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(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,019,812**
(22) 1990/06/26
(43) 1990/12/28
(45) 2000/11/21

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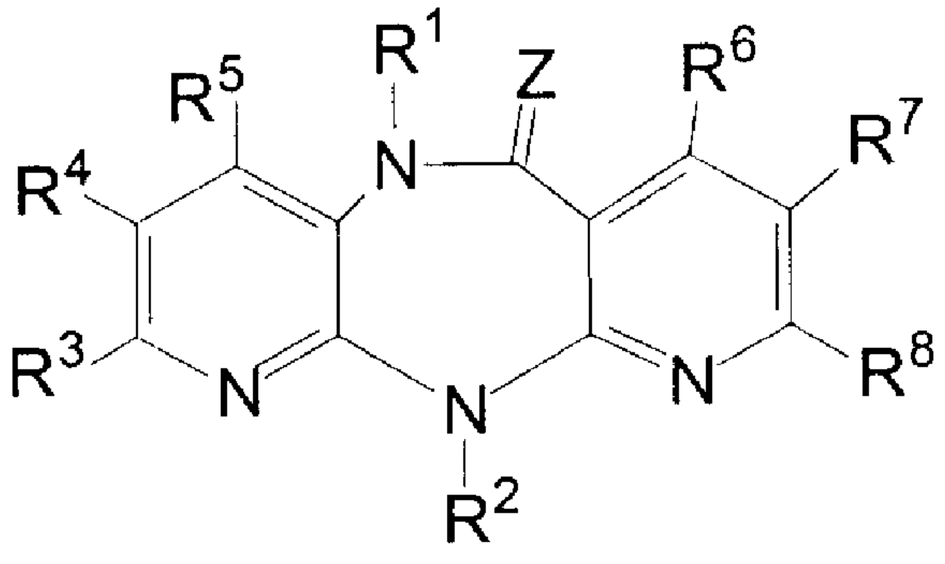
(51) Int.Cl.[5] C07D 471/14, A61K 31/55
(30) 1989/06/28 (372,974) US

(54) **NOUVEAU 5,11-DIHYDRO-6H-DIPYRIDO[3,2-B:2',3'-E][1,4]DIAZEPIN-6-ONES ET LEUR UTILISATION DANS LA PREVENTION ET LE TRAITEMENT DU SIDA**

(54) **NOVEL 5,11-DIHYDRO-6H-DIPYRIDO[3,2-B:2',3'-E][1,4]DIAZEPIN-6-ONES AND THEIR USE IN THE PREVENTION OR TREATMENT OF AIDS**



(57) Disclosed are novel 5,11-dihydro-6H-dipyrido(3,2-b; 2',3'-e][1,4] diazepin-6-ones and -thiones. These are useful in the prevention or treatment of AIDS.

ABSTRACT

Disclosed are novel 5,11-dihydro-6H-dipyrido[3,2-b; 2',3'-e][1,4] diazepin-6-ones and -thiones. These are useful in the prevention or treatment of AIDS.

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NOVEL 5,11-DIHYDRO-6H-DIPYRIDO[3,2-b:2',3'-e][1,4]DIAZEPIN-6-ONES AND THIONES AND THEIR USE IN THE PREVENTION OR TREATMENT OF AIDS

Field of the Invention

The invention relates to novel 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-ones and -thiones and pharmaceutically acceptable acid addition salts thereof, methods for preparing these compounds, the use of these compounds in the prevention or treatment of AIDS, and to pharmaceutical compositions containing these compounds.

Background of the Invention

The human disease, Acquired Immune Deficiency Syndrome (AIDS), is caused by the Human Immunodeficiency Virus (HIV), particularly the strain known as HIV-1.

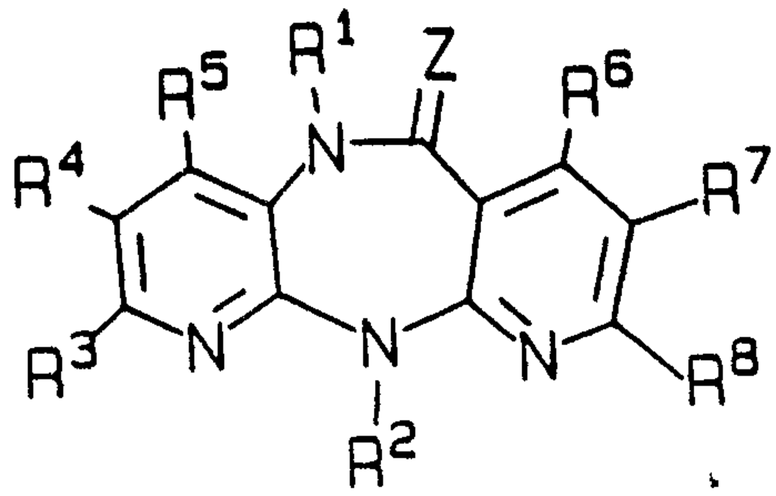
Like other viruses, HIV-1 cannot replicate without commandeering the biosynthetic apparatus of the host cell it infects. It causes this apparatus to produce the structural proteins which make up the viral progeny. These proteins are coded for by the genetic material contained within the infecting virus particle, or virion. Being a retrovirus, however, the genetic material of HIV is RNA, not DNA as in the host cell's genome. Accordingly, the viral RNA must first be converted into DNA, and then integrated into the host cell's genome, in order for the host cell to produce the required viral proteins.

The conversion of the RNA to DNA is accomplished through the use of the enzyme reverse transcriptase (RT), which is included within the infecting virion along with the RNA. Reverse transcriptase has three enzymatic functions; it acts as an RNA-dependent DNA polymerase, as a ribonuclease, and as a DNA-dependent DNA polymerase. Acting first as an RNA-dependent DNA polymerase, RT makes a single-stranded DNA copy of the viral RNA. Next, acting as a ribonuclease, RT frees the DNA just produced from the original viral RNA and then destroys the original RNA. Finally, again acting as a DNA-dependent DNA polymerase, RT makes a second, complementary DNA strand, using the first DNA strand as a template. The two strands form double-stranded DNA, which is integrated into the host cell's genome by another enzyme called an integrase.

Compounds which inhibit the enzymatic functions of HIV-1 reverse transcriptase will inhibit replication of HIV-1 in infected cells. Such compounds are useful in the prevention or treatment of HIV-1 infection in human subjects.

Description of the Invention

In one of its composition of matter aspects, the invention comprises 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-ones and -thiones of the formula



I

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wherein,

Z is oxygen or sulfur;

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 5 carbon atoms, trihalomethyl, alkenyl or alkynyl of 3 to 5 carbon atoms, 2-halo-propen-1-yl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl which is either unsubstituted or substituted by methyl, methoxy or halogen), alkanoyl of 2 to 3 carbon atoms, or alkoxyalkyl or alkythioalkyl of 2 to 4 carbon atoms;

R^2 is a hydrogen, alkyl or fluoroalkyl of 1 to 5 carbon atoms, alkenyl or alkynyl of 2 to 5 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, hydroxyalkyl of 2 to 5 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or halogen), phenyl (which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxy or halogen or alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms; and

R^3 through R^8 are each hydrogen; or,

one of R^3 through R^8 is alkyl of 1 to 4 carbon atoms, alkoxy or alkylthio of 1 to 4 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkanoylamino of 1 to 4 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, carboxyalkyl of 2 to 4 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, cyano, nitro, hydroxyl, carboxyl, amino, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, azido or halogen, with the other five substituents being hydrogen; or

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R^3, R^4, and R^5 are each independently hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that at least one of these substituents is hydrogen, or one of R^3, R^4 and R^5 is butyl with the remaining two substituents being hydrogen; and,

R^6, R^7, and R^8 are each independently hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that at least one of these substituents is hydrogen, or one of R^6, R^7 and R^8 is butyl with the remaining two substituents being hydrogen with the proviso that when Z is oxygen and R^1 and R^2 are the same or different and are hydrogen or straight chained or branched alkyl of 1 to 5 carbon atoms at least one of R^3 through R^8 is other than hydrogen.

A subgeneric aspect of the invention comprises compounds of Formula I, wherein,

Z is oxygen or sulfur;

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 5 carbon atoms, trihalomethyl, alkenyl or alkynyl of 2 to 4 carbon atoms, 2-halo-propen-1-yl, or alkoxyalkyl or alkylthioalkyl of 2 to 3 carbon atoms;

R^2 is alkyl or fluoroalkyl of 1 to 4 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl or 2 to 3 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl or thienyl, which is either unsubstituted or substituted by methyl, methoxy, hydroxyl or halogen), phenyl (which is either unsubstituted or substituted with

methyl, methoxy, hydroxyl or halogen) or alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms;

R^3, R^4, and R^5 are each independently hydrogen or methyl, with the proviso that at least one of these substituents is hydrogen, or R^5 is ethyl, propyl or butyl with the remaining two substituents being hydrogen; and,

R^6, R^7, and R^8 are each independently hydrogen or methyl, with the proviso that at least one of these substituents is hydrogen, or R^6 is ethyl, propyl or butyl with the remaining two substituents being hydrogen.

A particular subgeneric aspect of the invention comprises compounds of formula I wherein,

Z is oxygen or sulfur;

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 4 carbon atoms or allyl;

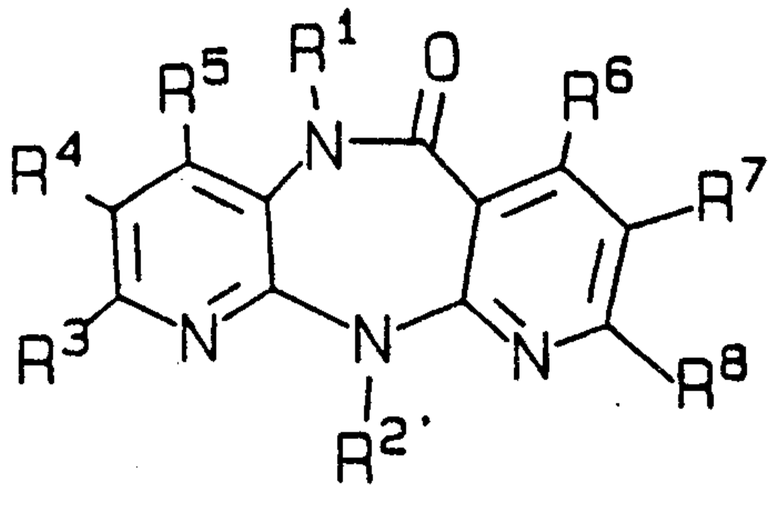
R^2 is alkyl or fluoroalkyl of 1 to 4 carbon atoms, allyl or benzyl; and

R^3 through R^9 are each hydrogen.

The compounds of Formula I can be prepared by known methods or obvious modifications theréof. Methods A, B, C, D, and E, described below, are illustrative of the methods for preparing the compounds.

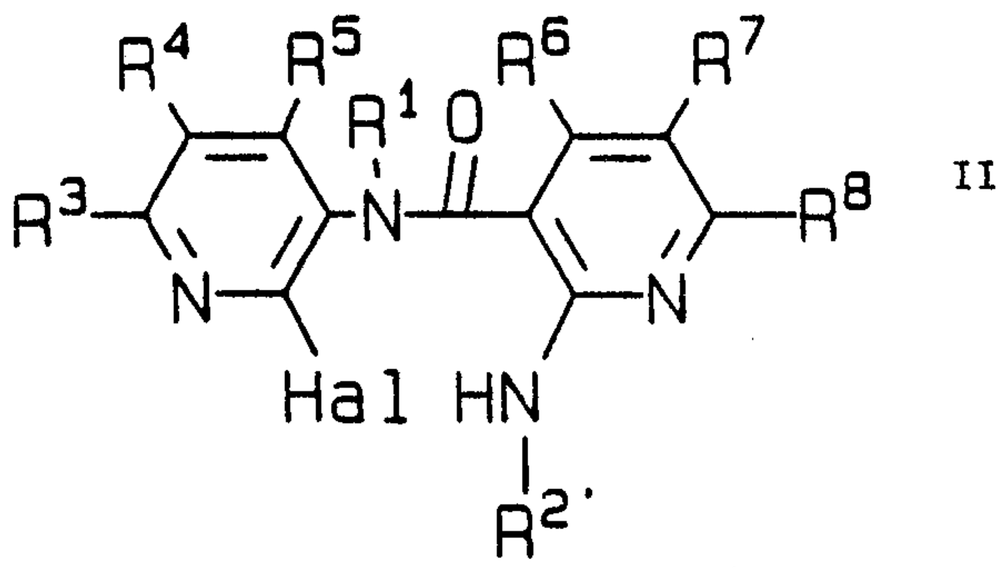
Method A

Compounds of the general formula Ia



Ia

wherein R^1 and R^3 through R^8 are defined as above and $R^{2'}$ has the same definitions as R^2 with the exception of hydrogen, can be obtained by cyclizing carboxylic acid amides of general formula II



II

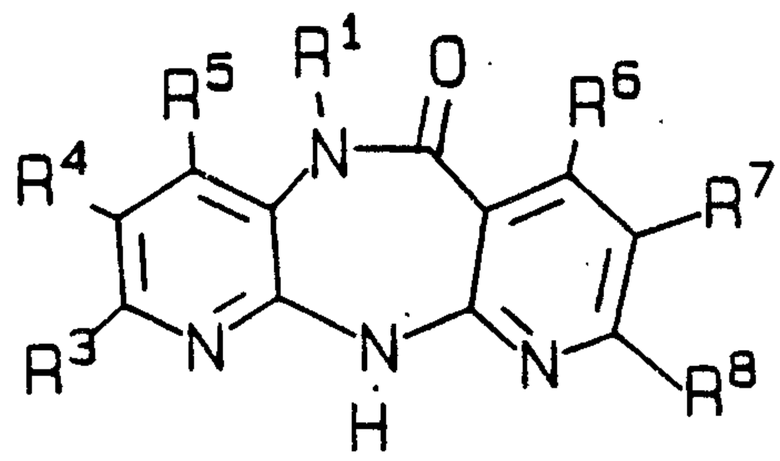
wherein R^1, R^3 through R^8 and $R^{2'}$ have the same definitions set forth with respect to Formula Ia and Hal represents fluorine, chlorine, bromine or iodine. Cyclisation is preferably carried out by converting the compounds of general formula II into their alkaline metal salts and subsequent condensation at temperatures between 0°C and the boiling point of the reaction mixture.

If, in the starting compounds of general formula II, R^1 is different from hydrogen, metallation requires at least 1 mole of the metallating agent. If on the other hand, R^1 is hydrogen, at least 2 moles of this agent must be used. For metallation, lithium, sodium and potassium hydrides, lithium alkyls, such as n-butyl lithium, are preferably used.

The reaction is usually carried out in inert solvents, e.g. in tetrahydrofuran, 1,4-dioxane, glycoldimethyl ether, diethyleneglycoldimethyl ether, triethyleneglycoldimethyl ether, dimethylformamide, benzene or anisole. Cyclisation may also be effected by heating carboxylic acid amides of general formula II in dipolar aprotic solvents, preferably in sulfolane or dimethylsulfone. Catalytic quantities of strong acids, e.g. sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, polyphosphoric acid, methanesulfonic acid or p-toluenesulfonic acid, have proved to be of use. The necessary reaction temperature is usually between 110 and 220°C, the preferred range of temperature being between 130 and 170°C.

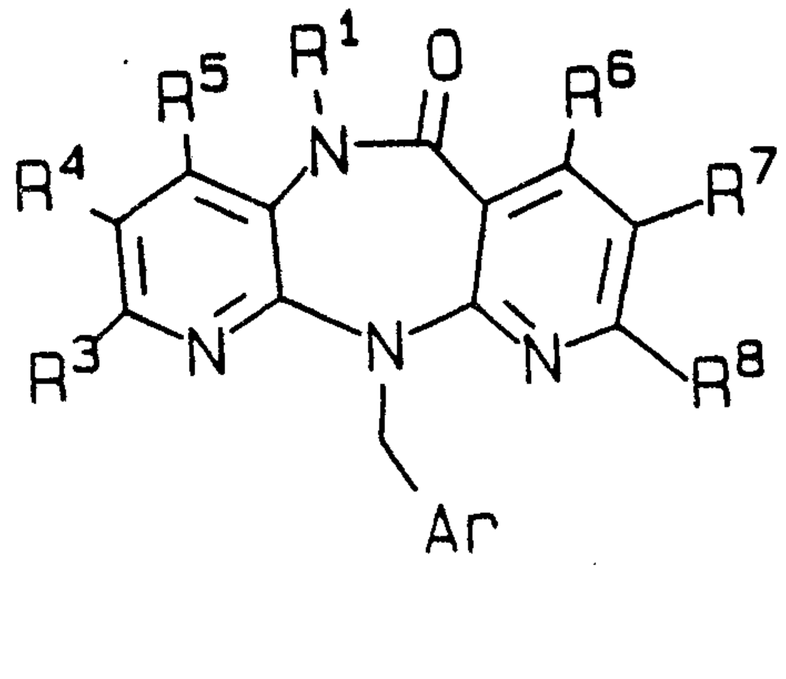
Method B

Compounds of general formula Ib



Ib

wherein R^1 and R^3 through R^8 are defined as above, can be prepared by hydrolytic cleavage of the arylmethyl group in compounds of general formula III



III

wherein R^1 and R^3 through R^8 are defined as mentioned above and Ar can be, for example, a phenyl or 4-methoxyphenyl group. Hydrolysis is effected by moderate to strong acids or Lewis-acids at temperatures between -20 and +150°C. Such acids can be, for example, sulfuric acid, methanesulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, phosphoric or polyphosphoric acid. When using phosphoric or polyphosphoric acid, the addition of solvents such as benzene, toluene, phenol, anisole or veratrole has proved to be of advantage.

If Lewis acids, such as aluminum chloride or bromide are used to eliminate the arylmethyl group, solvents such as aromatic hydrocarbons, e.g. benzene, toluene, anisole, or mixtures thereof with dichloromethane are suitable.

It will be obvious to those skilled in the art that Method B is not preferred in those cases wherein any of R^1 and R^3 through R^8 are readily hydrolyzable substituents, for example, wherein R^1 is alkanoyl or any of R^3 through R^8 are alkanoylamino or alkoxycarbonyl. In cases wherein R^1 is alkanoyl or any of R^3 through R^8 are alkoxycarbonyl, for example, it is preferable to utilize method A described above; when R^1 is hydrogen two equivalents of base must be used. In cases wherein any of R^3 through R^8 are alkanoylamino, for example, it is preferable to carry out the hydrolysis (and subsequent acylation) on the corresponding nitro derivative, and then reduce the nitro moiety to the amine, followed by acylation to yield the desired product.

Method C

compound of general formula Ic

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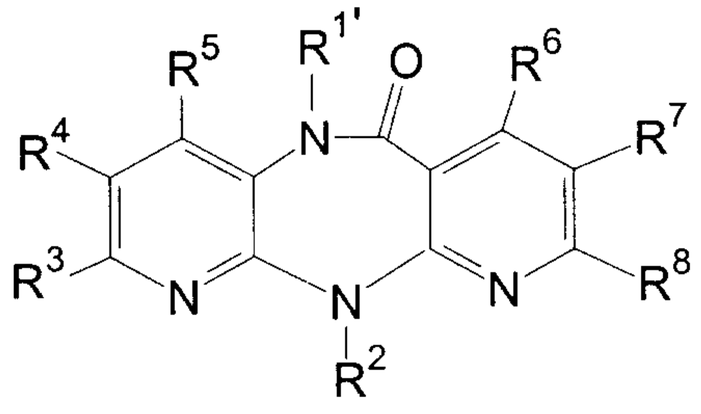
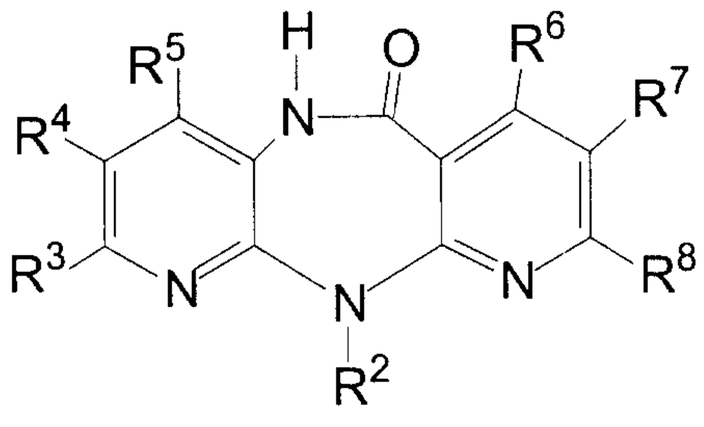


(Ic)

wherein $R^{1'}$ has the same definitions as R^1 with the exception of hydrogen and R^2 through R^8 are defined as above, may be obtained by converting a 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one of the formula IV



(IV)

wherein R^2 through R^8 are defined as above, into the corresponding 5-alkali or alkaline earth metal compound and subsequently reacting the alkali metal compound with a compound of the Formula V

$$R^{1'}X \qquad (V)$$

wherein $R^{1'}$ has the same meanings as in Formula Ic and X is the radical of a reactive ester, a halogen atom, the group $OSO_2OR^{1'}$, the methanesulfonyloxy or ethanesulfonyloxy group or an aromatic sulfonyloxy group. Instead of converting the compound of the general Formula IV into its corresponding alkali metal salt in the first step, the alkylation of a compound of Formula IV may also be performed by reaction with a compound of Formula V in the presence of amines, such as triethylamine, diazabicycloundecene or 4-(dimethylamino)-pyridine, or of alkali

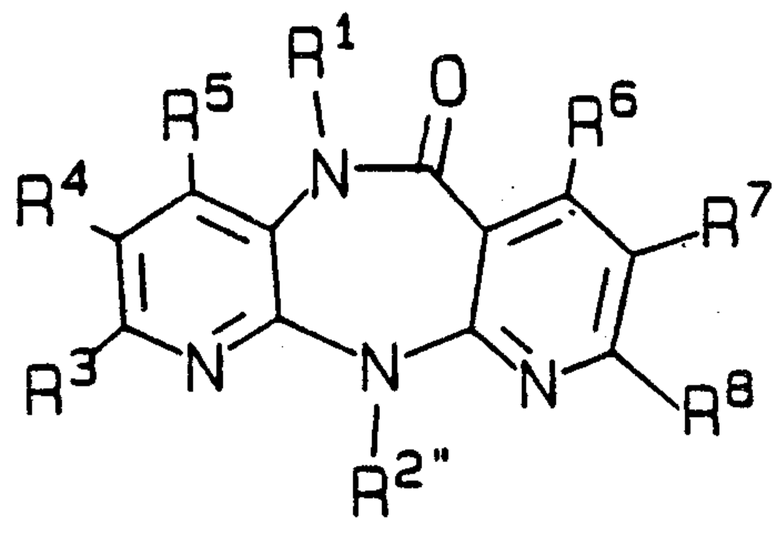
carbonates or bicarbonates, such as sodium and potassium carbonate or sodium bicarbonate.

The conversion of a compound of general formula IV into the corresponding alkali metal or alkaline earth metal compound may be effected by reacting a compound of formula IV with an alkali metal or alkaline earth metal hydroxide, such as lithium hydroxide, barium hydroxide, sodium hydroxide or potassium hydroxide, with an alkali metal alcoholate, such as sodium methanolate or potassium tert-butoxide, with an alkali metal amide, such as sodium amide or potassium amide, or with an alkali metal hydride such as sodium hydride or potassium hydride. The reaction is preferably carried out at elevated temperatures and in the presence of a suitable organic solvent. Inert organic solvents, such as tetrahydrofuran or glycoldimethyl ether are preferred if alkali metal hydrides are used as the metallating agents, whereas, if an alkali or alkaline earth metal hydroxide is used, an aqueous mixture with an organic solvent, such as methanol or tetrahydrofuran, may also be employed. For conversion of the alkali or alkaline earth metal-substituted 5,11-dihydro-6H-dipyrido [3,2-b:2',3'-e][1,4]diazepin-6-one thus obtained into a compound of general formula Ic, the solution or suspension of the alkali or alkaline earth metal compound is reacted directly, i.e. without isolation, with a compound of formula V at -20°C or at elevated temperatures, up to the boiling point of the solvent or reaction medium, whichever is lower. The substitution takes place almost exclusively at the nitrogen atom in the 5-position of the dihydrodipyridodiazepinone, even if R^2 in the starting material of formula IV is a hydrogen atom, provided that one equivalent of base and one equivalent of a compound of formula V are used.

It will be obvious to those skilled in the art that the presence of nucleophilic substituents in the compounds of formula Ic may require the use of an intermediate of formula Ic having substituents which are, other than the 11-position nitrogen, not nucleophilic but which can be derivatized to yield the required group. For example, amino or monoalkylamino substituents at any of R^3 through R^8 are preferably obtained by alkylating or acylating an intermediate of formula Ic having a nitro group at any of R^3 through R^8, and subsequently reducing the nitro group, and alkylating, if appropriate, to yield the final product.

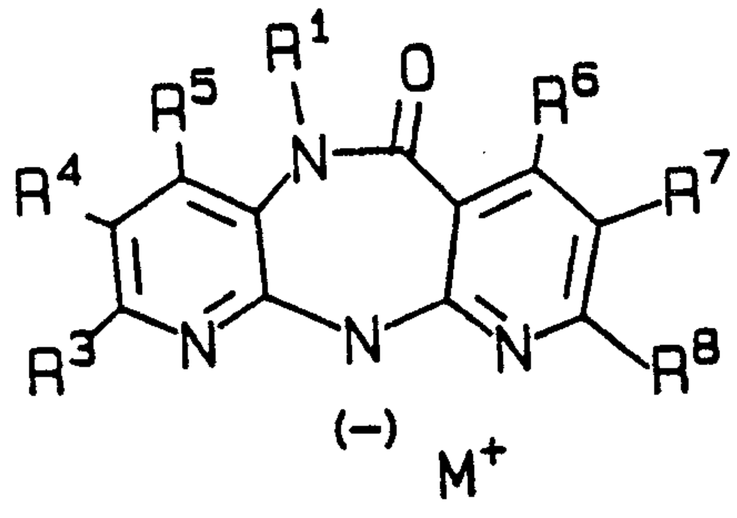
Method D

A compound of general formula Id



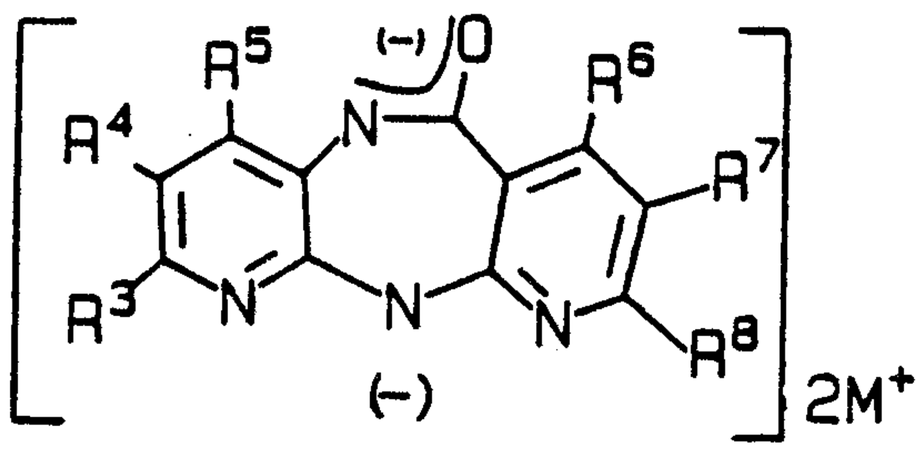
(Id)

wherein $R^{2"}$ has the meanings of R^2 with the exception of alkanoyl, hydroxyalkyl or alkoxycarbonylmethyl, and R^1 and R^3 through R^8 represent the groups mentioned above, can be obtained by converting a 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-3][1,4]diazepin-6-one of general formula Ib into the corresponding metal salt of general formula VIa or - in the case of R^1 in the compound of formula Ib being hydrogen - into a compound of formula VIb



(VIa)

VIb



wherein M represents an alkali metal, such as lithium, sodium, potassium, rubidium or cesium, or M represents the group MgHal+, wherein Hal is a chlorine, bromine or iodine atom, and subsequently alkylating with a compound of general formula VII

$$R^{2"}X \qquad \text{VII}$$

wherein $R^{2"}$ and X are as hereinbefore defined.

The conversion of a compound of general formula Ib into the corresponding alkali metal compound of formulae VId and VIb may be effected by reacting a compound of formula Ib with a lithium alkyl (e.g. n-butyl lithium, or t-butyl lithium) optionally in the presence of tetramethylethylenediamine, a lithium dialkylamide, (e.g. lithium

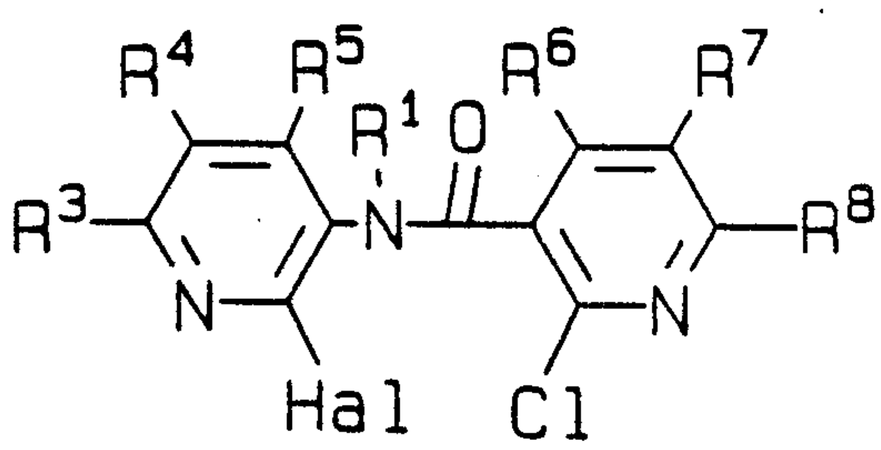
diisopropylamide, lithium dicyclohexylamide and lithium isopropyl-cyclohexylamide), a lithium aryl (e.g. phenyl lithium), an alkali metal hydroxide (e.g. lithium, sodium or potassium hydroxide), an alkali metal hydride (e.g. sodium or potassium hydride), an alkali metal amide (e.g. sodium or potassium amides) or a Grignard reagent (e.g. methyl magnesium iodide, ethyl magnesium bromide or phenyl magnesium bromide). One equivalent of base is required for the formation of compounds of formula VIa, whereas two equivalents of base are required for the formation of compounds of formula VIb. The metallation is conveniently carried out in an inert organic solvent at temperatures of between -78°C and the boiling point of the reaction mixture in question. If a lithium alkyl, lithium aryl, lithium dialkylamide or Grignard reagent is used for the metallation, the preferred solvents are ethers such as tetrahydrofuran, diethyl ether or dioxane, optionally in a mixture with aliphatic or aromatic hydrocarbons, such as hexane or benzene, and the operation may be carried out at temperatures of between -20 and +80°C. When metallation is effected with an alkali metal hydride or alkali metal amide, in addition to the solvents mentioned hereinbefore it is also possible to use xylene, toluene, acetonitrile, dimethylformamide and dimethylsulfoxide, while if an alkali metal hydroxide is used it is also possible to use alcohols such as ethanol, methanol and aliphatic ketones such as acetone, as well as mixtures of these solvents with water.

For conversion of the alkali metal salt thus obtained into a compound of formula Id, the solution or suspension of the alkali metal compound is reacted directly, i.e. without isolation of the reaction product, with a compound of formula VII at -20°C or at elevated temperatures, preferably

at the boiling point of the solvent or suspension medium or at the boiling point of the compound VII, whichever is lower.

It will be obvious to those skilled in the art that the presence of nucleophilic substituents in the compounds of formula Id may require the use of an intermediate of formula Id having substituents which are, other than the 11-position nitrogen, not nucleophilic but which can be derivatized to yield the required group. For example, amino or monoalkylamino substituents at any of R^3 through R^8 are preferably obtained by alkylating or acylating an intermediate of formula Ic having a nitro group at any of R^3 through R^8, and subsequently reducing the nitro group, and alkylating, if appropriate, to yield the final product.

The carboxylic acid amides of general formula II used as starting materials are obtained, for example, by amination of 2-chloro-nicotinic acid amides of general formula VIII



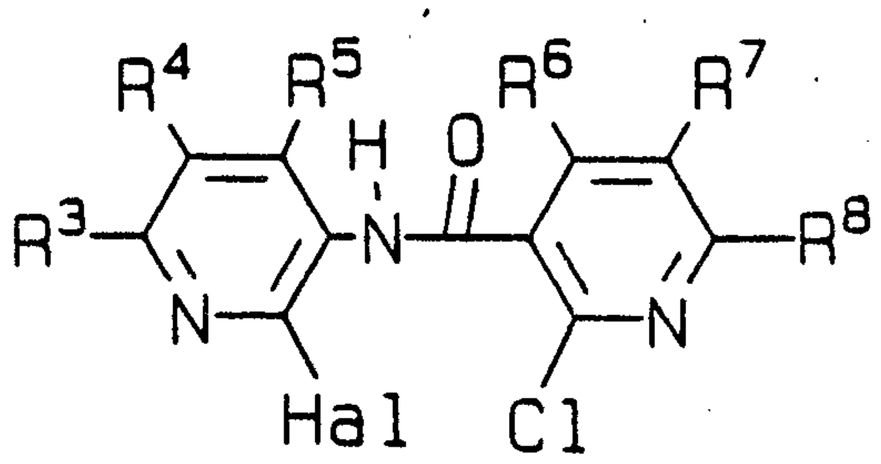
(VIII)

wherein R^1 through R^8 and Hal are as hereinbefore defined, with primary amines of general formula IX

$$H_2N\text{-}R^{2'} \qquad \text{(IX)}$$

wherein $R^{2'}$ is as hereinbefore defined. The reaction can also be carried out in the presence of inorganic or organic auxiliary bases, such as

triethylamine, N,N-dimethylaniline, or sodium or potassium carbonate. The reaction can be carried out without using a solvent; it is of some advantage, however, to use inert organic solvents at temperatures of between 0°C and 150°C, preferably at reflux temperature. Suitable inert solvents that can be used include an excess of the primary amine of general formula IX, open chain or cyclic ethers, such as tetrahydrofuran, 1,4-dioxane, glycoldimethyl ether, diethyleneglycoldimethyl ether; aromatic hydrocarbons, such as benzene, toluene, xylene, chlorobenzene or pyridine; alcohols such as methanol, ethanol, isopropanol; dipolar aprotic solvents such as dimethylformamide; 1,3-dimethyl-2-imidazolidinone, 1,3-dimethyl-tetrahydro-2(1H)- pyrimidinone and sulfolane. Starting materials of general formula VIII, wherein R^1 is different from hydrogen, can be prepared from 2-chloronicotinic acid amides of general formula X



(X)

by reaction with alkylating agents of general formula V in the presence of proton acceptors, for example of amines, such as triethylamine, diazabicycloundecene, 4-(dimethylamino)pyridine, or alkali or alkaline earth metal hydroxides, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, of alkali carbonates, or alkaline earth metal carbonates or hydrogencarbonates, such as sodium carbonate or potassium carbonate, or potassium hydrogen carbonate.

2-Chloronicotinic acid amides of general formula X can be obtained by condensation of 2-chloronicotinic acid chloride with 3-amino-2-halopyridines, under well known reaction conditions.

All the other starting materials are known from the literature or may be purchased or may be obtained by procedures known from the literature.

Method E

In Method E, a compound of Formula I, wherein Z is sulfur, is obtained by reacting a compound of Formula I, wherein Z is oxygen, with a sulfurating agent, such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide; bis(tricyclohexyltin)sulfide; bis(tri-n-butyltin)sulfide; bis (triphenyltin)sulfide; bis(trimethylsilyl)sulfide or phosphorous pentasulfide. The reaction is carried out in an inert organic solvent such as carbon disulfide, benzene or toluene, at room temperature or higher, preferably at an elevated temperature up to the boiling point of the reaction mixture, and preferably under anhydrous conditions. When using the above mentioned tin or silyl sulfides, it is preferable to carry out the sulfurization reaction in the presence of a Lewis acid such as boron trichloride.

It will be obvious to those skilled in the art that the presence of another carbonyl moiety in a compound of formula I, for example, a compound wherein Z is oxygen and any of R^3 through R^8 is alkanoyl, will require that the ketone carbonyl be protected via known methods by a suitable protecting group prior to the sulfurization reaction; deprotection subsequent to the sulfurization reaction provides the desired compound. Similarly, in cases wherein R^2 is, for example, alkanoyl, it will be obvious that the sulfurization reaction should be

performed prior to the acylation of the 11-position nitrogen. In those cases wherein the substituents at any of R^3 through R^8 can be derived from nitro, for example, alkanoylamino, the sulfurization reaction can be performed on the corresponding nitro derivative, followed by an appropriate (known) reduction and finally acylation to yield the desired product.

Compounds of formula I may, if desired, be converted into their non-toxic, pharmaceutically acceptable acid addition salts by conventional methods; for example, by dissolving a compound of formula I in a suitable solvent and acidifying the solution with one or more molar equivalents of the desired acid. The invention also comprises such salts.

Examples of inorganic and organic acids which may form nontoxic, pharmaceutically acceptable acid addition salts with a compound of the formula I are the following: hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, tartaric acid, citric acid, methanesulfonic acid, and the like. Compounds of general formula I usually form acid addition salts with one molar equivalent of the acid.

The above described compounds of Formula I possess inhibitory activity against HIV-1 reverse transcriptase. When administered in suitable dosage forms, they are useful in the prevention or treatment of AIDS, ARC and related disorders associated with HIV infection. Another aspect of the invention, therefore, is a method for preventing or treating HIV-1 infection which comprises administering to a human being, exposed to or

infected by HIV-1, a prophylactically or therapeutically effective amount of a novel compound of Formula I, as described above.

The compounds of formula I may be administered in single or divided doses by the oral, parenteral or topical routes. A suitable oral dosage for a compound of formula I would be in the range of about 10 to 500 mg per day. In parenteral formulations, a suitable dosage unit may contain from 1 to 50 mg of said compounds, whereas for topical administration, formulations containing 0.01 to 1% active ingredient are preferred. It should be understood, however, that the dosage administration from patient to patient will vary and the dosage for any particular patient will depend upon the clinician's judgement, who will use as criteria for fixing a proper dosage the size and condition of the patient as well as the patient's response to the drug.

When the compounds of the present invention are to be administerted by the oral route, they may be administered as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. Such carrier material can be an inert organic or inorganic carrier material suitable for oral administration. Examples of such carrier materials are water, gelatin, talc, starch, magnesium stearate, gum arabic, vegetable oils, polyalkylene-glycols, petroleum jelly and the like.

The pharmaceutical preparations can be prepared in a conventional manner and finished dosage forms can be solid dosage forms, for example, tablets, dragees, capsules, and the like, or liquid dosage forms, for example solutions, suspensions, emulsions and the like. The pharmaceutical preparations may be subjected to conventional

pharmaceutical operations such as sterilization. Further, the pharmaceutical preparations may contain conventional adjuvants such as preservatives, stabilizers, emulsifiers, flavor-improvers, wetting agents, buffers, salts for varying the osmotic pressure and the like. Solid carrier material which can be used include, for example, starch, lactose, mannitol, methyl cellulose, microcrystalline cellulose, talc, silica, dibasic calcium phosphate, and high molecular weight polymers (such as polyethylene glycol).

For parenteral use, a compound of formula I can be administered in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable oil or a mixture of liquids, which may contain bacteriostatic agents, antioxidants, preservatives, buffers or other solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Additives of this type include, for example, tartrate, citrate and acetate buffers, ethanol, propylene glycol, polyethylene glycol, complex formers (such as EDTA), antioxidants (such as sodium bisulfite, sodium metabisulfite, and ascorbic acid), high molecular weight polymers (such as liquid polyethylene oxides) for viscosity regulation and polyethylene derivatives of sorbitol anhydrides. Preservatives may also be added if necessary, such as benzoic acid, methyl or propyl paraben, benzalkonium chloride and other quaternary ammonium compounds.

The compounds of this invention may also be administered as solutions for nasal application and may contain in addition to the compounds of this invention suitable buffers, tonicity adjusters, microbial preservatives, antioxidants and viscosity-increasing agents in an aqueous vehicle. Examples of agents used to increase viscosity are polyvinyl alcohol,

cellulose derivatives, polyvinylpyrrolidone, polysorbates or glycerin. Microbial preservatives added may include benzalkonium chloride, thimerosal, chlorobutanol or phenylethyl alcohol.

Additionally, the compounds provided by the invention can be administered by suppository.

As stated before, the compounds provided by the invention inhibit the enzymatic activity of HIV-1 RT. Based upon testing of these compounds, as described below, it is known that they inhibit the RNA-dependent DNA polymerase activity of HIV RT. Based upon other testing, not described herein, it is believed that they also inhibit the DNA-dependent DNA polymerase activity of HIV RT.

Utilizing the Reverse Transcriptase (RT) Assay described below, compounds can be tested for their ability to inhibit the RNA-dependent DNA polymerase activity of HIV RT. Certain specific compounds described in the Examples which appear below, were so tested. The results of this testing appears in Table I, below.

REVERSE TRANSCRIPTASE (RT) ASSAY

Assay Theory:

Among the enzymes for which Human Immunodeficiency Virus (HIV-1) encodes is a reverse transcriptase (1), so-named because it transcribes a DNA copy from an RNA template. This activity can be quantitatively measured in a cell-free enzyme assay which has been previously described (2), and is based upon the observation that reverse transcriptase is able to use a synthetic template [poly r(C) primed with oligo d(G)] to transcribe a

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radio-labelled, acid-precipitable DNA strand utilizing ^{3}H-dGTP as a substrate.

Materials:

a) Preparation of the enzyme

Reverse transcriptase enzyme from the LAV strain of Human Immunodeficiency Virus (HIV-1) (1) was isolated from the bacterial strain JM109 (3) expressing the DNA clone pBRTprt1+ (2) which is under the control of the lac promoter in the expression vector pIBI21 (4). An overnight culture grown in 2XYT medium (37°C, 225 rpm) (5) supplemented with 100 µg/ml ampicillin for positive selection is inoculated at a 1:40 dilution into M9 medium supplemented with 10 µg/ml thiamine, 0.5% casamino acids, and 50 µg/ml ampicillin (5). The culture is incubated (37°C, 225 rpm) until it reaches an OD540 of 0.3-0.4. At that time the repressor inhibitor IPTG (isopropyl b-D-thiogalactopyranoside) is added to 0.5mM and incubated for 2 additional hours. Bacteria are pelleted, resuspended in a 50mM Tris, 0.6mM EDTA, 0.375M NaCl buffer and digested by the addition of lysozyme (1mg/ml) for 30 minutes on ice. The cells are lysed by the addition to 0.2% NP-40 and brought to 1M NaCl.

After removal of the insoluble debris by centrifugation, the protein is precipitated by the addition of 3 volumes of saturated aqueous ammonium sulfate. The enzyme is pelleted, resuspended in RT buffer (50 mM Tris pH 7.5, 1mM EDTA, 5mM DTT, 0.1% NP-40, 0.1M NaCl, and 50% glycerol), and stored at -70°C for further use.

b) Composition of 2X concentrated stock reaction mixture

Stock Reagent	2X Mix Concentration
1M Tris pH 7.4	100mM
1M Dithiothrietol	40mM
1M NaCl	120mM
1% Nonidet P-40	0.1%
1M MgCl	4mM
[poly r(C) /oligo d(G)](5:1)	2µg/ml
^{3}H-dGTP (81µM)	0.6µM

Assay Procedure:

The 2X concentrated stock reaction mixture is aliquoted and stored at -20°C. The mixture is stable and thawed for use in each assay. This enzyme assay has been adapted to a 96 well microtiter plate system, and has been previously described (6). Tris buffer (50 mM, pH 7.4), vehicle. (solvent diluted to match the compound dilution), or compounds in vehicle are dispensed into 96-well microtiter plates (10µl/well; 3 wells/ compound). The HIV RT enzyme is thawed, diluted in 50mM Tris pH 7.4 so that fifteen µl of diluted enzyme contain 0.001 Unit (one unit is that amount of enzyme to transform 1 micromole of substrate per minute at 25°C), and fifteen µl are dispensed per well. Twenty µl of 0.12-0.5M EDTA are added to the first three wells of the microtiter plate. EDTA chelates the Mg^{++} present and prevents reverse transcription. This group serves as background polymerization which is subtracted from all other groups. Twenty-five ul of the 2X reaction mixture are added to all wells and the assay is allowed to incubate at room temperature for 60 minutes. The assay is terminated by precipitating the DNA in each well with 50ul of 10% trichloracetic acid (TCA) in 1% sodium pyrophosphate. The microtiter plate is incubated for 15 minutes at 4°C and the precipitate

is fixed onto #30 glass fiber paper (Schleicher & Schuell) using a Skatron semi-automatic harvester. The filters are then washed with additional 5% TCA containing 1% sodium pyrophosphate, rinsed with 70% aqueous ethanol, dried, and transferred to scintillation vials (6). Each vial receives 2 mls of scintillation cocktail and is counted in a Beckman beta counter.

Calculations for percent inhibition are as follows:

$$\%\text{inhibition} = \frac{\text{CPM Mean Test Value - CPM Mean Control Value}}{\text{CPM Mean Control Value}} \times 100$$

References:

1. Benn, S., et al., SCIENCE 230:949, 1985

2. Farmerie, W.G. et. al., SCIENCE 236:305, 1987

3. Yanisch-Perron, C., Viera, J., and Messing, J., GENE 33:103, 1985

4. International Biotechnologies, Inc., New Haven, CT 06535

5. Maniatis, T, Fritsch, E.F., and J. Sambrook, eds. MOLECULAR CLONING: A LABORATORY MANUAL, Cold Spring Harbor Laboratory, 1982

6. Spira, T., et. al. J. Clinical Microbiology, 25:97, 1987.

In order to confirm that compounds which are active in the RT Assay also have the ability to inhibit HIV replication in a living system, compounds according to the invention were also tested in the human T-Cell Culture Assay described below. The results of this testing appear in Table I.

HUMAN T CELL CULTURE ASSAY

Assay Theory: Formation of syncytia is a feature of *in vitro* cultures of CD4+ T-cells infected with HIV-1. In this assay, T-cells are treated with a putative replication inhibiting compound and then infected with

HIV-1. After incubation the culture is checked for the formation of syncytia. The absence or reduction is the number of syncytia is used as a measure of the test compound's ability to inhibit HIV replication.

Assay Method: The target cells, designated C8166, are a subclone of human lymphoma cells of T-cell origin and are established at an initial density of $5x10^4$ per 100 ul in RPMI 1640 (+ 10% fetal bovine serum) culture medium in 96 well flat bottom plates. A selected amount of test compound, dissolved in DMSO is included. After 24 hours, 50-100 $TCID_{50}$'s (the dose that results in induced effect in 50% of test cultures) of the HTLV-IIIB strain of HIV-1 (2) are innoculated into each culture. Control cultures receive compound or virus only. Four days after virus challenge, cultures are visually examined for the frequency and distribution of virus-induced giant cell syncytia. The percent inhibition by the test compound is determined by comparison with control values. Confirmation of the presence or absence of virus replication is accomplished by harvesting the cell free culture fluids from all experimental groups to determine the presence or absence of infectious progeny through the induction of syncytia formation in secondary human T-cell cultures after 3 days.

References:

(1) M. Somasundaran and H.L. Robinson, Science 242, 1554 (1998)

(2) G.M. Shaw, R.H. Hahn, S.K. Arya, J.E. Groopman, R.C. Gallo and F. Wong-Staal, Science 226, 1165 (1984)

In order to assess the specificity of the enzyme inhibitory activity of the compounds provided by the invention, a few were tested, using known *per se* assay methods, for their ability to inhibit Feline Leukemia Virus-

derived reverse transcriptase and Calf Thymus-derived DNA alpha-polymerase. None of the compounds so tested was observed to possess any inhibitory activity against these enzymes. These results indicate that the enzyme inhibitory activity of the compounds provided by the invention is directed rather specifically against HIV RT.

In order to roughly assess the cytotoxicity of the compounds provided by the invention, several such compounds were tested in the MTT Cellular Cytotoxicity Assay described below. The results of this testing are reported in Table I, below. Compounds having a relatively high EC_{50} are preferred.

MTT ASSAY FOR CELLULAR CYTOTOXICITY

Assay Theory:

The MTT [3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl tetrazolium bromide] assay is based on cleavage of tetrazolium bromide by metabolically active cells, resulting in a highly quantitative blue color. This assay has been previously described (1) but has been optimized for the purposes of the testing reported herein.

Assay Method:

The H9 cell line (2), an established human lymphoma suspension cell line grown in RPMI 1640 supplemented with 10% fetal bovine serum is used as the target cell line in the assay. Cells (100µl) are plated in microtest plate wells at a concentration of 10^5 cells per ml in the presence of varying concentrations of inhibitor. The cells are incubated at 37°C in a humidified CO_2 incubator. Five days later, 20µl of MTT (5 mg/ml in RPMI 1640, sonicated, 0.2 micron filtered, and stored at 4°C) is added to each well. After 4 hours additional incubation at 37°C, 60 µl of Triton-X is added to each well and thoroughly mixed to aid the solubilization of the crystals. Absolute ethanol (5 µl) is incubated for 30 minutes at 60°C and immediately read on a plate reader (Dynatech) at a wavelength of 570nm.

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Data from this assay are used to generate a nonlinear regression analysis which yields an EC_{50}.

References:

1. Mosmann, Tim, J. Immunol. Methods, 65:55, 1983.

2. Jacobs, J.P., J. Natl. Cancer Inst., 34:231, 1965.

The following examples further illustrate the present invention and will enable others skilled in the art to understand it more completely. It should be understood, however, that the invention is not limited to the particular examples given below.

Example 1

5-11-Dihydro-11-ethyl-5-methyl-6H-dipyrido[3.2-b:2',3',-e][1,4]diazepin-6-thione

A mixture of 2.66g (0.01 mol) of 5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one and 2.10g (0.005 mol) of Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in 50ml of toluene was refluxed for 2 1/2 h. The solvent was then removed in vacuo and water was added to the residue. The product was extracted with ethyl acetate, dried (anhydrous sodium sulfate) and concentrated in vacuo. Purification was effected on a silica gel column using methylene chloride as the first eluent, followed by ethyl acetate/hexane (1:4). Removal of the solvent in vacuo gave 2.20g (74% of theory) of 5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-thione as a yellow powder which was recrystallized from 10% hexane/ethyl acetate to provide 1.1g of yellow needles, m.p. 157-158°C.

The resulting compound was tested using the Reverse Transcriptase Inhibition Assay (at 10 μg/ml) and T-Cell Culture Assay (at 3 μg/ml) and demonstrated 100% inhibition in both tests.

Preparation of starting compound

5,11-Dihydro-6H-dipyrido[3,2-b:2',3'-4][1,4]diazepin-6-one

a) 2-Chloro-N-(2-chloro-3-pyridinyl)-3-pyridinecarboxamide

In a three-necked round-bottomed flask, fitted with an efficient reflux condenser, mechanical stirrer and dropping funnel, were placed 215 g (1.672 mol) of 3-amino-2-chloropyridine, dissolved in a mixture of 400 ml dioxane, 500 ml cyclohexane and 130 ml pyridine. The solution of 299.2 g (1.7 mol) of freshly prepared 2-chloro-3-pyridinecarboxylic acid chloride in 200 ml dioxane was added at such a rate as to keep the vigorous reaction under control. Thereafter, the reaction mixture was allowed to cool to room temperature and the resulting crystalline precipitate was filtered off and washed successively with cyclohexane and ether.

The dark brown product was dissolved in 5 l of a 3% aqueous solution of sodium hydroxide. The resulting solution was treated with charcoal, suction filtered, and the filtrate was acidified by addition of 50% aqueous acetic acid. The resulting precipitate was collected by filtration and thoroughly washed with water. After being dried overnight in a stream of nitrogen at room temperature the almost colorless product had a m.p. of 156-159°C and was sufficiently pure for further reactions. The yield was 376.0 g (84% of theory).

b) N-(2-Chloro-3-pyridinyl)-2-[[(4-methoxyphenyl)methyl]amino]-3-pyridinecarboxamide

13.4 g (0.05 mol) of the product obtained in step a) were dissolved in 20 ml of xylene, and the resulting solution was admixed with 13.8 g (0.1 mol) of p-methoxybenzylamine. Thereafter, the mixture was refluxed for two hours. The reaction mixture was then evaporated in vacuo, and the residue was purified by column chromatography on silica gel (0.2-0.5 mm) using dichloromethane/ethyl acetate 10/1 (v/v) as an eluent. Colorless crystals, melting at 122-124°C (after recrystallization from acetonitrile). The yield was 17.2 g (93% of theory).

c) 5,11-Dihydro-11-[(4-methoxyphenyl)methyl]-6H-dipyrido-[3,2-b:2',3'-e][1,4]diazepin-6-one

16.7 g (0.0453 mol) of the product obtained in step b) were dissolved in 150 ml of absolute dioxane, and the resulting solution was admixed with 6.7 g (0.14 mol) of a 50% dispersion of sodium hydride in mineral oil.

Thereafter, the mixture - while protected against the external atmosphere by a low flow of nitrogen - was refluxed until no starting material could be detected by TLC. The surplus of sodium hydride was decomposed by cautious addition of 10 ml of a mixture of methanol and tetrahydrofuran (50/50 v/v). The reaction mixture was neutralized by addition of acetic acid and then was evaporated in vacuo. The residue was purified by column chromatography on silica gel (0.2-0.5 mm) using successively dichloromethane/ethyl acetate 10/1 (v/v) and dichloromethane/ethyl acetate 1/1 (v/v) as eluents. The crystalline product obtained by evaportion of suitable fractions was recrystallized from acetonitrile and

2-propanol. The product had a m.p. of 213-215°C and was identified as 5,11-dihydro-11-[(4-methoxyphenyl)methyl]-6H-dipyrido[3,2-b:2',3' -e][1,4]diazepin-6-one. The yield was 10.3 g (68% of theory). R_F 0.7 (Macherey-Nagel, Polygram^R SIL G/UV_{254}, precoated plastic sheets for TLC; dichloromethane/ethyl acetate 1/1 v/v).

d) 5,11-Dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

10.0 g (0.3 mol) of the product obtained in step c) were dissolved in 50 ml of trifluoroacetic acid whereby the mixture became slightly warm. Thereafter, the reaction mixture was stirred at 60°C for 1 hour. No starting material could be detected by TLC at that time. The mixture was then evaporated in vacuo. The residue thus obtained was thoroughly stirred with 0.5% aqueous ammonia and then was filtered by suction. The raw product was recrystallized from 150 ml of dimethyl sulfoxide to provide colorless crystals of m.p. of > 340°C. The yield was 4.8 g (75% of theory).

The product was identified as 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one.

e) Following step c) 10 g of the resulting compound can instead be reacted with trifluoroacetic acid, stirred for one hour at room temperature, the acid removed in vacuo and the residue stirred for one hour with 0.3% ammonia. The solid was filtered and dried to give 6.7 g of the 5-methyl substituted derivative.

2.0 g of a 50% dispersion of NaH in mineral oil was added to 5.75 g of the 5-methyl derivative in 100 ml dimethyl-

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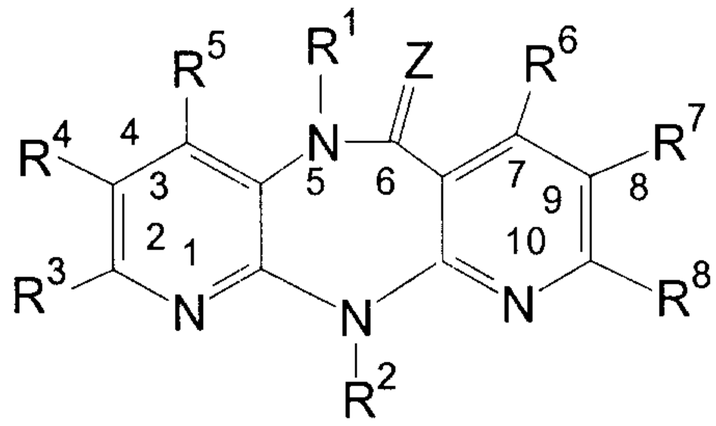
formamide. After cessation of hydrogen evolution the mixture was heated to 50°C for 30 min. and the mixture stirred overnight at room temperature. Excess sodium hydride was decomposed by the addition of ice followed by water. The product was extracted with ether, dried (anhydrous sodium sulfate) and evaporated to give 4.5 g of 5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

m.p. 130-132°C.

The following compounds were prepared analogously to Example 1 (preparation of starting materials) and according to methods C and D (for Z = O) and analogously to Example 1 (method E) (for Z = S), and were tested using the Reverse Transcription Inhibitory Assay described above.

Z is an oxygen atom unless the compound is noted to be a thiolactam.

The compounds are unsubstituted at the 2, 3, 4, 7, 8 and 9 positions unless noted in the column headed "OTHER"



Example	R^1	R^2	OTHER	Inhib. @ 10 µg/ml	M.P. °C
2	H	$-CH_2Ph-4-OMe$		81%	209-210
3	Me	$-CH_2Ph$		66%	-
4	Me	$-CH_2Ph-4-OMe$		45%	120-121.5
5	Me	$-CH_2CH_2F$		96%	117-118
6	H	-Ph		71%	220-222
7	H	Et	4-Et	100%	212-214
8	Me	Et	8-Cl	94%	105-106

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Example	R^1	R^2	OTHER	Inhib. @ 10 µg/ml	M.P. °C
9	Me	Et	4-Me	98%	157-159
10	Me	$-COCH_3$		73%	138-143
11	$-CH_2SCH_3$	Et		93%	118-120
12	H	Et	2,3-di Me	100%	212-214
13	H	Et	9-Me	86%	244-247
14	H	Et	2-Me	91%	263-266
15	H	Et	2,4-di Me	100%	210-211
16	H	Et	3-Me	95%	not avail.
17	Me	Et	3-Me	96%	94-96
18	H	$-COCH_3$		60%	>215 (dec).
19	Me	Et	2,9-di Me	98%	100-102
20	H	Et	2,4,9-tri Me	100%	228-230
21	Me	Et	2-Me	100%	124-126
22	H	Et	3,4-di Me	100%	265-266
23	Me	Et	3,4-di Me	99%	119-120
24	Me	Et	9-Me	96%	79-93
25	$-COCH_3$	Et		96%	123-124.5
26	Me	$-CH_2SCH_3$		99%	109-110
27	H	Et	3-Cl	92%	217-218
28	Me	Et	3-Cl	99%	124-125
29	$-CH_2Ph$	$-COCH_3$		37%	169-170
30	Me	$-CH_2CH=CH_2$		99%	93-95
31	H	Et	2-Cl	96%	252-254
32	Me	Et		100%	143-145
33	Me	$-CH_2C=CH$		94%	169-170
34	Me	Et	2-Cl	100%	125-126
35	H	Et	7-Me	80%	193-194
36	H	Et	8,9-di Me	42%	204-206
37	H	Et	8-Me	89%	182-183
38	H	Et	4-Cl	100%	184-186

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Example	R^1	R^2	OTHER	Inhib. @ 10 µg/ml	M.P. °C
39	H	Et	4-OMe	96%	156-157
40	H	Et	4-Et	100%	218-219
41	H	Et	8-Br	-	233.5-235.5
42	Me	Et	3-NO_2	-	154-156
43	Me	Et	3-NH_2	-	235-240
44	H	i-Pr	4-Me	-	188-189
45	Me	Et	2,4-di Me	-	151-153
46	Me	Et	7-Me	-	122-124
47	H	Et	4-Me (thiolactam)	-	158-159
48	H	Et	4-OH (2HBr salt)	-	295-296
49	Me	Et	2-OMe	-	116-118
50	Me	Et	2-OH	-	215-218
51	H	Et	2,4-di Me (thiolactam)	-	199-201
52	Me	Et	2-NH_2	-	197-199
53	Me	Et	2-NHMe	-	186-189

EXAMPLE A

Capsules or Tablets

A-1

Ingredients	Quantity
Active compound	50 mg
Starch	160 mg
Microcrys, Cellulose	90 mg
Sodium Starch Gluctate	10 mg
Magnesium Stearate	2 mg
Fumed colloidal silica	1 mg

A-2

Ingredients	Quantity
Active compound	50 mg
Dicalcium Phosphate	160 mg
Microcrys. Cellulose	90 mg
Stearic acid	5 mg
Sodium Starch Glycolate	10 mg
Fumed colloidal silica	1 mg

The compound of Example 2 is blended into a powder mixture with the premixed excipient materials as identified above with the exception of the lubricant. The lubricant is then blended in and the resulting blend compressed into tablets or filled into hard gelatin capsules.

EXAMPLE B

Parenteral Solutions

Ingredients	Quantity
Active compound	500mg
Tartaric acid	1.5g
Benzyl Alcohol	0.1% by weight
Water for injection	q.s. to 100ml

The excipient materials are mixed with the water and thereafter the active compound is added. Mixing is continued until the solution is clear. The pH of this solution is adjusted to 3.0 and is then

filtered into the appropriate vials or ampoules and sterilized by autoclaving.

EXAMPLE C

Nasal Solutions

Ingredients	Quantity
Active compound	100mg
Citric acid	1.92g
Benzalkonium chloride	0.025% by weight
EDTA	0.1 % by weight
Polyvinylalcohol	10% by weight
Water	q.s. to 100ml

The excipient materials are mixed with the water and thereafter the active compound is added and mixing is continued until the solution is clear. The pH of this solution is adjusted to 4.0 and is then filtered into the appropriate vials or ampoules.

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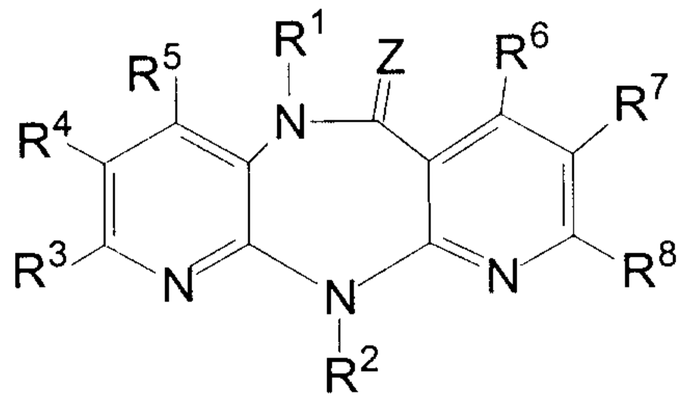
CLAIMS:

1. A compound of the formula



I

wherein,

Z is oxygen or sulfur;

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 5 carbon atoms, trihalomethyl, alkenyl or alkynyl of 3 to 5 carbon atoms, 2-halo-propen-1-yl, arylmethyl (wherein the aryl moiety is phenyl or thienyl or furanyl, which is either unsubstituted or substituted by methyl, methoxy or halogen), alkanoyl of 2 to 3 carbon atoms, or alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms;

R^2 is hydrogen, alkyl or fluoroalkyl of 1 to 5 carbon atoms, alkenyl or alkynyl of 2 to 5 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, hydroxyalkyl of 2 to 5 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or halogen), phenyl (which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms hydroxy or halogen) or alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms; and,

R^3 through R^8 are each hydrogen; or,

one of R^3 through R^8 is alkyl of 1 to 4 carbon atoms, alkoxy or alkylthio of 1 to 4 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkanoylamino of 1 to 4 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, carboxyalkyl

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of 2 to 4 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, cyano, nitro, hydroxyl, carboxyl, amino, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, azido or halogen, with the other five substituents being hydrogen; or

R^3, R^4, and R^5 are each independently hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that at least one of these substituents is hydrogen, or one of R^3, R^4 and R^5 is butyl with the remaining two substituents being hydrogen; and,

R^6, R^7, and R^8 are each independently hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that at least one of these substituents is hydrogen, or one of R^6, R^7 and R^8 is butyl with the remaining two substituents being hydrogen;

with the proviso that when Z is oxygen and R^1 and R^2 are the same or different and are hydrogen or straight chained or branched alkyl of 1 to 5 carbon atoms at least one of R^3 through R^8 is other than hydrogen, or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of Formula I, as set forth in claim 1, wherein,

Z is oxygen or sulfur;

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 5 carbon atoms, trihalomethyl, alkenyl or alkynyl of 2 to 4 carbon atoms, 2-halo-propen-1-yl, or alkoxyalkyl or alkylthioalkyl of 2 to 3 carbon atoms;

R^2 is alkyl or fluoroalkyl of 1 to 4 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 2 to 3 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl or thienyl, which is either unsubstituted or substituted by methyl, hydroxyl, methoxy or halogen), phenyl (which is either unsubstituted or substituted

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with methyl, methoxy, hydroxyl or halogen) or alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms;

R^3, R^4, and R^5 are each independently hydrogen or methyl, with the proviso that at least one of these substituents is hydrogen, or R^5 is ethyl, propyl or butyl with the remaining two substituents being hydrogen;

R^6, R^7, and R^8 are each independently hydrogen or methyl, with the proviso that at least one of these substituents is hydrogen, or R^6 is ethyl, propyl or butyl with the remaining two substituents being hydrogen;

or a pharmaceutically acceptable acid addition salt thereof.

3. A compound of formula I, as set forth in claim 1, wherein,

Z is oxygen or sulfur;

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 4 carbon atoms or allyl;

R^2 is straight or branched alkyl or fluoroalkyl of 1 to 4 carbon atoms, allyl or benzyl and,

R^3 through R^8 are each hydrogen;

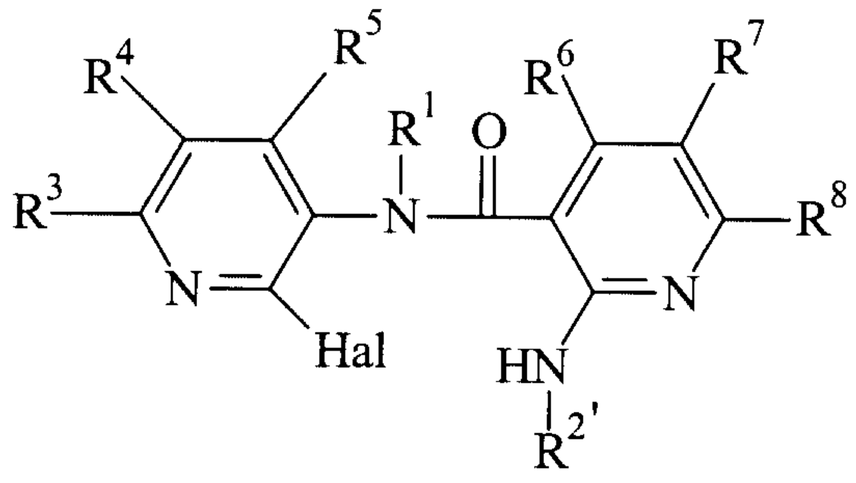
or a pharmaceutically acceptable acid addition salt thereof.

4. Use of a compound of formula I, as set forth in claims 1, 2 or 3 for preventing or treating HIV-I infection.

5. A pharmaceutical composition suitable for preventing or treating HIV-I infection which comprises a prophylactically or therapeutically effective amount of a compound of formula I, as set forth in claims 1, 2 or 3, and a pharmaceutically acceptable carrier.

6. A method of preparing a compound as defined in any one of claims 1 to 3, which comprises carrying out one of the following methods;

A. for preparing compounds in accordance with formula I in which R^2 is other than hydrogen, cyclising a carboxylic acid amide of the general formula II



II

wherein R^1 and R^3 through R^8 have the same meanings as set forth with respect to formula I, $R^{2'}$ has the same definitions as R^2 with the exception of hydrogen, and Hal represents fluorine, chlorine, bromine or iodine.

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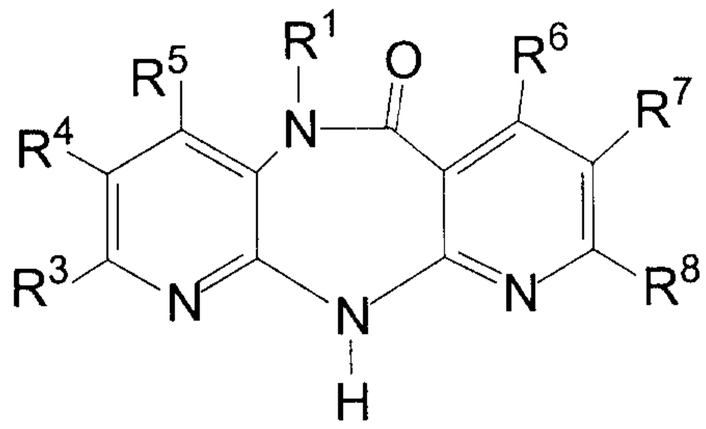
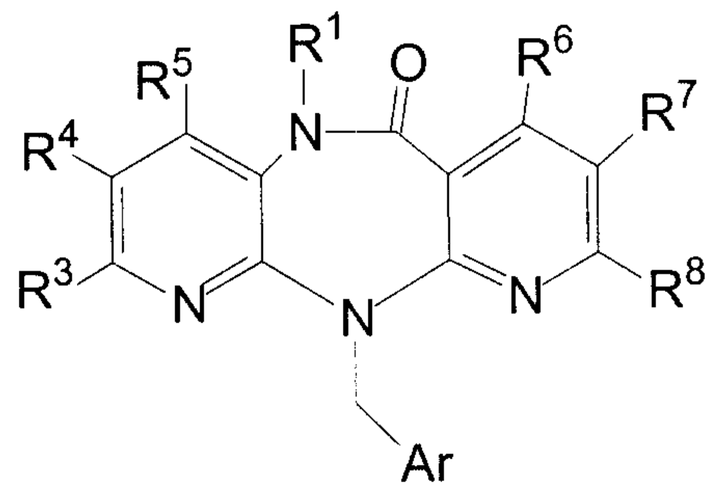
B. for producing compounds in accordance with Formula Ib



Ib

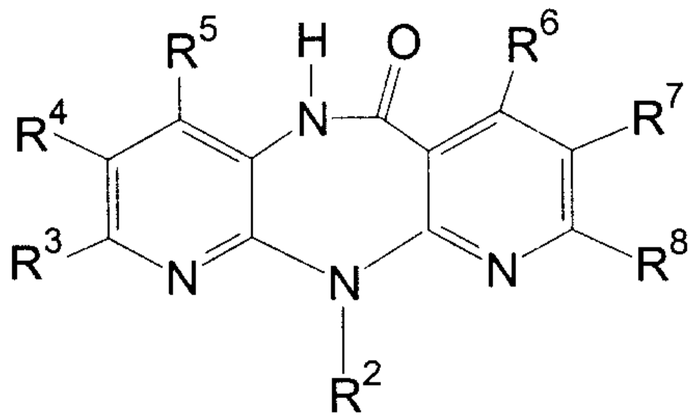
in which R^1 and R^3 through R^8 have the same meanings as set forth with respect to Formula I, hydrolytically cleaving the aryl methyl group in a compound of general Formula III



III

in which R^1 and R^3 through R^8 are as defined above and Ar is a phenyl or 4-methoxyphenyl group,

C. for preparing compounds in accordance with Formula I in which R^2 through R^8 are as defined with respect to Formula I and R^1 is other than hydrogen, by converting a 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one of the Formula IV



(IV)

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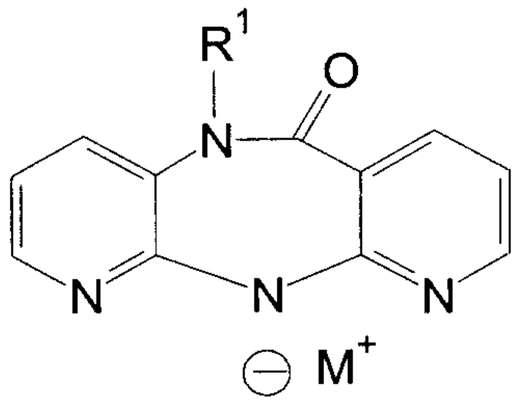
wherein R^2 through R^8 are as defined above, into the corresponding 5-alkali or alkaline earth metal compound and subsequently reacting the alkali metal compound with a reactive ester of the Formula V

$$R^{1'}X \qquad (V)$$

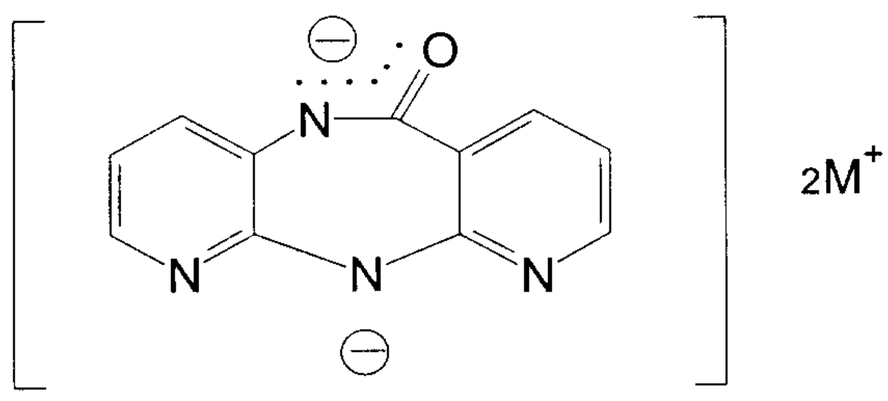
wherein $R^{1'}$ has the same definition as for R^1 with the exception of hydrogen and X is the radical of a reactive ester, a halogen atom, the group $OSO_2OR^{1'}$, the methanesulfonyloxy or ethanesulfonyloxy group or an aromatic sulfonyloxy group,

C'. for preparing compounds in accordance with Formula I in which R^2 through R^8 are as defined with respect to Formula I and R^1 is other than hydrogen, by reacting a compound of Formula IV as defined above with a compound of Formula V as defined above in the presence of an amine or of an alkali carbonate or bicarbonate,

D. for preparing a compound of Formula I in which R^2 is other than alkanoyl, hydroxyalkyl or alkoxycarbonyl and R^1 and R^3 through R^8 are as defined with respect to Formula I, by converting a compound of Formula I in which R^2 is hydrogen into the corresponding metal salt of general Formula VIa or, when R^1 is hydrogen - of Formula VIb



VIa



VIb

wherein R^1 is as hereinbefore defined and M represents an alkali metal, or M represents the group MgHal wherein Hal is a chlorine, bromine or iodine atom, and subsequently alkylating with a compound of the general formula VII

$$R^{2''}X \qquad \text{VII}$$

wherein $R^{2''}$ has the same definitions as for R^2 with the exception of alkanoyl, hydroxyalkyl, or alkoxycarbonyl and X is as defined above;

E. for preparing a compound of formula I in which Z is sulfur and R^1 through R^8 are as defined with respect to Formula I, by reacting a compound of formula I in which Z is oxygen with a sulfurating agent, and wherein in each of the foregoing processes any reactive group may be protected as desired or necessary, and thereafter as desired,

a) deprotecting any protected group,

b) hydrolysing a nitro group to an amino group,

c) acylating an amino group to form an alkanoylamino group,

d) alkylating an amino or aminoalkyl group to form a mono- or dialkylamino group or mono- or dialkylaminoalkyl group,

e) acylating the 11-position nitrogen atom of a compound of formula I in which R^2 is hydrogen,

and thereafter isolating the compound of formula I as such or as a pharmaceutically acceptable acid addition salt thereof.

7. A process as set forth in claim 6 wherein process E is carried out, followed by acylating the 11-position nitrogen atom of a compound of formula I in which R^2 is hydrogen.

8. A method of preparing a pharmaceutical composition which comprises mixing a compound as defined in any one of Claims 1 to 3, or prepared by a method according to Claim 6 or 7 with a pharmaceutically acceptable carrier or excipient.

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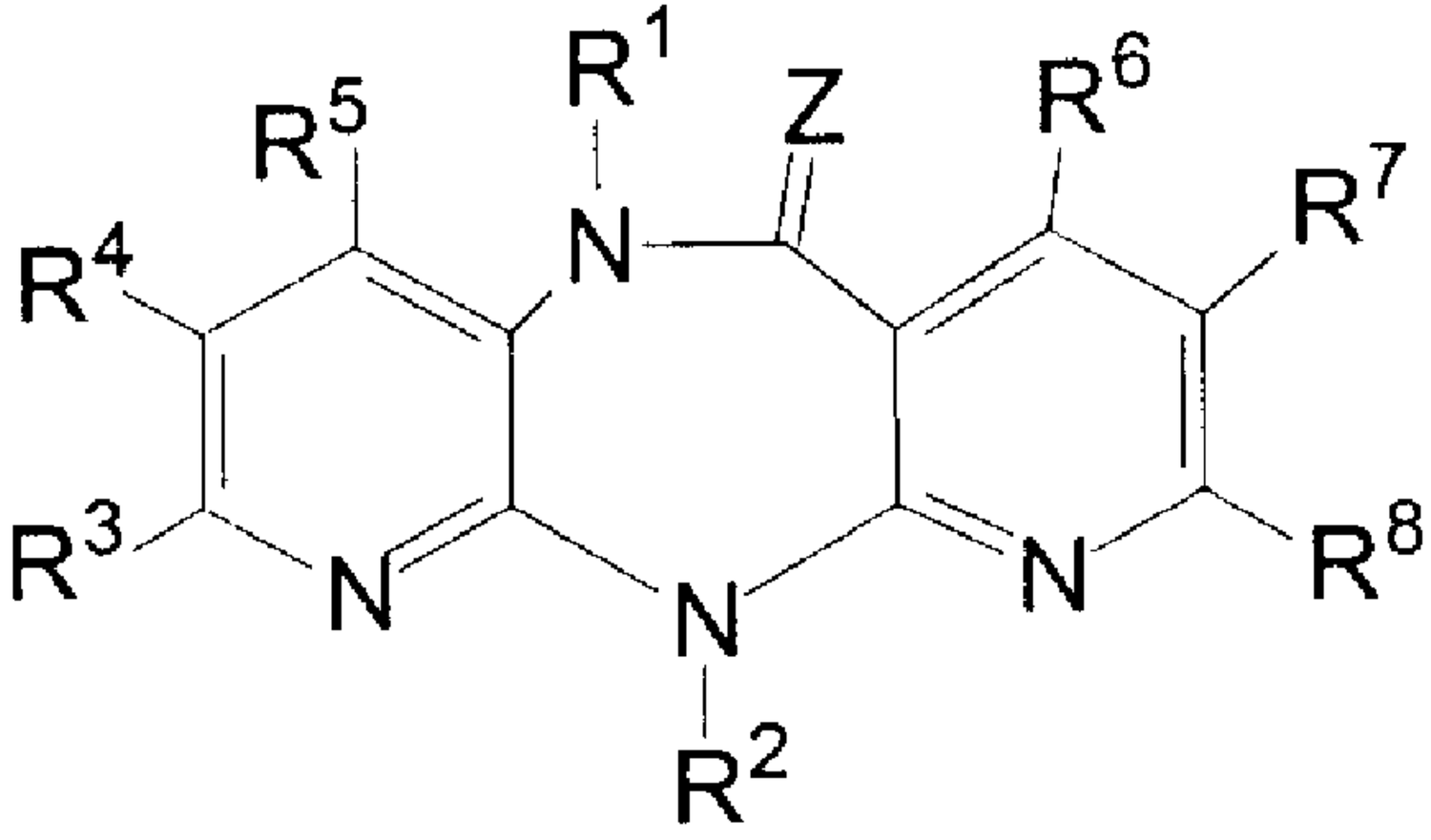
R1
Z
R6
R5
R7
R4
N
R3
N
N
N
R8
R2