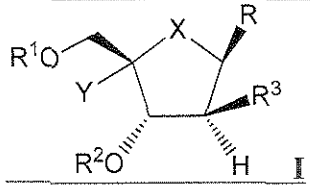
SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure is directed to 4'-substituted nucleoside derivatives and their use in the inhibition of HIV reverse transcriptase, the prophylaxis of infection by HIV, the treatment of infection by HIV, and the prophylaxis, treatment, and delay in the onset or progression of AIDS and/or ARC.

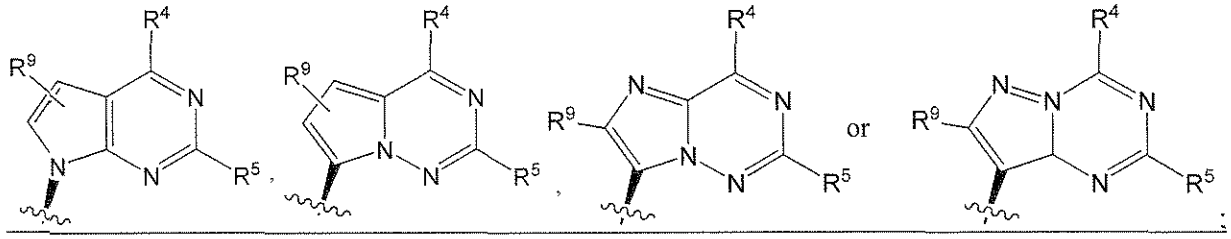
In one aspect, there is provided a compound of structural Formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

R is

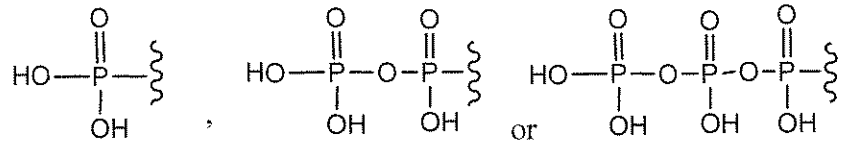


;

X is O, S, CH2 or CF2;

Y is –C≡C-R8 or -C≡N;

R1 is -H, -C(O)R6, -C(O)OR6, -C(O)N(R6)2,



,

or a pro-drug modification of the mono-, di- or triphosphate;

R2 is -H, -C(O)R6a, -C(O)OR6a or -C(O)N(R6a)2;

R3 is -H, -F, or -OH;

R4 is -H, -C1-C6 alkyl, -C2-C6 alkenyl, -C2-C6 alkynyl, -C1-C6 haloalkyl, -C3-C7 cycloalkyl, 5- or 6-membered monocyclic heteroaryl, a 9- or 10-membered bicyclic heteroaryl, halo, -CN, -NO2, -N(R^X)2, -NH(C1-C6alkylene)-(5- or 6-membered monocyclic heteroaryl), -NH(C1-C6 alkylene)-(9- or 10-membered bicyclic heteroaryl), aryl, -NHC(O)OR6b, -N(C(O)OR6b)2, -NHC(O)N(R6b)2, or -NHC(O)R6b, wherein each of said -C1-C6 alkyl group, said -C2-C6 alkenyl group or said -C2-C6 alkynyl group can be optionally substituted with halo;

R5 is -H, -C1-C6 alkyl, -C2-C6 alkenyl, -C2-C6 alkynyl, -C1-C6 haloalkyl, -C3-C7 cycloalkyl, 5- or 6-membered monocyclic heteroaryl, a 9- or 10-membered bicyclic heteroaryl, halo, -OR^X, -CN, -NO2, -N(R^X)2, -NH(C1-C6alkylene)-(5- or 6-membered monocyclic heteroaryl), -NH(C1-C6 alkylene)-(9- or 10-membered bicyclic heteroaryl), aryl,

-NHC(O)OR6b, -N(C(O)OR6b)2, -NHC(O)N(R6b)2, or -NHC(O)R6b, wherein each of said -C1-C6 alkyl group, said -C2-C6 alkenyl group or said -C2-C6 alkynyl group can be optionally substituted with halo;

R6, **R6a** and **R6b** are each independently selected at each occurrence from -H, -C1-C6 alkyl, -C1-C6 haloalkyl, -(C1-C3 alkylene)m-(C3-C7 cycloalkyl), -(C1-C3 alkylene)m-(aryl), -(C1-C3 alkylene)m-(4 to 7-membered heterocycloalkyl), -(C1-C3 alkylene)m-(5- or 6-membered monocyclic heteroaryl) or -(C1-C3 alkylene)m-(9- or 10-membered bicyclic heteroaryl), wherein each of said -C1-C6 alkyl, said C3-C7 cycloalkyl group, said aryl group, said 4 to 7-membered heterocycloalkyl group, said -(5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R7;

m is an integer selected from 0 (zero) or 1;

R7 represents from one to five substituent groups, each independently selected from -C1-C6alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 haloalkyl, aryl, or a 5-6-member heteroaryl;

R8 is -H, -C1-C6 alkyl, -C1-C6 haloalkyl, -C3-C7 cycloalkyl, aryl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl;

R9 is -H, halo, -C1-C6 alkyl, -C1-C6 haloalkyl, -CN, -OR^Y or -$N(R^Y)2$;

$\mathbf{R^X}$ is independently selected at each occurrence from -H, -C1-C6 alkyl, -C1-C6 haloalkyl, aryl, or 5- or 6- membered monocyclic heteroaryl;

or when either or both of **R4** or **R5** is -$N(R^X)2$, each R^X may optionally be joined together with the nitrogen to which they are both attached to form a 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl; and

$\mathbf{R^Y}$ is -H, -C1-C6 alkyl or -C1-C6 haloalkyl;

with the proviso that when **X** is O, **Y** is–C≡CH or -C≡N, **R1** is –H, **R2** is -H, **R4** is –NH2, **R5** is –H, -F, or –OH and **R9** is -F, then **R3** is not –F.

In another aspect, there is provided a pharmaceutical composition comprising an effective amount of a compound as defined herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

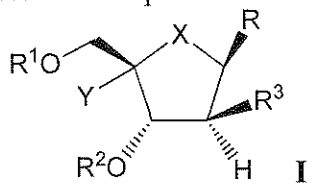
In another aspect, there is provided a pharmaceutical composition comprising an effective amount of a compound as defined herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier and further comprising an effective amount of an anti-HIV agent selected from an anti-HIV antiviral agent, an immunomodulator, or anti-infective agent.

In another aspect, there is provided use of the compound as defined herein or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof.

In another aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for the inhibition of HIV reverse transcriptase, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

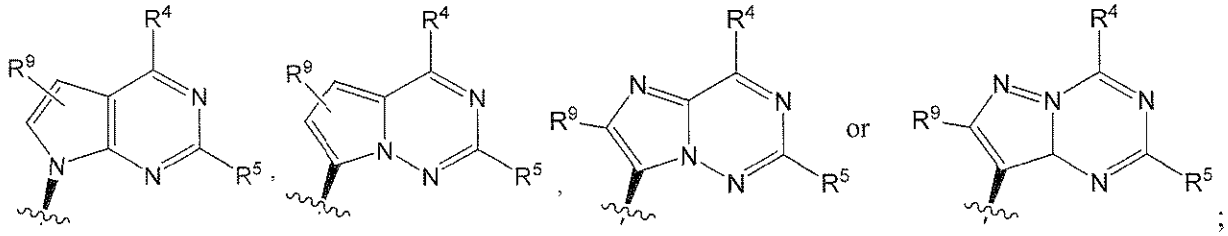
The present invention is directed to compounds having structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R is

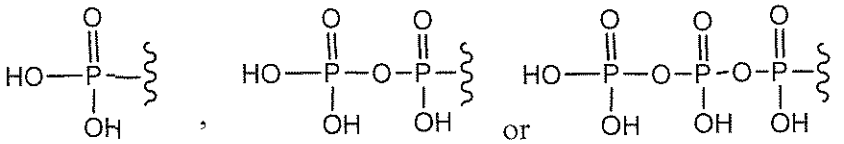


;

X is O, S, CH_2 or CF_2;

Y is $-C\equiv C-R^8$ or $-C\equiv N$;

R^1 is -H, $-C(O)R^6$, $-C(O)OR^6$, $-C(O)N(R^6)_2$,



,

or a pro-drug modification of the mono-, di- or triphosphate;

R^2 is -H, $-C(O)R^{6a}$, $-C(O)OR^{6a}$ or $-C(O)N(R^{6a})_2$;

R^3 is -H, -F, or -OH;

R^4 is -H, $-C_1$-C_6 alkyl, $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, $-C_1$-C_6 haloalkyl, $-C_3$-C_7 cycloalkyl, 5- or 6-membered monocyclic heteroaryl, a 9- or 10-membered bicyclic heteroaryl, halo, -CN, $-NO_2$, $-N(R^X)_2$, $-NH(C_1$-C_6alkylene)-(5- or 6-membered monocyclic heteroaryl), $-NH(C_1$-C_6 alkylene)-(9- or 10-membered bicyclic heteroaryl), aryl, $-NHC(O)OR^{6b}$, $-N(C(O)OR^{6b})_2$, $-NHC(O)N(R^{6b})_2$, or $-NHC(O)R^{6b}$, wherein each of said $-C_1$-C_6 alkyl group, said $-C_2$-C_6 alkenyl group or said $-C_2$-C_6 alkynyl group can be optionally substituted with halo;