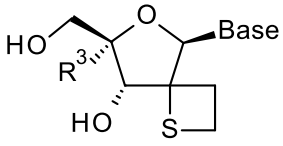
DESCRIPTION

The present disclosure provides 2'-spirothietane nucleosides and the monophosphate, diphosphate, triphosphate, and the prodrugs thereof; and the pharmaceutically acceptable salts and solvates thereof, having activity against *Flaviviridae*, in particular HCV and/or Dengue virus, and/or *alphaviruses*, in particular, Chikungunya virus and/or Sindbis virus and/or Simliki Forest virus.

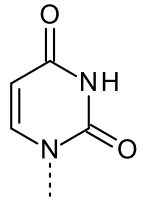
Thus, in one aspect the present disclosure provides spirothietane nucleosides of Formula (I)



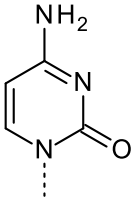
(I),

including all possible stereoisomeric forms thereof, wherein

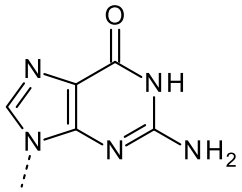
Base is selected from the group consisting of (B-1), (B-2), (B-3a), (B-3b), (B-4) and (B-5)



(B-1)



(B-2)



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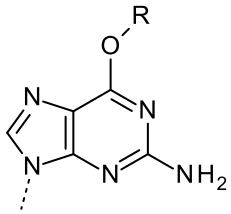
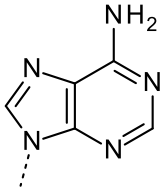
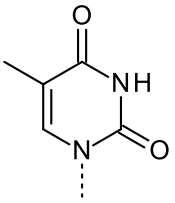


(B-3b)



(B-4)



(B-5)

wherein R is hydrogen or C_{1-6}alkyl; and

R^3 is selected from the group consisting of hydrogen, halo, methyl, CH_2Cl, CH_2F and N_3;

and the monophosphate, the diphosphate, the triphosphate, and the prodrugs thereof;

and the pharmaceutically acceptable salts and solvates thereof.

The present disclosure, in another aspect, relates to a pharmaceutical composition comprising a therapeutically effective amount, in particular an anti-virally effective amount, of the compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, and a pharmaceutically acceptable carrier or excipient.

Additionally, the disclosure, in another aspect, relates to a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, for use as a medicament. In particular for use in the treatment or in the prevention of *Flaviviridae* virus infections, particularly hepatitis C and/or Dengue virus infections, and/or in the treatment or in the prevention of *alphavirus* infections, particularly Chikungunya virus and/or Sindbis virus and/or Simliki Forest virus infections.

In another aspect, there is provided a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, for use in the treatment or prevention of *Flaviviridae* virus infections and/or in the treatment or in the prevention of *alphavirus* infections.

In another aspect, there is provided a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, for use as an inhibitor of HCV and/or dengue virus.

In another aspect, there is provided a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, for use as an inhibitor of chikungunya virus and/or Sindbis virus and/or Simliki Forest virus.

Additionally, the disclosure relates to the use of a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, in combination with an additional antiviral for use in the treatment or prevention of *Flaviviridae* virus infections, particularly hepatitis C and/or Dengue virus infections, and/or in the treatment or in the prevention of *alphavirus* infections, particularly Chikungunya virus and/or Sindbis virus and/or Simliki Forest virus infections.

In another aspect, there is provided use of a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment or prevention of *Flaviviridae* virus infections and/or in the treatment or in the prevention of *alphavirus* infections.

Furthermore, the disclosure, in another aspect, relates to a process for preparing a pharmaceutical composition according to the disclosure, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount, in particular an anti-virally effective amount, of a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof.

The disclosure also relates to a product comprising a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof, and an additional pharmaceutical agent, in particular an additional antiviral, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of *Flaviviridae* virus infections, particularly hepatitis C and/or Dengue virus

infections, and or in the treatment or in the prevention of *alphavirus* infections, particularly Chikungunya virus and/or Sindbis virus and/or Simliki Forest virus infections.

In another aspect, there is provided a product comprising a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof and an additional pharmaceutical agent, in particular an additional antiviral, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of *Flaviviridae* virus infections, and or in the treatment or in the prevention of *alphavirus* infections.

In another aspect, there is provided use of a product comprising a compound of Formula (I) or a stereoisomeric form thereof, or a phosphate (i.e. monophosphate, diphosphate or triphosphate) or a prodrug thereof, or a pharmaceutically acceptable salt or a solvate thereof and an additional pharmaceutical agent, in particular an additional antiviral, as a combined preparation in the manufacture of a medicament for the treatment or prevention of *Flaviviridae* virus infections, and or for the treatment or prevention of *alphavirus* infections.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the term “about” has the meaning known to the person skilled in the art. In certain embodiments, the term “about” may be left out and the exact amount is meant. In other embodiments the term “about” means that the numerical following the term “about” is in the range of ± 15%, or of ± 10%, or of ± 5%, or of ± 1%, of said numerical value.

As used herein "C_1-C_4alkyl" as a group or part of a group defines saturated straight or branched chain hydrocarbon radical having from 1 to 4 carbon atoms such as for example methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 2-methyl-2-propyl. "C_1-C_6alkyl" encompasses C_1-C_4alkyl radicals and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 2-methyl-1-butyl, 2-methyl-1-pentyl, 2-ethyl-1-butyl, 3-methyl-2-pentyl, and the like. Of interest amongst C_1-C_6alkyl is C_1-C_4alkyl. "C_1-C_{10}alkyl" encompasses C_1-C_6alkyl radicals and the higher homologues thereof having 7, 8, 9 or 10 carbon atoms such as, for example, heptyl, 2-heptyl, 3-heptyl, 2-methylhexyl, octyl, 2-octyl, 3-octyl, nonyl, 2-nonyl, 3-nonyl, 2-butylpentyl, decyl,

2-decyl, and the like. Of interest amongst C_1-C_{10}alkyl is C_1-C_6alkyl, and C_1-C_2alkyl defines methyl and ethyl.

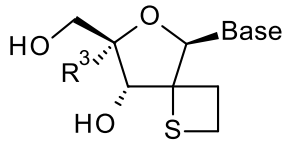
"C_1-C_6alkoxy" means a radical -O-C_1-C_6alkyl wherein C_1-C_6alkyl is as defined above. Examples of C_1-C_6alkoxy are methoxy, ethoxy, n-propoxy, or isopropoxy.

"C_3-C_7cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Of interest is cyclopropyl and cyclobutyl.

The term "C_2-C_6alkenyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having saturated carbon-carbon bonds and at least one double bond, and having from 2 to 6 carbon atoms, such as, for example, 1-propenyl, 2-propenyl (or allyl), 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-methyl-2-butenyl, 2-methyl-2-pentenyl and the like. Of interest amongst C_2-C_6alkenyl is C_3-C_6alkenyl, in particular C_3-

CLAIMS

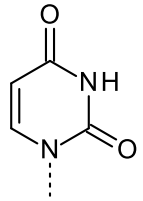
1. A compound of Formula (I)



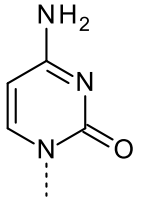
(I),

or a stereoisomeric form thereof, wherein

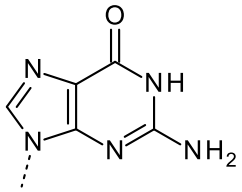
Base is selected from the group consisting of (B-1), (B-2), (B-3a), (B-3b), (B-4) and (B-5)



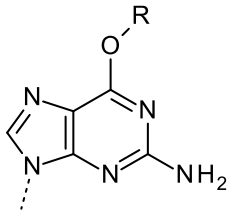
(B-1)



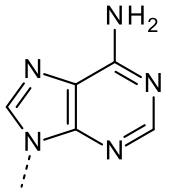
(B-2)



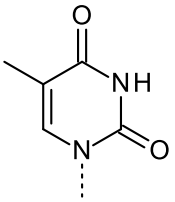
(B-3a)



(B-3b)



(B-4)



(B-5)

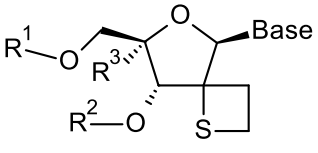
wherein R is hydrogen or C_{1-6}alkyl; and

R^3 is selected from the group consisting of hydrogen, halo, methyl, CH_2Cl, CH_2F and N_3;

or a monophosphate, diphosphate, triphosphate, or a prodrug thereof;

or a pharmaceutically acceptable salt or a solvate thereof.

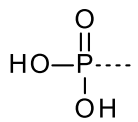
2. The compound according to claim 1, having Formula (I')



(I')

wherein

R^1 is selected from the group consisting of hydrogen,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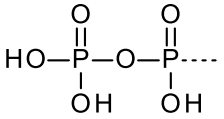
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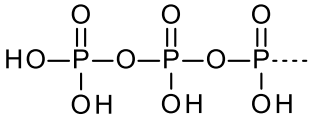
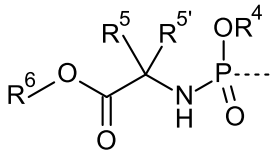
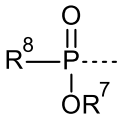
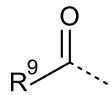
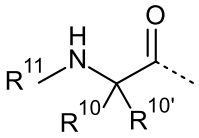

,

a group of formula (a-1), a group of formula (a-2), a group of formula (a-3), and a group of formula (a-4)

(a-1) (a-2) (a-3) (a-4), wherein

R^4 and R^7 are each independently selected from the group consisting of hydrogen, phenyl, naphthyl, quinolinyl, isoquinolinyl, and pyridyl, each of which being optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halo, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, hydroxy, and $NR^{16}R^{16'}$; or

R^4 and R^7 are each independently indolyl, optionally substituted at its nitrogen atom with C_1-C_6alkyl or C_1-C_6alkyloxycarbonyl and/or at any available carbon atom with 1, 2, or 3 substituents, each independently selected from the group consisting of halo, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, hydroxy, and $NR^{17}R^{17'}$;

R^5, $R^{5'}$, R^{10} and $R^{10'}$ are each independently selected from the group consisting of hydrogen, C_1-C_6alkyl, benzyl, and phenyl; or

R^5 and $R^{5'}$, or R^{10} and $R^{10'}$, together with the carbon atom to which they are attached form a C_3-C_7cycloalkanediyl or a 3- to 7-membered heterocyclic ring containing one oxygen atom;

R^6 is selected from the group consisting of C_1-C_{10}alkyl, C_3-C_7cycloalkyl, phenyl and phenyl-C_1-C_6alkyl-, wherein the phenyl moiety in phenyl or phenyl-C_1-C_6alkyl- is optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of hydroxy, C_1-C_6alkoxy, and $NR^{18}R^{18'}$;

R^8 is $–OR^{19}$ or $–NR^{20}R^{20'}$;

R^9 is selected from the group consisting of C_1-C_6alkyl, phenyl, and phenyl-C_1-C_6alkyl-, wherein the phenyl moiety in phenyl or phenyl-C_1-C_6alkyl- is optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of halo and C_1-C_6alkyloxy;

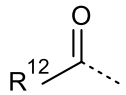
R^{11} is selected from the group consisting of hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, phenyl or phenyl-C_1-C_6alkyl-, wherein the phenyl moiety in phenyl or phenyl-C_1-C_6alkyl- is optionally substituted with 1, 2 or 3 substituents each independently selected from the group consisting of hydroxy, C_1-C_6alkoxy, and $NR^{23}R^{23'}$;

R^{19} is selected from the group consisting of C_1-C_6alkyl, C_3-C_7cycloalkyl, oxetanyl, (C_1-C_6alkoxy)C_1-C_6alkyl-, -CH_2-O-(C=O)C_1-C_6alkyl, and -CH_2-O-(C=O)OC_1-C_6alkyl;

R^{20} is selected from the group consisting of hydrogen, C_1-C_6alkyl, and C_3-C_7cycloalkyl; and $R^{20'}$ is selected from the group consisting of C_1-C_6alkyl, C_3-C_7cycloalkyl, and (C_1-C_6alkoxy)C_1-C_6alkyl-; or

–$NR^{20}R^{20'}$ together form an azetidinyl, a pyrrolidinyl or a piperidinyl ring, each of which may be optionally substituted with a group consisting of hydroxy, C_1-C_6alkyl, C_1-C_6alkyloxy, and (C=O)-OR^{21} wherein R^{21} is selected from the group consisting of C_1-C_{10}alkyl, C_3-C_7cycloalkyl, phenyl and phenyl-C_1-C_6alkyl-, wherein the phenyl moiety in phenyl or phenyl-C_1-C_6alkyl- is optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of hydroxy, C_1-C_6alkoxy, and $NR^{22}R^{22'}$;

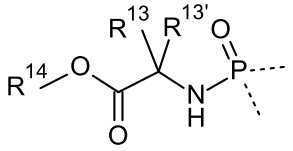
R^2 is hydrogen or a group of formula (b)

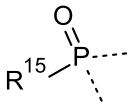


(b), wherein

R^{12} is selected from the group consisting of C_1-C_6alkyl, phenyl, and phenyl-C_1-C_6alkyl-, wherein the phenyl moiety in phenyl or phenyl-C_1-C_6alkyl- is optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of halo and C_1-C_6alkyloxy; or

R^1 and R^2 are bound to form a divalent radical of formula (c-1) or (c-2)





(c-1) (c-2), wherein

R^{13} and $R^{13'}$ are each independently selected from the group consisting of hydrogen, C_1-C_6alkyl, benzyl, and phenyl; or

R^{13} and $R^{13'}$, together with the carbon atom to which they are attached form a C_3-C_7cycloalkanediyl or a 3- to 7-membered heterocyclic ring containing one oxygen atom;

R^{14} is selected from the group consisting of C_1-C_{10}alkyl, C_3-C_7cycloalkyl, phenyl and phenyl-C_1-C_6alkyl-, wherein the phenyl moiety in phenyl or phenyl-C_1-C_6alkyl- is optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of hydroxy, C_1-C_6alkoxy, and $NR^{24}R^{24'}$;

R^{15} is –OR^{25} or –$NR^{26}R^{26'}$, wherein

R^{25} is selected from the group consisting of hydrogen; C_1-C_6alkyl; C_1-C_3alkyl substituted with 1, 2 or 3 substituents each independently selected from the group consisting of phenyl, naphthyl, C_3-C_7cycloalkyl, hydroxyl and C_1-C_6alkyloxy; C_3-C_7cycloalkyl; (C_1-C_6alkoxy)C_1-C_6alkyl-; -CH_2-O-(C=O)C_1-C_6alkyl; -CH_2-O-(C=O)OC_1-C_6alkyl; a 3- to 7-membered heterocyclic ring containing one oxygen atom; and Ar; wherein

Ar is selected from the group consisting of phenyl, naphthyl, quinolinyl, isoquinolinyl, and pyridyl, each of which being optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halo, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, hydroxy, and $NR^{27}R^{27'}$; or

Ar is indolyl, optionally substituted at its nitrogen atom with C_1-C_6alkyl or C_1-C_6alkyloxycarbonyl and/or at any available carbon atom with 1, 2, or 3 substituents, each independently selected from the group consisting of halo, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, hydroxy, and $NR^{28}R^{28'}$;

R^{26} is selected from the group consisting of hydrogen, C_1-C_6alkyl, and C_3-C_7cycloalkyl; and $R^{26'}$ is selected from the group consisting of C_1-C_6alkyl, C_3-C_7cycloalkyl, and (C_1-C_6alkoxy)C_1-C_6alkyl-; or

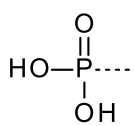
–$NR^{26}R^{26'}$ together form an azetidinyl, a pyrrolidinyl or a piperidinyl ring, each of which may be optionally substituted with a group consisting of hydroxy, C_1-C_6alkyl, C_1-C_6alkyloxy, and (C=O)-OR^{27} wherein R^{27} is selected from the group consisting of C_1-C_{10}alkyl, C_3-C_7cycloalkyl, phenyl and phenyl-C_1-C_6alkyl-, wherein the phenyl moiety in phenyl or phenyl-C_1-C_6alkyl- is optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of hydroxy, C_1-C_6alkoxy, and $NR^{29}R^{29'}$;

R^{16}, $R^{16'}$, R^{17}, $R^{17'}$, R^{18}, $R^{18'}$, R^{22}, $R^{22'}$, R^{23}, $R^{23'}$, R^{24}, $R^{24'}$, R^{27}, $R^{27'}$, R^{28}, $R^{28'}$, R^{29} and $R^{29'}$ are each independently selected from hydrogen and C_1-C_6alkyl; and

R^3 is selected from the group consisting of hydrogen, halo, methyl, CH_2Cl, CH_2F and N_3.

3. The compound according to claim 2, wherein

R^1 is selected from the group consisting of hydrogen,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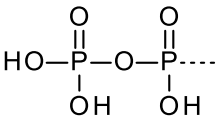
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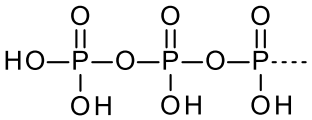

,

a group of formula (a-1), a group of formula (a-2) and a group of formula (a-3); wherein

R^4 and R^7 are each independently phenyl or naphthyl, each of which being optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halo, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, hydroxy, and $NR^{16}R^{16'}$; whereinR^{16} and $R^{16'}$ are each independently selected from hydrogen and C_1-C_6alkyl; or R^4 and R^7 are each independently indolyl;

R^5 and $R^{5'}$ are each independently selected from the group consisting of hydrogen, C_1-C_6alkyl, benzyl, and phenyl; or R^5 and $R^{5'}$ together with the carbon atom to which they are attached form a C_3-C_7cycloalkanediyl;

R^6 is selected from the group consisting of C_1-C_{10}alkyl, C_3-C_7cycloalkyl and phenyl-C_1-C_6alkyl-;

R^8 is $–OR^{19}$ or $–NR^{20}R^{20'}$; wherein R^{19} is C_1-C_6alkyl or C_3-C_7cycloalkyl;

R^{20} is hydrogen and $R^{20'}$ is C_1-C_6alkyl or C_3-C_7cycloalkyl; and

R^9 is C_1-C_6alkyl;

R^2 is hydrogen or a group of formula (b), wherein R^{12} is C_1-C_6alkyl; or

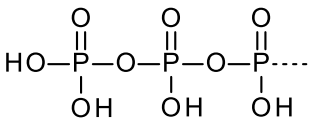
R^1 and R^2 are bound to form a divalent radical of formula (c-1) or (c-2), wherein

R^{13} and $R^{13'}$ are each independently selected from the group consisting of hydrogen, C_1-C_6alkyl, benzyl, and phenyl; or R^{13} and $R^{13'}$, together with the carbon atom to which they are attached form a C_3-C_7cycloalkanediyl;

R^{14} is selected from the group consisting of C_1-C_{10}alkyl, C_3-C_7cycloalkyl and phenyl-C_1-C_6alkyl-; and

R^{15} is $–OR^{25}$ or $–NR^{26}R^{26'}$, wherein R^{25} is selected from the group consisting of C_1-C_6alkyl; phenyl; C_3-C_7cycloalkyl; and C_1-C_3alkyl substituted with 1, 2 or 3 substituents each independently selected from the group consisting of phenyl, naphthyl, C_3-C_7cycloalkyl, hydroxyl and C_1-C_6alkyloxy; R^{26} is hydrogen; and $R^{26'}$ is C_1-C_6alkyl or C_3-C_7cycloalkyl.

4. The compound according to claim 2 or 3, wherein R^1 is selected from the group consisting of

hydrogen,  , and a group of formula (a-1);

or R^1 and R^2 are bound to form a divalent radical of formula (c-2).

5. The compound according to any one of claims 2 to 4, wherein

R^4 is phenyl, halophenyl, diC_1-C_4alkylphenyl, or naphthyl;

R^5 and $R^{5'}$ are each independently hydrogen, C_1-C_6alkyl, benzyl, or phenyl;

R^6 is C_1-C_6alkyl; and

R^{15} is $–OR^{25}$ wherein R^{25} is C_1-C_6alkyl or C_1-C_2alkyl substituted with phenyl, C_1-C_2alkyloxy or C_3-C_7cycloalkyl.

6. The compound according to any one of claims 1 to 5, wherein Base is (B-1), (B-2) or (B-3a) and R^3 is selected from the group consisting of hydrogen, halo, and N_3.

7. A pharmaceutical composition comprising a therapeutically effective amount, in particular an anti-virally effective amount, of a compound of Formula (I) as defined in any of claims 1 to 6 and a pharmaceutically acceptable carrier.

8. A process for preparing the pharmaceutical composition according to claim 7, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount, in particular an anti-virally effective amount, of a compound of Formula (I) as defined in any one of claims 1 to 6.

9. A compound as defined in any one of claims 1 to 6 or a pharmaceutical composition as defined in claim 7 for use as a medicament.

10. A compound according to any one of claims 1 to 6 or a pharmaceutical composition as defined in claim 7 for use in the treatment or prevention of *Flaviviridae* virus infections and/or in the treatment or in the prevention of *alphavirus* infections.

11. A compound according to any one of claims 1 to 6 or a pharmaceutical composition as defined in claim 7 for use as an inhibitor of HCV and/or dengue virus.

12. A compound according to any one of claims 1 to 6 or a pharmaceutical composition as defined in claim 7 for use as an inhibitor of chikungunya virus and/or Sindbis virus and/or Simliki Forest virus.

13. Use of a compound according to any one of claims 1 to 6 or a pharmaceutical composition as defined in claim 7 in the manufacture of a medicament for the treatment or prevention of *Flaviviridae* virus infections and/or in the treatment or in the prevention of *alphavirus* infections.

14. A product comprising a compound of Formula (I) as defined in any one of claims 1 to 6 and an additional pharmaceutical agent, in particular an additional antiviral, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of *Flaviviridae* virus infections, and or in the treatment or in the prevention of *alphavirus* infections.

15. Use of a product comprising a compound of Formula (I) as defined in any one of claims 1 to 6 and an additional pharmaceutical agent, in particular an additional antiviral, as a combined preparation in the manufacture of a medicament for the treatment or prevention of *Flaviviridae* virus infections, and or for the treatment or prevention of *alphavirus* infections.