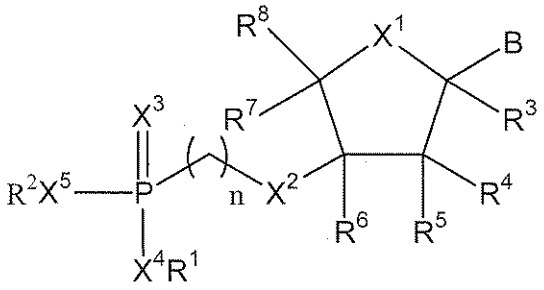
manufacture of medicaments for treating and/or preventing viral infections, in particular retroviral infections such as, but not limited to, HIV in humans. The invention also relates to methods for the preparation of all such compounds and to pharmaceutical compositions comprising them in an anti-viral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

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.

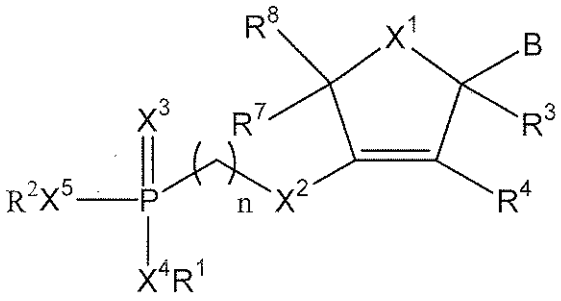
One particularly useful aspect of the present invention is the provision of new phosphonate nucleosides comprising a phosphonoalkoxy-substituted or phosphonothioalkyl-substituted five-membered, saturated or unsaturated, ring which is coupled to a heterocyclic nucleobase, preferably a pyrimidine or a 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 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, 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 each independently selected from the group consisting of oxygen and sulfur,
- 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;
- 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; acyloxy- C_1-C_{18} alkyl; acyloxy-C_2-C_{18} alkenyl; acyloxy-C_2-C_{18} alkynyl; acyloxy-

C_6-C_{30} aryl; acyloxy- C_6-C_{30} aryl-C_1-C_{18} alkyl; acyloxy-C_6-C_{30} aryl-C_2-C_{18} alkenyl; acyloxy-C_6-C_{30} aryl-C_2-C_{18} alkynyl; di-C_1-C_{18} alkylcarbonate; C_1-C_{18} alkyl-C_6-C_{30} arylcarbonate; C_1-C_{18} alkyl-C_2-C_{18} alkenylcarbonate; C_1-C_{18} alkyl-C_2-C_{18} alkynylcarbonate; C_2-C_{18} alkenyl-C_6-C_{30} arylcarbonate; C_2-C_{18} alkynyl-C_6-C_{30} arylcarbonate; C_2-C_{18} alkenyl-C_2-C_{18} alkynylcarbonate; di-C_2-C_{18} alkenylcarbonate; di- C_2-C_{18} alkynyl-carbonate; wherein said C_1-C_{18} alkyl, C_2-C_{18} alkenyl and C_2-C_{18} 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;

- R^3, R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, azido, halogen, cyano, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, SR^{14} and OR^{14};
- R^7 and R^8 are both hydrogen;
- R^{14} is selected from hydrogen; 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_3-C_{15} heterocyclic; C_6-C_{30} arylalkyl; C_3-C_{15} heterocyclic-C_1-C_{18} alkyl; acyloxy-C_1-C_{18} alkyl; wherein said C_1-C_{18} alkyl, C_2-C_{18} alkenyl and C_2-C_{18} 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;
- R^{16}, R^{17} and R^{18} are independently selected from the group consisting of hydrogen; 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 ring; C_3-C_{15} heterocyclic ring-C_1-C_{18} alkyl; acyloxy-C_1-C_{18} alkyl; wherein said C_1-C_{18} alkyl, C_2-C_{18} alkenyl and C_2-C_{18} 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, 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};
- 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, 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 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,

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.

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