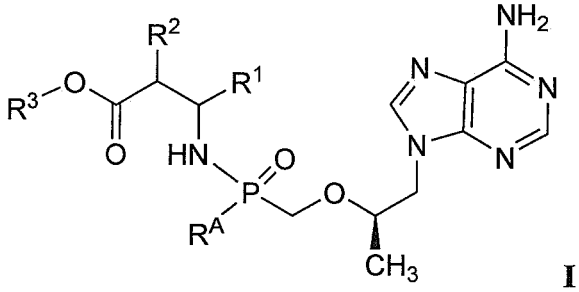
strains of HIV. Accordingly, there is a particular need for new RT inhibitors that are effective against mutant HIV strains.

SUMMARY

The present disclosure is directed to beta-amino acid ester phosphodiamide prodrugs of tenofovir and their use in the inhibition of nucleotide reverse transcriptase. In addition to the use of said compounds in the inhibition of HIV reverse transcriptase, the disclosure is also directed to the use of said compounds for prophylaxis of infection by HIV, the treatment of infection by HIV, and the prophylaxis, treatment, and/or 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 pharmaceutically acceptable salt thereof, wherein:

R1 and **R2** are each independently selected from (a) H, (b) -C1-4alkyl, (c) -C1-4alkyl substituted with -OH, -SH, -SCH3, -NH2 or –NH-C(=NH)-NH2, (d) -CH2-phenyl, (e) -CH2-phenol, (f) -(CH2)1-2-COOH, (g) -(CH2)1-2-CONH2, (h) -CH2-1*H*-indole, (i) -CH2-imidazole, (j) aryl or (k) heteroaryl;

R3 is

(a) -C1-10alkyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR10a, -SH, -NR11R12, -C3-6cycloalkyl or spiro-C3-6cycloalkyl,

(b) -CH2-phenyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15a, -SH, -NR11R12 or -C1-3alkyl,

(c) -C3-8cycloalkyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15a, -SH, -NR11R12 or -C1-3alkyl,

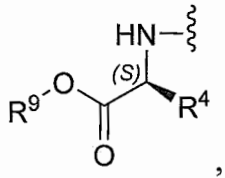
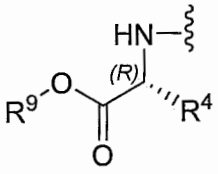
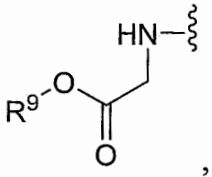
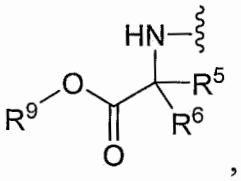
(d) aryl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15a, -SH, -NR11R12 or -C1-3alkyl,

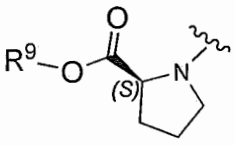
(e) -C1-5alkyl-X-C1-5alkyl wherein X is O, S or NH,

(f) heteroaryl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15a, -SH, -NR11R12 or -C1-3alkyl, or

(g) a heterocyclic ring unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15a, -SH, -NR11R12 or -C1-3alkyl;

RA is an L-amino acid ester residue of formula (i), a D-amino acid ester residue of formula (ii), a glycine ester residue of formula (iii), a geminally di-substituted amino acid ester residue of formula (iv), , or an L-proline ester residue of formula (vi):

(i) , (ii) , (iii) , (iv) ,

or (vi) ;

R4 is (a) -C1-4alkyl, (b) -C1-4alkyl substituted with -OH, -SH, -SCH3, -NH2, –NH-C(=NH)-NH2, (c) -CH2-phenyl, (d) -CH2-phenol, (e) -(CH2)1-2-COOH, (f) -(CH2)1-2-CONH2, (g) -CH2-1*H*-indole, (h) -CH2-imidazole, (i) aryl or (j) heteroaryl;

R5 and **R6** are each independently selected from (a) -C1-4alkyl, (b) -C1-4alkyl substituted with -OH, -SH, -SCH3, -NH2, –NH-C(=NH)-NH2, (c) -CH2-phenyl, (d) -CH2-phenol, (e) -(CH2)1-2-COOH, (f) -(CH2)1-2-CONH2, (g) -CH2-1*H*-indole, (h) -CH2-imidazole, (i) aryl or (j) heteroaryl;

or **R5** and **R6** are joined together with the carbon to which they are both attached to form -C3-6cycloalkyl or a 4 to 6-membered heterocyclic ring;

R9 is

(a) -C1-10alkyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR10b, -SH, -NR13R14, -C3-6cycloalkyl or spiro-C3-6cycloalkyl,

(b) -CH2-phenyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15b, -SH, -NR13R14 or -C1-3alkyl,

(c) -C3-8cycloalkyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15b, -SH, -NR13R14 or -C1-3alkyl,

(d) aryl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15b, -SH, -NR13R14 or -C1-3alkyl,

(e) -C1-5alkyl-X-C1-5alkyl wherein X is O, S or NH;

(f) heteroaryl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15b, -SH, -NR13R14 or -C1-3alkyl, or

(g) a heterocyclic ring unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR15b, -SH, -NR13R14 or -C1-3alkyl;

R10a and **R10b** are each independently selected from -H or -C3-6cycloalkyl;

R11 and **R12** are each independently selected from –H, -C1-3alkyl or -C3-6cycloalkyl;

R13 and **R14** are each independently selected from –H, -C1-3alkyl or -C3-6cycloalkyl; and

R15a and **R15b** are each independently selected from –H, -C1-3alkyl or -C3-6cycloalkyl.

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

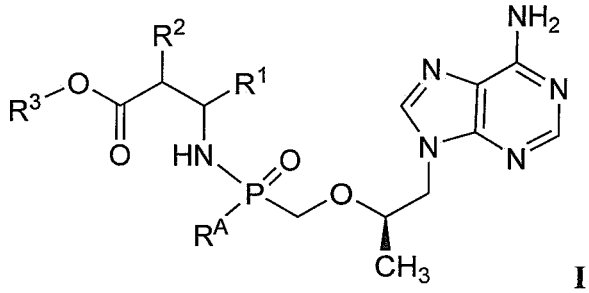
In another aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt thereof, for use in the prophylaxis or treatment of infection by HIV or for use in the prophylaxis, treatment, or delay in the onset of AIDS in a subject in need thereof.

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

In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of infection by HIV or for the treatment 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 of structural Formula I:



I

or pharmaceutically acceptable salt thereof, wherein:

R1 and **R2** are each independently selected from (a) H, (b) -C_{1-4}alkyl, (c) -C_{1-4}alkyl substituted with -OH, -SH, -SCH_3, -NH_2 or –NH-C(=NH)-NH_2, (d) -CH_2-phenyl, (e) -CH_2-phenol,

(f) -$(CH_2)_{1-2}$-COOH, (g) -$(CH_2)_{1-2}$-$CONH_2$, (h) -CH_2-1*H*-indole, (i) -CH_2-imidazole, (j) aryl (for example but not limited to phenyl or naphthyl) or (k) heteroaryl (for example but not limited to pyridine);

R3 is

(a) -C_{1-10}alkyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR^{10a}, -SH, -$NR^{11}R^{12}$, -C_{3-6}cycloalkyl or spiro-C_{3-6}cycloalkyl,

(b) -CH_2-phenyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR^{15a}, -SH, -$NR^{11}R^{12}$ or -C_{1-3}alkyl,

(c) -C_{3-8}cycloalkyl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR^{15a}, -SH, -$NR^{11}R^{12}$ or -C_{1-3}alkyl,

(d) aryl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR^{15a}, -SH, -$NR^{11}R^{12}$ or -C_{1-3}alkyl,

(e) -C_{1-5}alkyl-X-C_{1-5}alkyl wherein X is O, S or NH,

(f) heteroaryl unsubstituted or substituted with one to three substituents independently selected from fluoro, chloro, bromo, -OR^{15a}, -SH, -$NR^{11}R^{12}$ or -C_{1-3}alkyl, or