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 phosphonomethoxy-methoxymethyl 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~~ disclosure 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~~ disclosure 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 phosphonylated nucleosides of the invention can be considered as mono-, di- or triphosphate mimics. By varying the length of this linking structure, the present ~~invention~~ disclosure makes it possible to further finely tune the antiviral activity of the novel class of compounds. Also, this ~~invention~~ disclosure 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 disclosure~~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~~ disclosure 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~~ disclosure 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~~ disclosure furthermore relates to the use of such compounds as medicines, more specifically as anti-viral agents, and to their use for the

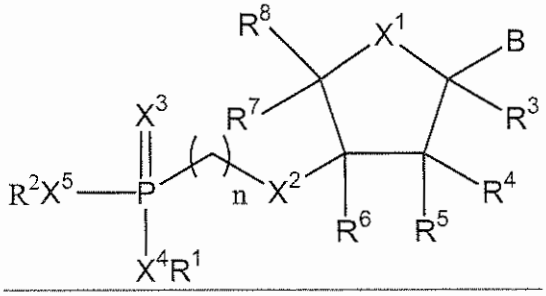
manufacture of medicaments for treating and/or preventing viral infections, in particular retroviral infections such as, but not limited to, HIV in humans. The ~~invention~~ disclosure also relates to methods for the preparation of all such compounds and to pharmaceutical compositions comprising them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

The present ~~invention~~ 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.

One particularly useful ~~aspect of the present invention~~embodiment 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 dihydrofuranyl and tetrahydrofuranyl.

An~~other~~ embodiment ~~of the invention~~ relates to novel 3'-phosphonalkoxy-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 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 of the present disclosure, there is provided a process for preparing a compound represented by the general formula (II):



wherein: X^1, X^2, X^3, X^4 and X^5 are each --O--,

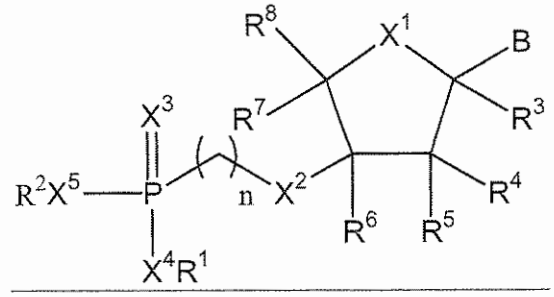
B is selected from the group consisting of adeninyl, thyminyl, uracilyl, cytosinyl and guaninyl,

R^1 and R^2 are each independently selected from the group consisting of hydrogen, alkyl and P(O)(OH)--O--PO_3H_2, provided that when one of R^1 and R^2 is P(O)(OH)--O--PO_3H_2, the other one is hydrogen; R^4 and R^5 are each independently selected from the group consisting of hydrogen and OR^{14};

R^3, R^6, R^7 and R^8 are each hydrogen;

R^{14} is hydrogen or arylalkyl; and

n is an integer representing the number of methylene groups between X_2 and P, and is selected from 1, 2, 3, 4, 5 and 6; or a pharmaceutically acceptable salt thereof, the process comprising the step of coupling a nucleobase B selected from the group consisting of adenine, thymine, uracil, cytosine and guanine, in the presence of a Lewis acid catalyst, with a precursor represented by the general formula



wherein X^1, X^2, X^3, X^4 and X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{14}, and n are as defined in formula (II) and wherein R^9 is an O-acyl group

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