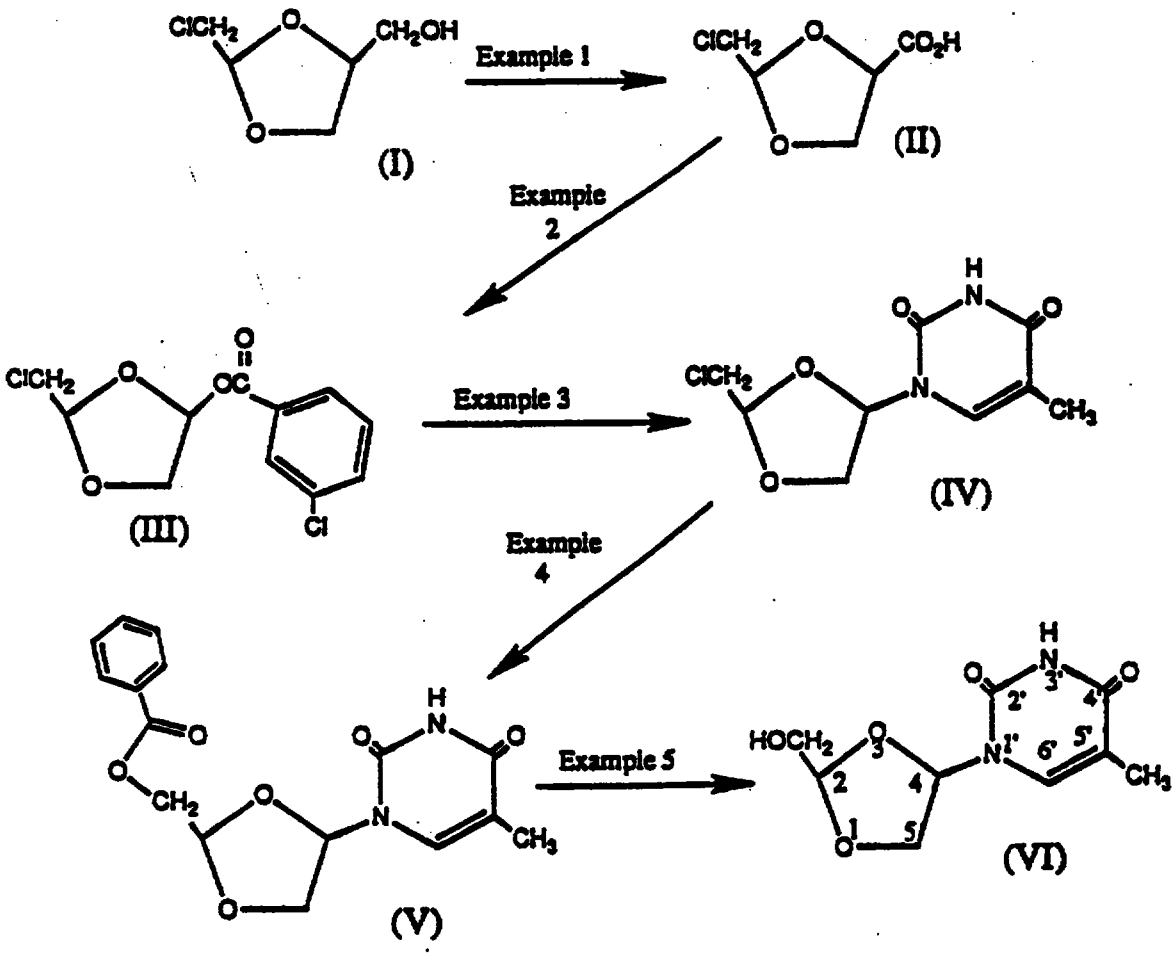
Also in accordance with the present invention, there is provided a pharmaceutical composition for administration to persons infected with the AIDS virus or other infectious agent which comprises a therapeutically effective amount of the 2,4-disubstituted dioxolane of Formula (L) or pharmaceutically acceptable salt in association with a pharmaceutically acceptable excipient. The amount of active ingredient which is contained in a single dosage form will vary depending upon the host treated as well as the frequency and the mode of administration.

Also within the scope of the present invention is a method for treating AIDS-infected persons which comprises administering to said persons a therapeutically effective amount of 2,4-disubstituted-1,3-dioxolane of Formula (L). Also within the scope of the present invention is any combination of a 2,4-disubstituted-1,3-dioxolane of Formula (L) with another drug where such combination is therapeutically more advantageous than either drug given above.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention are prepared starting from glycerol and 2-halo- (or an equivalent leaving group such as aryl- or alkyl-sulfonyloxy) acetaldehyde preferably in the form of an acetal derivative according to the reported procedure of E.G. Hallonquist and H. Hibbert, Can. J. Res. 1933, 7, 129. For the purpose of this disclosure, the term acyl is an alkanoyl radical of 2 to 16 carbon atoms, e.g., acetyl, propionyl, isobutyryl, myristoyl, etc. The compounds of the instant invention are prepared by a total synthesis comprising a few steps. The synthesis is practical and is commercially feasible. The process for preparing one specific compound of the present invention is outlined in the following Flowsheet 1:

Flowsheet 1



The various steps involved in the synthesis illustrated in Flowsheet 1 may be briefly described as follows:

Step 1 The primary alcohol function of the starting dioxolane I is treated with an oxidizing reagent such as chromic acid (which may be complexed with pyridine) in a compatible organic solvent to give the corresponding dioxolane carboxylic acid II.

Step 2 The acid II is converted to a mixed anhydride using an alkyl chloroformate and submitted to a Bayer-Villiger oxidation with an organic peracid such as m-chloroperbenzoic acid to yield the corresponding aroyloxydioxolane III.

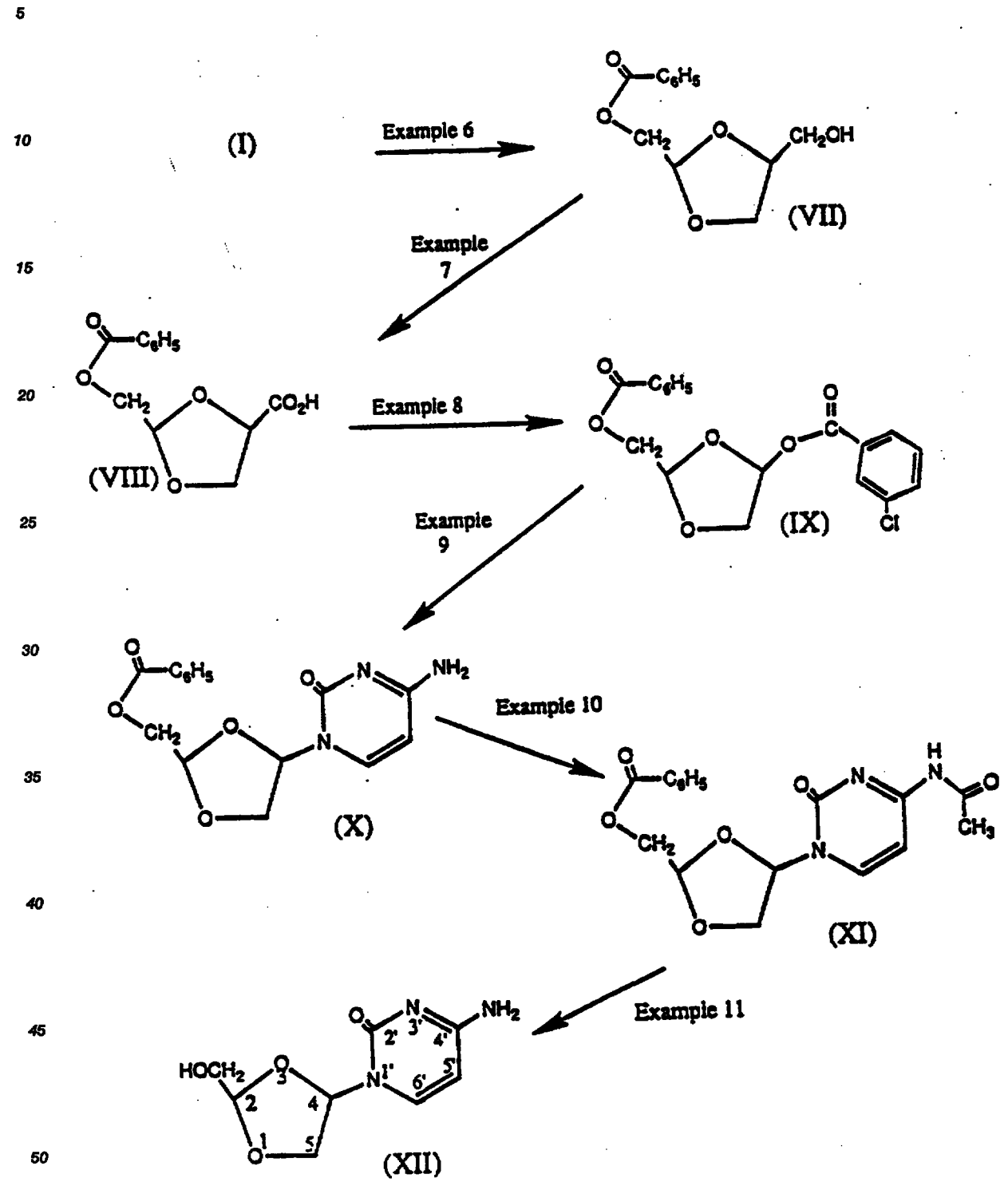
Step 3 Intermediate III is then reacted with thymine previously silylated with hexamethyldisilazane in a compatible solvent and the reaction catalyzed by a Lewis acid or preferably by trimethylsilyltriflate to give the thymin-1'-yl dioxolane IV.

Step 4 The chlorine atom of IV is displaced by reaction with a benzoic acid salt in a compatible solvent such as dimethylformamide to give intermediate V.

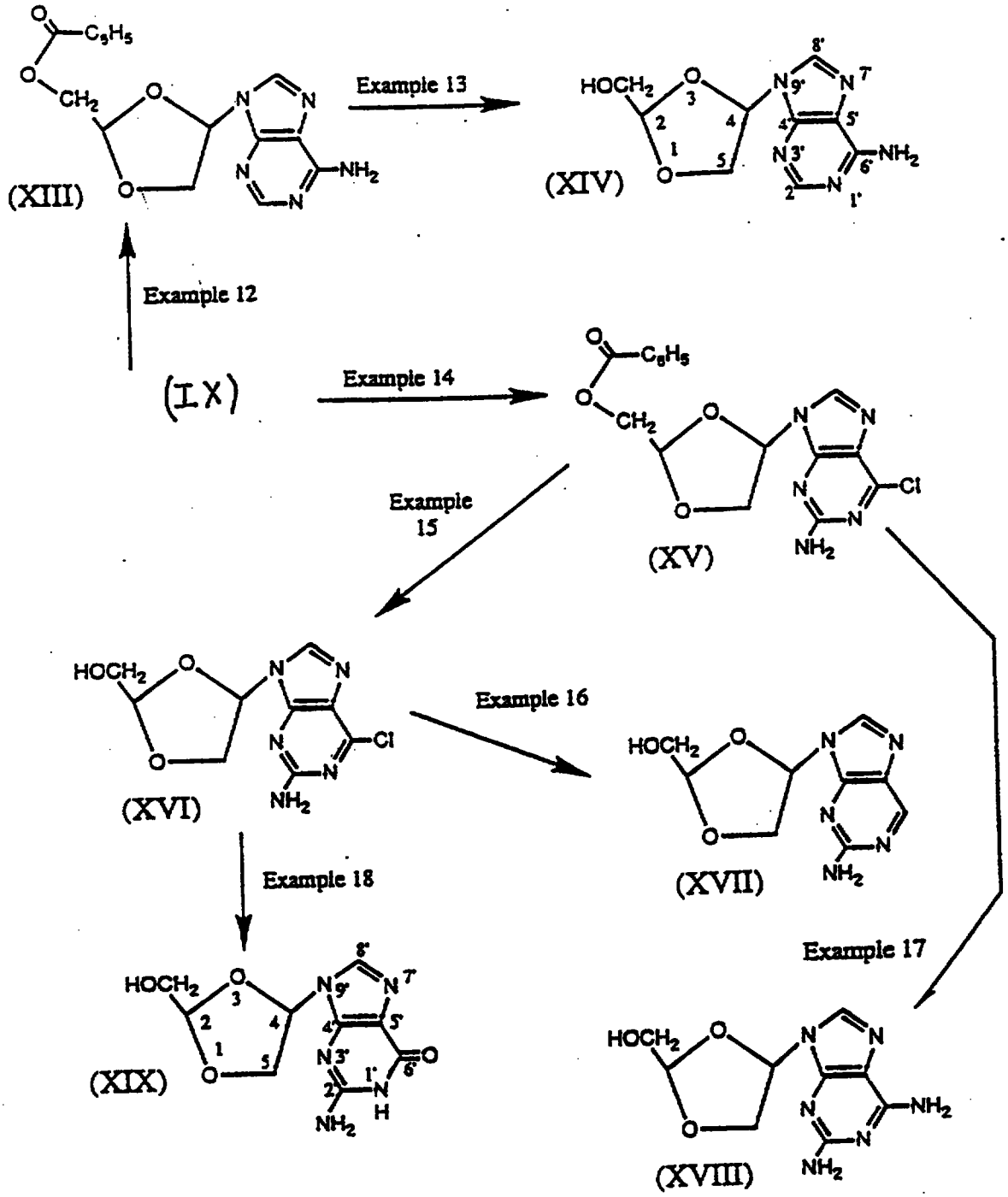
Step 5 The benzoate ester function is then hydrolyzed under basic conditions to yield the desired end-product VI.

An alternate process for preparing further specific compounds of the present invention is illustrated in Flowsheet II:

Flowsheet II



Flowsheet II (Continued)



The various steps involved in the synthesis illustrated in Flowsheet II may be briefly described as follows:

Step 1 The chlorine atom of starting dioxolane I is displaced by a benzoic (or acetic) acid salt in a solvent such a dimethylformamide to yield the diol monoester VII.

Step 2 The hydroxymethyl group of VII is oxidized with a suitable reagent such as chromic acid (which may be complexed with pyridine) in a compatible organic solvent to give the dioxolane carboxylic acid VIII.

Step 3 The acid VIII is then submitted to Bayer-Villiger oxidation by the procedure outlined in Step 2 (Flowsheet 1) above to give the corresponding aroyloxy-dioxolane IX.

Step 4 The key intermediate IX is reacted with cytosine previously silylated under the reaction conditions outlined in Step 3 (Flowsheet 1) to give the cytosin-1'-yl dioxolane X.

Step 5 The amine function of X is acylated with acetic anhydride in pyridine to give XI which provides for easier separation of isomers.

Step 6 The ester and acetyl functions of XI are hydrolyzed under basic conditions to yield the desired end-product XII.

Step 7 (IX to XIII) Key intermediate IX is reacted with adenine by the procedure outlined above in Step 3 (Flowsheet 1) to give XIII.

Step 8 (XIII to XIV) The ester function of XIII is hydrolyzed under basic conditions to yield the desired end-product XIV.

Step 9 (IX to XV) Intermediate IX is reacted with 2-amino-6-chloropurine under the conditions outlined in Step 3 (Flowsheet 1) to give compound XV.

Step 10 (XV to XVI) The preceding intermediate is hydrolyzed under basic conditions to yield the desired end-product XVI.

Step 11 (XVI to XVII) The chlorine atom of XVI is removed by catalytic hydrogenation over Pd/C to give the 2'-amino-purin-9'-yl dioxolane XVII.

Step 12 The above intermediate XV is reacted with excess ammonia under pressure whereupon the 2',6'-diamino-purin-9'-yl dioxolane XVIII is generated.

Step 13 Compound XVI is submitted to boiling sodium hydroxide to give the desired end-product guanin-9'-yl dioxolane XIX.

ANTIVIRAL ACTIVITY

All of the compounds of the preferred embodiments are novel and some are valuable for their properties as non-toxic inhibitors of the primary replication of HIV-1 in previously uninfected T-lymphocytes over a prolonged period of time.

In particular, the compounds having the formula XII possess desirable properties, i.e., antagonism of HIV infectivity towards T-lymphocytes in the absence of cytotoxicity.

In vitro testing was conducted on the compounds to determine their inhibitory properties. Table 1 represents the results of a typical experiment. The figures reported are the micromolar concentrations in the incubation media which effect the ability of T-lymphocyte H-9 cells to be infected by HIV-1 following the protocol of H. Mitsuya and S. Broder, Proc. Natl. Acad. Sci. U.S.A. 1986, 83, 1911-1915; the level of infection being measured by the level of reverse transcriptase activity (RTA) as assayed in the usual manner with tritiated thymidine triphosphate (TTP). As a control drug, 2',3'-dideoxy-3'-azido-thymidine (AZT) was used and the RTA measured in the incubation medium after 8, 12 and 26 days of exposure to the inhibitor. The values in Table 1 reflect the total number of virus particles in the incubation medium.

Table 1

Example of the effects of prototype compounds trans-XII, cis-XIV and AZT on ability of H-9 cells to be infected by HIV-1.

Expt.#	Inhibitor	Conc.-	RTA activity (cpm) after:		
			8 days	12 days	26 days
1	none	-	198,612	327,570	239,019
	trans-XII	10µM	4,608	83,462	312,478
	trans-XII	50µM	1,319	758	1,732
	AZT	20µM	633	419	821
2	none	-	64,769	119,580	227,471
	cis-XIV	20µM	2,618	130,563	210,583
	cis-XIV	50µM	1,132	39,752	231,609
	AZT	20µM	587	1,316	679

It is apparent from the table that prototype compound trans-XII exhibits potent inhibitory activity. Other analogues displayed variable degrees of antiviral activity. Accordingly, as it is the rule for certain analogues of nucleosides, trans-XII and selected analogues are expected to demonstrate in vivo activity as inhibitors of

retroviruses. Such compounds may also be used in combination with other antiviral agents at reduced doses, thus lowering their toxicity potential.

TOXICITY

In contrast to the results obtained with AZT or with other di-deoxynucleosides analogues, in vitro toxicity experiments showed that the compound trans-XII is non toxic even at concentration as high as 200µM. In spite of the AZT activity, its serious bone marrow toxicity limits its therapeutic usefulness. It is then highly desirable to provide with new active antiviral agents which would be devoided of toxic side effects.

EXAMPLES

Example 1. Preparation of 2-chloromethyl-1,3-dioxolane-4-carboxylic acid (II).

Starting material I (40 g; prepared according to E.G. Hallonquist and H. Hibbert, Can. Res. J. 1933, 7, 129) was treated with pyridinium dichromate (PDC; 345 g) in dimethyl formamide (DMF; 690ml) at 0° according to the procedure of E.J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399 and product II obtained as a crude mixture of cis- and trans-isomers (20 g) was identified by its ^{1}H NMR spectrum [200 MHz, $CDCl_3$; tetramethyl silane (TMS) as internal reference]
δ(ppm): 3.6-3.8 (m,2H;CH_2Cl);
4.1-4.5 (m,2H;C_5H_2);
4.72-4.797 (gg,1H;C_4-H);
5.29-5.46 (tt,1H;C_2-H).
The product was used as such in the next step.

Example 2. Preparation of 2-chloromethyl-4-m.chlorobenzoyloxy-1,3-dioxolane (III).

The preceding product II (5.26 g) was treated in CH_2Cl_2 at -20° with 3.6 ml of ethyl chloroformate in the presence of 4.5 mg of triethylamine. To the solution was added 8.85 g of m.chloroperbenzoic acid at room temperature according to the procedure of D.H.R. Barton, I.H. Coates and P.G. Sammes, J. Chem. Soc., Perkin 1, 1973, 599 to give III as a mixture of cis- and trans-isomers. These were separated and purified by flash chromatography on silica gel using a mixture of hexane and ethyl acetate as the eluent. The isomers were identified by their ^{1}H NMR spectra (recorded as in example 1): trans-isomer of III: δ-(ppm):
3.66 (q,2H;CH_2-Cl);
4.36 (qq,2H;C_5-H_2);
5.57 (t,1H;C_2-H);
6.7 (q,1H;C_4-H);
7.39-8.0 (m,4H;aromatic H);
cis-isomer of III: δ(ppm):
3.66 (q,2H;CH_2-Cl);
4.24 (qq,2H;C_5-H_2);
5.43 (t,1H;C_2-H);
6.63 (q,1H;C_4-H);
7.42-8.04 (m,4H;aromatic H).

Example 3. Preparation of 2-chloromethyl-4-(thymin-1'-yl)-1,3-dioxolane (IV).

Reaction of the preceding compound with thymine was carried out according to the procedure of D.S. Wise and L.B. Townsend, in Nucleic Acid Chemistry, Eds. L.B. Townsend and R.S. Tipson, John Wiley & Sons, Inc., New York, 1978, Part 1, pp. 413-419. The product was a mixture of cis- and trans-isomers of IV (37.3 mg from 131 mg of III) which had the following ^{1}H NMR characteristics (obtained as in example 1):
δ(ppm): 1.93 (d,3H;5'-CH_3);
3.64 and 3.85 (dd,2H;CH_2Cl);
4.17-4.46 (m,2H;C_5-H_2);
5.26 and 5.72 (tt,1H;C_2-H);
6.6 and 6.66 (qq,1H;C_4-H);
7.40 and 7.49 (dd,1H;C_6-H);

U.V.: (CH_3OH)λmax.264 nm.

Example 4. Preparation of 2-acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane (V).

The preceding compound IV (35 mg) was reacted with anhydrous potassium acetate (70 mg) in boiling DMF (3 ml) for 4h to give after conventional workup a cis- and trans-mixture of V (25 mg). These isomers were purified and separated by flash chromatography on silica using a mixture of hexane and ethyl acetate as the eluent. Their ^1H NMR spectra were as follows:

trans-isomer of V: δ(ppm):

1.94 (d,3H;C_5-CH_3);
2.12 (s,3H;CH_3CO_2-);
4.05-4.43 (m,4H;C_2-CH_2-O_2CCH_3 and C_5-H_2);
5.65 (t,1H;C_2-H);
6.31 (q,1H;C_4-H);
7.14 (d,1H;C_6-H);
8.18 (m,1H;N_3-H).

cis-isomer of V: δ(ppm):

1.97 (d,3H;C_5-CH_3);
2.14 (s,3H;CH_3CO-O);
4.13-4.49 (m,4H;2-CH_2OCOCH_3 and C_5H_2);
5.19 (t,1H;C_2-H);
6.40 (q,1H;C_4H);
7.43 (d,1H;C_6-H);
8.12 (m,1H;N_3-H).

U.V.: (CH_3OH) λmax.264 nm.

Example 5. Preparation of 2-hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane (VI).

The preceding trans- and cis-isomers of V (10 mg) were respectively treated with a catalytic amount of potassium carbonate in methanol (5 ml) at room temperature for 5-6 h and the mixture worked up in the usual manner and the respective products purified by flash chromatography on silica gel using a mixture of ethyl acetate and methanol as the eluent The ^1H NMR spectrum of the pure trans-isomer of VI was as follows (in CD_3COCD_3 as solvent);

trans-VI: δ(ppm):

1.87 (d,3H;C_5-CH_3);
3.61 (q,2H;C_2-CH_2OH);
4.30 (qq,2H;C_5-H_2);
5.56 (t,1H;C_2-H);
6.31 (q,1H;C_4-H);
7.41 (d,1H;C_6-H).

U.V.: (CH_3OH) λmax.265 nm.

cis-isomer of VI (in CD_3COCD_3): δ(ppm):

1.82 (d,3H;C_5-CH_3);
3.82 (q,2H;C_2CH_2OH);
4.24 (qq,2H;C_5-H_2);
5.02 (t,1H;C_2-H);
6.34 (q,1H;C_4-H);
7.81 (d,1H;C_6-H).

U.V.: (CH_3OH) λmax.264nm.

Example 6. Preparation of 2-benzoyloxymethyl-4-hydroxymethyl-1,3-dioxolane (VII).

Starting material I (41.6 g) was treated with potassium benzoate (65.56 g) in boiling dimethyl formamide containing 100 mg of 18-crown-6 for 24 h after which time the mixture was worked up in the usual manner and the product (51.02 g) characterized by its ^1H NMR spectrum ($CDCl_3$;TMS):

δ(ppm): 3.5-4.8 (m,H;C_5-H_2;C_2-$CH_2OCOC_6H_5$,C_4-CH_2OH and C_2-H);
5.05 and 5.16 (tt,1H;C_4-H);
7.27-8.10 (m,5H; aromatic H).

Similar results were obtained using potassium acetate instead of potassium benzoate.

Example 7. Preparation of 2-benzoyloxymethyl-1,3-dioxolane-4-carboxylic acid (VIII).

The preceding compound VII (51.02 g) was treated at 0° with pyridinium dichromate (282.5 g) in dimethyl formamide (565 ml) and the mixture worked up in the usual manner to give 35 g of crude VIII which was used as such in the next example.

Example 8.

A 10 g portion of crude VIII was treated with 6.03 ml of ethyl chloroformate in the presence of 8.6 ml of triethylamine followed by the addition of 16.81 g of m.chloroperbenzoic acid exactly as described in example 2 for the case of the preparation of intermediate III. The isomers of product IX thus obtained were purified by flash chromatography on silica gel using a mixture of hexane and ethyl acetate as the eluent. They were characterized by their ^{1}H NMR spectra ($CDCl_3$):

trans-isomer of IX: δ(ppm):

4.29 (qq,2H;C_5-H_2);
4.49 (d,2H;C_2-$CH_2OCOC_6H_5$);
5.66 (t,1H;C_2-H);
6.70 (q,1H;C_4-H);
7.27-8.10 (m,9H; aromatic).

cis-isomer of IX: δ(ppm):

4.27 (qq,2H;C_5-H_2);
4.51 (d,2H;C_2-$CHOCOC_6H_5$);
5.51 (t,1H;C_2-H);
6.59 (d,1H;C_4-H);
7.26-8.09 (m,9H; aromatic).

Example 9. Preparation of 2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane (X).

Following the procedure described by T. Ueda and S.I. Watanabe, Chem. Pharm. Bull. (Japan), 1985, 33, 3689-3695 and by G. Gosselin, M.C. Bergogne, J. DeRudder, E. DeClercq and J.L. Imbach, J. Med. Chem., 1987, 30, 982-991, cytosine (139 mg) and either isomer of the proceding compound IX (363 mg) yielded a mixture of cis- and trans-isomers (390 mg) X which were used as such in the following step.

Example 10.

Treatment of cis- and trans-X with excess acetic anhydride in pyridine at room temperature yielded after work up in the conventional manner, a mixture of the cis- and trans-isomers of XI which were separated and purified by flash chromatography on silica gel using a mixture of hexane and ethyl acetate as the eluent. They were characterized by their ^{1}H NMR spectra ($CDCl_3$):

trans-isomer of XI: δ(ppm):

2.15 (s,3H;C_4-NH-$COCH_3$);
4.16 and 4.46 (m,4H;C_5-H_2 and C_2-CH_2OCOC_6-H_5);
5.96 (t,1H;C_2-H);
6.24 (q,1H;C_4-H);
7.55-8.09 (m,5H;aromatic);
8.15 (d,1H;C_6-H).

cis-isomer of XI: δ(ppm):

2.15 (s,3H;C_4-NH-$COCH_3$);
4.26 and 4.56 (m,4H;C_5-H_2 and C_2-CH_2OCOC_6-H_5);
5.35 (t,1H;C_4-H);
6.25 (q,1H;C_4-H);
7.18 (d,1H;C_5-H);
7.58-8.04 (m,5H; aromatic);
8.17 (d,1H;C_6-H).

Example 11. Preparation of cis- and trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane (XII).

Each of the preceding isomers of XI (25 mg) was treated with potassium carbonate (20 mg) in methanol at room temperature for several hours and the mixtures worked in the usual manner to yield each isomer of XII which were purified by chromatography on silica gel using a mixture of ethyl acetate and methanol as eluent. They were crystallized from methanol and characterized by their respective ^{1}H NMR spectra (D_3CCOCD_3):

trans-isomer of XII: δ(ppm):
3.62 (q,2H;C_2-C$\underline{H}_2$OH);
m.p.179-180° 4.21 (qq,2H;C_5-$\underline{H}_2$);
5.50 (t,1H;C_2-$\underline{H}$);
5.93 (d,1H;C_5-$\underline{H}$,J=7.5Hz);
6.18 (q,1H;C_4-$\underline{H}$);
7.66 (d,1H;C_6-$\underline{H}$,J=7.5Hz).
U.V.: (CH_3OH) λmax.271 nm.

cis-isomer of XII: δ(ppm):
3.82 and 4.15 (m,4H;C_5-$\underline{H}_2$ and C_2-C$\underline{H}_2$OH);
m:p.173-174° 5.04 (t,1H;C_2-$\underline{H}$);
5.83 (d,1H;C_5-$\underline{H}$);
6.23 (q,1H;C_4-$\underline{H}$);
8.05 (d,1H;C_6-$\underline{H}$).
U.V.: (CH_3OH) λmax.270nm.

Example 12. Preparation of 2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane (XIII).

Following the same procedure as in example 9, adenosine (135 mg) was coupled with either isomer of intermediate IX (545 mg) in dimethylformamide at 120° in the presence of trimethylsilyl triflate (0.45 ml) and the mixture worked up in the usual manner to yield a mixture of cis- and trans-isomers of XIII (540 mg) which were purified and separated by chromatography on silica gel using a mixture of hexane and ethyl acetate as the eluent. They were characterized by their respective ^{1}H NMR spectra ($CDCl_3$):

trans-isomer of XIII: δ(ppm):
4.5 and 4.59 (m,4H;C_5-$\underline{H}_2$ and C_2-C$\underline{H}_2$OCOC_6H_5);
6.00 (t,1H;C_2-$\underline{H}$);
6.65 (q,1H;C_4-$\underline{H}$);
6.75 (m,2H;C_6-$\underline{H}_2$);
7.68-8.21 (m,5H;aromatic);
8.36 (s,1H;C_2-$\underline{H}$);
8.37 (s,1H;C_8-$\underline{H}$).

cis-isomer of XIII: δ(ppm):
4.62 (d,2H;C_2-C$\underline{H}_2$OCOC_6H_5);
4.65 (qq,2H;C_5-$\underline{H}_2$);
5.52 (t,1H;C_2-$\underline{H}$);
6.59 (q,1H;C_4-$\underline{H}$);
6.85 (m,2H;C_6-N$\underline{H}_2$);
6.96-7.71 (m,5H;aromatic);
7.66 (d,2H;C_2-$\underline{H}$ and C_8-$\underline{H}$).

Example 13. Preparation of 2-hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane (XIV).

Each isomer of the preceding compound XIII was treated with potassium carbonate in methanol at room temperature by the same procedure described in example 5 and each product purified by column chromatography on silica gel using a mixture of ethyl acetate and methanol as the eluent. The isomers were further purified by crystallization from methanol and characterized by their ^{1}H NMR spectra (CD_3SOCD_3):

trans-isomer of XIV: δ(ppm):
3.50 (d,2H;C_2-C$\underline{H}_2$OH);
4.70 (m,2H;C_5-$\underline{H}_2$);
5.52 (t,1H;C_2-$\underline{H}$);
6.44 (q,1H;C_4-$\underline{H}$);

8.18 (s,1H;C_2-H);
8.31 (s,1H;C_8-H).
U.V.: (CH_3OH) λmax.269 nm.
cis-isomer of XIV: δ(ppm):
4.63 (d,2H;C_2-CH_2OH);
4.29 (qq,2H;C_5-H_2);
5.08 (t,1H;C_2-H);
6.43 (q,1H;C_4-H);
8.18 (s,1H;C_2-H);
8.36 (s,1H;C_8-H).
U.V.: (CH_3OH) λmax.269 nm.

Example 14. Preparation of 2-benzoyloxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane (XV).

A solution of 2-amino-6-chloropurine (600 mg; 3.54 mmol) in 20 ml of hexamethyldisilazane (HMDS) containing 0.5 ml of trimethylsilyl chloride (TMS-Cl) was heated under reflux for 3 h after which time the mixture was evaporated to dryness in vacuo. The residue was dissolved in 75 ml of dichloroethane containing 910 mg of compound IX and 0.6 ml of trimethylsilyl triflate (TMS-T_f) added. After refluxing under argon for 4 h, the mixture was collected, 2 g of solid $NaHCO_3$ added followed by 50 ml of saturated aqueous $NaHCO_3$. The organic layer was collected and after work-up in the usual manner, crude XV was obtained as an oil which was purified and separated into its isomer by chromatography on silica gel using hexane-ethyl acetate (3:7) as the eluent to give 230 mg of pure trans- and 250 mg or pure cis-isomer as colorless foams. They were characterized by their ^1H NMR spectra ($CDCl_3$):
trans-isomer of XV (R :0.40; hexane-EtOAc 3:7):
δ(ppm): 4.45-4.52 (m,4H;C_5-H_2,C_2-$CH_2OCOC_6H_5$);
5.16 (b,2H;C_2-NH_2);
5.83 (t,1H;C_2-H,J = 3.8 Hz);
6.39 (dd,1H;C_4-H);
7.41-7.58 (m,3H;aromatic);
7.92 (s,1H;C_8-H);
8.06 (d,2H;aromatic,J = 7Hz).
U.V.: (CH_3OH) λmax. 312 nm.
cis-isomer of XV (R :0.26; hexane-EtOAc 3:7):
δ(ppm): 4.25-4.33 (dd,1H;C_5-H,J = 5.43 Hz);
4.59-4.64 (m,3H;C_5-H and C_2-CH_2-$OCOC_6H_5$);
5.17 (b,2H;C_2-NH_2);
5.42 (t,1H;C_2-H,J = 3.50 Hz);
6.33-6.53 (dd,1H;C_4-H);
7.38-7.57 (m,3H;aromatic);
7.93-7.98 (d,2H;aromatic);
8.00 (s,1H;C_8-H).
U.V.: (CH_3OH) λmax.312 nm.

Example 15. Preparation of trans- and cis-2-hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane (XVI).

The preceding trans-isomer of XV (180 mg) was dissolved in 30 ml of methanol, the solution cooled to 0° and dry ammonia bubbled through for 15 min. After stirring at room temperature for 15 h, the solvent was removed in vacuo and the residue crystallized from ether. After recrystallization from ethanol-ether, 98 mg of pure trans-XVI, m.p. 155-156°, was obtained (R_f: 0.23, EtOAc). It was characterized by ^1H NMR (DMSO-d_6):
trans-XVI: δ(ppm): 3.44-3.49 (m,2H;C_2-CH_2OH);
4.37-4.45 (m,2H;C_5-H_2);
5.01 (t,1H;C_5-CH_2OH,J = 6.2Hz);
5.46 (t,1H;C_2-H,J = 3.6 Hz);
6.27-6.32 (dd,1H;C_4-H,J = 4,1 Hz);
7.00 (b,2H;C_2-NH_2);
8.26 (s,1H;C_8-H).

U.V.: (CH_3OH) λmax.247 and 308 nm.
The cis-isomer of XVI was obtained in similar yield from the cis-isomer of XV by the same preceding procedure. After recrystallization from ethanol-ether, the pure product had m.p. 145-147° (R_f:0.24, EtOAc). It was characterized by ^1H NMR (DMSO-d_6):
cis-XVI: δ(ppm): 3.54-3.59 (m,2H;C_2-CH_2OH);
4.12-4.19 (dd,1H;C_5-H,J=5.3 Hz and 9.8 Hz);
4.48-4.53 (d,1H;C_5-H,J=9.8 Hz);
5.01 (t,1H;C_2-H,J=2.8 Hz);
5.09 (t,1H;C_2-CH_2-OH,J=6.0 Hz);
6.24 (d,1H;C_4-H,J=5.1 Hz);
6.96 (b,2H;C_2-NH_2);
8.23 (s,1H;C_8-H).
U.V.: (CH_3OH) λmax.247 and 308 nm.

Example 16. Preparation of trans-and cis-2-hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane (XVII).

The preceding trans-isomer of XVI (50 mg) was submitted to hydrogenation conditions under 345 kPa [50 (psi)] of hydrogen over 10% Pd/C (30 mg) in 30 ml of ethanol containing 0.5 ml of triethylamine. After 3 h of shaking, the mixture was worked up in the usual manner to yield a solid which was recrystallized from ethanol-ether to give 36 mg of pure trans-XVII, m.p. 153-155°, R_f:0.25 (EtOAc: MeOH 85:15). It was characterized by ^1H NMR (DMSO-d_6):
trans-XVII: δ(ppm): 3.44-3.49 (m,2H;C_2-CH_2OH);
4.38-4.44 (m,2H;C_5-H_2);
4.99 (t,1H;C_2-CH_2-OH,J=6.1 Hz);
5.45 (t,1H;C_2-H,J=3.6 Hz);
6.29-6.34 (dd,1H;C_4-H);
6.59 (b,2H;C_2-NH_2);
8.19 (s,1H;C_8-H);
8.59 (s,1H;C_6-H).
The cis-isomer of XVII was obtained in similar yield from the cis-isomer of XVI by the same preceding procedure. After recrystallisation from ethanol- ether, the pure product had m.p. 145-148°, R_f: 0.25 (EtOAc:MeOH 85:15). It was characterized by ^1H NMR (DMSO-d_6):
cis-XVII: δ(ppm): 3.55-3.60 (dd,2H;C_2-CH_2H,J=2.10
and 6.1 Hz);
4.14-4.22 (dd,1H;C_5-H,J=5.4 and 9.7 Hz);
4.47-4.53 (dd,1H;C_5-H,J=1.38 and 9.7 Hz);
5.02 (t,1H;C_2-H,J=3 Hz);
5.11 (t,1H;C_2-CH_2OH,J=7.2 Hz);
6.58 (b,2H;C_2-NH_2);
8.19 (s,1H;C_8-H);
8.57 (s,1H;C_6-H).
U.V.: (CH_3OH) λmax. 255, 308 nm.

Example 17. Preparation of trans- and cis-2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane (XVIII):

The above compound trans-XV (200 mg) was dissolved in 30 ml of methanol saturated at 0° with dry ammonia and the solution heated in a steel bomb to 105-110° for 16h. The solution was evaporated to dryness and the residue purified by chromatography on silica gel using chloroform-methanol 4:1 as the eluent to give 101 mg of product which was recrystallized from methanol-ether to yield pure trans-XVIII, m.p. 165-168°, R_f:0.30($CHCl_3$:CH_3OH 4:1). It was characterized by ^1H NMR (DMSO-d_6):
trans-XVIII: δ(ppm):3.43-3.48 (m,2H;C_2-CH_2OH);
4.34-4.49 (m,2H;C_5-H_2);
4.97 (t,1H;C_2-CH_2OH);
5.42 (t,1H;C_2-H);
5.82 (b,2H;C_2-or C_6-NH_2);
6.18-6.23 (dd,1H;C_4-H);
6.72 (b,2H;C_2- or C_6-NH_2);
7.84 (s,1H;C_8-H).

U.V.: (CH_3OH) λmax.255,280 nm.

The cis-isomer of XVIII was obtained by the same preceding procedure from compound cis-XV. After recrystallization from methanol-ether, pure cis-XVIII, m.p. 180-182°, R_f:0.32($CHCl_3$:CH_3OH 4:1) was obtained in a similar yield. It was characterized by ^1H NMR (DMSO-d_6):

cis-XVIII: δ(ppm): 3.56-3.58 (d,2H;C_2-CH_2OH,J = 4.2Hz);
4.11-4.19 (dd,1H;C_5-H,J = 4.5 and 9.7Hz);
4.38-4.44 (dd,1H;C_5-H,J = 1.6 and 11.2Hz);
5.00 (t,1H;C_2-H,J = 3.1 Hz);
5.91 (b,2H;C_2- or C_6-NH_2);
6.15-6.19 (dd,1H;C_4-H);
6.84 (b,2H;C_2- or C_6-NH_2);
7.86 (s,1H;C_8-H).

U.V.: (CH_3OH) λmax.254,279 nm.

Example 18. Preparation of cis- and trans-2-hydroxymethyl-4-(guanosin-9'-yl)-1,3-dioxolane (XIX).

The above cis-XVI (40 mg) was dissolved in a mixture of 15 ml of methanol, 2 ml of water and 2 g of sodium hydroxide and the solution heated under reflux for 5 h after which time it was diluted with 100 ml of water and excess pyridinium sulfonate resin added. The slurry was filtered, the resin washed with water and the combined aqueous filtrates evaporated to dryness in vacuo to leave a residue which was taken up in 50% aqueous methanol. The solution was treated with activated charcoal, filtered and the filtrate evaporated to dryness in vacuo to give a solid residue that was recrystallized from ethanol-water to yield pure cis-XIX (27 mg) m.p. > 250° decomp., R_f:0.23 ($CHCl_3$:CH_3OH 7:3). It was characterized by ^1H NMR (DMSO-d_6):

cis-XIX: δ(ppm): 3.55 (m,2H;C_2CH_2OH);
4.10-4.17 (dd,1H;C_5-H,J = 5.6 and 9.8 Hz);
4.37-4.42 (dd,1H;C_5-H,J = 1.4 and 9.6 Hz);
4.98 (t,1H;C_2-H,J = 3.2 Hz);
5.15 (b,1H;C_2-CH_2OH);
6.10-6.13 (dd,1H;C_4-H,J = 2.4 and 5.3 Hz);
6.66 (b,2H;C_2-NH_2);
7.78 (s,1H;C_8-H);
11.02 (b,1H;N_1-H). U.V.: (CH_3OH) λmax.252, 270 nm (shoulder).

The isomer trans-XIX was obtained in similar yield from the above trans-XVI by the same preceding procedure. After recrystallization from ethanol-water, pure trans-XIX, m.p. > 260°(dec.), R_f:0.23 ($CHCl_3$:CH_3OH 7:3) was obtained and characterized by ^1H NMR (DMSO-d_6):

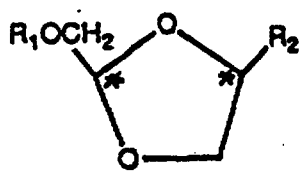
trans-XIX: δ(ppm): 3.42-3.47 (m,2H;C_2-CH_2OH);
4.34 (d,2H;C_5-H_2,J = 4.8Hz);
4.99 (t,1H;C_2-CH_2OH);
5.40 (t,1H;C_2-H,J = 3.5 Hz);
6.15-6.20 (t,1H;C_4-H,J = 4.8 Hz);
6.49 (b,2H;C_2-NH_2);
7.83 (s,1H;C_8-H);
10.64 (b,1H;N_1-H).

U.V.: (CH_3OH) λmax.252, 270 (shoulder)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A 1,3-dioxolane derivative of the general formula (L), the geometric and optical isomers thereof, and mixtures of these isomers:



(L)

U.V.: (CH_3OH) λmax.255,280 nm.

The cis-isomer of XVIII was obtained by the same preceding procedure from compound cis-XV. After recrystallization from methanol-ether, pure cis-XVIII, m.p. 180-182°, R_f:0.32($CHCl_3$:CH_3OH 4:1) was obtained in a similar yield. It was characterized by ^1H NMR (DMSO-d_6):

cis-XVIII: δ(ppm): 3.56-3.58 (d,2H;C_2-CH_2OH,J = 4.2Hz);
4.11-4.19 (dd,1H;C_5-H,J = 4.5 and 9.7Hz);
4.38-4.44 (dd,1H;C_5-H,J = 1.6 and 11.2Hz);
5.00 (t,1H;C_2-H,J = 3.1 Hz);
5.91 (b,2H;C_2- or C_6-NH_2);
6.15-6.19 (dd,1H;C_4-H);
6.84 (b,2H;C_2- or C_6-NH_2);
7.86 (s,1H;C_8-H).

U.V.: (CH_3OH) λmax.254,279 nm.

Example 18. Preparation of cis- and trans-2-hydroxymethyl-4-(guanosin-9'-yl)-1,3-dioxolane (XIX).

The above cis-XVI (40 mg) was dissolved in a mixture of 15 ml of methanol, 2 ml of water and 2 g of sodium hydroxide and the solution heated under reflux for 5 h after which time it was diluted with 100 ml of water and excess pyridinium sulfonate resin added. The slurry was filtered, the resin washed with water and the combined aqueous filtrates evaporated to dryness in vacuo to leave a residue which was taken up in 50% aqueous methanol. The solution was treated with activated charcoal, filtered and the filtrate evaporated to dryness in vacuo to give a solid residue that was recrystallized from ethanol-water to yield pure cis-XIX (27 mg) m.p. > 250° decomp., R_f:0.23 ($CHCl_3$:CH_3OH 7:3). It was characterized by ^1H NMR (DMSO-d_6):

cis-XIX: δ(ppm): 3.55 (m,2H;C_2CH_2OH);
4.10-4.17 (dd,1H;C_5-H,J = 5.6 and 9.8 Hz);
4.37-4.42 (dd,1H;C_5-H,J = 1.4 and 9.6 Hz);
4.98 (t,1H;C_2-H,J = 3.2 Hz);
5.15 (b,1H;C_2-CH_2OH);
6.10-6.13 (dd,1H;C_4-H,J = 2.4 and 5.3 Hz);
6.66 (b,2H;C_2-NH_2);
7.78 (s,1H;C_8-H);
11.02 (b,1H;N_1-H). U.V.: (CH_3OH) λmax.252, 270 nm (shoulder).

The isomer trans-XIX was obtained in similar yield from the above trans-XVI by the same preceding procedure. After recrystallization from ethanol-water, pure trans-XIX, m.p. > 260°(dec.), R_f:0.23 ($CHCl_3$:CH_3OH 7:3) was obtained and characterized by ^1H NMR (DMSO-d_6):

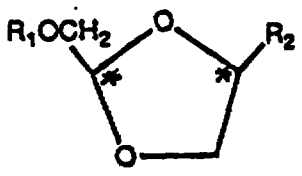
trans-XIX: δ(ppm): 3.42-3.47 (m,2H;C_2-CH_2OH);
4.34 (d,2H;C_5-H_2,J = 4.8Hz);
4.99 (t,1H;C_2-CH_2OH);
5.40 (t,1H;C_2-H,J = 3.5 Hz);
6.15-6.20 (t,1H;C_4-H,J = 4.8 Hz);
6.49 (b,2H;C_2-NH_2);
7.83 (s,1H;C_8-H);
10.64 (b,1H;N_1-H).

U.V.: (CH_3OH) λmax.252, 270 (shoulder)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A 1,3-dioxolane derivative of the general formula (L), the geometric and optical isomers thereof, and mixtures of these isomers:



(L)

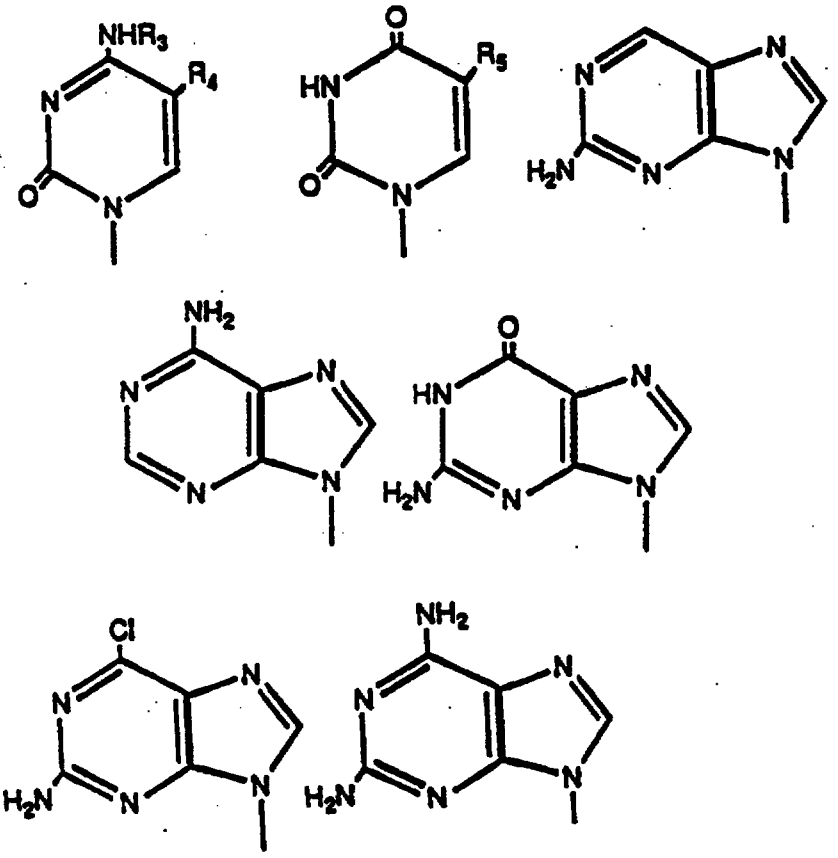
* C L M S *

wherein:

R_1 is selected from the group consisting of hydrogen, an acyl group having 1 to 16 carbon atoms, benzoyl and a benzoyl substituted in any position by at least one halogen, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, nitro and trifluoromethyl groups; and R_2 is any nucleoside base analog.

2. The compound of Claim 1 wherein:

R_2 is a heterocyclic radical selected from:



wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen and C_1 - C_3 alkyl; and

R_5 is selected from the group consisting of C_1 -C_3 alkyl and halogen.

3. The compound of Claim 2 which is 2-acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane.

4. The compound of Claim 2 which is 2-hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane.

5. The compound of Claim 2 which is 2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3dioxolane.

6. The compound of Claim 2 which is trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane.

7. The compound of Claim 2 which is 2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane.

8. The compound of Claim 2 which is 2-hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane.

9. The compound of Claim 2 which is 2-benzoyloxylmethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane.

10. The compound of Claim 2 which is 2-hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane.

* C L M S *

11. The compound of Claim 2 which is 2-hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane.

12. The compound of Claim 2 which is 2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane.

13. The compound of claim 2 which is 2-hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolane.

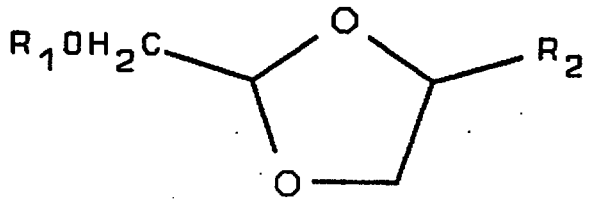
14. A pharmaceutical composition for treating viral infections comprising a 1,3-dioxolane derivative as claimed in any of Claims 1 to 13 and a pharmaceutically acceptable carrier.

15. The use of a 1,3-dioxolane derivative as claimed in any of Claims 1 to 13 in the manufacture of a pharmaceutical composition for treating viral infections.

Claims for the following Contracting State : ES

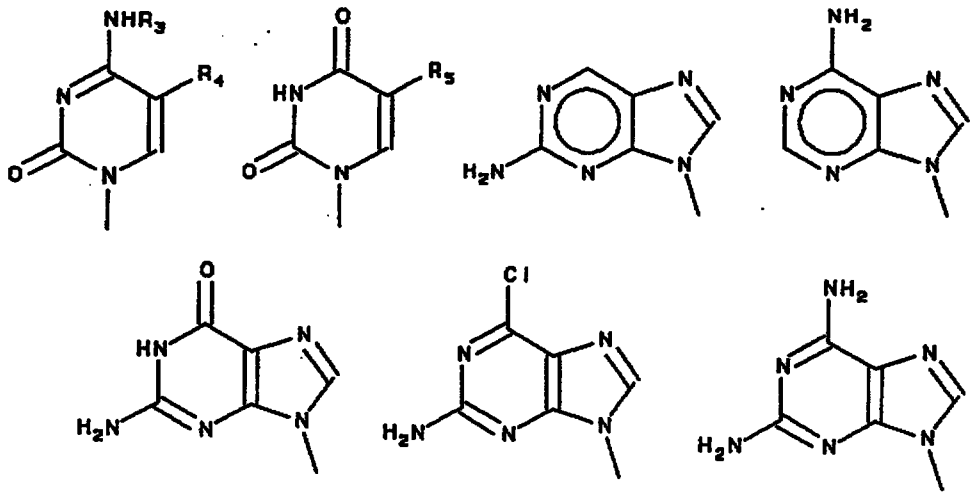
1. A process for manufacture of a pharmaceutical composition comprising mixing a 1,3-dioxolane derivative of general formula (L), the geometric and optical isomers thereof, or mixtures of these isomers:

(L)



wherein R_1 is selected from the group consisting of hydrogen, an acyl group having 1 to 16 carbon atoms, benzoyl and a benzoyl substituted in any position by at least 1 halogen, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, nitro and trifluoromethyl groups; and R_2 is any nucleoside base analogue, with a pharmaceutically acceptable carrier.

2. A process according to Claims 1 wherein R_2 is a heterocylic radical selected from:



wherein R_3 and R_4 are independently selected from the group consisting of hydrogen and C_1 - C_3 alkyl; and R_5 is selected from the group consisting of C_1 -C_3 alkyl and halogen.

3. A process according to Claim 1 or 2 wherein the 1,3-dioxolane derivative of general formula (L) is selected from the following:-
2 - acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane,

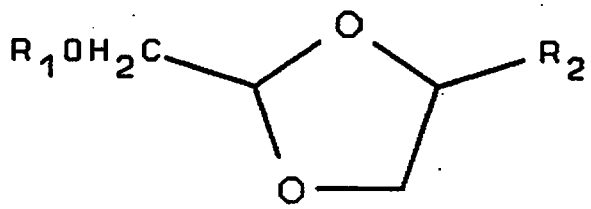
* C L M S *

2 - benzoyloxymethyl-4-(cytosin-1'-yl)-1',3-dioxolane
trans-2-hydroxymethyl-4-(cytosin-1'yl)-1,3-dioxolane,
2 - benzoloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane,
2 - benzoyloxylmethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane, and
2 - hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolane.

Claims for the following Contracting State : GR

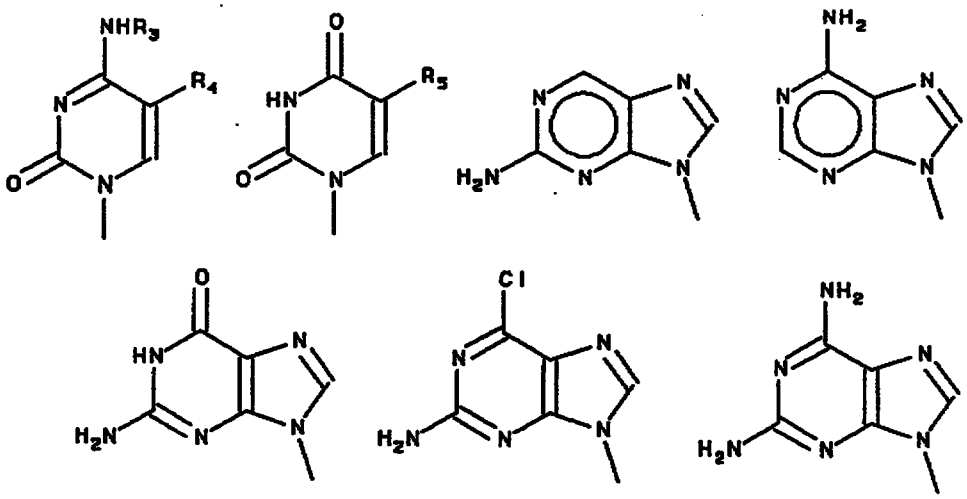
1. A process for manufacture of a pharmaceutical composition comprising mixing a 1,3-dioxolane derivative of general formula (L), the geometric and optical isomers thereof, or mixtures of these isomers:

(L)



wherein R_1 is selected from the group consisting of hydrogen, an acyl group having 1 to 16 carbon atoms, benzoyl and a benzoyl substituted in any position by at least 1 halogen, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, nitro and trifluoromethyl groups; and R_2 is any nucleoside base analogue,
with a pharmaceutically acceptable carrier.

2. A process according to Claims 1 wherein R_2 is a heterocylic radical selected from:



wherein R_3 and R_4 are independently selected from the group consisting of hydrogen and C_1 - C_3 alkyl; and R_5 is selected from the group consisting of C_1 -C_3 alkyl and halogen.

3. A process according to Claim 1 or 2 wherein the 1,3-dioxolane derivative of general formula (L) is selected from the following:-
2 - acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane,
2 - benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane
trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane,
2 - benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane,

* C L M S *

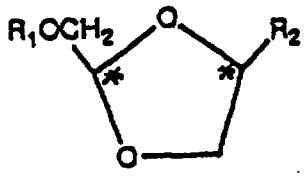
2 - hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane,
2 - benzoyloxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane,
2 - hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane, and
2 - hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolane.

4. Use of a 1,3-dioxolane derivative of general formula (L) according to any of Claims 1-3 in the manufacture of a medicament for treating viral infections.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. 1,3-Dioxolanderivat der allgemeinen Formel (L),

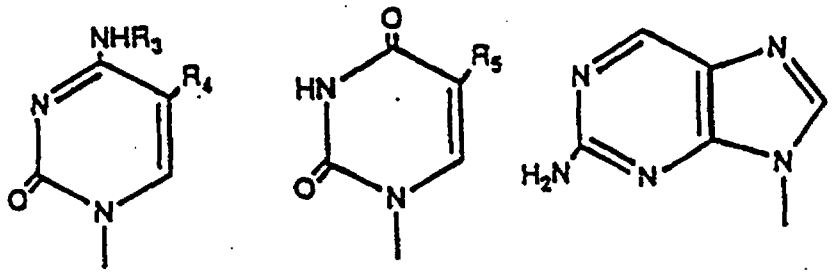


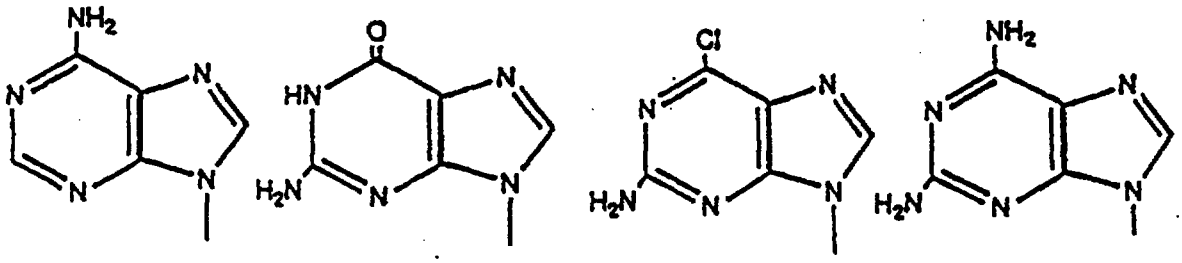
(L)

in der

R_1 aus der aus Wasserstoff, einer Acylgruppe mit 1 bis 16 Kohlenstoffatomen, Benzoyl und in beliebiger Position durch mindestens eine Halogen-, C_{1-3}-Alkyl-, C_{1-3}-Alkoxy-, Nitro- oder Trifluormethylgruppe substituiertem Benzoyl bestehenden Gruppe ausgewählt ist, und R_2 ein beliebiges Analogon einer Nukleosidbase darstellt, sowie
geometrische und optische Isomere desselben und Gemische dieser Isomere.

2. Verbindung gemäß Anspruch 1, in der R_2 einen aus





ausgewählten heterocyclischen Rest darstellt, wobei

R_3 und R_4 unabhängig voneinander aus der aus Wasserstoff und C_{1-3}-Alkyl bestehenden Gruppe und R_5 aus der aus C_{1-3}-Alkyl und Halogen bestehenden Gruppe ausgewählt ist.

* C L M S *

3. Verbindung gemäß Anspruch 2, bei der es sich um 2-Acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolan handelt.

4. Verbindung gemäß Anspruch 2, bei der es sich um 2-Hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolan handelt.

5. Verbindung gemäß Anspruch 2, bei der es sich um 2-Benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolan handelt.

6. Verbindung gemäß Anspruch 2, bei der es sich um trans-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolan handelt.

7. Verbindung gemäß Anspruch 2, bei der es sich um 2-Benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolan handelt.

8. Verbindung gemäß Anspruch 2, bei der es sich um 2-Hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolan handelt.

9. Verbindung gemäß Anspruch 2, bei der es sich um 2-Benzoyloxymethyl-4-(2'-amino-6'-chlorpurin-9'-yl)-1,3-dioxolan handelt.

10. Verbindung gemäß Anspruch 2, bei der es sich um 2-Hydroxymethyl-4-(2'-amino-6'-chlorpurin-9'-yl)-1,3-dioxolan handelt.

11. Verbindung gemäß Anspruch 2, bei der es sich um 2-Hydroxymethyl-4-(2'-aminopurin-9'-yl)-1,3-dioxolan handelt.

12. Verbindung gemäß Anspruch 2, bei der es sich um 2-Hydroxymethyl-4-(2',6'-diaminopurin-9'-yl)-1,3-dioxolan handelt.

13. Verbindung gemäß Anspruch 2, bei der es sich um 2-Hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolan handelt.

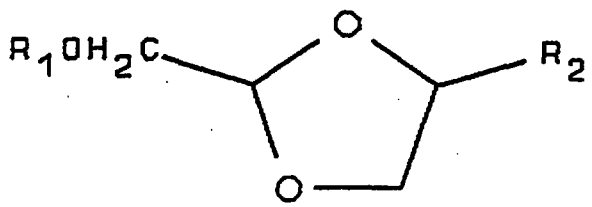
14. Arzneimittel zur Behandlung viraler Infektionen, das ein 1,3-Dioxolanderivat gemäß einem der Anprüche 1 bis 13 und einen pharmazeutisch geeigneten Träger enthält.

15. Verwendung eines 1,3-Dioxolanderivates gemäß einem der Ansprüche 1 bis 13 zur Herstellung eines Arzneimittels zur Behandlung viraler Infektionen.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung eines Arzneimittels, bei dem man ein 1,3-Dioxolanderivat der allgemeinen Formel (L),

(L)



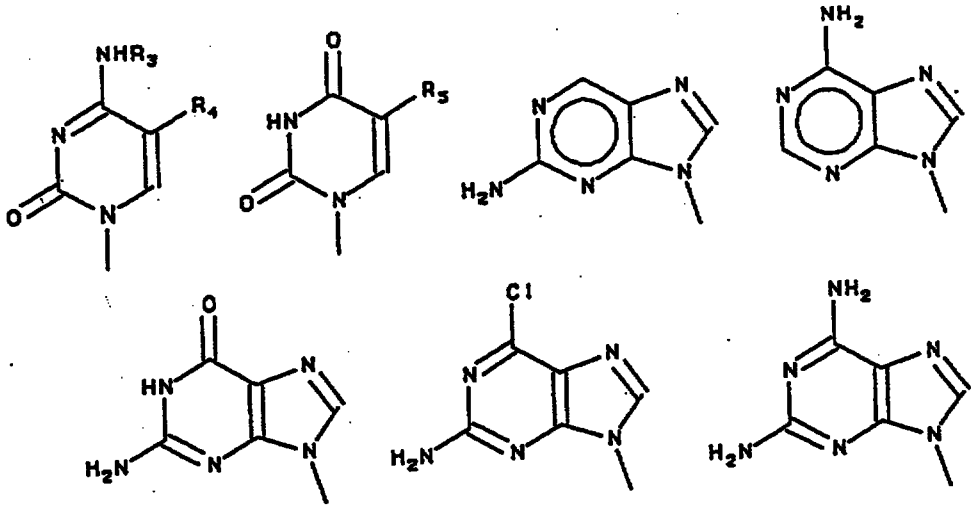
in der

R_1 aus der aus Wasserstoff, einer Acylgruppe mit 1 bis 16 Kohlenstoffatomen, Benzoyl und in beliebiger Position durch mindestens eine Halogen-, C_{1-3}-Alkyl-, C_{1-3} Alkoxy-, Nitro- oder Trifluormethylgruppe substituiertem Benzoyl bestehenden Gruppe ausgewählt ist und R_2 ein beliebiges Analogon einer Nukleosidbase darstellt, sowie deren
geometrische und optische Isomere und Gemische dieser Isomere

* C L M S *

mit einem pharmazeutisch geeigneten Träger mischt.

2. Verfahren gemäß Anspruch 1, wobei R_2 einen aus



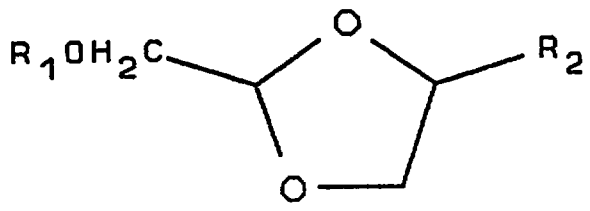
ausgewählten heterocyclischen Rest darstellt und

R_3 und R_4 unabhängig voneinander aus der aus Wasserstoff und C_{1-3}-Alkyl bestehenden Gruppe und R_5 aus der aus C_{1-3}-Alkyl und Halogen bestehenden Gruppe ausgewählt ist.

3. Verfahren gemäß Anspruch 1 oder 2, bei dem das 1,3-Dioxolanderivat der allgemeinen Formel (L) unter den folgenden gewählt wird:
   - 2-Acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolan
   - 2-Benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolan
   - trans-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolan
   - 2-Benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolan
   - 2-Benzoyloxymethyl-4-(2'-amino-6'-chlorpurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(2'-amino-6'-chlorpurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(2'-aminopurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(2',6'-diaminopurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolan

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung eines Arzneimittels, bei dem man ein 1,3-Dioxolanderivat der allgemeinen Formel (L),



(L)

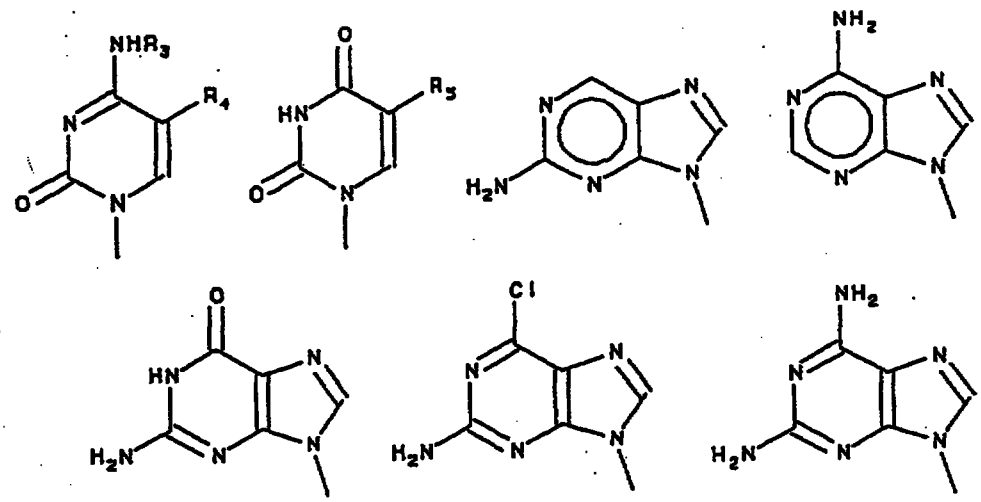
in der

R_1 aus der aus Wasserstoff, einer Acylgruppe mit 1 bis 16 Kohlenstoffatomen, Benzoyl und in beliebiger Position durch mindestens eine Halogen-, C_{1-3}-Alkyl-, C_{1-3}-Alkoxy-, Nitro- oder Trifluormethylgruppe substituiertem Benzoyl bestehenden Gruppe ausgewählt ist und R_2 ein beliebiges Analogon einer Nukleosidbase darstellt, sowie deren

* C L M S *

geometrische und optische Isomere und Gemische dieser Isomere mit einem pharmazeutisch geeigneten Träger mischt.

2. Verfahren gemäß Anspruch 1, wobei R_2 einen aus



ausgewählten heterocyclischen Rest darstellt und
R_3 und R_4 unabhängig voneinander aus der aus Wasserstoff und C_{1-3}-Alkyl bestehenden Gruppe und R_5 aus der aus C_{1-3}-Alkyl und Halogen bestehenden Gruppe ausgewählt ist.

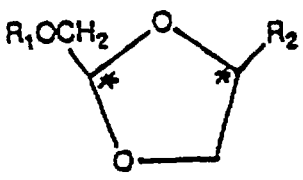
3. Verfahren gemaß Anspruch 1 oder 2, bei dem das 1,3-Dioxolanderivat der allgemeinen Formel (L) unter den folgenden gewählt wird:
   - 2-Acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4(thymin-1'-yl)-1,3-dioxolan
   - 2-Benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolan
   - trans-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolan
   - 2-Benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolan
   - 2-Benzoyloxymethyl4-(2'-amino-6'-chlorpurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(2'-amino-6'-chlorpurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(2'-aminopurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(2',6'-diaminopurin-9'-yl)-1,3-dioxolan
   - 2-Hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolan

4. Verwendung eines 1,3-Dioxolanderivates der allgemeinen Formel (L) gemäß einem der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels für die Behandlung viraler Infektionen.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivé de 1,3-dioxalane de formule générale (L), isomères géométriques et optiques de celui-ci, et mélanges de ces isomères :



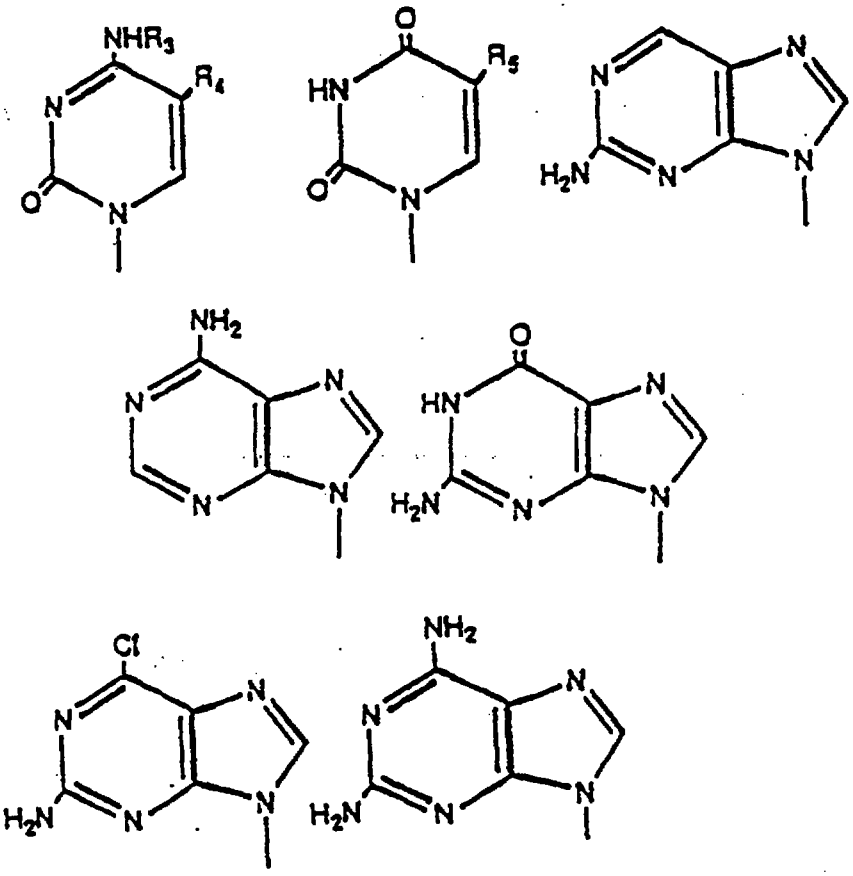
(L)

* C L M S *

dans laquelle :

- R_1 est choisi au sein du groupe comprenant l'hydrogène, un groupe acyle comportant 1 à 16 atomes de carbone, les groupes benzoyle et benzoyle substitué en une position quelconque par au moins un atome d'halogéne, et par les groupes alkyle C_1-C_3, alcoxy C_1-C_3, nitro et trifluorométhyle; et
- R_2 est un analogue d'une base nucléoside quelconque.

2. Composé selon la revendication 1, dans lequel :
   - R_2 est un radical hétérocyclique choisi parmi :



dans lequel :

- R_3 et R_4 sont choisis indépendamment au sein du groupe comprenant l'hydrogène et les groupes alkyle C_1-C_3; et
- R_5 est choisi parmi le groupe comprenant les groupes alkyle C_1-C_3 et un halogène.

3. Composé selon la revendication 2, qui est le 2-acétoxyméthyl-4-(thymin-1'-yl)-1,3-dioxalane.

4. Composé selon la revendication 2, qui est le 2-hydroxyméthyl-4-(thymin-1'-yl)-1,3-dioxalane.

5. Composé selon la revendication 2, qui est le 2-benzoyloxyméthyl-4-(cytosin-1'-yl)-1,3-dioxalane.

6. Composé selon la revendication 2, qui est le trans 2-hydroxyméthyl-4-(cytosin-1'-yl)-1,3-dioxalane.

7. Composé selon la revendication 2, qui est le 2-benzoyloxyméthyl-4-(adénin-9'-yl)-1,3-dioxalane.

8. Composé selon la revendication 2, qui est le 2-hydroxyméthyl-4-(adénin-9'-yl)-1,3-dioxalane.

9. Composé selon la revendication 2, qui est le 2-benzoyloxylméthyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxalane.

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10. Composé selon la revendication 2, qui est le 2-hydroxyméthyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxalane.

11. Composé selon la revendication 2, qui est le 2-hydroxyméthyl-4-(2'-amino-purin-9'-yl)-1,3-dioxalane.

12. Composé selon la revendication 2, qui est le 2-hydroxyméthyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxalane.

13. Composé selon la revendication 2, qui est le 2-hydroxyméthyl-4-(guanin-9'-yl)-1,3-dioxalane.

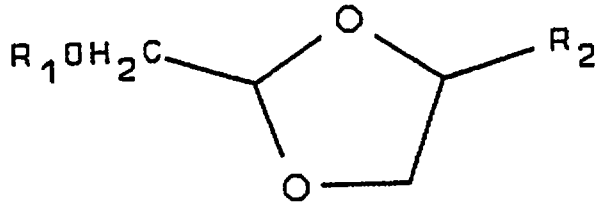
14. Composition pharmaceutique pour le traitement d'infections virales, comprenant un dérivé de 1,3-dioxalane selon l'une quelconque des revendications 1 à 13, et un véhicule pharmaceutiquement acceptable

15. Utilisation d'un dérivé de 1,3-dioxalane selon l'une quelconque des revendications 1 à 13, dans la fabrication d'une composition pharmaceutique pour le traitement d'infections virales.

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la fabrication d'une composition pharmaceutique, comprenant le mélange d'un dérivé de 1,3-dioxalane de formule générale (L), d'isomères géométriques et optiques de celui-ci, ou de mélanges de ces isomères :

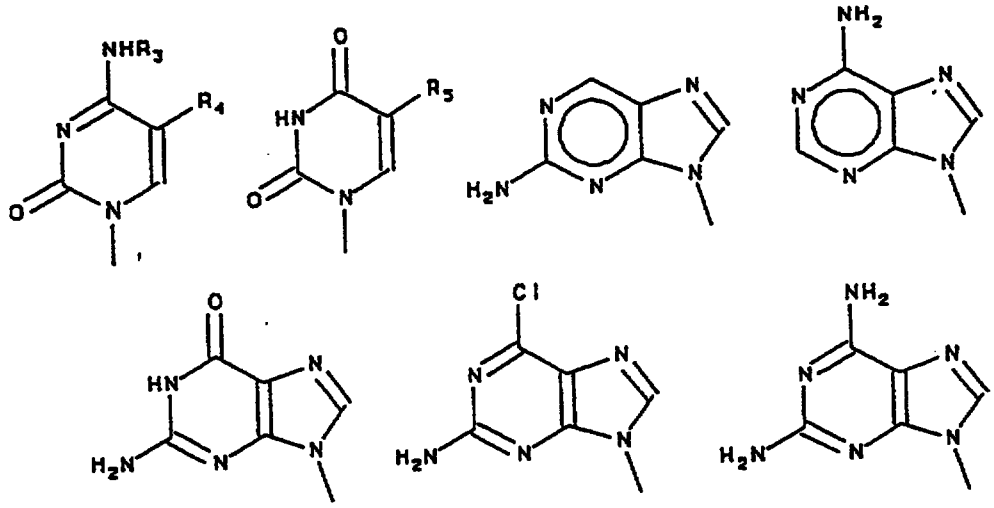
(L)



dans laquelle :
- R_1 est choisi au sein du groupe comprenant l'hydrogène, un groupe acyle comportant 1 à 16 atomes de carbone, les groupes benzoyle et benzoyle substitué en une position quelconque par au moins un atome d'halogène, et par les groupes alkyle C_1-C_3, alcoxy C_1-C_3, nitro et trifluorométhyle; et
- R_2 est un analogue d'une base nucléoside quelconque,

avec un véhicule pharmaceutiquement acceptable.

2. Procédé selon la revendication 1, dans lequel R_2 est un radical hétérocyclique choisi parmi :



dans lequel :

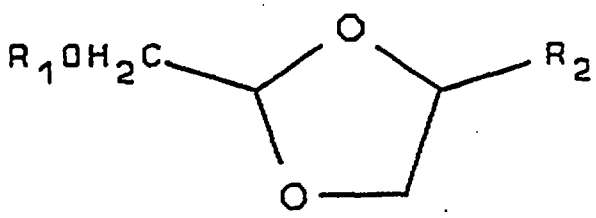
- R_3 et R_4 sont choisis indépendamment au sein du groupe comprenant l'hydrogène et les groupes alkyle C_1-C_3; et R_5 est choisi parmi le groupe comprenant les groupes alkyle C_1-C_3 et un halogène.

3. Procédé selon la revendication 1, ou la revendication 2, dans lequel le dérivé de 1,3-dioxalane de formule générale (L) est choisi parmi les composés suivants :
   - le 2-acétoxyméthyl-4-(thymin-1'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(thymin-1'-yl)-1,3-dioxalane,
   - le 2-benzoyloxyméthyl-4-(cytosin-1'-yl)-1,3-dioxalane,
   - le trans 2-hydroxyméthyl-4-(cytosin-1'-yl)-1,3-dioxalane,
   - le 2-benzoyloxyméthyl-4-(adénin-9'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(adénin-9'-yl)-1,3-dioxalane.
   - le 2-benzoyloxylméthyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(2'-amino-purin-9'-yl)-1,3-dioxalane.
   - le 2-hydroxyméthyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxalane, et
   - le 2-hydroxyméthyl-4-(guanin-9'-yl)-1,3-dioxalane.

Revendications pour l'Etat contractant suivant : GR

1. Procédé pour la fabrication d'une composition pharmaceutique, comprenant le mixage d'un dérivé de 1,3-dioxalane de formule générale (L), d'isomères géométriques et optiques de celui-ci, ou de mélanges de ces isomères :

(L)



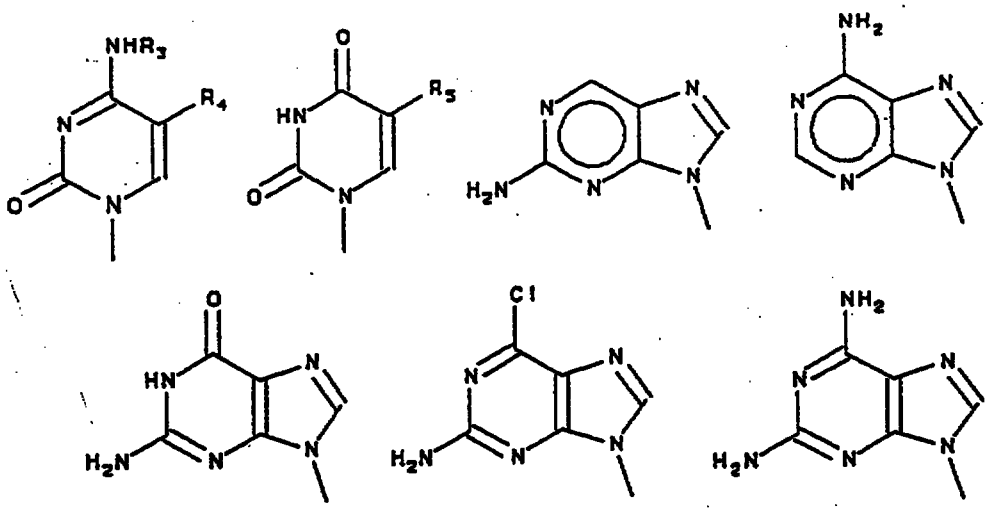
dans laquelle :

- R_1 est choisi au sein du groupe comprenant l'hydrogène, un groupe acyle comportant 1 à 16 atomes de carbone, les groupes benzoyle et benzoyle substitué en une position quelconque par au moins un atome d'halogène, et par les groupes alkyle C_1-C_3, alcoxy C_1-C_3, nitro et trifluorométhyle; et
- R_2 est un analogue d'une base nucléoside quelconque,

avec un véhicule pharmaceutiquement acceptable.

* C L M S *

2. Procédé selon la revendication 1, dans lequel R_2 est un radical hétérocyclique choisi parmi :



dans lequel :

- R_3 et R_4 sont choisis indépendamment au sein du groupe comprenant l'hydrogène et les groupes alkyle C_1-C_3; et R_5 est choisi parmi le groupe comprenant les groupes alkyle C_1-C_3 et un halogène.

3. Procédé selon la revendication 1, ou la revendication 2, dans lequel le dérivé de 1,3-dioxalane de formule générale (L) est choisi parmi les composés suivants :
   - le 2-acétoxyméthyl-4-(thymin-1'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(thymin-1'-yl)-1,3-dioxalane,
   - le 2-benzoyloxyméthyl-4-(cytosin-1'-yl)-1,3-dioxalane,
   - le trans 2-hydroxyméthyl-4-(cytosin-1'-yl)-1,3-dioxalane,
   - le 2-benzoyloxyméthyl-4-(adénin-9'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(adénin-9'-yl)-1,3-dioxalane.
   - le 2-benzoyloxylméthyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxalane,
   - le 2-hydroxyméthyl-4-(2'-amino-purin-9'-yl)-1,3-dioxalane.
   - le 2-hydroxyméthyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxalane, et
   - le 2-hydroxyméthyl-4-(guanin-9'-yl)-1,3-dioxalane.

4. Utilisation d'un dérivé de 1,3-dioxalane de formule générale (L) selon l'une quelconque des revendications 1 à 3, dans la fabrication d'un médicament pour le traitement d'infections virales.

* C L M S *