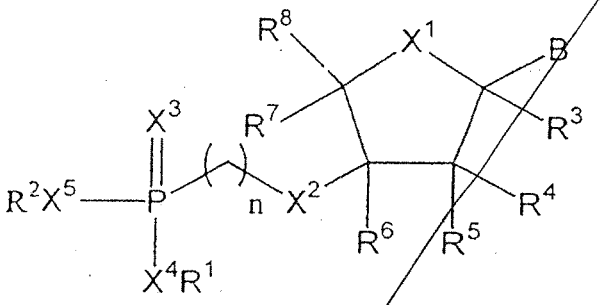
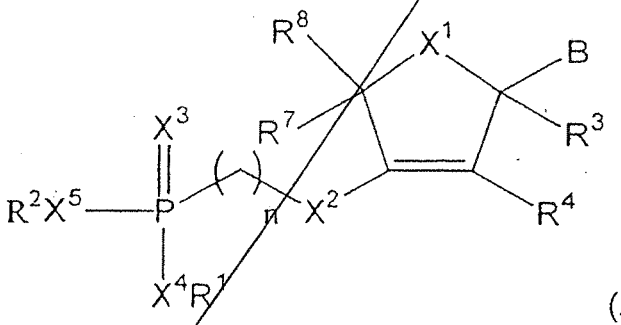
CLAIMS

1. A compound including a heterocyclic nucleobase attached to a first carbon atom of an optionally substituted five-member saturated or mono-unsaturated heterocyclic group selected from tetrahydrofuranyl, tetrahydrothienyl, dihydrofuranyl and dihydrothienyl and further including a phosphonoalkoxy or phosphonothioalkyl group attached to a second carbon atom of said five-member saturated or mono-unsturated heterocyclic group, said first carbon atom being adjacent to the heteroatom of said five-member saturated or mono-unsturated heterocyclic group, and said second carbon atom being adjacent neither to the heteroatom nor to the first carbon atom of said five-member saturated or mono-unsturated heterocyclic group, said compound being represented by one of the general formulae (II) and (XIX):



(II), and



(XIX)

wherein:

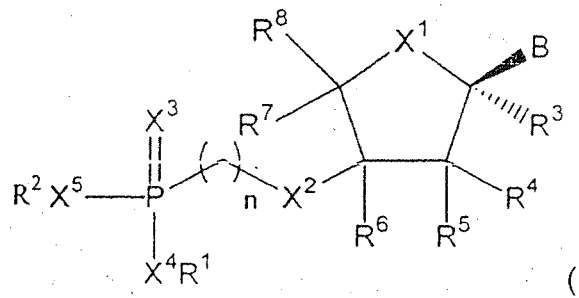
- X^1, X^2, X^3, X^4 and X^5 are each each independently selected from the group consisting of oxygen and sulfur,
- B is a natural or non-natural heterocyclic nucleobase,

- R^1 and R^2 are each independently selected from the group consisting of hydrogen; $(-PO_3R^{16})_m-PO_3R^{17}R^{18}$; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic; heterocyclic-alkyl; acyloxyalkyl; acyloxyalkenyl; acyloxyalkynyl; acyloxyaryl; acyloxyarylalkyl; acyloxyarylalkenyl; acyloxyarylalkynyl; dialkylcarbonate; alkylarylcarbonate; alkylalkenylcarbonate; alkylalkynylcarbonate; alkenylarylcarbonate; alkynylarylcarbonate; alkenylalkynylcarbonate; dialkenylcarbonate; dialkynylcarbonate; wherein said alkyl, alkenyl and 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, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, azido, halogen, cyano, alkyl, alkenyl, alkynyl, SR^{14} and OR^{14};
- R^{14} is selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heterocyclic; arylalkyl; heterocyclic-alkyl; acyloxyalkyl; wherein said alkyl, alkenyl and 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; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic ring; heterocyclic ring-alkyl; acyloxyalkyl; wherein said alkyl, alkenyl and 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 an amino-acid residue or polypeptide wherein a carboxyl function of said amino-acid residue being at a distance from the amidate nitrogen not further than 5 atoms is esterified;

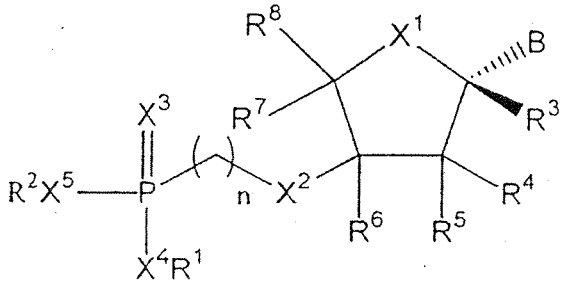
- X^4 and R^1 or X^5 and R^2 may together form a group having the formula – $OC(R^9)_2OC(O)Y(R^{10})_a$ wherein Y = N or O, a = 1 when Y is O and a = 1 or 2 when Y is N;
- R^9 is selected from the group consisting of hydrogen, alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl or alkylaryl, wherein each of said alkyl, alkenyl, alkynyl and 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, alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl and alkylaryl, wherein each of said alkyl, alkenyl, alkynyl and 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 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, stereoisomers and prodrugs thereof.

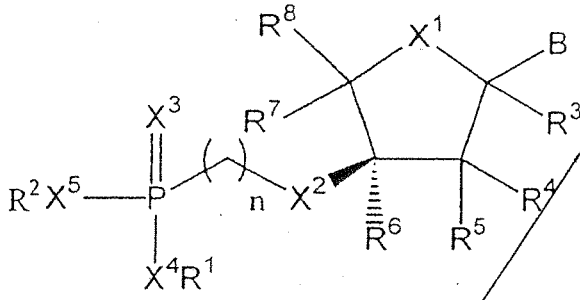
2. A compound according to claim 1, being represented by one of the general formulae (III) to (XVIII):



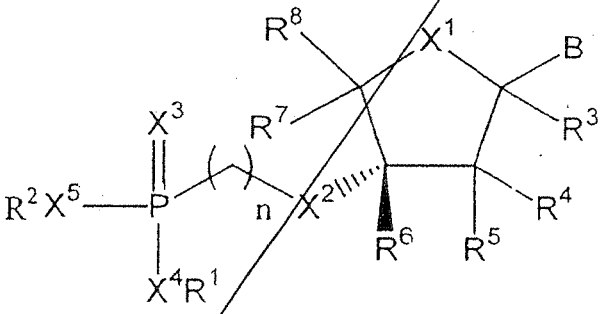
(III),



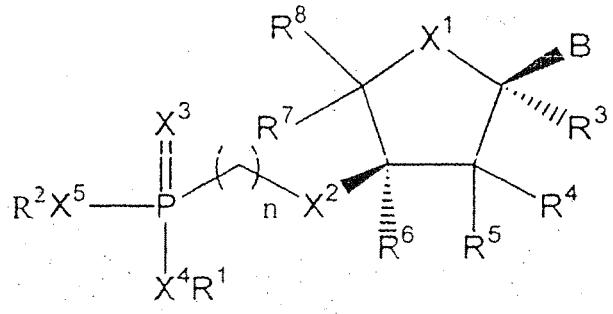
(IV),



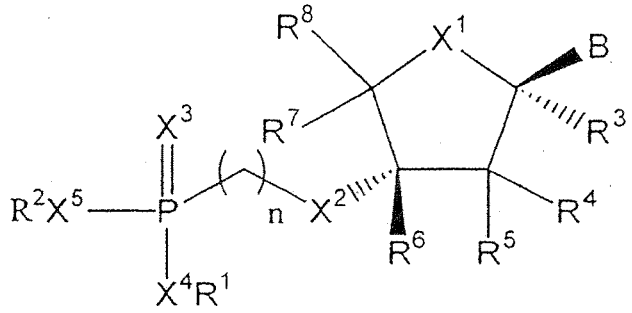
(V),



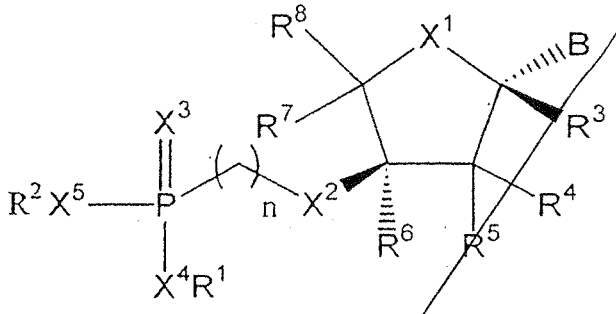
(VI),



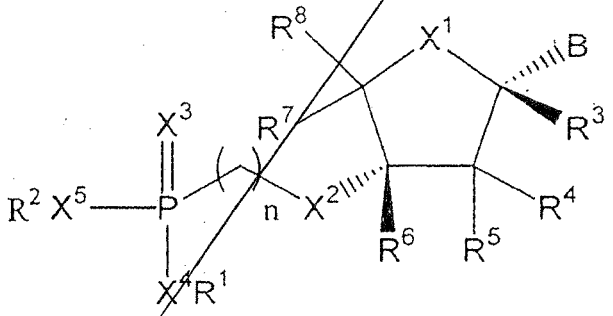
(VII),



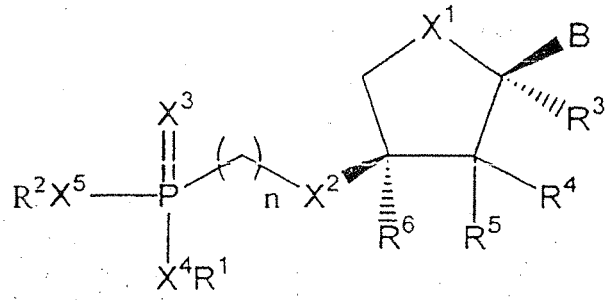
(VIII),



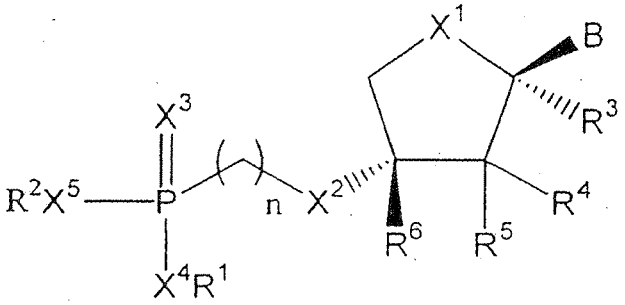
(IX),



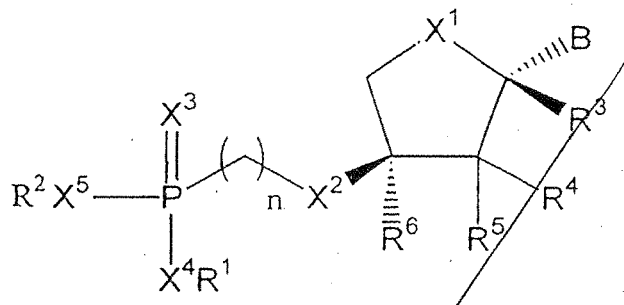
(X),



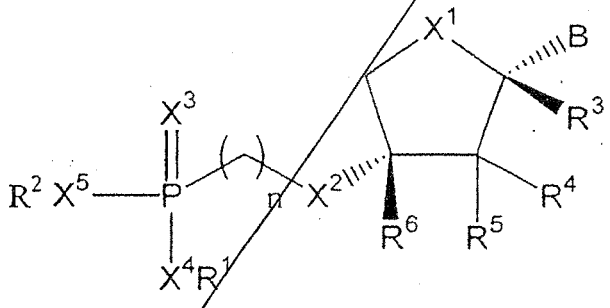
(XI),



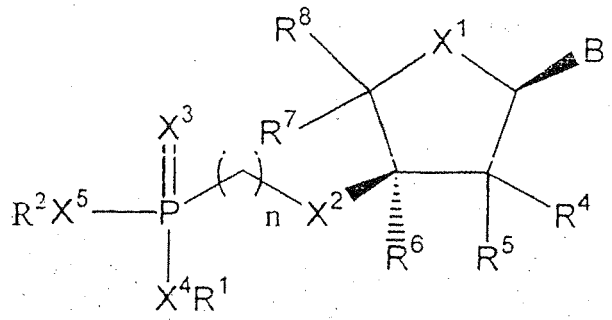
(XII)



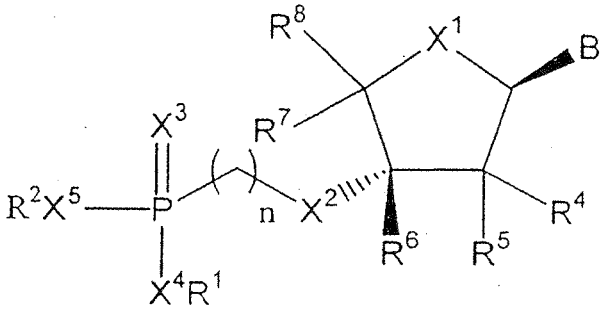
(XIII)



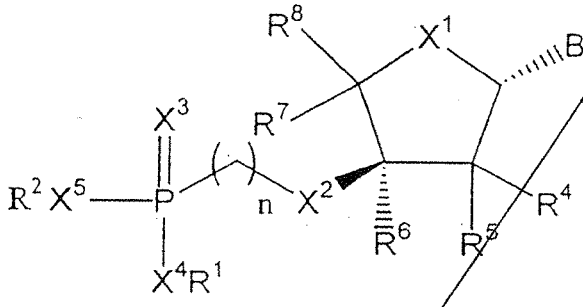
(XIV),



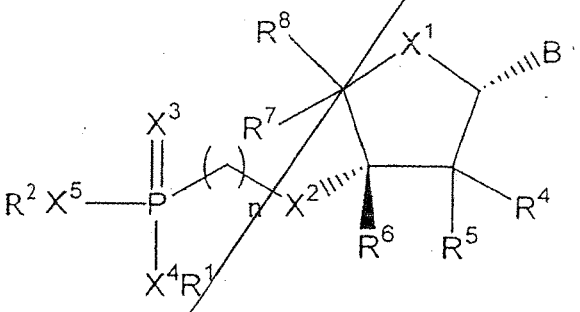
(XV),



(XVI)



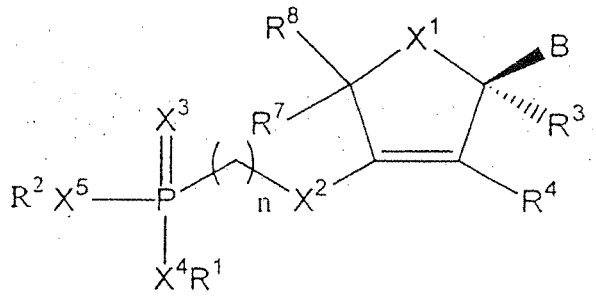
(XVII), and



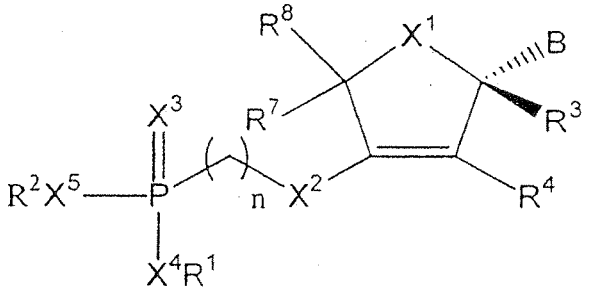
(XVIII)

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, stereoisomers and prodrugs thereof.

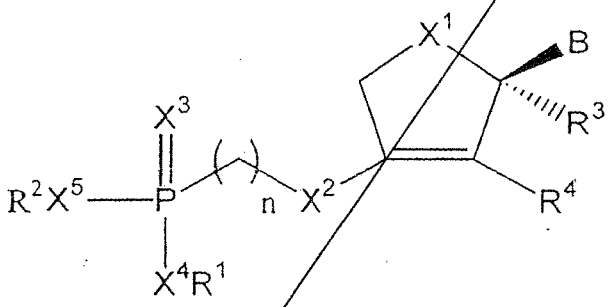
3. A compound according to claim 1, being represented by any of the following formulae (XX) to (XXVI):



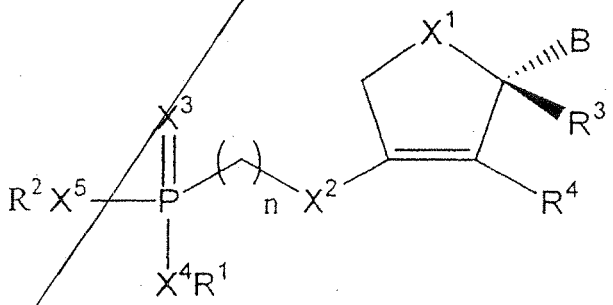
(XX),



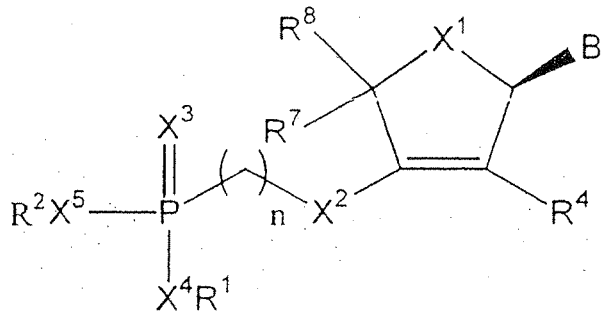
(XXI),



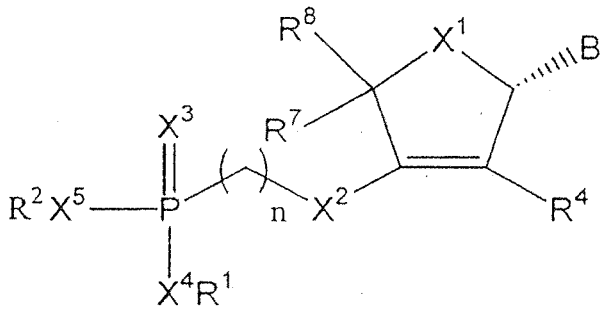
(XXII),



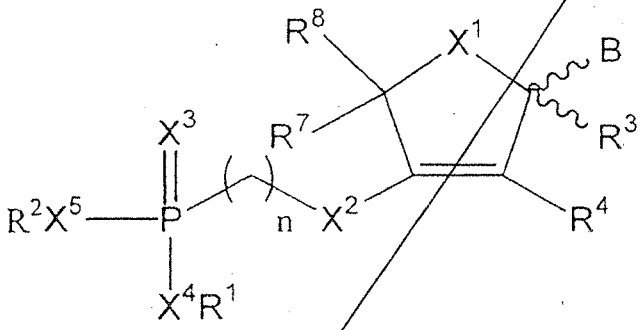
(XXIII),



(XXIV),



(XXV), and



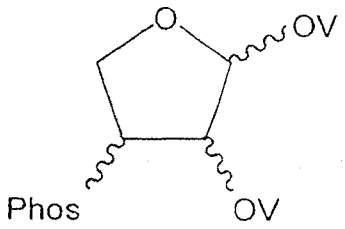
(XXVI),

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, stereoisomers and prodrugs thereof.

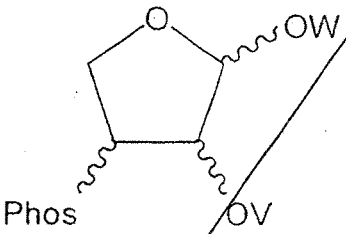
4. A compound according to any of claims 1 to 3, wherein B is selected from the group consisting of hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine;

7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and 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.

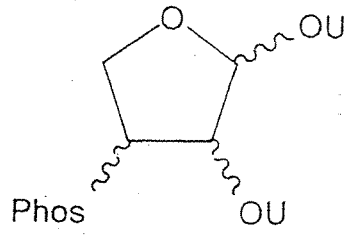
5. A compound represented by one of the following general formulae (XXXI) to (XXXVI):



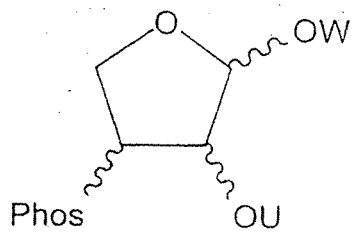
(XXXI),



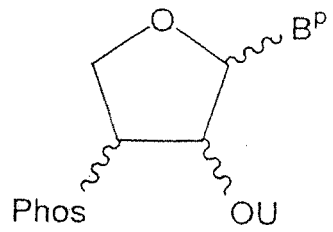
(XXXII),



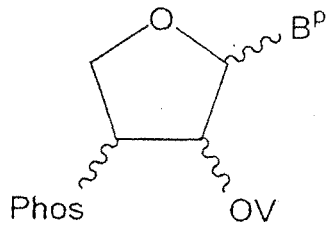
(XXXIII),



(XXXIV),



(XXXV), and



(XXXVI),

wherein:

- U is an acyl group,
- V is a silyl group,
- W is an alkyl group,
- the snake-like symbol means any stereochemical arrangement of the respective bond,
- B^P is an optionally protected heterocyclic nucleobase, and
- Phos is an O-protected phosphonoalkoxy group or phosphonothioalkyl group.

6. Use of a compound according to claim 5 as an intermediate for making a compound according to any of claims 1 to 4.

7. A compound according to any of claims 1 to 4, being selected from the group consisting of :

1-(N^6-benzoyladenin-9-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**11**);

1-(thymin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose(**12**);

1-(uracil-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**13**);

1-(N^4-acetylcytosin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**14**);

1-(adenin-9-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**15**);

1-(thymin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**16**);

1-(uracil-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**17**);

1-(cytosin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**18**);

1-(adenin-9-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**19**);

1-(thymin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**20**);

1-(uracil-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**21**);

1-(cytosin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**22**);

1-(adenin-9-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3a**);

1-(thymin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3b**);

1-(uracil-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3c**);

1-(cytosin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3d**);

1-(adenin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3e**);

1-(thymin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3f**);

1-(uracil-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3g**);

1-(cytidin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3h**);

a pharmaceutically acceptable salt , an stereoisomer, a solvate or a pro-drug thereof.

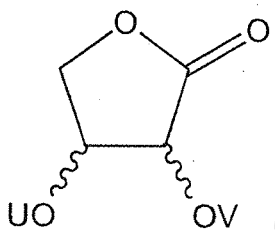
8. The use of a compound according to any of the claims 1 to 4, for the manufacture of a medicament for the prevention or treatment of a viral infection in a mammal.

9. The use according to claim 8, wherein said viral infection is an infection by the Human Immunodeficiency Virus (HIV).

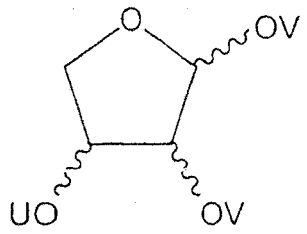
10. A pharmaceutical composition comprising a compound according to any of the claims 1 to 4 as an active ingredient in admixture with at least a pharmaceutically acceptable carrier.

11. A pharmaceutical composition according to claim 10, further comprising an antiviral agent.

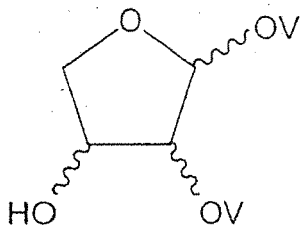
12. A compound represented by one of the following general formula (XXVIII) to (XXX):



(XXVIII),



(XXIX), and



(XXX),

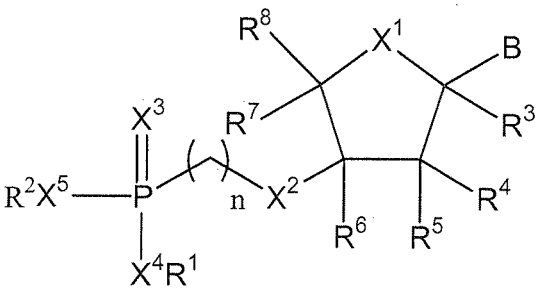
wherein:

- U is an acyl group,
- V is a silyl group, and
- the snake-like symbol means any stereochemical arrangement of the respective bond.

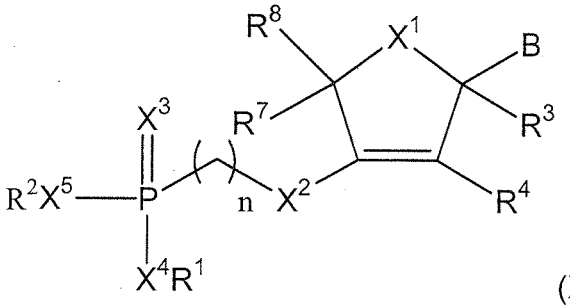
13. Use of a compound according to claim 12 as an intermediate for making a compound according to any of claims 1 to 4.

CLAIMS

1. 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;

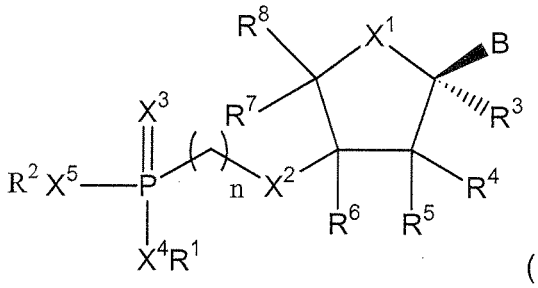
- R^3, R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, azido, halogen, cyano, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, SR^{14} and OR^{14};
- R^7 and R^8 are both hydrogen;
- R^{14} is selected from hydrogen; C_1-C_{18} alkyl; C_2-C_{18} alkenyl; 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};

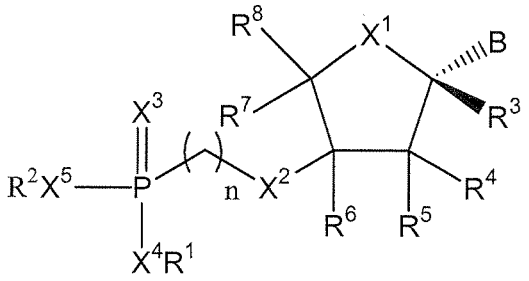
- R^{10} is selected from the group consisting of hydrogen, C_1-C_{18} alkyl, C_6-C_{30} aryl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, C_2-C_{18} alkenyl-C_6-C_{30} aryl, C_2-C_{18} alkynyl-C_6-C_{30} aryl and C_1-C_{18} alkyl-C_6-C_{30} aryl, wherein each of said C_1-C_{18} alkyl, C_2-C_{18} alkenyl, 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.

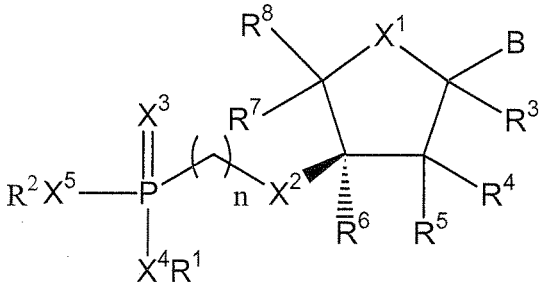
2. A compound according to claim 1, being represented by one of the general formulae (III) to (XVIII):



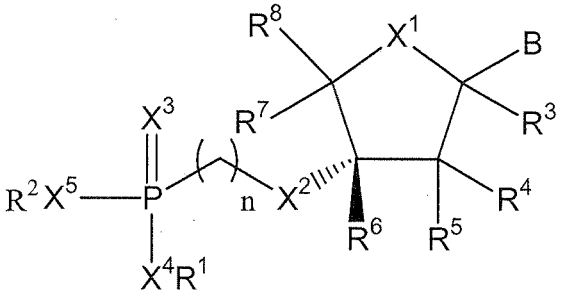
(III),



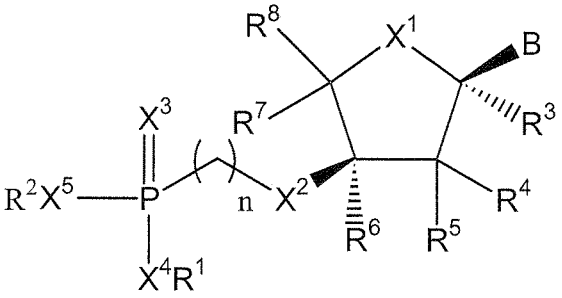
(IV),



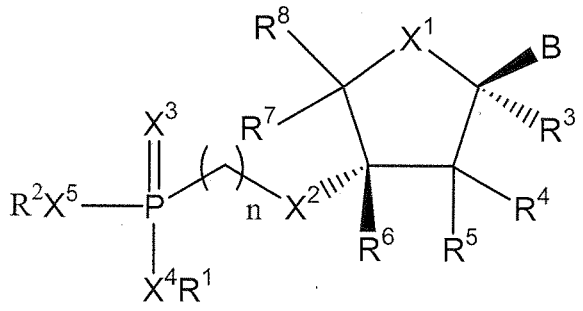
(V),



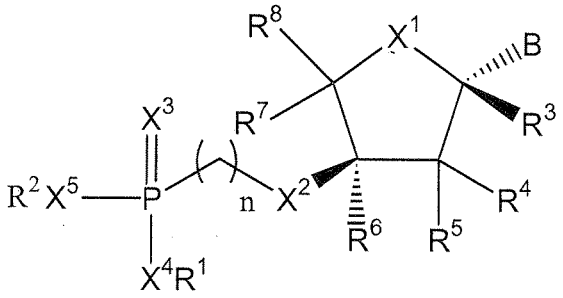
(VI),



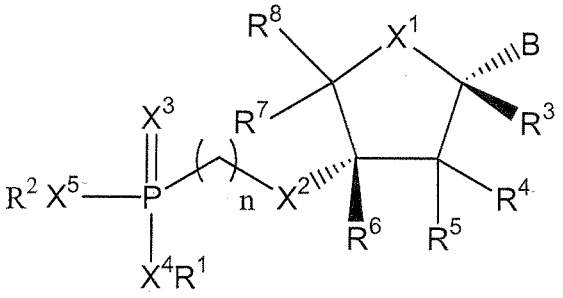
(VII),



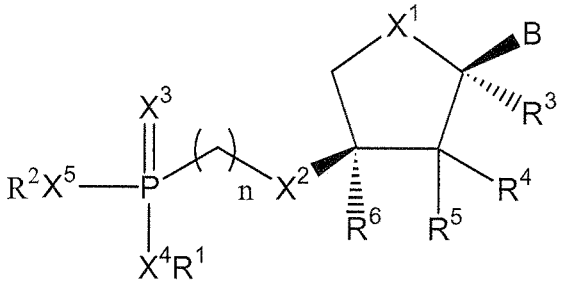
(VIII),



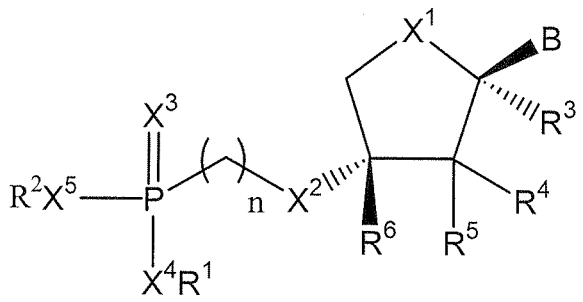
(IX),



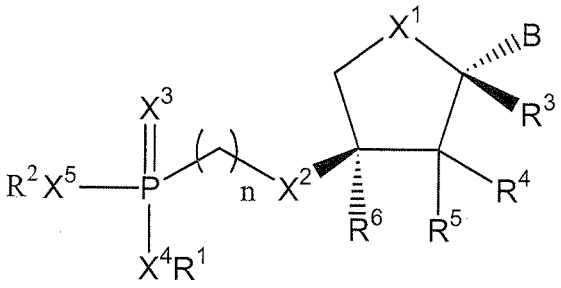
(X),



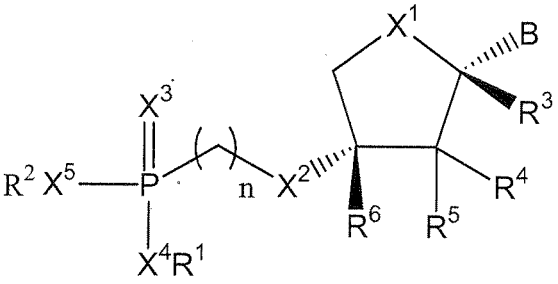
(XI),



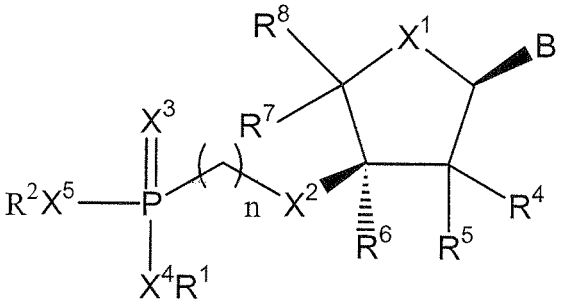
(XII)



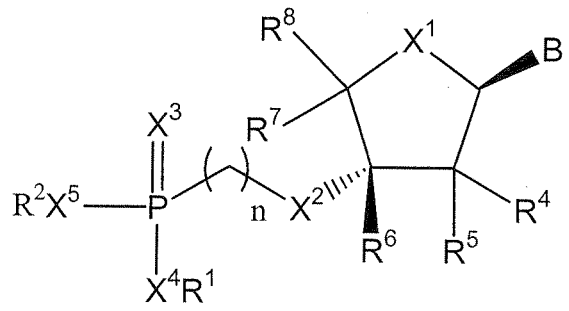
(XIII)



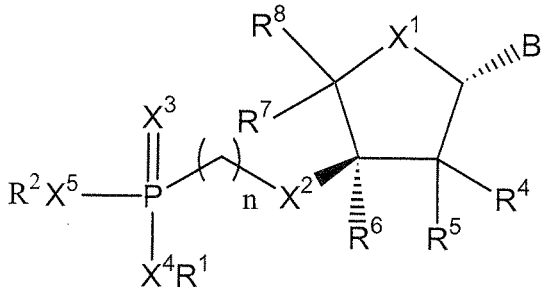
(XIV),



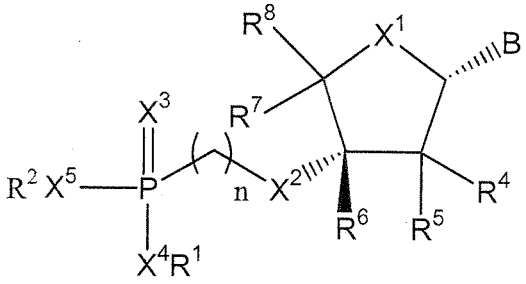
(XV),



(XVI)



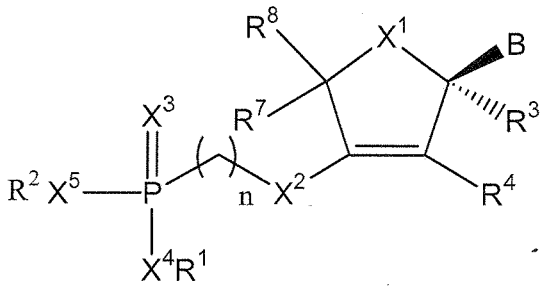
(XVII), and



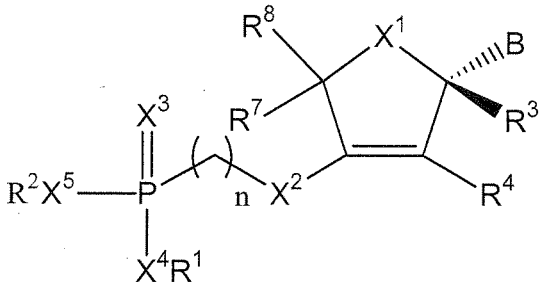
(XVIII)

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, and stereoisomers thereof.

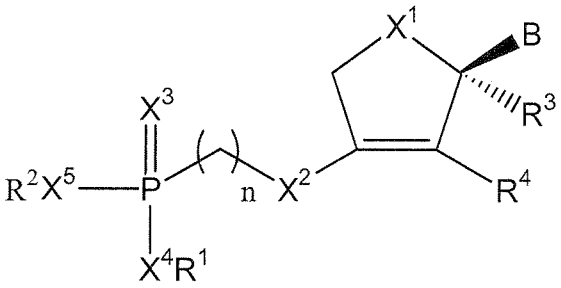
3. A compound according to claim 1, being represented by any of the following formulae (XX) to (XXVI):



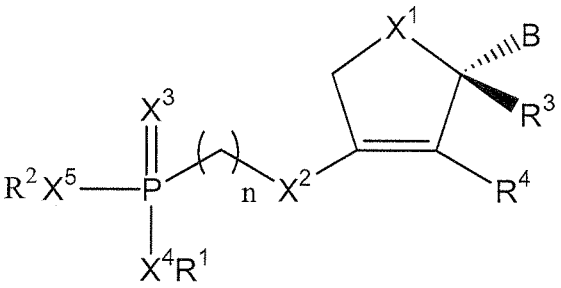
(XX),



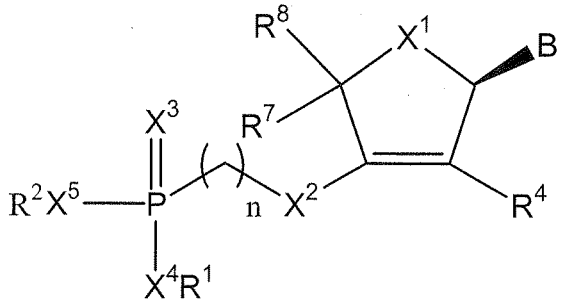
(XXI),



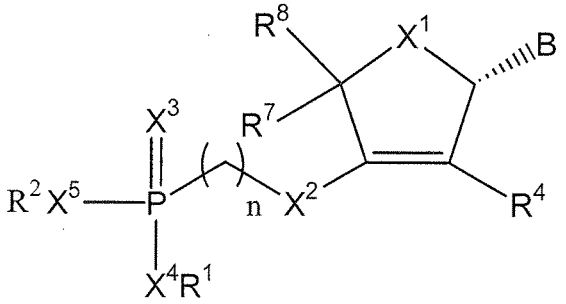
(XXII),



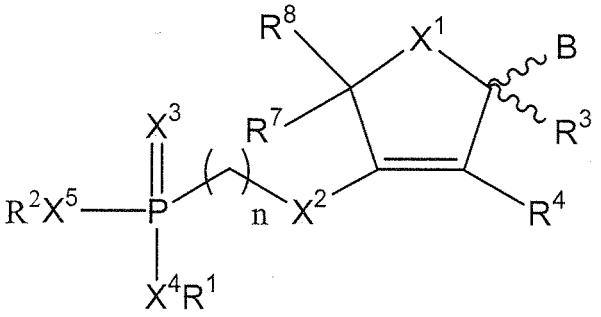
(XXIII),



(XXIV),



(XXV), and



(XXVI),

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, and stereoisomers thereof.

4. A compound according to any one of claims 1 to 3, wherein B is adenine or thymine.

5. A compound according to any one of claims 1 to 4, wherein R^4 is hydroxy

6. A compound according to any one of claims 1 to 5, wherein R^1 and R^2 are both isopropyl.

7. A compound according to any one of claims 1 to 4, being selected from the group consisting of :

1-(N^6-benzoyladenin-9-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**11**);

1-(thymin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose(**12**);

1-(uracil-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**13**);

1-(N^4-acetylcytosin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**14**);

1-(adenin-9-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**15**);

1-(thymin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**16**);

1-(uracil-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**17**);

1-(cytosin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**18**);

1-(adenin-9-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**19**);

1-(thymin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**20**);

1-(uracil-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**21**);

1-(cytosin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**22**);

1-(adenin-9-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3a**);

1-(thymin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3b**);

1-(uracil-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3c**);

1-(cytosin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3d**);

1-(adenin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3e**);

1-(thymin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3f**);

1-(uracil-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3g**);

1-(cytidin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3h**);

a pharmaceutically acceptable salt , an stereoisomer, or a solvate thereof.

8. The use of a compound according to any one of the claims 1 to 7, for the manufacture of a medicament for the prevention or treatment of a viral infection in a mammal.

9. The use according to claim 8, wherein said viral infection is an infection by the Human Immunodeficiency Virus (HIV).

10. A pharmaceutical composition comprising a compound according to any one of the claims 1 to 7 as an active ingredient in admixture with at least a pharmaceutically acceptable carrier.

11. A pharmaceutical composition according to claim 10, further comprising an antiviral agent.