

PHOSPHONATE NUCLEOSIDES USEFUL AS ACTIVE INGREDIENTS IN
PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF VIRAL
INFECTIONS, AND INTERMEDIATES FOR THEIR PRODUCTION

5 FIELD OF THE INVENTION

The present invention relates to a series of novel phosphonate nucleosides and thiophosphonate nucleosides, more specifically phosphonate nucleosides and thiophosphonate nucleosides comprising a phosphonalkoxy-substituted or phosphonothioalkyl-substituted five-membered, saturated or
10 unsaturated, oxygen-containing or sulfur-containing ring coupled to a heterocyclic nucleobase such as a pyrimidine or purine base. The invention further relates to certain phosphonate nucleosides and thiophosphonate nucleosides having antiviral activity, more specifically HIV (Human Immunodeficiency Virus) replication inhibiting properties. The invention also relates to methods for the
15 preparation of such phosphonate nucleosides and thiophosphonate nucleosides, as well as novel intermediates useful in one or more steps of such syntheses. The invention also relates to pharmaceutical compositions comprising an effective amount of such phosphonate nucleosides and thiophosphonate nucleosides as active ingredients. This invention further relates to the use of such
20 phosphonate nucleosides and thiophosphonate nucleosides as medicines or in the manufacture of a medicament useful for the treatment of mammals suffering from viral infections, in particular HIV infection. This invention further relates to methods for the treatment of viral infections in mammals by the administration of a therapeutical amount of such phosphonate nucleosides and thiophosphonate
25 nucleosides, optionally combined with one or more other drugs having anti-viral activity.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the
30 etiological agent of the complex disease that includes progressive destruction of

the immune system (acquired immune deficiency syndrome, hereinafter AIDS) and degeneration of the central and peripheral nervous system. There are two types of HIV, HIV-1 and HIV-2, the latter producing a less severe disease than the former. Being a retrovirus, its genetic material is in the form of RNA (ribonucleic acid) consisting of two single RNA strands. Coexisting with RNA are reverse transcriptase (having polymerase and ribonuclease activity), integrase, a protease and other proteins.

It is known in the art that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases. Drugs that are known and approved for the treatment of HIV-infected patients belong to one of the following classes:

- nucleoside reverse transcriptase inhibitors (NRTI) such as, but not limited to, azidothymidine, zidovudine, lamivudine, didanosine, abacavir, adefovir and the like,
- nucleotide reverse transcriptase inhibitors (NtRTI) such as, but not limited to, tenofovir (commercially available under the trade name Viread),
- non-nucleoside reverse transcriptase inhibitors such as, but not limited to, nevirapine, efavirenz and the like,
- protease inhibitors such as, but not limited to, nelfinavir, saquinavir, ritonavir, indinavir, amprenavir, fosamprenavir and the like, and
- fusion inhibitors such as enfuvirtide.

A relatively new target that was focused on lately is the integrase enzyme of HIV, while also many other proteins acting as enzymes or co-factors are being investigated.

Replication of the human immunodeficiency virus type 1 (hereinafter referred as HIV-1) can be drastically reduced in infected patients by combining potent antiviral drugs targeted at multiple viral targets, as reviewed by Vandamme *et al.* in *Antiviral Chem. Chemother.* (1998) 9:187-203.

Multiple-drug combination regimes can reduce viral load below the detection limit of the most sensitive tests. Nevertheless low level ongoing replication has

been shown to occur, possibly in sanctuary sites, leading to the emergence of drug-resistant strains, according to Perelson *et al.* in *Nature* (1997) 387:123-124.

Furthermore the selectivity of many antiviral agents is rather low, possibly making them responsible for side-effects and toxicity. Moreover, HIV can develop
5 resistance to most, if not all, currently approved antiviral drugs, according to Schmit *et al.* in *J. Infect. Dis.* (1996) 174:962-968. It is well documented that the ability of HIV to rapidly evolve drug resistance, together with toxicity problems resulting from known drugs, requires the development of additional classes of antiviral drugs.

10 As a summary, there is still a stringent need in the art for potent inhibitors of HIV. Therefore a goal of the present invention is to satisfy this urgent need by identifying efficient pharmaceutically active ingredients that are less toxic and/or more resistant to virus mutations than existing antiviral drugs and that can be useful, either alone or in combination with other active ingredients, for the
15 treatment of retroviral infections, in particular lentiviral infections, and more particularly HIV infections, in mammals and more specifically in humans. Furthermore, another goal of the present invention is complement existing antiviral drugs in such a way that the resulting drug combination has improved activity or improved resistance to virus mutation than each of the individual
20 compounds.

The family of the Flaviviridae consists of 3 genera, the pestiviruses, the flaviviruses and the hepaciviruses and also contains the hepatitis G virus (HGV/GBV-C) that has not yet been assigned to a genus. Pestiviruses such as the Classical Swine Fever Virus (CSFV), the Bovine Viral Diarrhea Virus (BVDV)
25 and the Border Disease Virus (BDV) cause infections of domestic livestock (respectively pigs, cattle and sheep) and are responsible for significant economic losses world-wide. Vaccines are used in some countries with varying degrees of success to control pestivirus disease. In other countries, animal culling and slaughter are used to contain pestivirus disease outbreaks.

The World Health Organization estimates that world-wide 170 million people (3% of the world's population) are chronically infected with HCV. These chronic carriers are at risk of developing cirrhosis and/or liver cancer. In studies with a 10 to 20 year follow-up, cirrhosis developed in 20 – 30 % of the patients, 1 to 5% of whom may develop liver cancer during the next then years. The only treatment option available today is the use of interferon α -2 (or its pegylated from) either alone or combined with ribavirin. However, sustained response is only observed in about 40% of the patients and treatment is associated with serious adverse effects. There is thus an urgent need for potent and selective inhibitors of the replication of the HCV in order to treat infections with HCV. Furthermore, the study of specific inhibitors of HCV replication has been hampered by the fact that it is not possible to propagate HCV (efficiently) in cell culture. Since HCV and pestiviruses belong to the same virus family and share many similarities (organisation of the genome, analogous gene products and replication cycle), pestiviruses have been adopted as a model and surrogate for HCV. For example BVDV is closely related to hepatitis C virus (HCV) and used as a surrogate virus in drug development for HCV infection.

In view of their important pharmacological value, there is a need for drugs having antiviral activity against viruses belonging to the family of Flaviviridae including hepatitis C virus.

Pioneering work on the chemistry of phosphonate nucleosides has already been carried out and includes certain important reaction schemes to synthesize phosphonate nucleosides. A review of chemistry and biology of phosphorous-modified nucleotide analogues is available for instance from A. Holy in *Advances in Antiviral Drug Design* (1993) 1:179-231. Phosphonate nucleosides can be divided in two categories. A first category are real nucleoside analogues since they contain a nucleobase and a sugar moiety. A second category of phosphonate nucleosides, represented for instance by 9-(2-phosphonyl-methoxyethyl)adenine (adefovir), can be considered as alkylated nucleobases since their sugar moiety is replaced by an alkoxyalkyl moiety. Surprisingly, up to

now, potent antiviral *in vivo* activity (HSV, CMV, HBV, HIV) has only been associated with certain phosphonalkoxyalkyl nucleobases and not with sugar containing phosphonate nucleosides. Several attempts to discover antiviral nucleoside phosphonates have led to synthetic schemes for the preparation of
5 furanose-, pyranose- and carbocyclic phosphonate nucleosides, all of them however lacking potent antiviral activity.

Phosphorylation by kinases and incorporation into nucleic acids (eventually leading to chain termination) is considered as an important mechanism which may explain the antiviral activity of nucleosides. The lack of antiviral activity of
10 phosphonate nucleosides of the first category is generally explained by their poor substrate properties for cellular and viral kinases. On the other hand, the potent antiviral activity of phosphonylated alkylated nucleobases of the second category has been ascribed to their intracellular phosphorylation into diphosphates and to an incorporation of the modified nucleosides into nucleic acids (enzymatic
15 incorporation into nucleic acids being almost irreversible) which has negative consequences downstream and thereby inhibits viral growth. A disadvantage of the acyclic nucleoside phosphonates are their low selectivity index in cellular screening systems. The selectivity of the triphosphates of anti-HIV nucleosides for HIV reverse transcriptase versus mitochondrial DNA polymerases is usually
20 regarded as an important factor determining *in vivo* toxicity. Thus there is still a need in the art for drug candidates having suitable selectivity for HIV reverse transcriptase. A less flexible structure such as is present in the nucleosides phosphonates is considered to improve both binding to polymerases and viral-versus-host selectivity. Consequently, nucleosides phosphonates retaining their
25 HIV reverse transcriptase affinity are considered as strong antiviral candidates.

Threose nucleosides have been previously synthesized because they can be assembled from natural precursor molecules. It has been demonstrated that threose nucleic acids (TNA) form duplexes with DNA and RNA exhibiting a thermal stability similar to that of the natural nucleic acids association.
30 Triphosphates of threose nucleosides are accepted as substrate by several

polymerases and can be enzymatically incorporated in DNA. A few 2,5-dihydro-5-(phosphonomethoxy)-2-furanyl nucleosides derived from thymine and adenine with antiretroviral activity have been disclosed by Kim et al. in *J. Org. Chem.* (1991) 56:2642-2647. EP-A-398,231 describes a family of phosphonomethoxymethoxymethyl purine/pyrimidine derivatives being effective in combating viral infections at a dose of 0.01 to 30 mg/kg bodyweight. U.S. Patent Publication No. 2004/0023921 discloses a pharmaceutical composition comprising a nucleotide analog with a phosphonate group at an amount effective to inhibit a viral polymerase of an hepatitis C virus (hereinafter referred as HCV) or to act as a substrate for the viral polymerase of the HCV virus. WO 98/20017 describes a family of modified nucleoside-5'-triphosphates which are inhibitors or substrates of DNA polymerases and antiviral agents, being in particular able to inhibit the reproduction of the human HIV virus in a culture of human lymphocytes.

Although, as is apparent from the prior art of record, numerous compounds were proposed for meeting the various above mentioned requirements in terms of retroviral therapy, it was observed that none of them does achieve such goals and, consequently, there is still a stringent need in the art for new compounds being able to solve these problems.

SUMMARY OF THE INVENTION

Without wishing to be bound by theory, the present invention is based on the unexpected finding that the above-mentioned problems can be solved by a novel class of compounds wherein the phosphonoalkoxy group or phosphonothioalkyl group of a furanose nucleoside phosphonate (or its sulfur analogue wherein furanyl is replaced with thienyl) is bound at the 3'-position, thus bringing the phosphorous atom and the nucleobase much closer to each other than in the previously known nucleoside phosphonates. This invention is also based on the unexpected finding that the absence of a hydroxymethyl substituent in the 4'-position of this class of compounds avoids steric hindrance during the enzymatic phosphorylation reaction, therefore avoiding the poor substrate

properties for cellular and viral kinases (leading to poor antiviral activity) of the nucleoside phosphonates of the prior art. In addition, depending on the length of the carbon-based linking structure between the 5-membered ring and the phosphorous atom, the phosphorylated nucleosides of the invention can be considered as mono-, di- or triphosphate mimics. By varying the length of this linking structure, the present invention makes it possible to further finely tune the antiviral activity of the novel class of compounds. Also, this invention is based on the unexpected finding that the presence of an anomeric centre in this novel class of threose nucleoside phosphonates provides them with similar stereo-electronic properties to that of natural nucleosides.

Based on the above unexpected findings, the present invention provides new anti-viral agents, especially anti-retroviral agents, and more particularly anti-HIV compounds. These compounds are phosphonate nucleosides, more particularly phosphonoalkoxy-substituted and phosphonothioalkyl-substituted nucleosides comprising a five-membered, saturated or unsaturated, oxygen-containing or sulfur-containing ring (preferably dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl or tetrahydrothienyl), or analogues or derivatives thereof, which have been shown that they possess anti-viral activity against various classes of viruses such as, but not limited to, retriviridae, flaviviridae and papoviridae, more specifically against the human HIV. The present invention demonstrates that these compounds efficiently inhibit the replication of HIV in mammals. Therefore, these phosphonate nucleosides constitute a useful class of new potent anti-viral compounds that can be used in the treatment and/or prevention of viral infections in animals such as mammals, and humans, more specifically for the treatment and/or prevention of HIV in humans.

The present invention also relates to compounds having antiviral activities with respect to one or more other viruses such as, but not limited to, hepatitis B virus, hepatitis C virus, papilloma virus, flaviviruses, picornaviruses and the like. The present invention furthermore relates to the use of such compounds as medicines, more specifically as anti-viral agents, and to their use for the

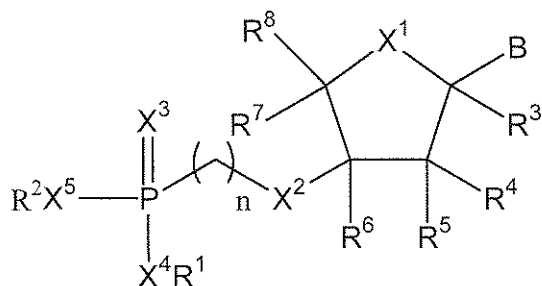
manufacture of medicaments for treating and/or preventing viral infections, in particular retroviral infections such as, but not limited to, HIV in humans. The invention also relates to methods for the preparation of all such compounds and to pharmaceutical compositions comprising them in an anti-viral effective amount.

5 The present disclosure also relates to a method of treatment or prevention of viral infections, in particular retroviral infections such as, but not limited to, HIV in humans by the administration of one or more such compounds, optionally in combination with one or more other anti-viral agents, to a patient in need thereof.

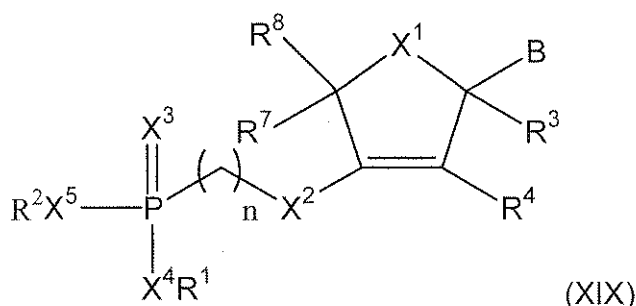
10 One particularly useful aspect of the present invention is the provision of new phosphonate nucleosides comprising a phosphonoalkoxy-substituted or phosphonothioalkyl-substituted five-membered, saturated or unsaturated, ring which is coupled to a heterocyclic nucleobase, preferably a pyrimidine or a purine base. In another particularly useful embodiment of the invention, the five-membered, saturated or unsaturated, ring is an oxygen-containing ring such as
15 dihydrofuranyl and tetrahydrofuranyl.

20 An embodiment of the invention relates to novel 3'-phosphonoalkoxy-substituted or 3'-phosphonothioalkyl-substituted, saturated or unsaturated, furanose nucleosides comprising a purine or pyrimidine base coupled to the 1' position of a furanose, whereby the 3' position of the furanose is substituted with a phosphonoalkoxy group or a phosphonothioalkyl group. These nucleosides can
25 also be derived from tetrahydrofuran or 3,4-dihydrofuran thereby substituted at the 2 position with a heterocyclic base such as, but not limited to, pyrimidine and purine bases, and at the 4 position with a phosphonoalkoxy group or phosphonothioalkyl group.

In one aspect, there is provided a compound represented by one of the general formulae (II) and (XIX):



(II), and



(XIX)

wherein:

- X^1 , X^2 , X^3 , X^4 and X^5 are each independently selected from the group consisting of oxygen and sulfur,
- 10 - B is a nucleobase selected from the group consisting of hypoxanthine, guanine, adenine, cytosine, thymine, uracil, xanthine, 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil;
- 15 - R^1 and R^2 are each independently selected from the group consisting of hydrogen; $(-PO_3R^{16})_m-PO_3R^{17}R^{18}$; C_1 - C_{18} alkyl; C_2 - C_{18} alkenyl; C_2 - C_{18} alkynyl; C_3 - C_{10} cycloalkyl; C_3 - C_{10} cycloalkenyl; C_3 - C_{10} cycloalkynyl; C_6 - C_{30} aryl; C_6 - C_{30} aryl- C_1 - C_{18} alkyl; C_3 - C_{15} heterocyclic; C_3 - C_{15} heterocyclic- C_1 - C_{18} alkyl;
- 20 acyloxy- C_1 - C_{18} alkyl; acyloxy- C_2 - C_{18} alkenyl; acyloxy- C_2 - C_{18} alkynyl; acyloxy-

- C₆-C₃₀ aryl; acyloxy- C₆-C₃₀ aryl-C₁-C₁₈ alkyl; acyloxy-C₆-C₃₀ aryl-C₂-C₁₈ alkenyl; acyloxy-C₆-C₃₀ aryl-C₂-C₁₈ alkynyl; di-C₁-C₁₈ alkylcarbonate; C₁-C₁₈ alkyl-C₆-C₃₀ arylcarbonate; C₁-C₁₈ alkyl-C₂-C₁₈ alkenylcarbonate; C₁-C₁₈ alkyl-C₂-C₁₈ alkynylcarbonate; C₂-C₁₈ alkenyl-C₆-C₃₀ arylcarbonate; C₂-C₁₈ alkynyl-C₆-C₃₀ arylcarbonate; C₂-C₁₈ alkenyl-C₂-C₁₈ alkynylcarbonate; di-C₂-C₁₈ alkenylcarbonate; di- C₂-C₁₈ alkynyl-carbonate; wherein said C₁-C₁₈ alkyl, C₂-C₁₈ alkenyl and C₂-C₁₈ alkynyl optionally contains one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;
- 10 - R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, azido, halogen, cyano, C₁-C₁₈ alkyl, C₂-C₁₈ alkenyl, C₂-C₁₈ alkynyl, SR¹⁴ and OR¹⁴;
- R⁷ and R⁸ are both hydrogen;
- R¹⁴ is selected from hydrogen; C₁-C₁₈ alkyl; C₂-C₁₈ alkenyl; C₂-C₁₈ alkynyl;
- 15 C₃-C₁₀ cycloalkyl; C₃-C₁₀ cycloalkenyl; C₃-C₁₀ cycloalkynyl; C₆-C₃₀ aryl; C₃-C₁₅ heterocyclic; C₆-C₃₀ arylalkyl; C₃-C₁₅ heterocyclic-C₁-C₁₈ alkyl; acyloxy-C₁-C₁₈ alkyl; wherein said C₁-C₁₈ alkyl, C₂-C₁₈ alkenyl and C₂-C₁₈ alkynyl optionally contain one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of
- 20 oxygen, sulfur and nitrogen;
- R¹⁶, R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen; C₁-C₁₈ alkyl; C₂-C₁₈ alkenyl; C₂-C₁₈ alkynyl; C₃-C₁₀ cycloalkyl; C₃-C₁₀ cycloalkenyl; C₃-C₁₀ cycloalkynyl; C₆-C₃₀ aryl; C₆-C₃₀ aryl-C₁-C₁₈ alkyl; C₃-C₁₅ heterocyclic ring; C₃-C₁₅ heterocyclic ring-C₁-C₁₈ alkyl; acyloxy-C₁-C₁₈
- 25 alkyl; wherein said C₁-C₁₈ alkyl, C₂-C₁₈ alkenyl and C₂-C₁₈ alkynyl optionally contain one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;

- X^4 and R^1 or X^5 and R^2 may together form a group having the formula – $OC(R^9)_2OC(O)Y(R^{10})_a$ wherein $Y = N$ or O , $a = 1$ when Y is O and $a = 1$ or 2 when Y is N ;
- R^9 is selected from the group consisting of hydrogen, C_1 - C_{18} alkyl, C_6 - C_{30} aryl,
5 C_2 - C_{18} alkenyl, C_2 - C_{18} alkynyl, C_2 - C_{18} alkenyl- C_6 - C_{30} aryl, C_2 - C_{18} alkynyl- C_6 - C_{30} aryl or C_1 - C_{18} alkyl- C_6 - C_{30} aryl, wherein each of said C_1 - C_{18} alkyl, C_2 - C_{18} alkenyl, C_2 - C_{18} alkynyl and C_6 - C_{30} aryl groups is optionally substituted with one or more atoms or groups selected from the group consisting of halo, cyano, azido, nitro and OR^{14} ;
- 10 - R^{10} is selected from the group consisting of hydrogen, C_1 - C_{18} alkyl, C_6 - C_{30} aryl, C_2 - C_{18} alkenyl, C_2 - C_{18} alkynyl, C_2 - C_{18} alkenyl- C_6 - C_{30} aryl, C_2 - C_{18} alkynyl- C_6 - C_{30} aryl and C_1 - C_{18} alkyl- C_6 - C_{30} aryl, wherein each of said C_1 - C_{18} alkyl, C_2 - C_{18} alkenyl, C_2 - C_{18} alkynyl and C_6 - C_{30} aryl groups is optionally substituted with one or more atoms or groups selected from the group consisting of halo,
15 cyano, azido, nitro, OR^{14} and $NR^{11}R^{12}$;
- R^{11} and R^{12} are each independently selected from the group consisting of hydrogen and C_1 - C_{18} alkyl, provided that at least one of R^{11} and R^{12} is not hydrogen;
- n is an integer representing the number of methylene groups between X_2 and
20 P , each of said methylene groups being optionally and independently substituted with one or two substituents selected from the group consisting of halogen, hydroxyl, sulhydryl and C_{1-4} alkyl, and n being selected from 1, 2, 3, 4, 5 and 6; and
- m is 0 or 1,
- 25 including pharmaceutically acceptable salts, solvates, and stereoisomers thereof.

In another aspect, there is provided the use of a compound as defined above, for the manufacture of a medicament for the prevention or treatment of a viral infection in a mammal.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above as an active ingredient in admixture with at least a pharmaceutically acceptable carrier.

5 BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 to 15 schematically show a number of alternative synthetic routes for making various embodiments of the nucleoside phosphonates of this invention, as well as intermediates involved in such synthetic routes. More specifically these synthetic routes relate to 2' substitution and, still more

specifically, to a different stereochemistry at the 1' and 3' positions of the molecule. Abbreviations used in the figures are defined in the specification herein after. In particular, " Nu " stands for a nucleophile.

5 DEFINITIONS

As used herein, and unless stated otherwise, the term " furanose " refers to five-membered cyclic monosaccharides and, by extension, to their sulfur analogues. The numbering of monosaccharides starts at the carbon next to the oxygen inclosed in the ring and is indicated with a prime (').

10 As used herein, and unless stated otherwise, the term " phosphonalkoxy " refers to a phosphonate coupled via an alkylgroup (such as defined herein after) to an oxygen atom which itself can be coupled to another molecule or group.

As used herein, and unless stated otherwise, the term " phospho-thioalkyl " refers to a phosphonate coupled via an alkylgroup (such as defined
15 herein after) to a sulfur atom which itself can be coupled to another molecule or group.

As used herein, and unless stated otherwise, the term " 3'-phosphono-alkoxy furanose nucleoside " refers to a heterocyclic base, such as a purine or pyrimidine base, coupled to the 1' position of a furanose whereby the 3' position
20 of said furanose is substituted with a phosphonoalkoxy group.

As used herein, and unless stated otherwise, the terms " heterocyclic nucleobase " and " pyrimidine and purine bases " include, but are not limited to, adenine, thymine, cytosine, uracyl, guanine and (2,6-)diaminopurine such as may be found in naturally-occurring nucleosides. The term also includes analogues
25 and derivatives thereof. An analogue thereof is a base which mimics such naturally-occurring bases in such a way that its structure (the kinds of atoms present and their arrangement) is similar to the above-listed naturally-occurring bases but is modified by either having additional functional properties with respect to the naturally-occurring bases or lacking certain functional properties of
30 the naturally-occurring bases. Such analogues include, but are not limited to,

those derived by replacement of a $-CH-$ moiety by a nitrogen atom (e.g. 5-azapyrimidines such as 5-azacytosine) or vice-versa (e.g. 7-deazapurines, such as 7-deaza-adenine or 7-deazaguanine) or both (e.g. 7-deaza, 8-azapurines). A derivative of naturally-occurring bases, or analogues thereof, is a compound wherein the heterocyclic ring of such bases is substituted with one or more conventional substituents independently selected from the group consisting of halogen, hydroxyl, amino and C_{1-6} alkyl. Some additional illustrative examples are provided in the specification herein after. Such purine or pyrimidine bases, analogues and derivatives thereof, are well known to those skilled in the art, e.g. from documents such as, but not limited to, WO 03/093290 and WO 04/028481.

As used herein, and unless stated otherwise, the term "alkyl" as used herein refers to linear or branched saturated hydrocarbon chains having from 1 to 18 carbon atoms such as, but not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl (isopropyl), 2-butyl (*sec*-butyl), 2-methyl-2-propyl (*tert*-butyl), 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, *n*-dodecyl, *n*-tridecyl, *n*-tetradecyl, *n*-pentadecyl, *n*-hexadecyl, *n*-heptadecyl, *n*-octadecyl, and the like; preferably the alkyl group has from 1 to 8 carbon atoms, more preferably from 1 to 4 carbon atoms.

As used herein, and unless stated otherwise, the term "cycloalkyl" means a monocyclic saturated hydrocarbon monovalent radical having from 3 to 10 carbon atoms, such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like, or a C_{7-10} polycyclic saturated hydrocarbon monovalent radical having from 7 to 10 carbon atoms such as, for instance, norbornyl, fenchyl, trimethyltricycloheptyl or adamantyl.

As used herein, and unless stated otherwise, the terms "alkenyl" and "cycloalkenyl" refer to linear or branched hydrocarbon chains having from 2 to 18 carbon atoms, respectively cyclic hydrocarbon chains having from 3 to 10

carbon atoms, with at least one ethylenic unsaturation (i.e. a carbon-carbon sp² double bond) which may be in the cis or trans configuration such as, but not limited to, vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂).

5 As used herein, and unless stated otherwise, the terms "alkynyl" and "cycloalkynyl" refer to linear or branched hydrocarbon chains having from 2 to 18 carbon atoms, respectively cyclic hydrocarbon chains having from 3 to 10 carbon atoms, with at least one acetylenic unsaturation (i.e. a carbon-carbon sp triple bond) such as, but are not limited to, ethynyl (-C≡CH), propargyl (-CH₂C≡CH), cyclopropynyl, cyclobutynyl, cyclopentynyl, or cyclohexynyl.

As used herein with respect to a substituting radical, and unless otherwise stated, the term "aryl" designates any mono- or polycyclic aromatic monovalent hydrocarbon radical having from 6 up to 30 carbon atoms such as but not limited to phenyl, naphthyl, anthracenyl, phenanthracenyl, fluoranthenyl, chrysenyl, pyrenyl, 15 biphenyl, terphenyl, picenyl, indenyl, biphenyl, indacenyl, benzocyclobutenyl, benzocyclooctenyl and the like, including fused benzo-C₄₋₈ cycloalkyl radicals (the latter being as defined above) such as, for instance, indanyl, tetrahydronaphthyl, fluorenyl and the like, all of the said radicals being optionally substituted with one or more substituents independently selected from the group 20 consisting of halogen, amino, trifluoromethyl, hydroxyl, sulfhydryl and nitro, such as for instance 4-fluorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-cyanophenyl, 2,6-dichlorophenyl, 2-fluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl and the like.

As used herein with respect to a substituting group, and unless otherwise 25 stated, the terms "arylalkyl", "arylalkenyl" and "heterocyclic-substituted alkyl" refer to an aliphatic saturated or ethylenically unsaturated hydrocarbon monovalent group (preferably a C₁₋₁₈ alkyl or C₂₋₁₈ alkenyl such as defined above) onto which an aryl or heterocyclic group (such as defined herein) is already bonded, and wherein the said aliphatic group and/or the said aryl or heterocyclic 30 group may be optionally substituted with one or more substituents independently

selected from the group consisting of halogen, amino, hydroxyl, sulfhydryl, C₁₋₇ alkyl, trifluoromethyl and nitro, such as but not limited to benzyl, 4-chlorobenzyl, 4-fluorobenzyl, 2-fluorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-*ter*-butylbenzyl, phenylpropyl, 1-naphthylmethyl, phenylethyl, 1-amino-2-phenylethyl, 1-amino-2-[4-hydroxy-phenyl]ethyl, 1-amino-2-[indol-2-yl]ethyl, styryl, pyridylmethyl (including all isomers thereof), pyridylethyl, 2-(2-pyridyl)isopropyl, oxazolylbutyl, 2-thienylmethyl, pyrrolylethyl, morpholinylethyl, imidazol-1-yl-ethyl, benzodioxolylmethyl and 2-furylmethyl.

As used herein with respect to a substituting group, and unless otherwise stated, the term " heterocyclic ring " or " heterocyclic " means a mono- or polycyclic, saturated or mono-unsaturated or polyunsaturated monovalent hydrocarbon group having from 3 up to 15 carbon atoms and including one or more heteroatoms in one or more heterocyclic rings, each of said rings having from 3 to 10 atoms (and optionally further including one or more heteroatoms attached to one or more carbon atoms of said ring, for instance in the form of a carbonyl or thiocarbonyl or selenocarbonyl group, and/or to one or more heteroatoms of said ring, for instance in the form of a sulfone, sulfoxide, N-oxide, phosphate, phosphonate or selenium oxide group), each of said heteroatoms being independently selected from the group consisting of nitrogen, oxygen, sulfur, selenium and phosphorus, also including radicals wherein a heterocyclic ring is fused to one or more aromatic hydrocarbon rings for instance in the form of benzo-fused, dibenzo-fused and naphtho-fused heterocyclic radicals; within this definition are included heterocyclic groups such as, but not limited to, pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothienyl, tetrahydrothienyl sulfoxide, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, bis-tetrahydrofuranyl, tetrahydropyranyl, bis-tetrahydropyranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-

1,5,2-dithiazinyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolyl, piperazinyl, indolyl, isoindolyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolyl, benzothienyl, benzothiazolyl and isatinoyl; heterocyclic groups may be sub-divided into heteroaromatic (or "heteroaryl") groups such as, but not limited to, pyridyl, dihydropyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl, and non-aromatic heterocyclic groups; when a heteroatom of the said non-aromatic heterocyclic group is nitrogen, the latter may be substituted with a substituent selected from the group consisting of alkyl, cycloalkyl, aryl, arylalkyl and alkylaryl (such as defined herein); by way of example, carbon-bonded heterocyclic rings may be bonded at position 2, 3, 4, 5, or 6 of a pyridine, at position 3, 4, 5, or 6 of a pyridazine, at position 2, 4, 5, or 6 of a pyrimidine, at position 2, 3, 5, or 6 of a pyrazine, at position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, at position 2, 4, or 5 of an oxazole, imidazole or thiazole, at position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, at position 2 or 3 of an aziridine, at position 2, 3, or 4 of an azetidine, at position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or at position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline; still more specific carbon-bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl; by way of example, nitrogen-bonded heterocyclic rings may be bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-

pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, at position 2 of an isoindole or isoindoline, at position 4 of a morpholine, and at position 9 of a carbazole or β -carboline, still more specific
 5 nitrogen-bonded heterocycles include 1-aziridyl, 1-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl and 1-piperidinyl.

The term " acyl " as used herein, unless otherwise stated, refers to a carbonyl group directly attached to an alkyl, alkenyl, alkynyl, aryl, heterocyclic, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic-alkyl, heterocyclic-alkenyl or
 10 heterocyclic-alkynyl group, such as for example alkanoyl (alkylcarbonyl), aroyl (arylcarbonyl), arylalkanoyl or alkylaroyl group, wherein the carbonyl group is coupled to another molecule. As an example, the term " acyloxyalkyl " refers to an acyl group coupled via an oxygen atom to an alkyl group, the latter being further coupled to another molecule or atom.

15 As an example, " alkylalkenylcarbonate " refers to a alkyl-OC(O)O-alkenyl group, thus a carbonate substituted at one side with an alkyl and on the other side with an alkenyl, one of the alkyl and alkenyl groups being further coupled to another molecule or atom.

As used herein and unless otherwise stated, the terms " alkoxy ", " cyclo-
 20 alkoxy ", " aryloxy ", " arylalkyloxy ", " oxyheterocyclic ", " thioalkyl ", " thio cycloalkyl ", " arylthio ", " arylalkylthio " and " thioheterocyclic " refer to substituents wherein an alkyl group, respectively a cycloalkyl, aryl, arylalkyl or heterocyclic group (each of them such as defined herein), are attached to an oxygen atom or a sulfur atom through a single bond, such as but not limited to
 25 methoxy, ethoxy, propoxy, butoxy, thioethyl, thiomethyl, phenyloxy, benzyloxy, mercaptobenzyl and the like.

As used herein and unless otherwise stated, the term halogen means any atom selected from the group consisting of fluorine, chlorine, bromine and iodine.

As used herein with respect to a substituting radical, and unless otherwise
 30 stated, the term " amino-acid " refers to a radical derived from a molecule having

the chemical formula $\text{H}_2\text{N}-\text{CHR}-\text{COOH}$, wherein R is the side group of atoms characterizing the amino-acid type; said molecule may be one of the 20 naturally-occurring amino-acids or any similar non naturally-occurring amino-acid.

As used herein and unless otherwise stated, the term " stereoisomer " refers to all possible different isomeric as well as conformational forms which the compounds of the invention may possess, in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds of the present invention may exist in different tautomeric forms, all of the latter being included within the scope of the present invention.

As used herein and unless otherwise stated, the term " enantiomer " means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

As used herein and unless otherwise stated, the term " solvate " includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like.

The term " pharmaceutically acceptable carrier or excipient " as used herein refers to any material or substance with which the active principle, i.e. a compound of this invention may be formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid.

As used herein and unless otherwise stated, the term " tetrose " refers to any of a class of monosaccharides containing four carbon atoms such as, but not limited to, erythrose or threose with the general formula $\text{C}_4\text{H}_8\text{O}_4$. Tetrose