Title: ANTIVIRAL PHOSPHONIC ACID DERIVATIVES OF PURINE ANALOGUES

Abstract

Compounds of formula (I), or a pharmaceutically acceptable salt thereof wherein X is -CH₂O, -CH₃ or -CH(CH₂OR₅)O where R₅ is hydrogen or acetyl; Y is O or S; R₁ is hydroxy or amino; R₂ is amino or hydrogen; R₃ is hydrogen or, when X is CH₂O and Y is O, R₃ may be CH₂OR₅ where R₅ is hydrogen or acetyl; and R₄ and R₅ are both phenyl, 4-bromophenyl, 4-methylphenyl, 4-methoxyphenyl, 2-acetoxyphenyl or 2-methylphenyl; and their pharmaceutical use in the treatment of viral diseases.
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Antiviral phosphonic acid derivatives of purine analogues

The present invention relates to novel compounds which are of potential use as antiviral agents, to processes for their preparation and to their use as pharmaceuticals.


EP-A-206459 (Ceskoslovenska akademie ved) discloses a group of 9-(phosphonomethoxyalkyl)adenines, which are described as having antiviral activity.

'Nucleotide Analogues as Antiviral Agents' ACS Symposium Series 401, Editor J.C. Martin, published by the American Chemical Society, Washington DC (1989) Chapters 4 and 5 discloses, a number of (phosphonomethoxyalkyl) derivatives of purines and pyrimidines and their antiviral activity.

Particular compounds of interest are adenine or guanine having a 9-substituent as follows:

\[(\text{HO})_2\text{POCH}_2\text{OCH}_2\text{CH}_2\text{O}^-\]  
Ex.1, EP-A-319228

\[(\text{HO})_2\text{POCH}_2\text{OCH}_2\text{CH(CH}_2\text{OH})\text{O}^-\]  
Ex.16, EP-A-206459

\[(\text{HO})_2\text{POCH}_2\text{OCH}_2\text{CH}_2^-\]  
PMEA/PMEG

\[(\text{HO})_2\text{POCH}_2\text{OCH(CH}_2\text{OH})\text{CH}_2^-\]  
HPMPA/HPMPG

It has now been discovered that certain derivatives of these compounds are prodrugs therefor, having improved gastrointestinal absorption properties.
Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:

\[
\begin{align*}
R_1 & \quad \text{or} \quad \text{(I)} \\
\text{X is } & \text{ -CH}_2\text{O, -CH}_2\text{ or -CH}_2(\text{CH}_2\text{OR}_6)\text{O where } R_6 \text{ is hydrogen or acyl;} \\
Y & \text{ is O or S;} \\
R_1 & \text{ is hydroxy or amino;} \\
R_2 & \text{ is amino or hydrogen;} \\
R_3 & \text{ is hydrogen or, when } X \text{ is CH}_2\text{O and } Y \text{ is O, } R_3 \text{ may be CH}_2\text{OR}_7 \text{ where } R_7 \text{ is hydrogen or acyl;} \text{ and} \\
R_4 & \text{ and } R_5 \text{ are both phenyl, 4-bromophenyl, 4-methylphenyl, 4-methoxyphenyl, 2-acetoxyphenyl or 2-methylphenyl.}
\end{align*}
\]

When \( R_1 \) is hydroxy and \( R_2 \) is amino, the compound of formula (I) is a guanine derivative;

When \( R_1 \) is amino and \( R_2 \) is hydrogen, the compound of formula (I) is an adenine derivative;

When \( R_1 \) is hydroxy and \( R_2 \) is hydrogen, the compound of formula (I) is a hypoxanthine derivative; and

When \( R_1 \) and \( R_2 \) are both amino groups, the compound of formula (I) is a 2,6-diaminopurine derivative.

Often, the compound of formula (I) is a guanine or adenine derivative.

\( R_4 \) and \( R_5 \) are preferably both phenyl.
Suitable examples of R₆/R₇ when acyl include carboxylic acyl, such as C₁₋₇ alkanoyl and benzoyl optionally substituted in the phenyl ring by one, two or three groups or atoms selected from halogen, such as fluoro, chloro, bromo, and C₁₋₄ alkyl or C₁₋₄ alkoxy wherein the alkyl moiety is selected from methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl. Preferred acyl groups include acetyl, propionyl, butyryl, heptanoyl and hexanoyl.

There are groups of compounds of interest wherein:

i) X is -CH₂O and R₃ is hydrogen.

ii) X is -CH₂O and R₃ is CH₂OR₇ as defined.

iii) X is -CH₂(CH₂OR₆)O as defined and R₃ is hydrogen.

iv) X is -CH₂ and R₃ is hydrogen.

v) X is -CH₂ and R₃ is CH₂OR₇ as defined.

Y is preferably O.

Examples of pharmaceutically acceptable salts of the compound of formula (I) are acid addition salts formed with a pharmaceutically acceptable acid such as hydrochloric acid, orthophosphoric acid and sulphuric acid. Pharmaceutically acceptable salts also include those formed with organic bases, preferably with amines, such as ethanolamines or diamines; and alkali metals, such as sodium and potassium.

It will be appreciated that some of the compounds of formula (I), especially those wherein R₃ is other than hydrogen, have an asymmetric centre, and therefore are capable of existing in more than one stereoisomeric form. The invention extends to each of these forms individually and to mixtures thereof, including racemates. The isomers may be separated conventionally by chromatographic methods or using a resolving agent. Alternatively, the individual isomers may be prepared by asymmetric synthesis using chiral intermediates.

The compounds of formula (I) including their alkali metal salts may form solvates such as hydrates and these are included wherever a compound of formula (I) or a salt thereof
is herein referred to.

It will be appreciated that, when R₁ is hydroxy in formula (I) the compound exists in the predominant tautomeric form of structure (IA):

![Formula IA](image)

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):

![Formula II](image)

with R₄OH and R₅OH and R₁, R₂, and R₃ are as defined in formula (I), and thereafter optionally forming a pharmaceutically acceptable salt thereof.

The reaction takes place in a suitable inert solvent such as dichloromethane at temperatures with cooling 0 to 3°C, under an inert atmosphere.

As appropriate or necessary, R₁/R₂/R₃ may be protected. Suitable examples of protecting groups and their removal, are as described in EP-A-242482. A particularly suitable protecting group for R₃ when other than hydrogen is the t-butyldiphenylsilyl
group removable by conventional methods.

The compounds of formula (II) may be generated from the corresponding compounds of formula (I), but wherein R₄/R₅ is replaced by an ethyl group, by treatment with bromotrimethylsilane in dichloromethane followed by chlorination with PCl₅ in dichloromethane: carbon tetrachloride.

It will be appreciated that the above conversions may take place in any desired or necessary order, having regard to the final desired compound of formula (I).

The R₄/R₅ = ethyl compounds of the formula (I) are prepared as described in EP-A-313289 and the aforementioned publications, the subject matter of which are incorporated herein by reference.

When R₆/R₇ is hydroxy, appropriate selective protection may be required, eg using acetate.

Pharmaceutically acceptable salts may be prepared in conventional manner, for example, in the case of acid addition salts, by reaction with the appropriate organic or inorganic acid.

It will be appreciated that the invention provides a process for the preparation of a compound of formula (I) wherein R₆/R₇ is hydrogen which process comprises the deprotection of a corresponding compound of formula (I) wherein R₈/R₉ is protected hydroxy. Methods for deprotection, are conventional for the protecting group concerned.

The compounds of the invention are of potential use in the treatment of infections caused by viruses, in particular DNA viruses and retroviruses. Examples of DNA viruses include herpesviruses such as herpes simplex types 1 and 2, varicella-zoster virus, Epstein-Barr virus and cytomegalovirus. Examples of retroviruses include lentiviruses such as visna virus and human immunodeficiency virus (strains 1 and 2).

The compounds may also be inhibitors of tumorigenic viruses and/or of potential use in the treatment of neoplastic diseases, i.e. cancer.
Compounds of the invention may be formulated for use in a pharmaceutical composition. Accordingly, in a further aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of formula (I) or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or excipient.

A composition which may be administered by the oral route to humans may be compounded in the form of a syrup, tablet or capsule. When the composition is in the form of a tablet, any pharmaceutical carrier suitable for formulating such solid compositions may be used, for example magnesium stearate, starch, lactose, glucose, rice, flour and chalk. The composition may also be in the form of an ingestible capsule, for example of gelatin, to contain the compound, or in the form of a syrup, a solution or a suspension. Suitable liquid pharmaceutical carriers include ethyl alcohol, glycerine, saline and water to which flavouring or colouring agents may be added to form syrups. The compounds may also be presented with a sterile liquid carrier for injection.

The composition may also be formulated for topical application to the skin or eyes.

For topical application to the skin, the composition may be in the form of a cream, lotion or ointment. These formulations may be conventional formulations well known in the art, for example, as described in standard books of pharmaceutics and cosmetics, such as Harry's Cosmetiology published by Leonard Hill Books and the British Pharmacopoeia.

The composition for application to the eyes may be a conventional eye-drop composition well known in the art, or an ointment composition. Preferably, the composition of this invention is in unit dosage form or in some other form that may be administered in a single dose. A suitable dosage unit might contain from 50 mg to 1 g of active ingredient, for example 100 to 500 mg.

Such doses may be administered 1 to 4 times a day or more usually 2 or 3 times a day. The effective dose of compound will in general be in the range of from 1.0 to 20 mg/kg of body weight per day or more usually 2.0 to 10 mg/kg per day.

No unacceptable toxicological effects are indicated at the above described dosage levels.
The invention also provides a method of treating viral infections/diseases in a human or non-human animal, which comprises administering to the animal an effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for the treatment of viral infections/diseases.

The compounds of the invention are also believed to exhibit a synergistic antiviral effect in conjunction with interferons; and combination products comprising these two components for sequential or concomitant administration, by the same or different routes, are therefore within the ambit of the present invention.

The following examples illustrate the invention.
Examples

The following compounds of formula (I) are prepared.

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<th>R₁</th>
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In examples I-VI, the following general synthetic procedure was used:

\[
\begin{align*}
\text{NH₂} & \xrightarrow{\text{i) TMSBr, CH₂Cl₂}} \text{NH₂} \\
\text{(EtO)₂P} & \xrightarrow{\text{ii) PCl₅, CH₂Cl₂, CCl₄}} \text{(RO)₂P} \\
\xrightarrow{\text{iii) ROH, Et₃N, CH₂Cl₂, 1-methylimidazole}} & \text{NH₂}
\end{align*}
\]

I \quad R = C₆H₅

II \quad R = 4-Br-C₆H₄

III \quad R = 4-CH₃-C₆H₄

IV \quad R = 4-CH₃O-C₆H₄

V \quad R = 2-CH₃CO₂-C₆H₄

VI \quad R = 2-CH₃-C₆H₄
Examples I-VI

To a solution of the diethyl ester (1.45 mmol) in dry dichloromethane (5 ml) bromotrimethylsilane (14.5 mmol) was added. The reaction mixture was stirred at RT for 2 h and the solvents were evaporated. The residue was coevaporated with dry toluene (2 x 5 ml) and the resulting glass was dissolved in dry dichloromethane: carbon tetrachloride solution (3:1, 10 ml). Phosphorus pentachloride (3.045 mmol) was then added and the reaction mixture was stirred at RT for 3 h. The solvents were evaporated, the residue was coevaporated with dry toluene (1 x 10 ml). The resulting phosphonyl dichloridate derivative was suspended in dry dichloromethane (10 ml), the appropriate alcohol (3.045 mmol) was added and the solution was cooled to 0°-3°C under argon. The reaction mixture was then treated with triethylamine (3.625 mmol) followed by 1-methylimidazole (5.8 mmol), stirred at 0°-3°C for 10 min and then at RT for 1.5 h. The precipitate was filtered, washed with dichloromethane and the solvents were evaporated. The residue was coevaporated with toluene (2 x 20 ml), dissolved in chloroform (80 ml), washed successively with aqueous sodium hydrogen carbonate (2 x 20 ml) and water (2 x 20 ml). The product was purified by column chromatography on silica gel eluting with chloroform-ethanol to give the compound examples I-VI in 12-40% yield.

Example I, \( R = \text{C}_6\text{H}_5 \), 36% yield

\[
\delta_H [(\text{CD}_3)_2\text{SO}] 3.97 (2H, m, \text{CH}_2\text{OCH}_2\text{P}), 4.35 (2H, d, J=7.15Hz, \text{CH}_2\text{P}), 4.55 (2H, m, \text{NOCH}_2), 7.21-7.44 (12H, m, Ar and \text{NH}_2, \text{D}_2\text{O exchangeable}), 8.15 (1H, s, H-2), 8.31 (1H, s, H-8).
\]

Found: C, 50.84; H, 4.20; N, 14.59%. \( \text{C}_{20}\text{H}_{20}\text{O}_5\text{P} \times 0.35 \text{CHCl}_3 \) requires C, 50.59, H, 4.24; N, 14.49%.

Example II, \( R = 4-\text{Br-C}_6\text{H}_4 \), 31% yield

\[
\delta_H [(\text{CD}_3)_2\text{SO}] 3.96 (2H, m, \text{CH}_2\text{OCH}_2\text{P}), 4.38 (2H, d, J=7.42Hz, \text{CH}_2\text{P}), 4.54 (2H, m, \text{NOCH}_2), 7.20-7.63 (8H, m, Ar), 7.39 (2H, brs, \text{D}_2\text{O exchangeable, NH}_2), 8.15 (1H, s, H-2), 8.31 (1H, s, H-8).
\]

Found: C, 38.50; H, 2.88; N, 10.84%. \( \text{C}_{20}\text{H}_{18}\text{N}_5\text{O}_5\text{PBr}_2 \times 0.3 \text{CHCl}_3 \) requires C, 38.4, H, 2.90; N, 10.87%.

Example III, \( R = 4-\text{CH}_3-\text{C}_6\text{H}_4 \), 12% yield
\[ \delta_H [(CD_3)_2SO] \ 3.31 \ (6H, s, C_H_3), \ 3.94 \ (2H, m, C_H_2OCH_2P), \ 4.38 \ (2H, d, J=7.15Hz, C_H_2P), \ 4.54 \ (2H, m, NOCH_2), \ 7.08-7.21 \ (8H, m, Ar), \ 7.38 \ (2H, br.s, D_2O exchangeable, N_H_2), \ 8.15 \ (1H, s, H-2), \ 8.31 \ (1H, s, H-8). \]

Found: M+H (C.I.) 470.1594; C_{22}H_{24}N_{5}O_{5}P requires M+H 470.1594.

Example IV, R=4-CH_3O-C_6H_4, 26% yield

\[ \delta_H [(CD_3)_2SO] \ 3.73 \ (6H, s, OCH_3), \ 3.95 \ (2H, m, C_H_2OCH_2P), \ 4.27 \ (2H, d, J=7.15Hz, C_H_2P), \ 4.55 \ (2H, m, NOCH_2), \ 6.68-7.32 \ (8H, m, Ar), \ 7.38 \ (2H, br.s, D_2O exchangeable, N_H_2), \ 8.15 \ (1H, s, 2-H), \ 8.33 \ (1H, s, 8-H). \]

Found: C, 50.37; H, 5.50; N, 13.92%, M+H (C.I.) 502.1492; C_{22}H_{24}N_{5}O_{7}P x H_2O requires C, 50.87; H, 5.05; N, 13.48%, M+H 502.1492.

Example V, R=2-CH_3CO_2-C_6H_4, 14% yield

\[ \delta_H [(CD_3)_2SO] \ 2.20 \ (6H, s, C_H_3CO_2), \ 3.96 \ (2H, m, C_H_2OCH_2P), \ 4.36 \ (2H, d, J=6.87Hz, C_H_2P), \ 4.55 \ (2H, m, NOCH_2), \ 7.27-7.84 \ (10H, m, Ar and N_H_2, D_2O exchangeable), \ 8.15 \ (1H, s, H-2), \ 8.30 \ (1H, s, H-8). \]

Found: C, 50.50; H, 4.31; N, 12.21%. C_{24}H_{24}N_{5}O_{9}P x 0.1 CHCl_3 requires C, 50.84; H, 4.26; N, 12.30%.

Example VI, R=2-CH_3-C_6H_4, 40% yield

\[ \delta_H [(CD_3)_2SO] \ 3.32 \ (6H, s, C_H_3), \ 3.98 \ (2H, m, C_H_2OCH_2P), \ 4.38 \ (2H, d, J=7.25Hz, C_H_2P), \ 4.54 \ (2H, m, NOCH_2), \ 7.09-7.25 \ (8H, m, Ar), \ 7.33 \ (2H, br.s, D_2O exchangeable, N_H_2), \ 8.15 \ (1H, s, H-2), \ 8.31 \ (1H, s, H-8). \]

Found: C, 53.14; H, 5.80; N, 13.87%. C_{22}H_{24}N_{5}O_{5}P x 1.5 H_2O requires C, 53.23; H, 5.48; N, 14.10%.
9-[2-(Bis(phenoxyl)methoxy)ethoxy]adenine
(alternative preparation method)

A mixture of 9-[(phosphonomethoxy)ethoxy]adenine (1.0 g, 3.46 mmol) and thionyl chloride (50 ml) was heated under reflux for 2 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure (with exclusion of moisture) to give an oily residue. The residue was coevaporated with dry dichloromethane and then it was redissolved in dry dichloromethane (15 ml). Phenol (0.72 g, 7.61 mmol) was added to the solution and the resulting mixture was cooled to 0°C under argon. Triethylamine (1.06 ml, 7.61 mmol) was added dropwise (over 2 min) followed by 1-methylimidazole (1.1 ml, 13.84 mmol). The reactants were stirred at 0°C for 15 min and then at room temperature for 1 h. The precipitate was filtered off, washed with cold dichloromethane (10 ml). The combined filtrate and washing were diluted with dichloromethane (100 ml), washed with saturated aqueous NaHCO₃ (30 ml), water (30 ml) and dried (MgSO₄). The solvent was removed under reduced pressure, the product was purified by column chromatography, eluting with 6% ethanol in chloroform, to give the title compound as a colourless gum; yield 0.52 g, 34%.

^1H NMR δ (DMSO-d₆)

3.97 (2H, m, CH₂CH₂O), 4.35 (2H, d, J=7.42, CH₂P), 4.55 (2H, m, CH₂CH₂O), 7.22-7.44 (12H, m, aromatic protons and NH₂-D₂O exchangeable), 8.15 and 8.31 (1H, s and 1H, s, H-2 and H-8). Found: (Cl),M⁺, 441.1202; C₂₀H₂₀N₅O₅ P requires M⁺, 441.1201. Anal. Calcd for C₂₀H₂₀N₅O₅ P·0.2 CHCl₃: C, 52.15; H, 4.38; N, 15.05. Found: C, 52.37; H, 4.42; N, 14.83.
9-[2-Bis(phenoxy)phosphorylmethoxy]ethoxy]adenine hydrochloride

9-[2-Bis(phenoxy)phosphorylmethoxy]ethoxy]adenine (1.5 g, 3.4 mmol) was dissolved in dry dichloromethane (10 ml) and a saturated (0°C) solution of hydrogen chloride in dichloromethane (30 ml) was added. After being stirred at room temperature for 5 min, the solution was concentrated (with exclusion of moisture) and the residue was coevaporated with dry dichloromethane (3 x 50ml) to give the diphenyl ester hydrochloride as a colourless solid; yield 1.6 g (99%). A sample of the compound (50 mg) was evaporated with dry toluene (20 ml) and dried *in vacuo* to give a crystalline solid, mp 139-143°C.

$^{1}H$ NMR $\delta$ (DMSO-$d_6$)

4.01 (2H, m, CH$_2$CH$_2$O), 4.32 (2H, d, J=7.42, CH$_2$P), 4.62 (2H, m, CH$_2$CH$_2$O), 7.16-7.44 (10H, m, aromatic protons), 8.49 and 8.69 (1H, s and 1H, s, H-2 and H-8), 8.7-9.25 (2H, v, b, d, NH$_2$, D$_2$O exchangeable). Found: (Cl), MH$^+$, 442.1280; C$_{20}$H$_{20}$N$_5$O$_5$ P requires MH$^+$, 442.1280. Anal. Calcd for C$_{20}$H$_{20}$N$_5$O$_5$ P.H$_2$O.1.2 HCl: C, 47.74; H, 4.64; N, 13.92; Cl, 8.45. Found: C, 47.42; H, 4.54; N, 13.90; Cl, 8.52.
Biological Evaluation Procedures

Compounds were administered by oral gavage to female Balb/C mice weighing 20g, as single 0.1ml doses of 0.2mmol/kg. These solutions were made by dissolving the compounds in DMF and diluting with 1% carboxymethyl cellulose and 1% Tween 80, to a final DMF concentration of 5%. Food was withheld from the mice for 18 hours prior to the start of the experiment. Blood was collected by cardiac puncture using heparinised syringes 15, 60 and 180 mins after dosing. Equal volumes (0.2ml) from 3 mice were pooled at each time point and 0.6ml of ice-cold ethanol was added.

Following chilling at -20°C and centrifugation, 0.5ml of supernatant was dried under reduced pressure. The sample was then reconstituted with 0.5ml of 0.4M NH₄OAc (pH 6.0) and analysed by HPLC.

The results are as shown in the table below:

9-[2-(Phosphonomethoxy)ethoxy]adenine concn. (µM) in blood at time (min) after dosing

<table>
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<tr>
<th>Compound of Example No.</th>
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<tr>
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<td>25</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
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</tr>
<tr>
<td>III</td>
<td>4</td>
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<td>VI</td>
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Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

   \[
   \begin{array}{c}
   \text{R}_1 \\
   \text{N} \\
   \text{N} \\
   \text{R}_2 \\
   \text{O} \text{PCH}_2 \text{YCH}_X \\
   \text{R}_3 \\
   \end{array}
   \]

   (I)

   wherein
   X is -CH$_2$O, -CH$_2$ or -CH(CH$_2$OR$_6$)O where R$_6$ is hydrogen or acyl;
   10 Y is O or S;
   R$_1$ is hydroxy or amino;
   15 R$_2$ is amino or hydrogen;
   R$_3$ is hydrogen or, when X is CH$_2$O and Y is O, R$_3$ may be CH$_2$OR$_7$ where R$_7$ is hydrogen or acyl; and
   R$_4$ and R$_5$ are both phenyl, 4-bromophenyl, 4-methylphenyl, 4-methoxyphenyl, 2-acetoxyphenyl or 2-methylphenyl.

2. A compound according to claim 1 wherein R$_1$ is hydroxy and R$_2$ is amino.

3. A compound according to claim 1 wherein R$_1$ is amino and R$_2$ is hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R$_4$ and R$_5$ are both phenyl.

5. A compound according to any one of claims 1 to 4 wherein X is -CH$_2$O and R$_3$ is hydrogen.
6. A compound according to any one of claims 1 to 4 wherein X is -CH₂O and R₃ is CH₂OR₇ as defined in claim 1.

7. A compound according to any one of claims 1 to 4 wherein X is -CH(CH₂OR₆)O as defined in claim 1 and R₃ is hydrogen.

8. A compound according to any one of claims 1 to 4 wherein X is -CH₂ and R₃ is hydrogen.

9. A compound according to any one of claims 1 to 4 wherein X is -CH₂ and R₃ is CH₂OR₇ as defined in claim 1.

10. A compound as described herein with reference to any one of the Examples.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, and a pharmaceutically acceptable carrier.

12. A compound according to any one of claims 1 to 10 for use as an active therapeutic substance.

13. A compound according to any one of claims 1 to 10 for use in treating viral diseases.

14. Use of a compound according to any one of claims 1 to 10 in the manufacture of a medicament for use in the treatment of viral diseases.

15. A method of treatment of viral diseases in mammals, which comprises the administration to mammal in need of such treatment, an effective amount of a compound according to any one of claims 1 to 10.

16. A compound, use or method according to any one of claims 13, 14 or 15 wherein the viral infection is a human immunodeficiency virus infection.

17. 9-[2-Bis(phenoxy)phosphorylmethoxy]ethoxy]adenine hydrochloride.
# INTERNATIONAL SEARCH REPORT

**International Application No**: PCT/GB 93/00560

## I. CLASSIFICATION OF SUBJECT MATTER

If several classification symbols apply, indicate all.

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

Int.Cl. 5 C07F9/6561; A61K31/675

## II. FIELDS SEARCHED

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Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched.

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CA,A, 2 051 239 (BRISTOL-MYERS SQUIBB CO.) 15 March 1992 see page 7, line 25 - line 35; claims 1-17; example 35</td>
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"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

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

"Z" document member of the same patent family

## IV. CERTIFICATION

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International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

BESLIER L.M.
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