

COMMONWEALTH OF AUSTRALIA

The Patents Act 1952

CONVENTION APPLICATION FOR A PATENT

620724

We, BOEHRINGER INGELHEIM PHARMACEUTICALS INC., and DR KARL THOMAE GMBH, a body corporate of USA, of 90 East Ridge, P.O. Box 368, Ridgefield, Connecticut, 06877, United States of America and a body corporate of Federal Republic of Germany, of D-7950 Biberach an der Riss, Federal Republic of Germany, hereby apply for the grant of a Patent for an invention entitled "DIPYRIDO DIAZEPIN-6-ONES AND -THIONES" which is described in the accompanying complete specification.

This application is a Convention application and is based on the Application Numbered 372,974 for a patent or similar protection made in United States of America on 28 June 1989.

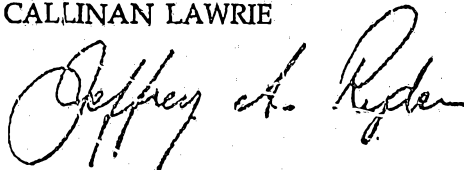
Our address for service is care of CALLINAN LAWRIE, Patent Attorneys, of 278 High Street, Kew, 3101, Victoria, Australia.

D A T E D this 28 day of June 1990.

BOEHRINGER INGELHEIM
PHARMACEUTICALS INC. and DR KARL
THOMAE GMBH

By their Patent Attorneys:

CALLINAN LAWRIE



To: The Commissioner of Patents.

Declaration in Support of an Application for Patent

In support of the Convention application made for a patent for an invention entitled
"DIPYRIDO DIAZEPIN-6-ONES AND -THIONES".

I, JEFFREY ALAN RYDER, of 278 High Street, Kew, 3101, Victoria, Australia, do solemnly
and sincerely declare as follows:-

1. I am authorised by BOEHRINGER INGELHEIM PHARMACEUTICALS INC. and
DR KARL THOMAE GmbH the applicant for the patent to make this declaration on its
behalf.

2. The basic application as defined by Section 141 of the Act is -

<u>Filing Date</u>	<u>Country</u>	<u>Applicant</u>
28 June 1989	United States of America	Dr K.D. Hargrave, Dr W. Eberlein, Dr G. Trummlitz, Dr W. Engel and Dr G. Schmidt

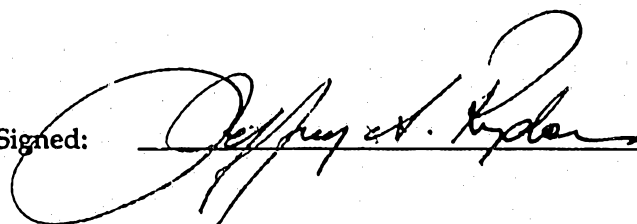
3. The basic application referred to in this Declaration was the first application made
in a Convention country in respect of the invention the subject of the application.

4. Karl D. HARGRAVE, of 4 Edna Drive, Brookfield, Connecticut, 06805, United
States of America; Wolfhard ENGEL, of Mozartstrasse 13, D-7950 Biberach 1, FDR; Wolfgang
EBERLEIN of Obere Au 6, D-7950 Biberach 1, FDR; Gunter TRUMMLITZ of Buchenweg 27,
D-7951 Warthausen, FDR; Gunther SCHMIDT, of Nymphenburger Strasse 155, D-8000,
Munchen 19, FDR are the actual inventors of the invention and the facts upon which the
applicant is entitled to make the application are as follows:-

The applicant would, if a patent were to be granted upon an
application made by the said actual inventors, be entitled to have the
patent assigned to it.

Declared at Kew this 5 day of February 1991.

Signed: _____

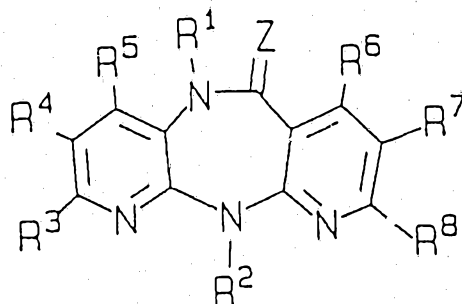


(12) PATENT ABRIDGMENT (11) Document No. AU-B-57921/90
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DIPYRIDO DIAZEPIN-6-ONES AND -THIONES
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- (21) Application No. : 57921/90 (22) Application Date : 29.06.90
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- (56) Prior Art Documents
AU 36448/89 C07D 471/14
AU 36446/89 C07D 471/04
AU 608641 20912/88 C07D 471/04
- (57) COMPOUNDS USED FOR TREATMENT OF HIV.

CLAIM

1. A compound of Formula I



(I)

(wherein,

Z is oxygen or sulphur;

R¹ is hydrogen, C₁₋₅alkyl optionally substituted by fluorine, trihalomethyl, C₃₋₅alkenyl or alkynyl, 2-halo-propen-1-yl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl and is optionally substituted

by methyl, methoxy or halogen), C_{2-3} alkanoyl or C_{2-4} -
(alkoxyalkyl) or C_{2-4} (alkylthioalkyl);

R^2 is hydrogen, C_{1-5} alkyl optionally substituted by
fluorine, C_{2-5} alkenyl or alkynyl, C_{2-4} (alkoxyalkyl) or
 C_{2-4} (alkylthioalkyl), C_{2-4} alkanoyl, C_{2-5} hydroxyalkyl,
arylmethyl (wherein the aryl moiety is phenyl, thienyl
or furanyl, and is optionally substituted by C_{1-3} alkyl
or alkoxy, hydroxyl or halogen), phenyl optionally
substituted by C_{1-3} alkyl or alkoxy groups, hydroxy or
halogen or (C_{1-5} alkoxy) carbonylmethyl; and

R^3 , R^4 , R^5 , R^6 , R^7 and R^8 is each hydrogen, or
one of R^3 , R^4 , R^5 , R^6 , R^7 and R^8 is an alkyl, alkoxy,
alkylthio, alkoxycarbonyl, hydroxyalkyl, alkanoyl,
alkanoyloxy, alkanoylamino, carboxyalkyl or aminoalkyl
group containing up to 4 carbon atoms, or a
(C_{1-2} alkoxy) carbonyl (C_{1-2} alkyl), mono- or di-
(C_{1-2} alkyl) amino, cyano, nitro, hydroxyl, carboxyl,
amino, mono- or di- (C_{1-2} alkyl) amino (C_{1-2} alkyl) or azido gro
up or a halogen atom and the remaining five of R^3 , R^4 ,
 R^5 , R^6 , R^7 and R^8 are each hydrogen, or

R^3 , R^4 and R^5 , are each independently hydrogen or C_{1-3} alkyl
with the proviso that at least one is hydrogen, or one
of R^3 , R^4 and R^5 is butyl with the remaining two being
hydrogen, and

R^6 , R^7 and R^8 are each independently hydrogen or C_{1-3} alkyl
with the proviso that at least one is hydrogen, or one
of R^6 , R^7 and R^8 is butyl with the remaining two being
hydrogen;

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with the proviso that when R^1 and R^2 are each independently hydrogen or straight-chained or branched C_{1-5} alkyl and R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are all hydrogen then Z is sulphur)

or an acid addition salts thereof.

AUSTRALIA

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Form 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number:
Lodged:

Complete Specification - Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS INC. and DR KARL THOMAE GmbH

Address of Applicant: a body corporate of USA, of 90 East Ridge, P.O. Box 368, Ridgefield, Connecticut, 06877, United States of America and a body corporate of Federal Republic of Germany, of D-7950 Biberach an der Riss, Federal Republic of Germany

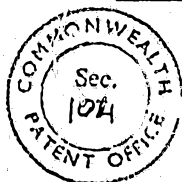
Actual Inventors: Karl D. HARGRAVE, Wolfgang EBERLEIN, Gunter TRUMMLITZ, Wolfhard ENGEL and Gunther SCHMIDT

Address for Service: CALLINAN LAWRIE, Patent & Trade Mark Attorney, 278 High Street, Kew, Victoria 3101, Australia.

Complete Specification for the invention entitled:

"DIPYRIDO DIAZEPIN-6-ONES AND -THIONES"

The following statement is a full description of this invention, including the best method of performing it known to me:-



55-553.517

DIAZEPIN-6-ONES AND -THIONES

This invention relates to novel 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-ones and -thiones and the use of these compounds to combat HIV infection.

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

Like other viruses, HIV-1 cannot replicate without utilizing the biosynthetic apparatus of the host cell it infects. The virus causes the biosynthetic apparatus to produce the proteins needed for viral progeny. The viral proteins are coded for by the genetic material contained within the infecting virus particle, or virion. In a retrovirus, such as HIV, the stable genetic material normally carried by the virus is RNA, compared to the host cell's DNA genome. The viral RNA must be converted into DNA and integrated into the host cell's genome, so that the host cell may produce the required viral proteins.

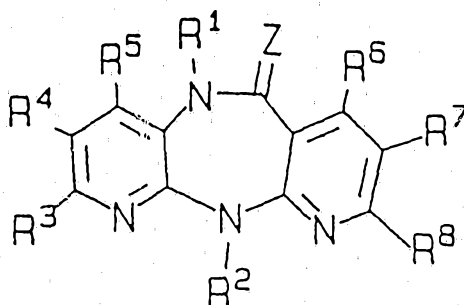
The conversion of the RNA to DNA is accomplished by the enzyme reverse transcriptase (RT), which is present within the infecting virion with the RNA. Reverse transcriptase has three identified enzymatic functions - it acts as an RNA-dependent DNA polymerase, as a ribonuclease, and as a DNA-dependent DNA polymerase. As an RNA-dependent DNA polymerase, RT produces a single-stranded DNA copy of the viral RNA. Next, as a ribonuclease, RT releases the newly-formed DNA produced from the original viral RNA and then destroys the original RNA. Finally, acting as a DNA-dependent DNA polymerase, RT makes a second, complementary DNA strand, using the first DNA strand as a template. The two DNA strands form a double-stranded DNA molecule, which is

integrated into the host cell's genome by another enzyme called an integrase.

The genetic information of the host cell is stably maintained as double-stranded DNA. In normal protein synthesis, a selected section of the DNA genome is first transcribed into single stranded messenger RNA which is subsequently translated to produce the encoded proteins. There is no reverse transcription involved in the normal metabolism of the host cell and an enzyme displaying a reverse transcriptase activity is not present.

Hence compounds which inhibit the enzymatic functions of HIV reverse transcriptase (especially HIV-1 reverse transcriptase) will inhibit replication of HIV in infected cells without affecting the host cell. Such compounds are useful in the prevention or treatment of HIV infection in human subjects.

Viewed from one aspect, the invention provides compounds of Formula I



(I)

(wherein,

Z is oxygen or sulphur;

R¹ is hydrogen, C₁₋₅alkyl optionally substituted by fluorine, trihalomethyl, C₃₋₅alkenyl or alkynyl, 2-halo-propen-1-yl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl and is optionally substituted by methyl, methoxy or halogen), C₂₋₃alkanoyl or C₂₋₄-



(alkoxyalkyl) or C_{2-4} (alkylthioalkyl);

R^2 is hydrogen, C_{1-5} alkyl optionally substituted by fluorine, C_{2-5} alkenyl or alkynyl, C_{2-4} (alkoxyalkyl) or C_{2-4} (alkylthioalkyl), C_{2-4} alkanoyl, C_{2-5} hydroxyalkyl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, and is optionally substituted by C_{1-3} alkyl or alkoxy, hydroxyl or halogen), phenyl optionally substituted by C_{1-3} alkyl or alkoxy groups, hydroxy or halogen or (C_{1-5} alkoxy)carbonylmethyl; and

R^3 , R^4 , R^5 , R^6 , R^7 and R^8 is each hydrogen, or

one of R^3 , R^4 , R^5 , R^6 , R^7 and R^8 is an alkyl, alkoxy, alkylthio, alkoxycarbonyl, hydroxyalkyl, alkanoyl, alkanoyloxy, alkanoylamino, carboxyalkyl or aminoalkyl group containing up to 4 carbon atoms, or a (C_{1-2} alkoxy)carbonyl(C_{1-2} alkyl), mono- or di-(C_{1-2} alkyl)amino, cyano, nitro, hydroxyl, carboxyl, amino, mono- or di-(C_{1-2} alkyl)amino(C_{1-2} alkyl) or azido group or a halogen atom and the remaining five of R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are each hydrogen, or

R^3 , R^4 and R^5 , are each independently hydrogen or C_{1-3} alkyl with the proviso that at least one is hydrogen, or one of R^3 , R^4 and R^5 is butyl with the remaining two being hydrogen, and

R^6 , R^7 and R^8 are each independently hydrogen or C_{1-3} alkyl with the proviso that at least one is hydrogen, or one of R^6 , R^7 and R^8 is butyl with the remaining two being hydrogen;

with the proviso that when R^1 and R^2 are each independently hydrogen or straight-chained or branched C_{1-5} alkyl and R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are all hydrogen then Z is sulphur)



and acid addition salts thereof.

Preferred compounds according to the invention include those of Formula I

wherein,

Z is oxygen or sulphur;

R¹ is hydrogen, C₁₋₅alkyl optionally substituted by fluorine, trihalomethyl, C₂₋₄alkenyl or alkynyl, 2-halo-propen-1-yl, or C₂₋₃(alkoxyalkyl) or C₂₋₃(alkylthioalkyl);

R² is C₁₋₄alkyl optionally substituted by fluorine, C₂₋₄alkenyl or alkynyl, C₂₋₄(alkoxyalkyl) or C₂₋₄(alkylthioalkyl), C₂₋₃alkanoyl, C₂₋₄hydroxyalkyl, arylmethyl (wherein the aryl moiety is phenyl or thienyl and is optionally substituted by methyl, methoxy, hydroxyl or halogen), phenyl (optionally substituted by methyl, methoxy, hydroxyl or halogen) or (C₁₋₅alkoxy)-carbonylmethyl;

R³, R⁴ and R⁵ are each independently hydrogen or methyl, with the proviso that at least one is hydrogen, or R⁵ is ethyl, propyl or butyl and R³ and R⁴ are hydrogen, and

R⁶, R⁷, and R⁸ are each independently hydrogen or methyl, with the proviso that at least one is hydrogen, or R⁶ is ethyl, propyl or butyl and R⁷ and R⁸ are hydrogen,

and the salts thereof.

Particularly preferred compounds according to the invention include those of Formula I

wherein,

Z is oxygen or sulphur;



R¹ is hydrogen, C₁₋₄alkyl optionally substituted by fluorine or allyl;

R² is C₁₋₄alkyl optionally substituted by fluorine, allyl or benzyl; and

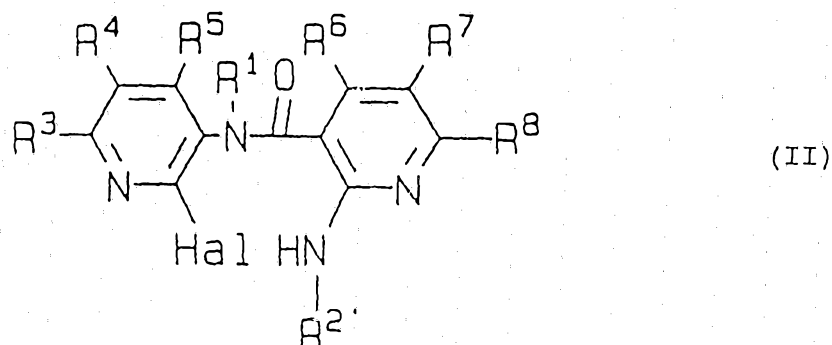
R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are each hydrogen,

and the salts thereof.

The compounds according to the invention can be prepared by known methods or modifications thereof.

Thus viewed from a further aspect the invention provides a process for preparing a compound of Formula I or salt thereof, said process comprising at least one of the following steps:

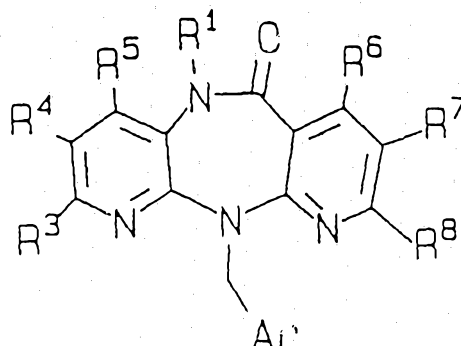
(A) (for preparing compounds of Formula I wherein R² is other than hydrogen) cyclizing a carboxylic acid amide of general Formula II



(wherein R¹, R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as hereinbefore defined, R² is as defined for R² with the exception of hydrogen, and Hal represents a fluorine, chlorine, bromine or iodine atom);

(B) (for producing compounds of Formula I wherein R² is hydrogen) hydrolytically cleaving an arylmethyl group from a compound of Formula III

(III)



(wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as hereinbefore defined and Ar represents an aryl group, for example, a phenyl or 4-methoxyphenyl group);

(C) (for preparing compounds of Formula I wherein R^1 is other than hydrogen)

converting a compound of Formula I wherein R^1 is hydrogen into a corresponding 5-alkali or alkaline earth metal compound and subsequently reacting said alkali or alkaline earth metal compound with a compound of Formula IV



(IV)

(wherein $R^{1'}$ is as hereinbefore defined for R^1 with the exception of hydrogen and X is the radical of a reactive ester, a halogen atom, a group $OSO_2OR^{1'}$, a methanesulphonyloxy or ethanesulphonyloxy group or an aromatic sulphonyloxy group);

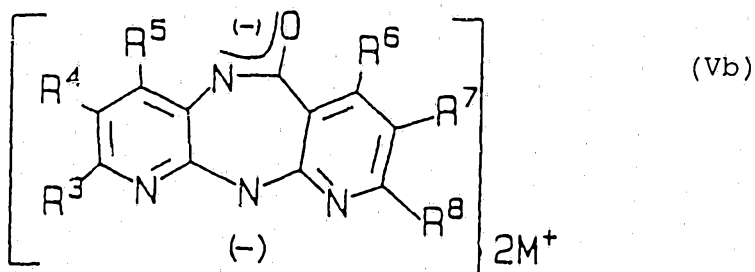
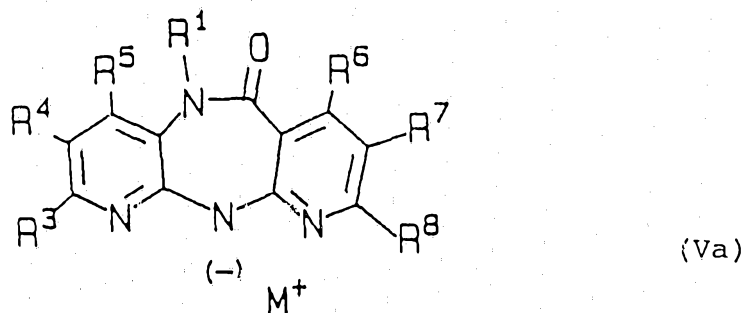
(D) (for preparing compounds of Formula I wherein R^1 is

other than hydrogen)

by reacting a compound of Formula I wherein R^1 is hydrogen with a compound of Formula IV (as defined above) in the presence of an amine or an alkali metal carbonate or bicarbonate;

(E) (for preparing a compound of Formula I wherein R^2 is other than an alkanoyl, hydroxyalkyl or alkoxy carbonylmethyl group)

converting a compound of Formula I wherein R^2 is hydrogen into a corresponding metal salt of Formula Va or, where R^1 represents hydrogen, Vb



(wherein M represents an alkali metal, such as lithium, sodium, potassium, rubidium or cesium, or M represents the group $MgHal^+$, wherein Hal is chlorine, bromine or iodine) and subsequently alkylating with a compound of

Formula VI



(VI)

(wherein X is as hereinbefore defined) and $R^{2''}$ is as defined for R^2 with the exception of alkanoyl, hydroxyalkyl and alkoxycarbonylmethyl);

(F) (to prepare a compound of Formula I, wherein Z is sulphur)

reacting a compound of Formula I, wherein Z is oxygen, with a sulphurating agent;

(G) subsequently if desired reacting a compound so obtained to

- (i) hydrolyse a nitro group to an amino group,
- (ii) acylate an amino group to an alkanoylamino group,
- (iii) alkylate an amino or aminoalkyl group to a mono- or di-alkylaminoalkyl group,
- (iv) acylate the 11-position nitrogen where R^1 is hydrogen, preferably subsequent to step (E); and

(H) converting a compound of Formula I into an acid addition salt thereof or a salt of a compound of Formula I into the free base, where in any of the foregoing steps reactive groups may if desired be protected by protecting groups which are subsequently removed.

In step A, cyclisation is preferably carried out by converting the compounds of 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 Formula II, R^1 does not represent hydrogen, metallation requires at least 1

mole of the metallating agent. If R^1 represents hydrogen, at least 2 moles of this agent must be used. For metalation, 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 Formula II in dipolar aprotic solvents, preferably in sulfolane or dimethylsulphone. The use of catalytic quantities of strong acids, e.g. sulphuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, polyphosphoric acid, methanesulphonic acid or p-toluenesulphonic acid, has proved to be advantageous. The reaction temperature is generally 110 to 220°C, the preferred range of temperature being 130 to 170°C.

In step B, hydrolysis may conveniently be effected by moderate to strong acids or Lewis-acids at temperatures of -20 to +150°C. Such acids can be, for example, sulphuric acid, methanesulphonic acid, trifluoroacetic acid, trifluoromethanesulphonic 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 aluminium 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 to R^8 are readily hydrolyzable substituents, for example, wherein R^1 is alkanoyl or any of R^3 to R^8

are alkanoylamino or alkoxycarbonyl. In cases wherein R^1 is alkanoyl or any of R^3 to 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 to 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.

In step C, the conversion of a compound of Formula I in which R^1 is hydrogen into the corresponding alkali metal or alkaline earth metal compound may be effected by reacting the compound of Formula I 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 an 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 compound thus obtained into a compound of Formula I in which R^1 is other than hydrogen, the solution or suspension of the alkali or alkaline earth metal compound may be reacted directly, i.e. without isolation, with a compound of Formula IV at -20°C or at higher 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 compound even if R^2 in the starting material of Formula I is a hydrogen atom, provided that one equivalent of base and one equivalent of a compound of Formula IV are used.

It will be obvious to those skilled in the art that the presence of nucleophilic substituents in the end product may require the use of an intermediate of Formula I where R^1 is other than hydrogen 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 to R^8 are preferably obtained by alkylating or acylating such an intermediate having a nitro group at any of R^3 to R^8 , and subsequently reducing the nitro group, and alkylating, if appropriate, to yield the final product.

In step D examples of amines that may be used include triethylamine, diazabicycloundecene or 4-(dimethylamino)pyridine, and examples of alkali carbonates or bicarbonates that may be used include those such as sodium and potassium carbonate or sodium bicarbonate.

In step E, the conversion of a compound of Formula I into the corresponding alkali metal compound of Formulae Va or Vb may conveniently be effected by reacting 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 isopropylcyclohexylamide), 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 Va, whereas two equivalents of base are required for the formation of compounds of Formula Vb. The metallation is conveniently carried out in an inert organic solvent at temperatures of -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 reaction may be carried out at temperatures of -20 to $+80^{\circ}\text{C}$. When metallation is effected with an alkali metal hydride or alkali metal amide, it is possible to use xylene, toluene, acetonitrile, dimethylformamide and dimethylsulphoxide, in addition to the solvents mentioned hereinbefore, 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.

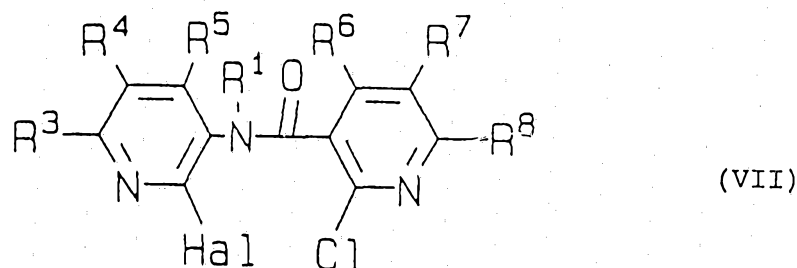
For conversion of the alkali metal salt thus obtained into a compound of Formula I in which R^2 is other than an alkanoyl, hydroxyalkyl or alkoxy carbonyl methyl group, the solution or suspension of the alkali metal compound may be reacted directly, i.e. without isolation of the reaction product, with a compound of Formula VI at -20°C or at higher temperatures, preferably at the boiling point of the solvent or suspension medium or at the boiling point of the compound of Formula VI, whichever is lower.

It will be obvious to those skilled in the art that the presence of nucleophilic substituents in the end product may require the use of an intermediate of Formula I where R^2 is other than alkanoyl, hydroxyalkyl or alkoxy carbonyl methyl which has substituents other

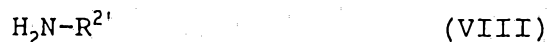
than the 11-position nitrogen, which are not nucleophilic but which can be deprotected to yield the required group. For example, amino or monoalkylamino substituents of R^3 to R^8 are preferably obtained by alkylating or acylating such an intermediate having a nitro group at any of R^3 to R^8 and subsequently reducing the nitro group, and alkylating, if appropriate, to yield the final product.

Methods (A) to (E) are particularly suited to the production of compounds of Formula I in which Z is oxygen, i.e. the diazepinone compounds.

The carboxylic acid amides of Formula II used as starting materials may be obtained, for example, by amination of 2-chloro-nicotinic amides of Formula VII



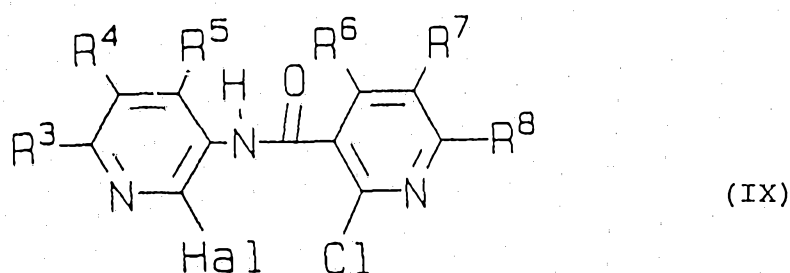
(wherein R^1 to R^8 and Hal are as hereinbefore defined) with primary amines of Formula VIII



(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 may be carried out without using a solvent; it is preferable, however, to use inert organic solvents at temperatures of 0°C to 150°C , preferably at reflux temperature. Suitable inert solvents include an excess of the primary amine of Formula VIII, 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 VII (wherein R¹ is other than hydrogen) can be prepared from 2-chloronicotinic acid amides of Formula IX



by reaction with alkylating agents of Formula IV in the presence of proton acceptors, for example amines, such as triethylamine, diazabicycloundecene, 4-(dimethylamino)pyridine, or alkali or alkaline earth metal hydroxides, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, or 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 Formula IX 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.

In step F a sulphurating agent such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-

disulphide; bis(tricyclohexyltin)sulphide; bis(tri-n-butyltin)sulphide; bis(triphenyltin)sulphide; bis(trimethylsilyl)sulphide or phosphorous pentasulphide may be used. The reaction is conveniently carried out in an inert organic solvent such as carbon disulphide, benzene or toluene, at ambient temperature or at an elevated temperature, preferably up to the boiling point of the reaction mixture, and preferably under anhydrous conditions. When using the above mentioned tin or silyl sulphides, it is preferable to carry out the sulphurization 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 to R^8 is alkanoyl, will require that the ketone carbonyl be protected via known methods by a suitable protecting group prior to the sulphurization reaction; deprotection subsequent to the sulphurization reaction provides the desired compound. Similarly, in cases wherein R^2 is, for example, alkanoyl, it will be obvious that the sulphurization reaction should be performed prior to the acylation of the 11-position nitrogen. In those cases wherein the substituents at any of R^3 to R^8 can be derived from nitro, for example, alkanoylamino, the sulphurization 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 acid addition salts, preferably the 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 non-toxic, pharmaceutically acceptable acid addition salts with a compound of Formula I include the following: hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, tartaric acid, citric acid, methanesulphonic acid, and the like. Compounds of Formula I usually form acid addition salts with one molar equivalent of the acid.

Viewed from a further aspect the invention provides a pharmaceutical composition comprising a compound of Formula I or a physiologically acceptable acid addition thereof together at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula I or their salts may be administered in single or divided doses by oral, parenteral or topical routes. A suitable oral dosage for a compound of Formula I or a salt thereof 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 the size and condition of the patient as criteria for fixing a proper dosage as well as the patient's response to the drug.

When the compounds of the present invention are to be administered 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 include 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, flavour-improvers, wetting agents, buffers, salts for altering 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 bisulphite, sodium metabisulphite 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 according to the invention can be administered by suppository.

The above described compounds of Formula I possess inhibitory activity against HIV 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.

Viewed from a yet further aspect, the present invention provides the use of a compound of Formula I or a physiologically acceptable acid addition salt thereof for the manufacture of a therapeutic agent for combatting HIV infection.

Viewed from a still further aspect, the present invention provides a method of treatment of the human body, to combat HIV infection, said method comprising administering to said body a compound of Formula I or a physiologically acceptable acid addition salt thereof.

As stated before, the compounds provided by the invention inhibit the enzymatic activity of HIV 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 (see Benn et al. Science 230:949 (1985)), so-named because it transcribes a single-stranded DNA copy from an RNA template. This activity can be quantitatively measured in a cell-free enzyme assay which has been previously described (see Farmerie et al. Science 236:305 (1987)), 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 radio-labelled, acid-precipitable DNA strand utilizing ^3H -dGTP as a substrate.

Materials:

a) Preparation of the enzyme

Reverse transcriptase enzyme from the LAV strain of Human Immuno-deficiency Virus (HIV-1) (see Benn et al. supra) is isolated from the bacterial strain JM109 (See Yanisch-Perron et al. Gene 33: 103 (1985)) expressing the DNA clone pBRTprt1+ (see Farmerie et al. supra) which is under the control of the lac promoter in the expression vector pIBI21 (International Biotechnologies Inc., New Haven, Connecticut 06535, USA). An overnight culture grown in 2XYT medium (37°C, 225 rpm) (see

Maniatis et al. eds "Molecular Cloning: A laboratory manual" Cold Spring Harbor Laboratory 1982) supplemented with 100 $\mu\text{g/ml}$ ampicillin for positive selection is inoculated at a 1:40 dilution into M9 medium supplemented with 10 $\mu\text{g/ml}$ thiamine, 0.5% casamino acids and 50 $\mu\text{g/ml}$ ampicillin (see Maniatis et al. supra). The culture is incubated (37°C, 225 rpm) until it reaches an OD^{540} of 0.3-0.4. At that time the repressor inhibitor IPTG (isopropyl β -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 sulphate. The enzyme is pelleted, resuspended in RT buffer (50mM 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

<u>Stock Reagent</u>	<u>2X Mix Concentration</u>
1M Tris pH 7.4	100mM
1M Dithiothreitol	40mM
1M NaCl	120mM
1% Nonidet P-40	0.1%
1M MgCl_2	4mM
[poly r(C)/oligo d(G)] (5:1)	2 $\mu\text{g/ml}$
^3H -dGTP (81 μM)	0.6 μM

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 (see Spira et al. J. Clinical Microbiology 25:97 (1987)). 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 ($10\mu\text{l}$ /well; 3 wells/compound). The HIV RT enzyme is thawed, diluted in 50mM Tris pH 7.4 so that $15\mu\text{l}$ of diluted enzyme contains 0.001 Unit (one Unit is that amount of enzyme needed to transform 1 micromole of substrate per minute at 25°C), and $15\mu\text{l}$ are dispensed per well. $20\mu\text{l}$ of 0.12-0.5M EDTA are added to the first three wells of the microtiter plate. EDTA chelates the Mg^{2+} present and prevents reverse transcription. This group serves as a control for the level of background polymerization which is subtracted from all other results. $25\mu\text{l}$ of the 2X reaction mixture are added to all wells and the assay is allowed to incubate at ambient temperature for 60 minutes. The assay is terminated by precipitating the DNA in each well with $50\mu\text{l}$ of 10% w/v trichloroacetic acid (TCA) in 1% w/v sodium pyrophosphate. The microtiter plate is incubated for 15 minutes at 4°C and the precipitate is fixed onto No. 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 (see Spira et al. supra). Each vial receives 2 mls of scintillation cocktail and is counted in a Beckman beta counter.

Calculations for percent inhibition are as follows:
% inhibition =

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

CPM Mean Control Value



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.

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 of 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 5×10^4 per 100 μ l 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, an excess of virus comprising 50-100 TCID₅₀'s (TCID₅₀ is the dose that results in infection in 50% of test cultures) of the HTLV-IIIB strain of HIV-1 (see Shaw et al. Science 226:1165 (1984)) are inoculated into each culture. Control cultures receive the test compound of the virus only. Four days after the viral challenge, the 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.

Regarding this assay, reference may also be had to Somasundaran et al. Science 242: 1554 (1998).

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 assess approximately the cytotoxicity of the compounds provided by the invention, several such compounds were tested in the MTT Cellular Cytotoxicity Assay described below. Compounds having a relatively high EC_{50} are preferred.

MTT ASSAY FOR CELLULAR CYTOTOXICITY

Assay Theory:

The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide] assay is based on cleavage of tetrazolium bromide by metabolically active cells, resulting in a highly quantitative blue colour. This assay has been previously described (see Mosmann, J. Immunol. Methods, 65: 55 (1983)) but has been optimized for the purposes of the testing reported herein.

Assay Method:

The H9 cell line (see Jacobs, J. Natl. Cancer Inst. 34:231 (1965)), 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 ($100\mu\text{l}$) 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, $20\mu\text{l}$ of MTT (5mg/ml in RPMI 1640, sonicated, 0.2 micrometer filtered, and stored at 4°C) is added to each well. After 4 hours additional incubation at 37°C , $60\mu\text{l}$ of Triton-X is added to each well and thoroughly mixed to aid the solubilization of the crystals. Absolute ethanol ($5\mu\text{l}$) is added, the wells are incubated for 30 minutes at 60°C and immediately read on the plate reader (Dynatech) at a wavelength of 570nm .

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

The following non-limiting Examples are provided to illustrate further the present invention and enable others skilled in the art to understand it more completely. Percentages, parts and ratios are by weight unless otherwise stated.

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-disulphide) in 50ml of toluene was refluxed for 2½ hours. The solvent was then removed in vacuo and water was added to the residue. The product was extracted with ethyl acetate, dried (anhydrous sodium sulphate) 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 by volume). 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 Assay (at 10µg/ml) and T Cell Culture Assay (at 3µg/ml) and demonstrated 100% inhibition in both tests.

Comparative Example 2

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 215g (1.672 mol) of 3-amino-2-chloropyridine, dissolved in a mixture of 400ml dioxane, 500ml cyclohexane and 130ml pyridine. The solution of 299.2g (1.7 mol) of freshly prepared 2-chloro-3-pyridinecarboxylic acid chloride in 200ml dioxane was added at such a rate as to keep the vigorous reaction under control. Thereafter, the reaction mixture was allowed to cool to ambient 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 ambient temperature the almost colourless product had a m.p. of 156-159°C and was sufficiently pure for further reactions. The yield was 376.0g (84% of theory).

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

13.4g (0.05 mol) of the product obtained in step a) were dissolved in 20ml of xylene, and the resulting solution was admixed with 13.8g (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. Colourless crystals, melting at 122-124°C (after recrystallization from acetonitrile) were obtained. The

yield was 17.2g (93% of theory).

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

16.7g (0.0453 mol) of the product obtained in step b) were dissolved in 150ml of absolute dioxane, and the resulting solution was admixed with 6.7g (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 10ml 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 evaporation of suitable fractions was recrystallized from acetonitrile and 2-propanol. The product has 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/UV₂₅₄, 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

10.0g (0.3 mol) of the product obtained in step c) were dissolved in 50ml 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 150ml of dimethyl sulphoxide to provide colourless crystals with m.p. of > 340°C. The yield was 4.8g (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 ambient 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 50% dispersion of NaH in mineral oil was added to 5.75 g of the 5-methyl derivative in 100 ml dimethylformamide. After cessation of hydrogen evolution the mixture was heated to 50°C for 30 minutes and the mixture stirred overnight at ambient temperatures. Excess sodium hydride was decomposed by the addition of ice followed by water. The product was extracted with ether, dried (anhydrous sodium sulphate) and evaporated to give 4.5 g of 5, 11-dihydro-11-ethyl-5-methyl-6-H dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one m.p. 130-132°C.

Examples 3 to 5

In the following Examples, compounds of Formula I were prepared analogously to Example 2 and according to Process Steps C and D (when Z represents oxygen) and analogously to Example 1 (Process Step F) (when Z represents sulphur), and were tested using the Reverse Transcription Assay described above.

Z is an oxygen atom unless the compound is specifically indicated to be a thiolactam

R³, R⁴, R⁵, R⁶, R⁷ and R⁸ all represent hydrogen except where other substituents are shown.



Example No.	R ¹	R ²	R ³ - R ⁸ Group	Substitution	Inhibit. at 10μg/ml	M.P.°C
3	H	-CH ₂ Ph-4-OMe	-		81%	209-210
4	Me	-CH ₂ Ph	-		66%	-
5	Me	-CH ₂ Ph-4-OMe	-		45%	120-121.5
6	Me	-CH ₂ CH ₂ F	-		96%	117-118
7	H	-Ph	-		71%	220-222
8	H	Et	R ⁵	Et	100%	212-214
9	Me	Et	R ⁷	Cl	94%	105-106
10	Me	Et	R ⁵	Me	98%	157-159
11	Me	-COCH ₃	-		73%	138-143
12	-CH ₂ SCH ₃	Et	-		93%	118-120
13	H	Et	R ³ ,R ⁴	Me	100%	212-214
14	H	Et	R ⁸	Me	86%	244-247
15	H	Et	R ³	Me	91%	263-266
16	H	Et	R ³ ,R ⁵	Me	100%	210-211
17	H	Et	R ⁴	Me	95%	not avail.
18	Me	Et	R ⁴	Me	96%	94-96
19	H	-COCH ₃	-		60%	>215(dec)
20	Me	Et	R ³ ,R ⁸	Me	98%	100-102
21	H	Et	R ³ ,R ⁵ ,R ⁸	Me	100%	228-230
22	Me	Et	R ³	Me	100%	124-126
23	H	Et	R ⁴ ,R ⁵	Me	100%	265-266
24	Me	Et	R ⁴ ,R ⁵	Me	99%	119-120
25	Me	Et	R ⁸	Me	96%	79-93
26	-COCH ₃	Et	-		96%	123-124.5

Example No.	R ¹	R ²	R ³ -R ⁸ Group	Substitution	Inhib. at 10μg/ml	M.P.°C
27	Me	-CH ₂ SCH ₃	-		99%	109-110
28	H	Et	R ⁴	Cl	92%	217-218
29	Me	Et	R ⁴	Cl	99%	124-125
30	-CH ₂ Ph	-COCH ₃	-		37%	169-170
31	Me	-CH ₂ CH=CH ₂	-		99%	93-95
32	H	Et	R ³	Cl	96%	252-254
33	Me	-CH ₂ C≡CH	-		94%	169-170
34	Me	Et	R ³	Cl	100%	125-126
35	H	Et	R ⁶	Me	80%	193-194
36	H	Et	R ⁷ ,R ⁸	Me	42%	204-206
37	H	Et	R ⁷	Me	89%	182-183
38	H	Et	R ⁵	Cl	100%	184-186
39	H	Et	R ⁵	OMe	96%	156-157
40	H	Et	R ⁵	Et	100%	218-219
41	H	Et	R ⁷	Br	-	233.5-235.5
42	Me	Et	R ⁴	NO ₂	-	154-156
43	Me	Et	R ⁴	NH ₂	-	235-240
44	H	i-Pr	R ⁵	Me	-	188-189
45	Me	Et	R ³ ,R ⁵	Me	-	151-153
46	Me	Et	R ⁶	Me	-	122-124
47 *	H	Et	R ⁵	Me	-	158-159
48 x	H	Et	R ⁵	OH	-	295-296
49	Me	Et	R ³	OMe	-	116-118



50	Me	Et	R ³	OH	-	215-218
51 *	H	Et	R ³ ,R ⁵	Me	-	199-201
52	Me	Et	R ³	NH ₂	-	197-199
53	Me	Et	R ³	NHMe	-	186-189

* compound is a thiolactam (Z represents sulphur)

≠ 2HBr salt

Example A

Capsules or Tablets

Composition A1

Composition A2

<u>Ingredients</u>	<u>Quantity</u>	<u>Ingredients</u>	<u>Quantity</u>
Active Compound	50 mg	Active compound	50mg
Starch	160 mg	Dicalcium Phosphate	160mg
Microcrystalline		Microcrystalline	
Cellulose	90 mg	Cellulose	90 mg
Sodium Starch		Stearic acid	5 mg
Gluctate	10 mg	Sodium Starch	
Magnesium Stearate	2 mg	Glycolate	10 mg
Fumed colloidal		Fumed colloidal	
silica	1 mg	silica	1 mg

The compound of Example 2 is blended into a powder mixture with the premixed excipient materials identified above with the exception of the stearic acid or magnesium stearate lubricant. The lubricant is then



blended in and the resulting blend is compressed into tablets or filled into hard gelatin capsules.

Example B

Parenteral Solutions

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

The excipient materials are mixed with the water and the active compound is then added. Mixing is continued until the solution is clear. The pH of this solution is adjusted to 3.0 and it is then filtered into the appropriate vials or ampoules and sterilized by autoclaving.

Example C

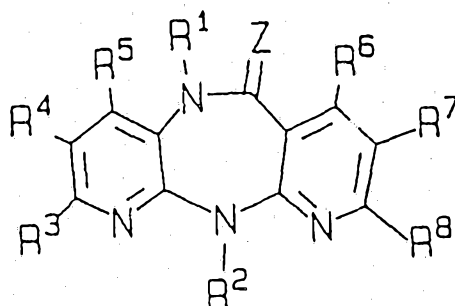
Nasal Solutions

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

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

CLAIMS

1. A compound of Formula I



(I)

(wherein,

Z is oxygen or sulphur;

R¹ is hydrogen, C₁₋₅alkyl optionally substituted by fluorine, trihalomethyl, C₃₋₅alkenyl or alkynyl, 2-halo-propen-1-yl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl and is optionally substituted by methyl, methoxy or halogen), C₂₋₃alkanoyl or C₂₋₄-(alkoxyalkyl) or C₂₋₄(alkylthioalkyl);

R² is hydrogen, C₁₋₅alkyl optionally substituted by fluorine, C₂₋₅alkenyl or alkynyl, C₂₋₄(alkoxyalkyl) or C₂₋₄(alkylthioalkyl), C₂₋₄alkanoyl, C₂₋₅hydroxyalkyl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, and is optionally substituted by C₁₋₃alkyl or alkoxy, hydroxyl or halogen), phenyl optionally substituted by C₁₋₃alkyl or alkoxy groups, hydroxy or halogen or (C₁₋₅alkoxy)carbonylmethyl; and

R³, R⁴, R⁵, R⁶, R⁷ and R⁸ is each hydrogen, or



one of R^3 , R^4 , R^5 , R^6 , R^7 and R^8 is an alkyl, alkoxy, alkylthio, alkoxycarbonyl, hydroxyalkyl, alkanoyl, alkanoyloxy, alkanoylamino, carboxyalkyl or aminoalkyl group containing up to 4 carbon atoms, or a $(C_{1-2}\text{alkoxy})\text{carbonyl}(C_{1-2}\text{alkyl})$, mono- or di- $(C_{1-2}\text{alkyl})\text{amino}$, cyano, nitro, hydroxyl, carboxyl, amino, mono- or di- $(C_{1-2}\text{alkyl})\text{amino}(C_{1-2}\text{alkyl})$ or azido group or a halogen atom and the remaining five of R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are each hydrogen, or

R^3 , R^4 and R^5 , are each independently hydrogen or $C_{1-3}\text{alkyl}$ with the proviso that at least one is hydrogen, or one of R^3 , R^4 and R^5 is butyl with the remaining two being hydrogen, and

R^6 , R^7 and R^8 are each independently hydrogen or $C_{1-3}\text{alkyl}$ with the proviso that at least one is hydrogen, or one of R^6 , R^7 and R^8 is butyl with the remaining two being hydrogen;

with the proviso that when R^1 and R^2 are each independently hydrogen or straight-chained or branched $C_{1-5}\text{alkyl}$ and R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are all hydrogen then Z is sulphur)

or an acid addition salts thereof.

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

Z is oxygen or sulphur;

R^1 is hydrogen, $C_{1-5}\text{alkyl}$ optionally substituted by fluorine

ne, trihalomethyl, C_{2-4} alkenyl or alkynyl, 2-halo-propen-1-yl, or C_{2-3} (alkoxyalkyl) or C_{2-3} (alkylthioalkyl);

R^2 is C_{1-4} alkyl optionally substituted by fluorine, C_{2-4} alkenyl or alkynyl, C_{2-4} (alkoxyalkyl) or C_{2-4} (alkylthioalkyl), C_{2-3} alkanoyl, C_{2-4} hydroxyalkyl, arylmethyl (wherein the aryl moiety is phenyl or thienyl and is optionally substituted by methyl, methoxy, hydroxyl or halogen), phenyl (optionally substituted by methyl, methoxy, hydroxyl or halogen) or (C_{1-5} alkoxy)carbonylmethyl;

R^3 , R^4 and R^5 are each independently hydrogen or methyl, with the proviso that at least one is hydrogen, or R^5 is ethyl, propyl or butyl and R^3 and R^4 are hydrogen, and

R^6 , R^7 , and R^8 are each independently hydrogen or methyl, with the proviso that at least one is hydrogen, or R^6 is ethyl, propyl or butyl and R^7 and R^8 are hydrogen,

or an acid addition salt thereof.

3. A compound of Formula I as claimed in claim 1, wherein,

Z is oxygen or sulphur;

R^1 is hydrogen, C_{1-4} alkyl optionally substituted by fluorine or allyl;

R^2 is C_{1-4} alkyl optionally substituted by fluorine, allyl or benzyl; and

R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are each hydrogen,

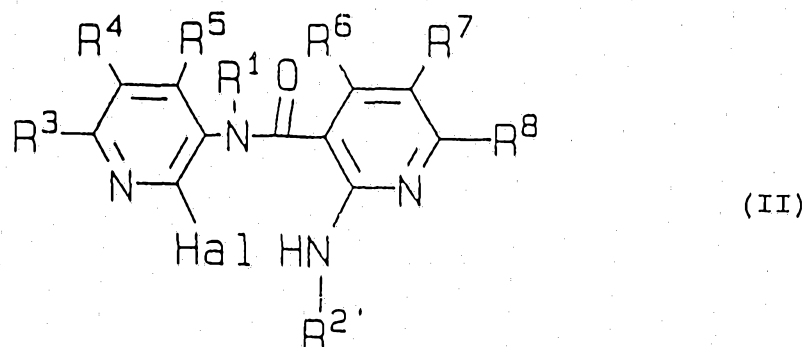
or an acid addition salt thereof.

4. A compound as claimed in any one of claims 1 to 3 being a physiologically acceptable acid addition salt of a compound of Formula I (as defined in claim 1).

5. A pharmaceutical composition comprising a compound of Formula I or a physiologically acceptable acid addition salt thereof as claimed in any of claims 1 to 4 together with at least one pharmaceutically acceptable carrier or excipient.

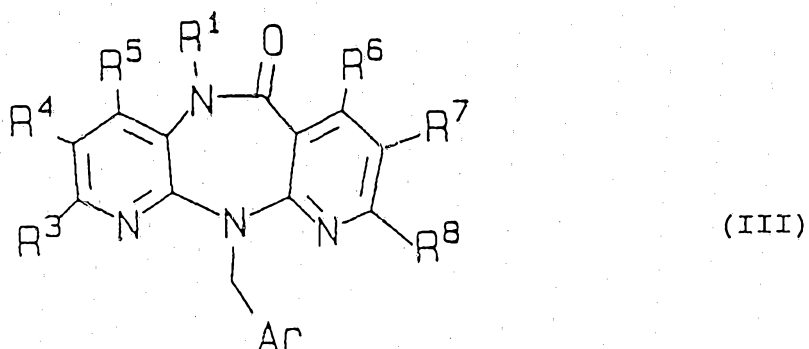
6. A process for preparing a compound as defined in any of claims 1 to 4, said process comprising at least one of the following steps:

(A) (for preparing compounds of Formula I wherein R^2 is other than hydrogen) cyclizing a carboxylic acid amide of general Formula II



(wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as hereinbefore defined, $R^{2'}$ is as defined for R^2 with the exception of hydrogen, and Hal represents a fluorine, chlorine, bromine or iodine atom);

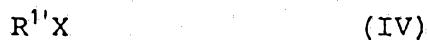
(B) (for producing compounds of Formula I wherein R^2 is hydrogen) hydrolytically cleaving an arylmethyl group from a compound of Formula III



(wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as hereinbefore defined and Ar represents an aryl group);

(C) (for preparing compounds of Formula I wherein R^1 is other than hydrogen)

converting a compound of Formula I wherein R^1 is hydrogen into a corresponding 5-alkali or alkaline earth metal compound and subsequently reacting said alkali or alkaline earth metal compound with a compound of Formula IV



(wherein R^1 is as hereinbefore defined for R^1 with the exception of hydrogen and X is the radical of a reactive

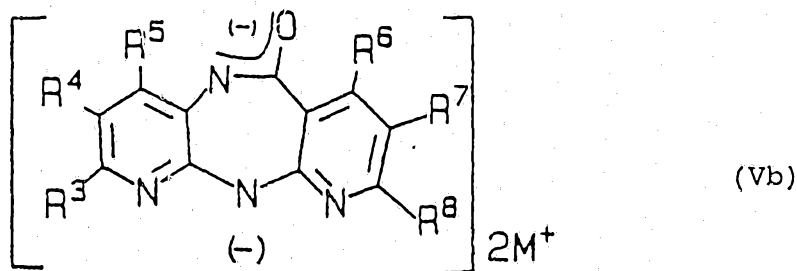
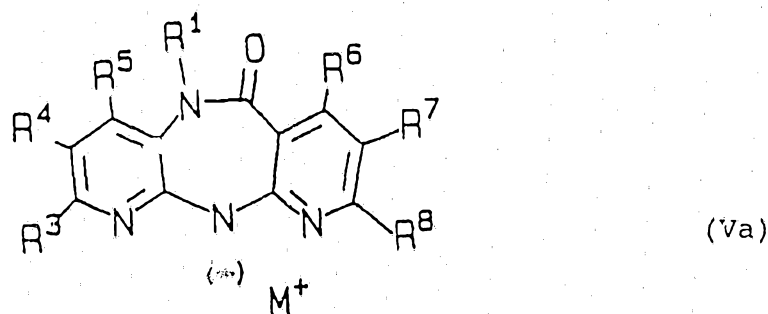
ester, a halogen atom, a group $\text{OSO}_2\text{OR}^{1'}$, a methanesulphonyloxy or ethanesulphonyloxy group or an aromatic sulphonyloxy group);

(D) (for preparing compounds of Formula I wherein R^1 is other than hydrogen)

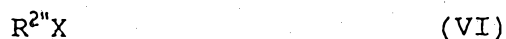
by reacting a compound of Formula I wherein R^1 is hydrogen with a compound of Formula IV (as defined above) in the presence of an amine or an alkali metal carbonate or bicarbonate;

(E) (for preparing a compound of Formula I wherein R^2 is other than an alkanoyl, hydroxyalkyl or alkoxy-carbonylmethyl group)

converting a compound of Formula I wherein R^2 is hydrogen into a corresponding metal salt of Formula Va or, where R^1 represents hydrogen, Vb



(wherein M represents an alkali metal, such as lithium, sodium, potassium, rubidium or cesium, or M represents the group $MgHal^+$, wherein Hal is chlorine, bromine or iodine) and subsequently alkylating with a compound of Formula VI



(wherein X is as hereinbefore defined) and $R^{2''}$ is as defined for R^2 with the exception of alkanoyl, hydroxyalkyl and alkoxycarbonylmethyl);

(F) (to prepare a compound of Formula I, wherein Z is sulphur)

reacting a compound of Formula I, wherein Z is oxygen, with a sulphurating agent.

7. Use of a compound of Formula I or a physiologically acceptable acid addition salt thereof as claimed in any of claims 1 to 4 for the manufacture of a therapeutic agent for combatting HIV infection.

8. A method of treatment of the human body, to combat HIV infection, said method comprising administering to said body a compound of Formula I as claimed in any of claims 1 to 3 or a physiologically acceptable acid addition salt thereof.

9. A compound of Formula I or salt thereof substantially as herein disclosed in any one of the Examples.

~~10. Each and every novel compound, composition,
process, use or method herein disclosed.~~

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