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WO 2006/094347 A1

(54) Title: BICYCLIC NUCLEOSIDES AND NUCLEOTIDES AS THERAPEUTIC AGENTS

(57) Abstract: The invention relates to the use of bicyclic nucleosides and nucleotides based on formula (II) for the treatment of infectious diseases, and in particular, viral infections.

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BICYCLIC NUCLEOSIDES AND NUCLEOTIDES AS THERAPEUTIC AGENTSField of the Invention

The present invention relates to the use of bicyclic nucleosides and nucleotides for the treatment of infectious diseases, including viral infections, novel bicyclic nucleosides and nucleotides and methods for their manufacture.

Background of the Invention

Viral infections are a major threat to human health and account for many serious infectious diseases. The most notable viruses are the blood-borne viruses (BBV), which include hepatitis C virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV) which are all linked by their mode of transmission, ie. through blood or bodily fluids.

The Flaviviridae is a group of positive single-stranded RNA viruses with a genome size from 9-15 kb. The Flaviviridae consists of various genera including:

1. Flaviviruses: This genus includes the Dengue virus, Japanese Tick-Borne and the Yellow Fever virus. Apart from these major groups, there are some additional Flaviviruses that are unclassified.

2. Hepaciviruses: This genus contains only one species, the Hepatitis C virus (HCV), which is composed of many genotypes and subtypes.

HCV is a major cause of viral hepatitis and has infected more than 200 million people worldwide. Current treatment for HCV infection is restricted to immunotherapy with interferon- α alone or in combination with ribavirin, a nucleoside analog. This treatment is effective in only about half the patient population. Therefore, there is an urgent need for new HCV drugs. Hepatitis C virus comprises a positive-strand RNA genome enclosed in a nucleocapsid and lipid envelope and consists of approximately 9600 ribonucleotides, which encodes a polyprotein of about 3000 amino acids (Dymock *et al. Antiviral*

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Chemistry & Chemotherapy **2000**, 11, 79). A HCV protein, NS5B, released from the polyprotein, possesses polymerase activity and is involved in the synthesis of double-stranded RNA from the single-stranded viral RNA genome that serves as the template. The reproduction of HCV virus may be prevented through the manipulation of NS5B's
5 polymerase activity. The inhibition of NS5B protein would suppress or prevent the formation of the double-stranded HCV RNA. Alternatively, a nucleoside analog also may be incorporated into the extending RNA strand and act as a chain-terminator. Furthermore, a deteriorating nucleoside analog also may be incorporated into the extending RNA, which may cause mutagenic damage to the viral genome. Recently, several PCT patent
10 applications (WO 99/43691, WO 01/32153, WO 01/60315, WO 01/79246, WO 01/90121, WO 01/92282, WO 02/18404, WO 02/057287, WO 02/057425) have described nucleoside analogs as anti-HCV agents in *in vitro* assays.

HBV has acutely infected almost a third of the world's human population, and about 5% of
15 the infected are chronic carriers of the virus (Delaney IV *et al.*, *Antiviral Chemistry & Chemotherapy* **2001**, 12, 1-35). Chronic HBV infection causes liver damage that frequently progresses to cirrhosis and/or liver cancer later in the life. Despite the availability and widespread use of effective vaccines and chemotherapy, the number of chronic carriers approaches 400 million worldwide. Therefore, more effective anti-HBV
20 drugs need to be developed.

HIV causes progressive degeneration of the immune system, leading to the development of AIDS. A number of drugs have been used clinically, including reverse transcriptase inhibitors and protease inhibitors. Currently, combination therapies are used widely for the
25 treatment of AIDS in order to reduce the drug resistance. Despite the progress in the development of anti-HIV drugs, AIDS is still one of the leading epidemic diseases.

Apart from the BBV's discussed above certain other acute viral infections also impose a great threat to human life, including the HSV, CMV, influenza viruses, West Nile virus,
30 SARS virus, small pox, EBV, VZV and RSV. Accordingly, this highlights the continued need for the development of different antiviral drugs.

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Bacterial infections have long been the sources of many infectious diseases. The widespread use of antibiotics has produced many new strains of life-threatening antibiotic resistant bacteria. Fungal infections are another type of infectious diseases, some of which
5 also can be life-threatening. There is an ever increasing demand for the treatment of bacterial and fungal infections. As such, antimicrobial drugs based on new mechanisms of action are especially important.

Nucleoside drugs have been used clinically for decades for the treatment of viral infections
10 and proliferative disorders such as cancer. Most of the nucleoside drugs are classified as antimetabolites. After they enter cells, nucleoside analogs are phosphorylated successively to nucleoside 5'-monophosphates, 5'-diphosphates, and 5'-triphosphates. In most cases, nucleoside triphosphates, *e.g.*, 3'-azido-3'-deoxythymidine triphosphate (AZT, an anti-HIV
15 chemical entities that inhibit DNA or RNA synthesis, through a competitive inhibition of polymerases and subsequent incorporation of modified nucleotides into DNA or RNA sequences. In a few cases, nucleoside analogs exert effects at lower phosphate levels. For instance, 5-fluoro-2'-deoxyuridine 5'-monophosphate (an anticancer drug) and 2',2'-difluoro-2'-deoxycytidine 5'-diphosphate (an anticancer drug) have been shown to inhibit
20 thymidylate synthase and ribonucleotide reductase, respectively. Although nucleoside analogs themselves may act at the nonphosphate level such as the inhibitors of adenosine kinases and the ligands of adenosine receptors, currently, clinically-useful nucleoside drugs primarily depend on cellular activation by nucleoside kinases and nucleotide kinases.

25 At least, two criteria are pertinent for nucleoside antiviral drugs: 1) nucleoside analogs should anabolise to nucleotides in cells; and 2) the anabolised nucleotides should target selectively viral enzymes. In order to be phosphorylated in cells and selectively target preferred enzymes, nucleoside analogs should have favourable modifications on their sugar and base moieties. To obtain such favourable nucleoside analogs, a general approach is to
30 generate diverse nucleoside analogs by modifying the base or the sugar, or by modifying both base and sugar moieties. Numerous examples exist in the literature for the synthesis

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of a variety of modified nucleosides (*Chemistry of Nucleosides and Nucleotides* Vol. 1 (1988), Vol. 2 (1991), Vol. 3 (1994), edited by L.B. Townsend, Plenum Press; *Handbook of Nucleoside Synthesis* by H. Vorbrüggen and C. Ruh-Pohlenz, John Wiley & Sons, Inc., 2001; *The Organic Chemistry of Nucleic Acids* by Y. Mizuno, Elsevier, 1986).

5

However, there are certain classes of nucleoside compounds that were not explored intensively for their antiviral activities before the present invention. A class of such compounds is bicyclic nucleosides which are not derived from purine bases. Disclosures of bicyclic nucleosides are very limited considering that natural adenine and guanine
10 (purines) based ribonucleotides and deoxy derivatives thereof, have bicyclic base moieties. WO 01/92282 A2, WO 01/90121 A2 and WO 04/058792 disclose derivatives of purine nucleosides. In contrast to these publications, the present invention discloses that a certain new class of bicyclic nucleosides and nucleotides display biological activity which may be particularly useful for the treatment of infectious diseases, including viral infections.

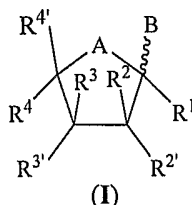
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Summary of the Invention

The present invention relates to a particular class of bicyclic nucleosides, nucleotides, and derivatives thereof and their use in the treatment of microbial infections, and specifically viral infections.

20

In particular, the present invention provides a method for the treatment of a microbial infection, comprising administering an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof;



25

wherein:
A is O, S, CH₂, CHF, CF₂ or NR;

- 5 -

R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, halogen, OH, N₃, CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted
5 heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkyloxy, optionally substituted alkenyloxy, optionally substituted alkynoxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted arylalkoxy, optionally substituted heterocycloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkoxy,
10 optionally substituted cycloalkenoxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted oxyacylimino, optionally substituted aminothioacyl, optionally substituted thioacylamino,
15 optionally substituted aminosulfinyl, optionally substituted aminosulfonyl, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacyloxy, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted phosphorylamino, optionally substituted sulfinyl, optionally substituted sulfonyl, optionally substituted sulfinylamino, optionally substituted sulfonylamino,
20 optionally substituted oxysulfinylamino, and optionally substituted oxysulfonylamino, or R² and R^{2'} together or R³ and R^{3'} together represents =O, =S, or =L-Y' where L is N, CH, CF, CCl or CBr and Y' is H, halogen, N₃, methyl, ethyl or CN;

R⁴ is -CY₂SH, -CY₂OH, -CY₂NH₂, or -L'-R⁵;
25

L' is selected from the group consisting of -CY₂-, -CY₂CY₂-, -CY₂OCY₂-, -CY₂SCY₂- and -CY₂NHCY₂-;

each Y is independently selected from the group consisting of H, F, Cl, Br, OR, C₁-
30 C₆alkyl, C₂-C₆alkenyl and C₂-C₆alkynyl, wherein C₁-C₆alkyl, C₂-C₆alkenyl, and C₂-C₆alkynyl may be optionally substituted with one or more groups selected from F, Cl, Br,

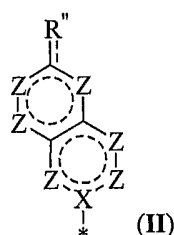
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OH, COOH, COOCH₃, SH, SCH₃, NH₂, NHCH₃, N(CH₃)₂, CN, NO₂, C(O)NH₂, C(O)NHCH₃, N₃, C(S)NH₂, OCH₃, and OCH₂CH₃;

R⁵ is selected from the group consisting of OR, NR₂, monophosphate, diphosphate, and
5 triphosphate, or a mono, di or triphosphate mimic;

each R is independently selected from the group consisting of H, CF₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted cycloalkyl, optionally
10 substituted cycloalkenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl;

B is a group of formula (II)



15

wherein, if Z is a participant in a π bond (double bond), Z is independently selected from N or C-G; or, if Z is not a participant in a π bond (double bond), Z is independently selected from O, S, Se, NR, NOR, NNR₂, CO, CS, CNR, SO, S(O)₂, SeO, Se(O)₂ or C(G)₂, wherein each G is independently selected from the group
20 consisting of H, halogen, OR, SR, NR₂, NROR, N₃, COOR, CN, CONR₂, C(S)NR₂, C(=NR)NR₂, and R; and

where any two adjacent Z are not both selected from O, S, and Se, or not both selected from CO, CS, CNR, SO, S(O)₂, SeO, and Se(O)₂;

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wherein, if X is a participant in a π bond (double bond), X is C; or if X is not a participant in a π bond (double bond), X is CR or N;

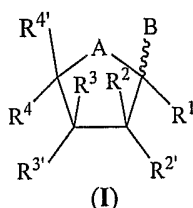
wherein, if R'' is a participant in a π bond (double bond), R'' is O, S, Se, NR, NOR or NNR₂; or if R'' is not a participant in a π bond (double bond), R'' is OR, SR, F, Cl, R, or SeR; and

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dashed lines (---) indicate a possible π or double bond;

optionally in combination with one or more antiviral or antibacterial agents.

- 5 The present invention also further provides the use of a compound of formula (I) or a salt thereof;



wherein:

A is O, S, CH₂, CHF, CF₂ or NR;

10

- R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, halogen, OH, N₃, CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted
- 15 heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkyloxy, optionally substituted alkenyloxy, optionally substituted alkynoxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted arylalkoxy, optionally substituted heterocycloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkoxy,
- 20 optionally substituted cycloalkenoxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted oxyacylimino, optionally substituted aminothioacyl, optionally substituted thioacylamino,
- 25 optionally substituted aminosulfinyl, optionally substituted aminosulfonyl, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacyloxy, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted phosphorylamino, optionally substituted sulfinyl, optionally substituted

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sulfonyl, optionally substituted sulfinylamino, optionally substituted sulfonylamino, optionally substituted oxysulfinylamino, and optionally substituted oxysulfonylamino, or R^2 and $R^{2'}$ together or R^3 and $R^{3'}$ together represents =O, =S, or =L-Y' where L is N, CH, CF, CCl or CBr and Y' is H, halogen, N_3 , methyl, ethyl or CN;

5

R^4 is $-CY_2SH$, $-CY_2OH$, $-CY_2NH_2$, or $-L^1-R^5$;

L^1 is selected from the group consisting of $-CY_2-$, $-CY_2CY_2-$, $-CY_2OCY_2-$, $-CY_2SCY_2-$ and $-CY_2NHCY_2-$;

10

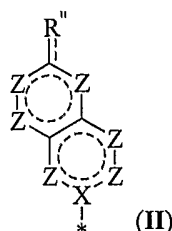
each Y is independently selected from the group consisting of H, F, Cl, Br, OR, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl may be optionally substituted with one or more groups selected from F, Cl, Br, OH, COOH, COOCH₃, SH, SCH₃, NH₂, NHCH₃, N(CH₃)₂, CN, NO₂, C(O)NH₂,
15 C(O)NHCH₃, N_3 , C(S)NH₂, OCH₃, and OCH₂CH₃;

R^5 is selected from the group consisting of OR, NR₂, monophosphate, diphosphate, and triphosphate, or a mono, di or triphosphate mimic;

20 each R is independently selected from the group consisting of H, CF₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl;

25

B is a group of formula (II)



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wherein, if Z is a participant in a π bond (double bond), Z is independently selected from N or C-G; or, if Z is not a participant in a π bond (double bond), Z is independently selected from O, S, Se, NR, NOR, NNR₂, CO, CS, CNR, SO, S(O)₂, SeO, Se(O)₂ or C(G)₂, wherein each G is independently selected from the group
5 consisting of H, halogen, OR, SR, NR₂, NROR, N₃, COOR, CN, CONR₂, C(S)NR₂, C(=NR)NR₂, and R; and

where any two adjacent Z are not both selected from O, S, and Se, or not both selected from CO, CS, CNR, SO, S(O)₂, SeO, and Se(O)₂;

wherein, if X is a participant in a π bond (double bond), X is C; or if X is not a
10 participant in a π bond (double bond), X is CR or N;

wherein, if R" is a participant in a π bond (double bond), R" is O, S, Se, NR, NOR or NNR₂; or if R" is not a participant in a π bond (double bond), R" is OR, SR, F, Cl, R, or SeR; and

dashed lines (---) indicate a possible π or double bond;

15

in the manufacture of a medicament for the treatment of a microbial infection.

Description of the Preferred Embodiments

"Alkyl" refers to monovalent alkyl groups which may be straight chained or branched and
20 preferably have from 1 to 10 carbon atoms or more preferably 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group having a single ring (eg.,
25 phenyl) or multiple condensed rings (eg., naphthyl or anthryl), preferably having from 6 to 14 carbon atoms. Examples of aryl groups include phenyl, naphthyl and the like.

"Arylene" refers to a divalent aryl group wherein the aryl group is as described above.

30 "Aryloxy" refers to the group aryl-O- wherein the aryl group is as described above.

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"Arylalkyl" refers to -alkylene-aryl groups preferably having from 1 to 10 carbon atoms in the alkylene moiety and from 6 to 10 carbon atoms in the aryl moiety. Such arylalkyl groups are exemplified by benzyl, phenethyl and the like.

5 "Arylalkoxy" refers to the group arylalkyl-O- wherein the arylalkyl group are as described above. Such arylalkoxy groups are exemplified by benzyloxy and the like.

"Alkoxy" refers to the group alkyl-O- where the alkyl group is as described above. Examples include, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-
10 butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

"Alkenyl" refers to a monovalent alkenyl group which may be straight chained or branched and preferably have from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and have at least 1 and preferably from 1-2, carbon to carbon, double bonds. Examples
15 include ethenyl (-CH=CH₂), *n*-propenyl (-CH₂CH=CH₂), *iso*-propenyl (-C(CH₃)=CH₂), but-2-enyl (-CH₂CH=CHCH₃), and the like.

"Alkenyloxy" refers to the group alkenyl-O- wherein the alkenyl group is as described above.

20

"Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1, and preferably from 1-2, carbon to carbon, triple bonds. Examples of alkynyl groups include ethynyl (-C≡CH), propargyl (-CH₂C≡CH), pent-2-ynyl (-CH₂C≡CCH₂-CH₃), and the like.

25

"Alkynyloxy" refers to the group alkynyl-O- wherein the alkynyl groups is as described above.

"Acyl" refers to groups H-C(O)-, alkyl-C(O)-, cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-
30 C(O)- and heterocyclyl-C(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

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"Oxyacyl" refers to groups H-OC(O)-, alkyl-OC(O)-, cycloalkyl-OC(O)-, aryl-OC(O)-, heteroaryl-OC(O)-, and heterocyclyl-OC(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

5

"Amino" refers to the group $-NR''R'''$ where each R'' is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

10 "Aminoacyl" refers to the group $-C(O)NR''R'''$ where each R'' is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Acylamino" refers to the group $-NR''C(O)R'''$ where each R'' is independently hydrogen, 15 alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Acyloxy" refers to the groups $-OC(O)-H$, $-OC(O)-alkyl$, $-OC(O)-aryl$, $-C(O)O-$ heteroaryl, and $-C(O)O-$ heterocyclyl where alkyl, aryl, heteroaryl and heterocyclyl are 20 as described herein.

"Aminoacyloxy" refers to the groups $-OC(O)NR''-H$, $-OC(O)NR''-alkyl$, $-OC(O)NR''-aryl$, $-OC(O)NR''-heteroaryl$, and $-OC(O)NR''-heterocyclyl$ where R'' is 25 independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Oxyacylamino" refers to the groups $-NR''C(O)OH$, $-NR''C(O)O-alkyl$, $-NR''C(O)O-$ aryl, $-NR''C(O)O-$ heteroaryl, and $NR''C(O)O-$ heterocyclyl where R'' is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where alkyl, 30 cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

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"Oxyacyloxy" refers to the groups $-\text{OC}(\text{O})-\text{OH}$, $-\text{OC}(\text{O})\text{O-alkyl}$, $-\text{O-C}(\text{O})\text{O-aryl}$, $-\text{OC}(\text{O})\text{O-heteroaryl}$, and $-\text{OC}(\text{O})\text{O-heterocyclyl}$ where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

5 "Acylimino" refers to the groups $-\text{C}(\text{NR}''')-\text{R}'''$ where each R''' is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Acyliminoxy" refers to the groups $-\text{O-C}(\text{NR}''')-\text{R}'''$ where each R''' is independently
10 hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Oxyacylimino" refers to the groups $-\text{C}(\text{NR}''')-\text{OR}'''$ where each R''' is independently
15 hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Cycloalkyl" refers to cyclic alkyl groups having a single cyclic ring or multiple condensed rings, preferably incorporating 3 to 8 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl,
20 cyclopentyl, cyclohexyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

"Cycloalkenyl" refers to cyclic alkenyl groups having a single cyclic ring and at least one point of internal unsaturation, preferably incorporating 4 to 8 carbon atoms.
25 Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclohex-4-enyl, cyclooct-3-enyl and the like.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

30 "Heteroaryl" refers to a monovalent aromatic heterocyclic group which fulfils the Hückel criteria for aromaticity (ie. contains $4n + 2 \pi$ electrons, is planar and

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conjugated) and preferably has from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen, selenium, and sulfur within the ring (and includes oxides of sulfur, selenium and nitrogen). Such heteroaryl groups can have a single ring (eg., pyridyl, pyrrolyl or N-oxides thereof or furyl) or multiple condensed rings (eg.,
5 indoliziny, benzoimidazolyl, coumarinyl, quinolinyl, isoquinolinyl or benzothiényl).

"Heterocyclyl" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, preferably from 1 to 8 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur, oxygen, selenium or phosphorous within
10 the ring. The most preferred heteroatom is nitrogen.

Examples of heterocyclyl and heteroaryl groups include, but are not limited to, oxazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline,
15 phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isothiazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiadiazoles, oxadiazole, oxatriazole,
20 tetrazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, piperidinyl, pyrrolidine, tetrahydrofuranyl, triazole, and the like.

"Thio" refers to groups H-S-, alkyl-S-, cycloalkyl-S-, aryl-S-, heteroaryl-S-, and heterocyclyl-S-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as
25 described herein.

"Thioacyl" refers to groups H-C(S)-, alkyl-C(S)-, cycloalkyl-C(S)-, aryl-C(S)-, heteroaryl-C(S)-, and heterocyclyl-C(S)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

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"Oxythioacyl" refers to groups HO-C(S)-, alkylO-C(S)-, cycloalkylO-C(S)-, arylO-C(S)-, heteroarylO-C(S)-, and heterocyclylO-C(S)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

5 "Oxythioacyloxy" refers to groups HO-C(S)-O-, alkylO-C(S)-O-, cycloalkylO-C(S)-O-, arylO-C(S)-O-, heteroarylO-C(S)-O-, and heterocyclylO-C(S)-O-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Phosphorylamino" refers to the groups $-NR'''-P(O)(R''')(OR''')$ where R''' represents
10 H, alkyl, cycloalkyl, alkenyl, or aryl, R'''' represents OR'''' or is hydroxy or amino and R'''' is alkyl, cycloalkyl, aryl or arylalkyl, where alkyl, amino, alkenyl, aryl, cycloalkyl, and arylalkyl are as described herein.

"Thioacyloxy" refers to groups H-C(S)-O-, alkyl-C(S)-O-, cycloalkyl-C(S)-O-, aryl-
15 C(S)-O-, heteroaryl-C(S)-O-, and heterocyclyl-C(S)-O-, where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Sulfinyl" refers to groups H-S(O)-, alkyl-S(O)-, cycloalkyl-S(O)-, aryl-S(O)-, heteroaryl-S(O)-, and heterocyclyl-S(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and
20 heterocyclyl are as described herein.

"Sulfonyl" refers to groups H-S(O)₂-, alkyl-S(O)₂-, cycloalkyl-S(O)₂-, aryl-S(O)₂-, heteroaryl-S(O)₂-, and heterocyclyl-S(O)₂-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

25

"Sulfinylamino" refers to groups H-S(O)-NR''', alkyl-S(O)-NR''', cycloalkyl-S(O)-NR''', aryl-S(O)-NR''', heteroaryl-S(O)-NR''', and heterocyclyl-S(O)-NR''', where R''' is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

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- 15 -

"Sulfonylamino" refers to groups $\text{H-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{alkyl-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{cycloalkyl-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{aryl-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{heteroaryl-S(O)}_2\text{-NR}^{\text{'''}}$ -, and $\text{heterocyclyl-S(O)}_2\text{-NR}^{\text{'''}}$ -, where $\text{R}^{\text{'''}}$ is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

5

"Oxysulfinylamino" refers to groups $\text{HO-S(O)-NR}^{\text{'''}}$ -, $\text{alkylO-S(O)-NR}^{\text{'''}}$ -, $\text{cycloalkylO-S(O)-NR}^{\text{'''}}$ -, $\text{arylO-S(O)-NR}^{\text{'''}}$ -, $\text{heteroarylO-S(O)-NR}^{\text{'''}}$ -, and $\text{heterocyclylO-S(O)-NR}^{\text{'''}}$ -, where $\text{R}^{\text{'''}}$ is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as

10 described herein.

"Oxysulfonylamino" refers to groups $\text{HO-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{alkylO-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{cycloalkylO-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{arylO-S(O)}_2\text{-NR}^{\text{'''}}$ -, $\text{heteroarylO-S(O)}_2\text{-NR}^{\text{'''}}$ -, and $\text{heterocyclylO-S(O)}_2\text{-NR}^{\text{'''}}$ -, where $\text{R}^{\text{'''}}$ is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

15

"Aminothioacyl" refers to groups $\text{R}^{\text{'''}}\text{R}^{\text{'''}}\text{N-C(S)-}$ -, where each $\text{R}^{\text{'''}}$ is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, where heterocyclic and alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

20

"Thioacylamino" refers to groups $\text{H-C(S)-NR}^{\text{'''}}$ -, $\text{alkyl-C(S)-NR}^{\text{'''}}$ -, $\text{cycloalkyl-C(S)-NR}^{\text{'''}}$ -, $\text{aryl-C(S)-NR}^{\text{'''}}$ -, $\text{heteroaryl-C(S)-NR}^{\text{'''}}$ -, and $\text{heterocyclyl-C(S)-NR}^{\text{'''}}$ -, where $\text{R}^{\text{'''}}$ is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and where heterocyclyl and alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

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
"Aminosulfinyl" refers to groups $\text{R}^{\text{'''}}\text{R}^{\text{'''}}\text{N-S(O)-}$ -, where each $\text{R}^{\text{'''}}$ is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

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"Aminosulfonyl" refers to groups $R''R'''N-S(O)_2-$, where each R'' is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

5 In this specification "optionally substituted" is taken to mean that a group may or may not be further substituted or fused (so as to form a condensed polycyclic group) with one or more groups selected from hydroxyl, acyl, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, alkynyloxy, amino, aminoacyl, thio, arylalkyl, arylalkoxy, aryl, aryloxy, acylamino, cyano, halogen, nitro, sulfo, phosphono, phosphorylamino, phosphinyl, heteroaryl, 10 heteroaryloxy, heterocyclyl, heterocycloxy, oxyacyl, acyloxy, oxime, oxime ether, hydrazone, oxyacylamino, aminoacyloxy, trihalomethyl, trialkylsilyl, pentafluoroethyl, trifluoromethoxy, difluoromethoxy, trifluoromethanethio, trifluoroethenyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclyl amino, and unsymmetric di- 15 substituted amines having different substituents selected from alkyl, aryl, heteroaryl and heterocyclyl, and the like. For instance, an "optionally substituted amino" group may include amino acid and peptide residues.

The term "base", unless otherwise specified, refers to the base moiety of a nucleoside or 20 nucleotide. The base moiety is the nitrogen-heterocycle portion of a nucleoside or nucleotide. The base moiety of a nucleotide of formula (I) is a bicyclic heterocycle represented by formula (II) and designated "B". The nucleoside base is attached to the sugar moiety of a nucleoside in such ways that both α and β anomers of D or L nucleosides can be produced. This is denoted by use of the  bond which links the base to the 25 sugar moiety.

The term "sugar" refers to the furanose portion of a nucleoside. The sugar moiety of formula (I) nucleosides, nucleotides and nucleotides mimics and/or prodrugs thereof may contain one or more substituents at their C1-, C2-, C3- and C4-position of the furanose. 30 Substituents may be directed to either the α - or β -face of the furanose. The nucleoside base can be considered as a substituent at the C-1 position of the furanose and is preferably

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directed to the β -face of the sugar. The β -face is the side of a furanose on which a purine or pyrimidine base of natural β -D-nucleosides is present. The α -face is the side of the sugar opposite to the β -face.

- 5 Examples of a "protecting group" for O, S, or N moieties such as hydroxy or NH_2 , includes acyl groups, silyl groups, and the like. Suitable protecting groups for these and other moieties are described by T.W., Greene and P.G.M. Wuts; *Protecting Groups in Organic Synthesis*, 3rd Ed, John Wiley & Sons, Inc. (1999), incorporated herein by reference.
- 10 The term "infection" or "microbial infection" refers to the infection caused by an infectious agent or microbe, such as bacteria, parasite (including protozoan), virus or fungus (including unicellular and multicellular). Examples of microbes that cause such infection include: Acanthamoeba, African Sleeping Sickness (Trypanosomiasis), amebiasis, American Trypanosomiasis (Chagas Disease), Bilharzia (Schistosomiasis),
- 15 cryptosporidiosis (diarrheal disease, *Cryptosporidium Parvum*), Giardiasis (diarrheal disease, *Giardia lamblia*), hepatitis A, B, C, D, E, leishmaniasis (skin sores and visceral), malaria (*Plasmodium falciparum*), Salmonella enteritides infection (stomach cramps, diarrhea and fever), tuberculosis (mycobacterium tuberculosis), varicella (chicken pox), yellow fever, pneumonias, urinary tract infections (Chlamydia and Mycoplasma),
- 20 meningitis and meningococcal septicemia, skin and soft tissue infections (*Staphylococcus aureus*), lower respiratory tract infections (bacterial pathogens or viral pathogens).

Common infections caused by microbes are further outlined in the following chart:

Infection	Bacteria	Fungus	Protozoa	Virus
AIDS				X
Athlete's Foot		X		
Chicken Pox				X
Common Cold				X
Diarrheal Disease	X		X	X
Dengue				X
Flu				X
Genital Herpes				X
Malaria	X		X	

Infection	Bacteria	Fungus	Protozoa	Virus
Meningitis	X			
Pneumonia	X	X		
Sinusitis	X	X		
Skin Disease	X	X	X	X
Strep Throat	X			
Tuberculosis	X			
Urinary Tract Infections	X			
Vaginal Infections	X	X		
Viral Hepatitis				X

In relation to the therapeutic methods of the present invention the compounds of formula (I) may be particularly useful for treating a microbial infection which is a viral infection caused by an RNA virus, such as a virus belonging to group Flaviviridae, for instance
 5 Flaviviruses or HCV, or a DNA or retrovirus such as HBV or HIV. In a preferred embodiment the method of the present invention treats a viral infection caused by an RNA virus of the group Flaviviridae and in particular HCV.

The compounds of formula (I) are administered to the subject in a therapeutic effective
 10 amount. As used herein, a therapeutic effective amount is intended to include at least partially attaining the desired effect, or delaying the onset of, or inhibiting the progression of, or halting or reversing altogether the onset or progression of the particular disease of condition being treated.

15 As used herein, the term "effective amount" relates to an amount of compound which, when administered according to a desired dosing regimen, provides the desired therapeutic activity. Dosing may occur at intervals of minutes, hours, days, weeks, months or years or continuously over any one of these periods. Suitable dosages lie within the range of about 0.1 ng per kg of body weight to 10 g per kg of body weight per dosage. The dosage may
 20 be in the range of 1 µg to 10 g per kg of body weight per dosage, such as is in the range of 1 mg to 10 g per kg of body weight per dosage. In one embodiment, the dosage may be in the range of 1 mg to 500 mg per kg of body weight per dosage. In another embodiment, the dosage may be in the range of 1 mg to 250 mg per kg of body weight per dosage. In

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yet another preferred embodiment, the dosage may be in the range of 1 mg to 100 mg per kg of body weight per dosage, such as up to 50 mg per body weight per dosage.

Suitable dosage amounts and dosing regimens can be determined by the attending
5 physician and may depend on the particular condition being treated, the severity of the condition as well as the general age, health and weight of the subject.

The active ingredient may be administered in a single dose or a series of doses. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a
10 composition, preferably as a pharmaceutical composition. The formulation of such compositions is well known to those skilled in the art. The composition may contain any suitable carriers, diluents or excipients. These include all conventional solvents, dispersion media, fillers, solid carriers, coatings, further antifungal and antibacterial agents, dermal penetration agents, surfactants, isotonic and absorption agents and the like. It will be
15 understood that the compositions of the invention may also include other supplementary physiologically active agents.

The carrier must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the subject. Compositions
20 include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parental (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which
25 constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as
30 capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-

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aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. inert diluent, preservative disintegrant (e.g. sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured base, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatine and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions suitable for topical administration to the skin may comprise the compounds dissolved or suspended in any suitable carrier or base and may be in the form of lotions, gel, creams, pastes, ointments and the like. Suitable carriers include mineral oil, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol, benzyl alcohol and water. Transdermal patches may also be used to administer the compounds of the invention.

30

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Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter, glycerin, gelatine or polyethylene glycol.

5 Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

10 Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bactericides and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example
15 water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

20 Finally, formulations of these compositions in dry powder form for delivery by a dry powder inhaler offer yet another means of administration. This overcomes many of the disadvantages of the oral and intravenous routes.

25 Preferred unit dosage compositions are those containing a daily dose or unit, daily sub-dose, as herein above described, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the active ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as binders, sweeteners, thickeners, flavouring agents
30 disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable

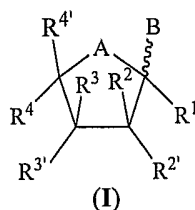
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disintegrating agents include cornstarch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

10

In a further embodiment, the present invention provides novel compounds, pharmaceutical compositions of said novel compounds and therapeutic applications of said novel compounds for the treatment of microbial infections.

15 Accordingly, in another aspect the present invention provides a compound of the formula (I) or a salt thereof;



wherein:

A is O, S, CH₂, CHF, CF₂ or NR;

20

R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, halogen, OH, N₃, CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkyloxy, optionally substituted alkenyloxy, optionally substituted alkynoxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted arylalkoxy, optionally substituted

heterocycloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkoxy, optionally substituted cycloalkenoxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted oxyacylimino, optionally substituted aminothioacyl, optionally substituted thioacylamino, optionally substituted aminosulfinyl, optionally substituted aminosulfonyl, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacyloxy, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted phosphorylamino, optionally substituted sulfinyl, optionally substituted sulfonyl, optionally substituted sulfinylamino, optionally substituted sulfonylamino, optionally substituted oxysulfinylamino, and optionally substituted oxysulfonylamino, or R^2 and R^2 together or R^3 and R^3 together represents =O, =S, or =L-Y' where L is N, CH, CF, CCl or CBr and Y' is H, halogen, N_3 , methyl, ethyl or CN;

15

R^4 is $-CY_2SH$, $-CY_2OH$, $-CY_2NH_2$, or $-L^1-R^5$;

L^1 is selected from the group consisting of $-CY_2-$, $-CY_2CY_2-$, $-CY_2OCY_2-$, $-CY_2SCY_2-$ and $-CY_2NHCY_2-$;

20

each Y is independently selected from the group consisting of H, F, Cl, Br, OR, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl may be optionally substituted with one or more groups selected from F, Cl, Br, OH, COOH, COOCH₃, SH, SCH₃, NH₂, NHCH₃, N(CH₃)₂, CN, NO₂, C(O)NH₂, C(O)NHCH₃, N_3 , C(S)NH₂, OCH₃, and OCH₂CH₃;

25

R^5 is selected from the group consisting of OR, NR₂, monophosphate, diphosphate, and triphosphate, or a mono, di or triphosphate mimic;

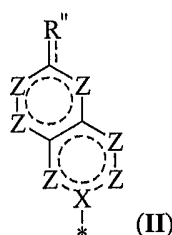
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each R is independently selected from the group consisting of H, CF₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally

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substituted aryl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl;

5 B is a group of formula (II)



wherein, if Z is a participant in a π bond (double bond), Z is independently selected from N or C-G; or, if Z is not a participant in a π bond (double bond), Z is
 10 independently selected from O, S, Se, NR, NOR, NNR₂, CO, CS, CNR, SO, S(O)₂, SeO, Se(O)₂ or C(G)₂, wherein each G is independently selected from the group consisting of H, halogen, OR, SR, NR₂, NROR, N₃, COOR, CN, CONR₂, C(S)NR₂, C(=NR)NR₂, NCONR₂, NCSNR₂ and R; and

where any two adjacent Z are not both selected from O, S, and Se, or not both
 15 selected from CO, CS, CNR, SO, S(O)₂, SeO, and Se(O)₂;

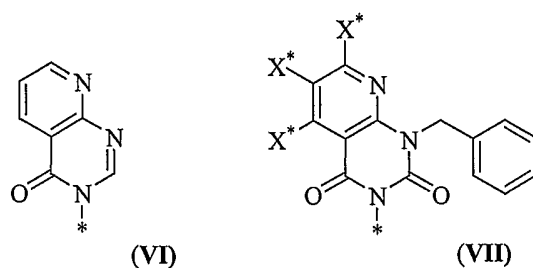
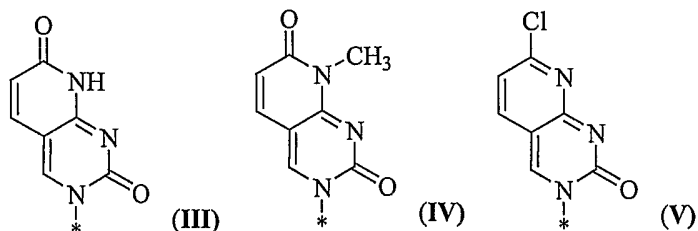
wherein, if X is a participant in a π bond (double bond), X is C; or if X is not a participant in a π bond (double bond), X is CR or N;

wherein, if R'' is a participant in a π bond (double bond), R'' is O, S, Se, NR, NOR, and NNR₂; or if R'' is not a participant in a π bond (double bond), R'' is OR, SR, F,
 20 Cl, R, or SeR;

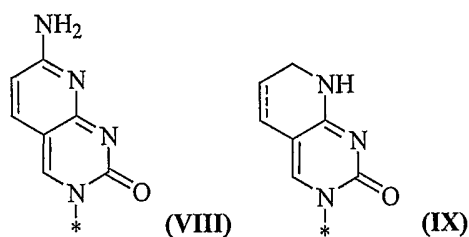
dashed lines (---) indicate a possible π or double bond; and

wherein when R², R³, and R⁵ are OH or OC(O)CH₃, L' is CH₂, A is O, and R¹, R², R³ and R⁴ are H, B is not the group of formula (III), formula (IV), formula (V), formula (VI), or
 25 formula (VII)

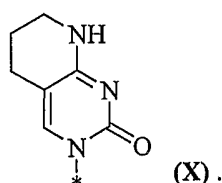
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- 5 (where all X^* are H, or one of X^* is CH_3 and the other two X^* are H);
when B is a group of formula (III), formula (VIII), or formula (IX)



- R^2 and $R^{2'}$ are not both H;
10 when R^2 , $R^{3'}$ and R^5 are OH, L' is CH_2 , A is O and R^1 , $R^{2'}$, R^3 and R^4 are H, B is not the group of formula (IV); and
when $R^{2'}$ is F, $R^{3'}$ is OH, R^5 is triphosphate, L' is CH_2 , A is O, and R^1 , R^2 , R^3 and R^4 are H, B is not a group of formula (X)

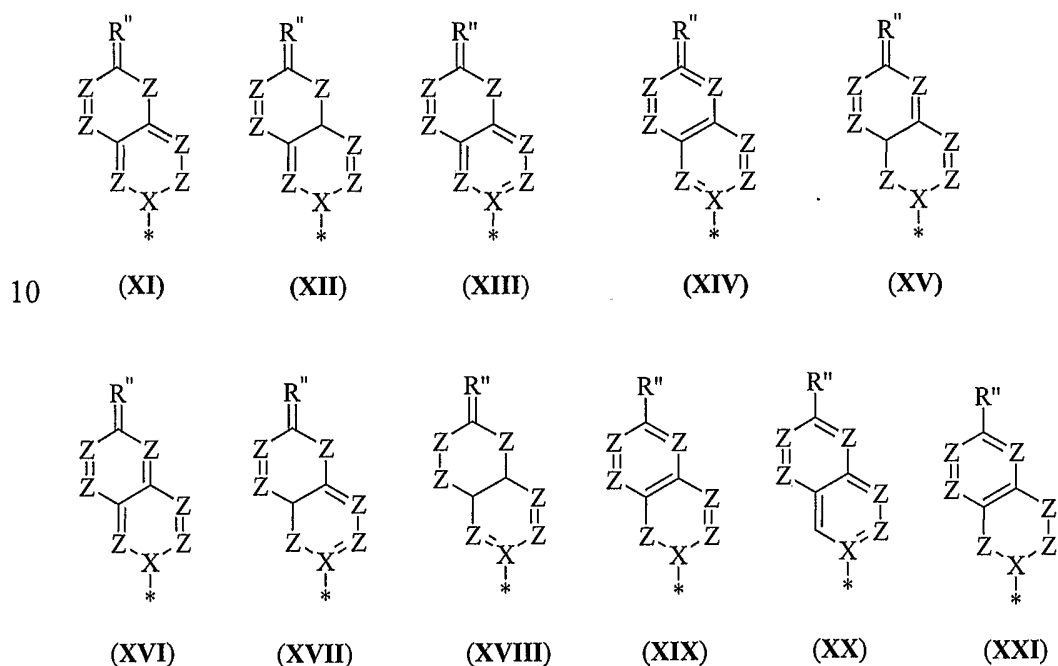


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In some preferred embodiments of the invention one or more of the following definitions apply:

The bicyclic base structure B of formula II may have one or more ring double bonds and, in some instances, may have two or more ring double bonds. Preferably, the base structure has at least two double bonds and more preferably three or more double bonds.

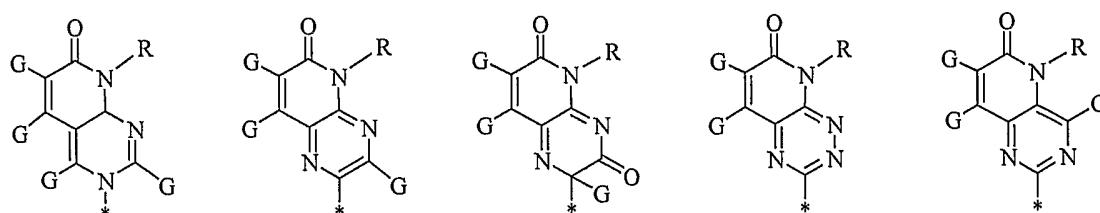
Preferably the base structure B is selected from the following formulae (XI) to (XXI)



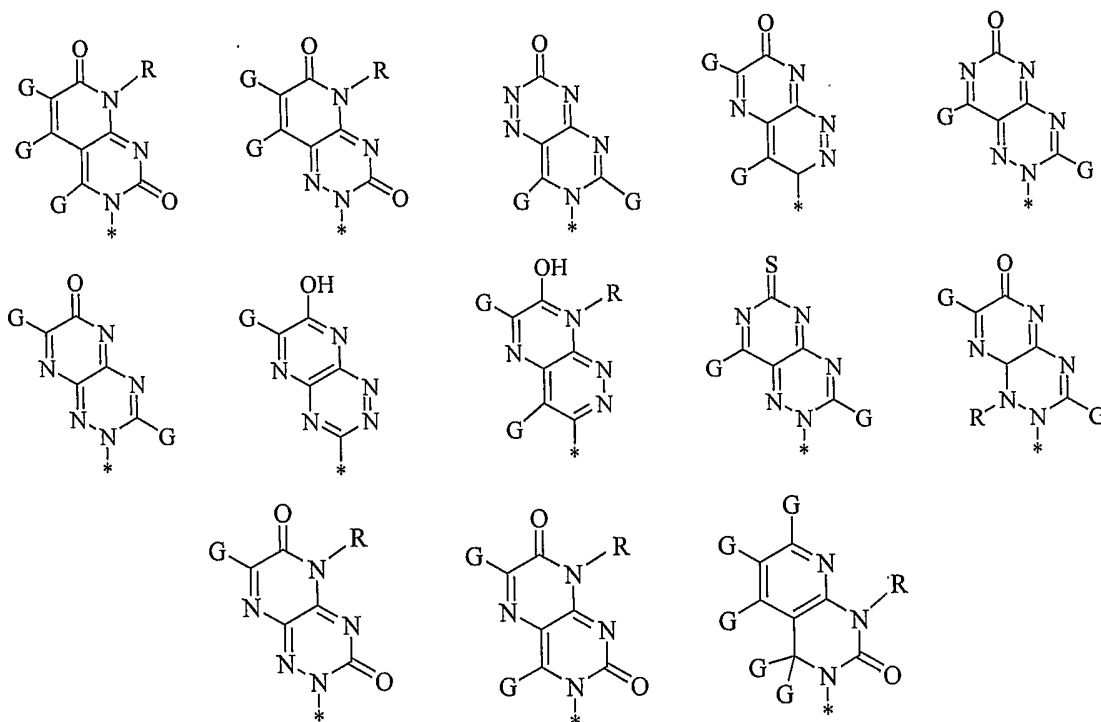
wherein Z, X and R'' are as defined above.

15

Examples of preferred base structures (B) are as follows:



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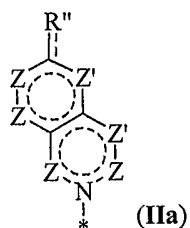


5 wherein G and R are as defined above.

Preferably X is N.

More preferably, the structure of formula **II** is represented by the structure of formula **IIa**

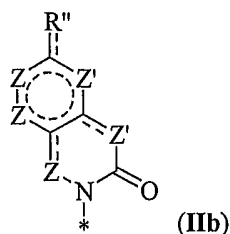
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wherein each Z' is independently N (if a participant in a π bond) or NR (if not a participant in a π bond), and R'', R and Z are as defined above.

15 Even more preferably, the structure of formula **II** is represented by the structure of formula **IIb**

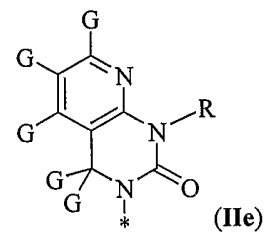
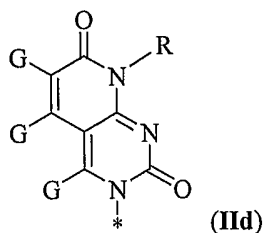
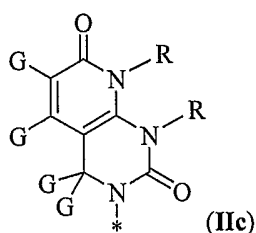
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wherein R'' and Z' are as defined above and each Z is independently CG (if a participant is π bond) or $>C(G)_2$ (if not a participant in a π bond).

5

Most preferably, the structure of formula II is represented by the structures of formulae IIc, II d and IIe



10 wherein R and G are as defined above.

Preferably, for the compounds of formulae IIc, II d and IIe each R is independently selected from H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl and each G is independently selected from H, halogen, CF₃, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl.

In a further preferred embodiment L' is -CH₂-.

20

In yet a further preferred embodiment R⁴ is selected from -CH₂-OH, -CF₂OH, -CCl₂-OH, -C(CH₃)(CH₃)₃OH, -CH(CH₃)OH, -CH₂-CH₂-P(O)(OH)₂, -CH₂-CH₂-P(O)(OH)₂, -CH₂SP(O)(OH)₂, -CH₂SH, -CF₂SH, and -CH₂-O-P(O)(OPh)(NHCH(CH₃)(CO₂Me)).

- 29 -

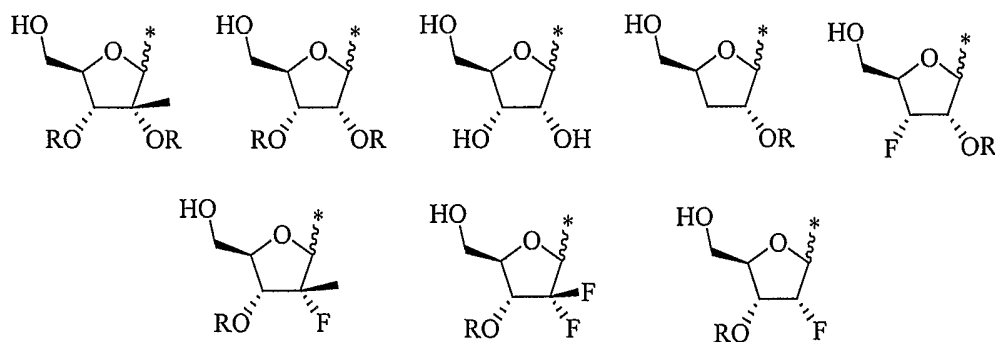
More preferably R⁴ is -CH₂-OH.

Preferably, R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, halogen (more preferably F), OH, N₃, CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkyloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino, optionally substituted thio, or R² and R^{2'} together or R³ and R^{3'} together represents =O, =S, or =L-Y' where L is N, CH, CF, CCl or CBr and Y' is H, halogen, N₃, methyl, ethyl or CN.

Even more preferably R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, F, Cl, Br, I, OH, SH, NH₂, NHOH, NHNH₂, N₃, COOH, CN, CONH₂, C(S)NH₂, COOR, R, OR, SR, SSR, NHR, and NR₂ wherein at least one of R² or R^{2'} is a substituent other than H, and wherein R is selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, and optionally substituted arylalkyl.

20

In yet another preferred embodiment, the sugar moiety is selected from the following formulae:



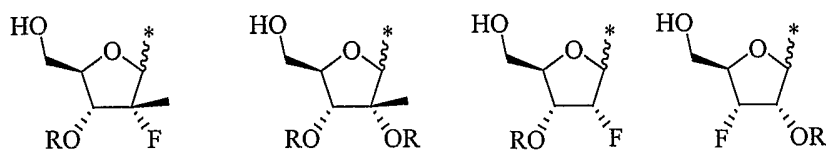
25 or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

- 30 -

In another preferred embodiment, at least one of R^2 and $R^{2'}$ is methyl, hydroxyl or F.

More preferably, the sugar moiety is selected from the following formulae:

5

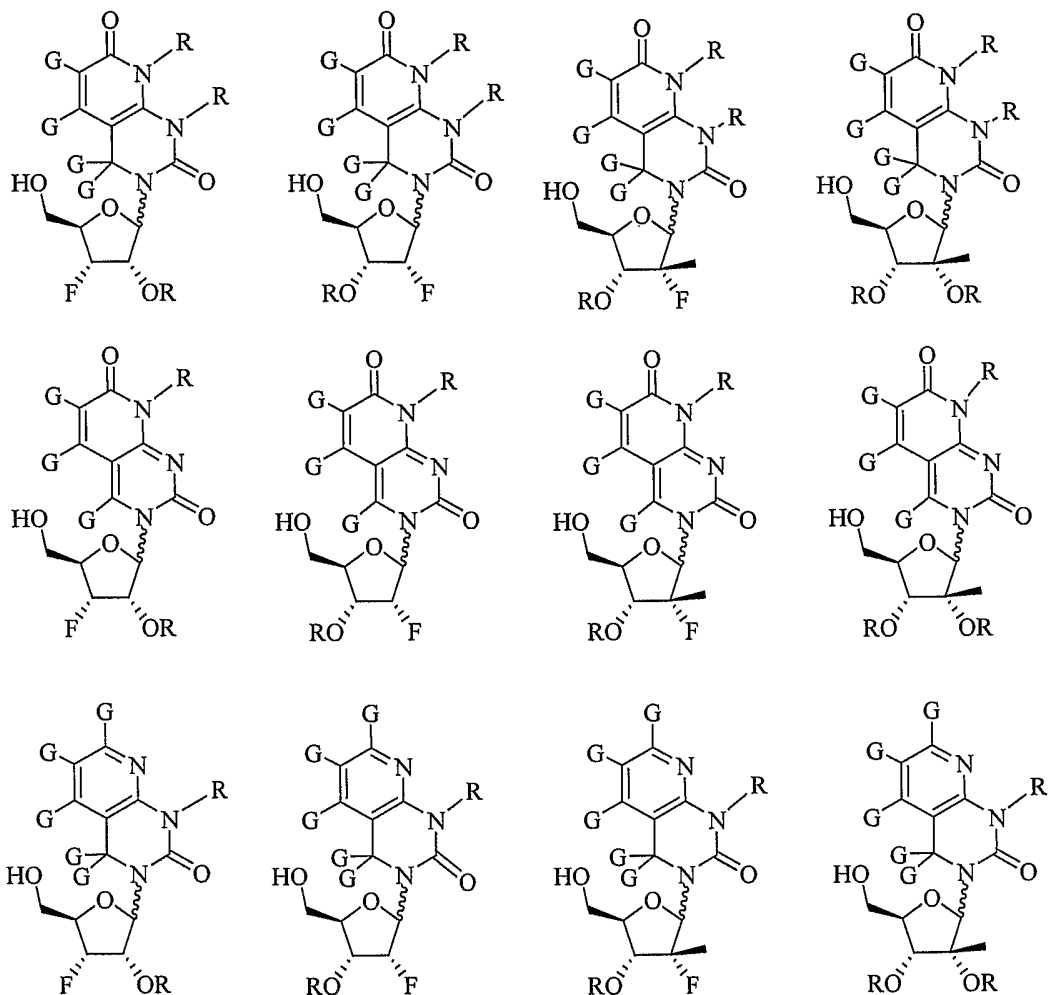


or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

10

Accordingly, in a preferred embodiment the compound of formula (I) is selected from the following formulae, or salts thereof:

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wherein:

- each R on the sugar moiety is independently selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl and optionally substituted arylalkyl;
- each R on the base moiety is independently selected from H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl;
- each G is independently selected from H, halogen, CF_3 , optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl; and
- C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

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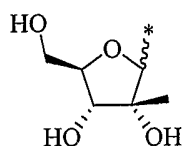
While nucleosides incorporating a variety of sugar moieties have been found to be useful for the inhibition of viral polymerases, in the case of the Flaviviridae, and in particular, the Hepatitis C virus, 2'-C-methyl ribnucleosides have been found to be particularly useful (see
5 Eldrup, A.B. et al., J. Med. Chem. 2004, 47(21), 5284-97, which is incorporated herein by reference).

Accordingly, even more preferably, the sugar moiety is represented by the following formula:



or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

15 Most preferably, the sugar moiety is represented by the following formula:



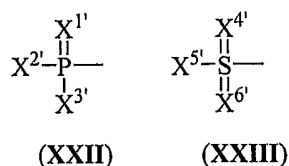
or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

20

The bicyclic nucleosides of the present invention also include derivatives such as nucleotides, and nucleotide mimics and/or prodrugs thereof.

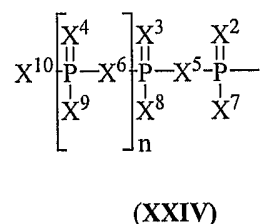
In some embodiments, nucleotide mimics of the compounds of the present invention of
25 formula (I) discussed above include a compound in which R⁵ is a monophosphate or monophosphate mimic of formula (XXII) or (XXIII):

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where $X^{1'}$, $X^{4'}$, and $X^{6'}$, independently are O, S, NR; $X^{2'}$, $X^{3'}$, and $X^{5'}$ are selected independently from the group consisting of H, F, NROR, N_3 , CN, $(BH_2G)^-M^+$, $(BH_3)^-M^+$, R, OR, SR, and NR_2 . The substituents $(BH_2G)^-M^+$ and $(BH_3)^-M^+$ are ion pairs, which are
 5 linked to phosphorus through the negatively charged boron. M^+ is a cation, preferably a pharmaceutically acceptable cation such as Ca^{2+} , ammonium, trialkylammonium or tertaalkylammonium, *e.g.*, NH_4^+ , Et_3NH^+ , Bu_3NH^+ , and Bu_4N^+ .

In some embodiments, nucleotide mimics of the compounds of formula (I) as discussed
 10 above include di- and triphosphates and di- and tri-phosphate mimics including a compound in which R^5 is a di- or tri-phosphate moiety of formula (XXIV):



X^2 , X^3 , and X^4 are selected independently from the group consisting of O, S, Se, and NR;

15 X^5 and X^6 are selected independently from the group consisting of -O-, -S-, -Se-, - $CY_2C(O)$ -, -CH(OH)-, -C(OH) $_2$ -, -CH $_2O$ -, -CH $_2CH_2$ -, -CH $_2CH(NH_2)$ -, -CH $_2CH_2CH(NH_2)$ -, - CY_2OCY_2 -, - CY_2 -, -CRY-, - CY_2CY_2 -, -CHR-, -C \equiv C-, -HC=CH-, -NH-, -NR-, >NOH, >NOR, >NNH $_2$, and >NNHR;

X^7 , X^8 , X^9 , and X^{10} are selected independently from the group consisting of H, F,
 20 OR, SR, NR_2 , NROR, NRNR $_2$, CN, N_3 , $(BH_3)^-M^+$, $(BH_2G)^-M^+$, R and SeR;

Y, R, $(BH_2G)^-M^+$ and $(BH_3)^-M^+$ are as defined above; and
 n is 0 or 1.

Additional nucleotide phosphate mimics and methods of making the phosphate mimics
 25 appropriate for the compounds of the present invention are described, *inter alia*, in WO 2003/072757 and WO 2003/073989, the entire contents of which are incorporated herein

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by reference. Many of the nucleotide mimics discussed herein can be prepared by similar approaches as published or by using well-known knowledge of organophosphorous chemistry. Generally, phosphate mimics of the nucleosides and nucleotides of the present invention can inhibit enzyme function without phosphorylation and/or have enhanced
5 nuclease stability relative to nucleotides with unmodified phosphate.

Accordingly, the term "phosphate mimic", unless otherwise specified, refers to a phosphate analog, including, but not limited to, phosphonate, phosphothiolate, phosphoselenoate, selenophosphate, thiophosphate, P-boranophosphate, phosphoramidate, sulfamate,
10 sulfonate, and sulfonamide and/or a combination thereof. Preferred embodiments of the phosphate mimics include phosphonate, phosphoramidate, phosphorothioate, methylphosphonate, fluoromethylphosphonate, difluoromethylphosphonate, vinylphosphonate, phenylphosphonate, sulfonate, fluorophosphate, dithiophosphorothioate, 5'-methylenephosphonate, 5'-difluoromethylenephosphonate, 5'-deoxyphosphonate, 5'-
15 aminophosphoramidate, and 5'-thiophosphate. More preferred is phosphonate and phosphoramidate.

Also, it will be appreciated that the term "diphosphate mimic" and "triphosphate mimic" specifically refer to a diphosphate analog and a triphosphate analog, respectively, which
20 comprises at least one of the phosphate mimics, one of the modifications at the bridging site of diphosphate and triphosphate (eg. X⁵, X⁶ and X¹⁰), and/or replacements of non-bridging phosphate oxygens (eg. X⁴, X³ and X²).

The α -P, β -P, and γ -P in the mono, di- and triphosphate mimics may independently adopt
25 either *R* or *S* configurations when chiral.

Accordingly, in compounds of formula (I) where a chiral centre is present, the invention encompasses enantiomers, or stereoisomers and mixtures thereof, such as enantiomerically enriched mixtures. It will also be appreciated that the base moieties of the present
30 invention may exist as rapidly interconvertible mixtures of isomers. Isomerism of this kind is known in the art as tautomerism. Individual isomers are called tautomers. Where

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tautomerism is possible the present invention covers all possible tautomers of the compounds of formula (I).

The compounds of the present invention can be administered to a subject as a pharmaceutically acceptable salt thereof. It will be appreciated however that non-pharmaceutically acceptable salts also fall within the scope of the present invention since these may be useful as intermediates in the preparation of pharmaceutically acceptable salts.

10 Suitable pharmaceutically acceptable salts include, but are not limited to salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, maleic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, 15 methanesulphonic, toluenesulphonic, benzenesulphonic, salicylic sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable 20 cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium. In particular, the present invention includes within its scope cationic salts eg sodium or potassium salts, or alkyl esters (eg methyl, ethyl) of the phosphate group.

25 Basic nitrogen-containing groups may be quarternised with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

In some embodiments, the bicyclic nucleosides and nucleotides of the present invention 30 also include their prodrug derivatives. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the compounds of the

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invention. Prodrugs of the compounds of the present invention may be prepared by modification of the sugar moiety or of the phosphate or phosphate mimic to include a prodrug substituent. Such prodrug modification is generally performed to enhance drug absorption and/or drug delivery into cells.

5

Prodrugs substituents include, but are not limited to residues of: proteins; antibiotics; D- and L-amino acids which may be attached to a phosphate moiety or a phosphate mimic moiety via a carbon atom (phosphonates), a nitrogen atom (phosphoamidates), or an oxygen atom (phosphoesters) or may be attached to the sugar moiety through any one or more of the R¹-R⁵ groups; peptides (preferably up to 10 amino acids) attached to a phosphate moiety or a phosphate mimic moiety via a carbon atom (phosphonates), a nitrogen atom (phosphoamidates), or an oxygen atom (phosphoesters), or may be attached to the sugar moiety through any one or more of the R¹-R⁵ groups; drug moieties attached to a phosphate moiety or a phosphate mimic moiety via a carbon atom (phosphonates), a nitrogen atom (phosphoamidates), or an oxygen atom (phosphoesters), or may be attached to the sugar moiety through any one or more of the R¹-R⁵ groups; as well as including steroids; vitamins; polyamines; carbohydrates; polyethylene glycols (PEGs); cycloaligenyls; substituted 4 to 8-membered rings, with or without heteroatom substitutions, 1,3-phosphoamidate attachments to a terminal phosphate or phosphate mimic moiety (γ or β) or connecting between an α,β or β,γ of a phosphate moiety or phosphate mimic moiety, and so on.

In addition to those described herein, prodrug derivatives of nucleosides, nucleotides and nucleotide phosphate mimics and methods of making the prodrugs appropriate for use in the present invention are described, *inter alia*, in PCT Publications WO 2003/072757 and WO 2003/073989.

The prodrug of a nucleoside 5'-monophosphate mimic can mask the negative charges of the phosphate mimic moiety entirely or partially, or mask the negative charges of the di-phosphate mimic or tri-phosphate mimic moiety or phosphate moiety in order to enhance drug absorption and/or drug delivery into cells.

30

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In one embodiment a combination of prodrug substituents may be attached to one or more X^2 , X^3 and X^5 positions on a nucleoside mono-phosphate mimic or to one or more X^7 - X^{10} positions on a nucleoside di- or tri-phosphate mimic. Preferred prodrug substituents in positions X^2 , X^3 or X^5 position include 2,3-O-diacylglyceryloxy, 2,3-O-dialkylglyceryloxy, 1-O-alkyl-2-O-acylglyceryloxy, 1-O-acyl-2-O-alkylglyceryloxy, 1-S-alkyl-2-O-acyl-1-thioglyceryloxy, acyloxymethoxy, *S*-acyl-2-thioethoxy, *S*-pivaloyl-2-thioethoxy, acyloxymethoxy, pivaloyloxymethoxy, alkoxycarbonyloxymethoxy, *S*-alkyldithio-*S'*-ethoxy acyloxymethoxy, *S*-acyl-2-thioethoxy, *S*-pivaloyl-2-thioethoxy, pivaloyloxymethoxy, alkoxycarbonyloxymethoxy, and *S*-alkyldithio-*S'*-ethoxy.

In a further embodiment, the prodrug substituent is a substituent on a hydroxyl group of the sugar moiety (that is, for instance, any one of R^1 - R^5). Preferably, the modification results in the formation of an ester and in this regard the preferred prodrug substituents are C_1 - C_6 acyl groups for example, acetyl, propionyl, pivaloyl, etc. Also preferred are substituted C_1 - C_6 acyl moieties, for example, fluoroacetyl, difluoroacetyl, etc. More preferably the substituted C_1 - C_6 acyl group is represented as a residue of a L or D amino acid consisting of alanine, asparagine, cysteine, glutamine, glycine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, aspartic acid, glutamic acid, arginine, histidine, and lysine. Most preferably the prodrug substituent is an amino acid residue of D or L-valine.

The prodrug can be activated either by cellular enzymes such as lipases, esterases, reductases, oxidases, nucleases or by chemical cleavage such as hydrolysis to release (liberate) either the nucleoside, nucleotide or nucleotide mimic after the prodrug enters cells.

In addition to using prodrug approaches, the delivery of the nucleosides and nucleotides may be assisted by using a therapeutically acceptable carrier such as liposomal suspensions, cationic lipids, and polyimines.

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The novel nucleosides, nucleotides, nucleotide mimics and prodrugs thereof, of the present invention can be prepared by those who are skilful in synthetic organic and nucleoside chemistry using established synthetic methodology (*Chemistry of Nucleosides and Nucleotides* Vol. 1 (1988), Vol. 2 (1991), Vol. 3 (1994), edited by L.B. Townsend, Plenum Press; *Handbook of Nucleoside Synthesis* by H. Vorbrüggen and C. Ruh-Pohlenz, John Wiley & Sons, Inc., 2001; *The Organic Chemistry of Nucleic Acids* by Y. Mizuno, Elsevier, 1986).

The nucleosides of the present invention can be converted to their corresponding monophosphate, diphosphate, and triphosphate nucleosides by established phosphorylation procedures. Similarly, known methods in the art can be used to synthesise the nucleotide and phosphate mimics and prodrugs. The following schemes and description serve as representative syntheses of the nucleosides and nucleotides of the present invention. As such, other compounds such as those having $-CY_2SH$, $-CY_2OH$ or $-L'-R^5$ groups other than CH_2R^5 may similarly be made.

The bicyclic nucleosides of the present invention may be prepared by modification of optionally protected and functionalised cytosine, uracil and other base analogues followed by Stille, Heck, Sonogashira or other metal-mediated cross coupling chemistry to introduce an α,β -unsaturated ester, alkyne or other functional group. Such processes allow for stereoselective synthesis of an intermediate capable of efficient cyclisation to form the bicyclic compounds of the present invention. Cyclisation and optional deprotection of the product delivers the target bicyclic nucleoside.

Any compound capable of metal-mediated cross coupling may be used, such as a tin derivative like trialkyltin. More preferably tributyltin. Preferably the reactions are carried out using a palladium based coupling agent. Suitable coupling agents are known in the art and include $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd(dibenzylideneacetone)$, and $PdCl_2(CH_3CN)_2$. Also, preferably the palladium catalysed coupling reactions may also include a co-catalyst, for instance, CuI which may be in the presence of a suitable non-nucleophilic base such as a trialkylamine.

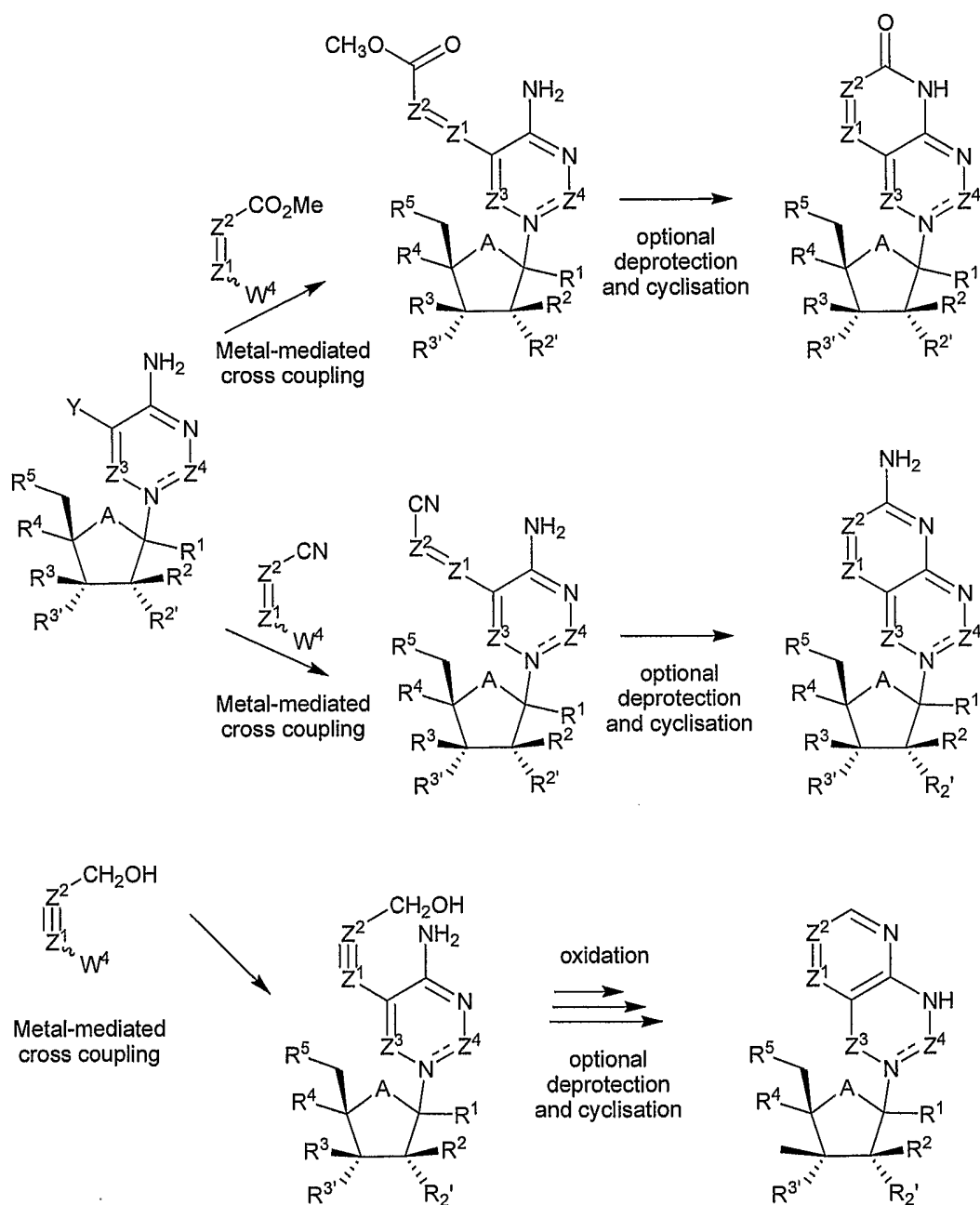
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Coupling reactions are generally performed at temperatures around room temperature. Elevated temperatures such as temperatures between 30-80°C can be employed to effect coupling and cyclisation in a single step. It is also preferred that such reactions are carried
5 out under an inert atmosphere of either nitrogen or argon. Suitable solvents include ether solvents such as THF and diethylether or polar solvents such as DMF.

For example, Schemes 1 and 2 illustrates some preferred cyclisation methods for forming the 6-membered ring portions of the bicyclic bases (B) of the compounds of the present
10 invention.

- 40 -

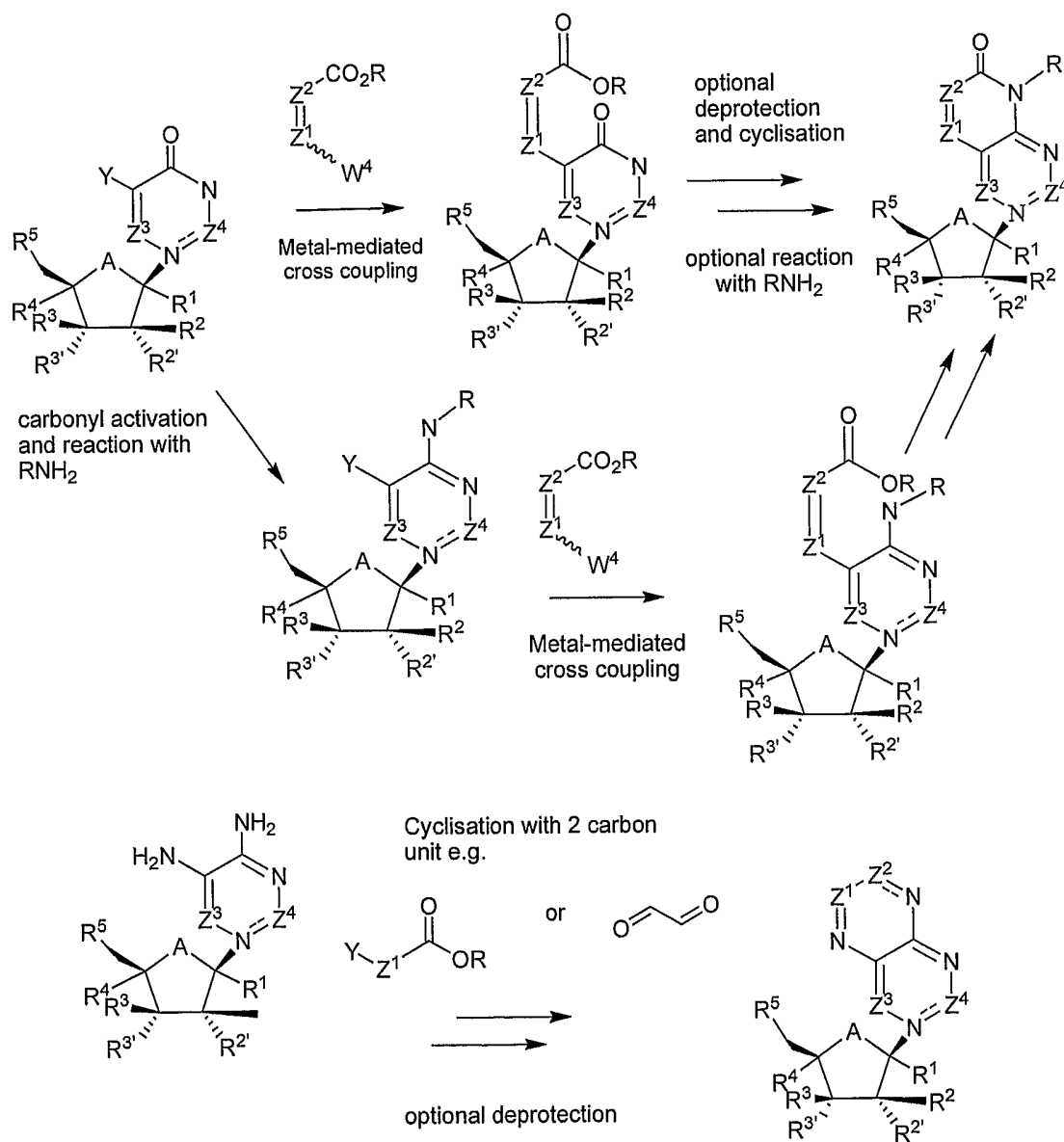
Scheme 1



Methodologies other than metal-mediated cross-coupling and cyclisation can also be used to prepare the bicyclic nucleosides. For example, the final process in scheme 2 depicts how a bifunctional two atom unit (such as an α -halocarboxylic ester or glyoxal) can be used to form the second 6-membered ring portion of a suitable nucleoside intermediate.

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Scheme 2



- 5 In the cyclisation methodology depicted in Schemes 1 and 2 each of Z^1 – Z^4 is independently Z.

Preferably, in this process A is O, CH_2 or optionally protected N; Y is halogen or other appropriate group such as trifluoromethanesulfonate; W^4 is H or trialkyltin; Z^1 and Z^2 are
 10 each independently C, CH, C-halogen, C-alkyl, C-aryl, C-heteroaryl, C-O-alkyl or C-S-

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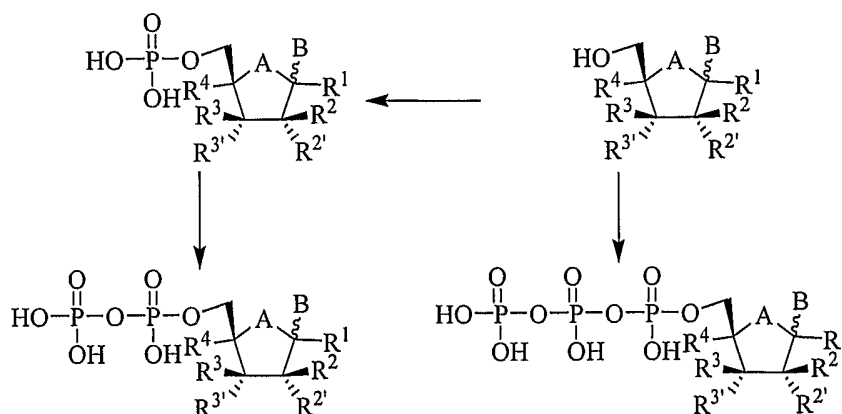
alkyl; Z^3 is CH, C-alkyl, C-halogen, N, CNHR, CNH₂, CNR₂, C=O, or C=S; Z^4 is CH, C-halogen, C-alkyl, C-aryl, C-heteroaryl, C-O-alkyl, C-S-alkyl, C-OH, C-NH₂, C-NHR, CNR₂ or C=O; R¹, R², R^{2'}, R³, R^{3'}, R⁴ are each independently H, halogen, alkyl, O-alkyl, OH, optionally protected O, methyl, H or F; and R⁵ is an optionally protected OH or NH₂; and
 5 (--) denotes an optional double bond.

The bicyclic bases of the present invention can be further modified either prior to being added to the sugar moiety or once attached. Such modification may involve transformations through functionalisation, defunctionalisation, or functional group
 10 interconversion. Modifications may include esterification, the preparation of enol ethers, o-alkylation, bromination, hydrogenation, dihydroxylation, epoxidation, oximation, and amination.

The compounds described herein can also be converted into their corresponding mono-, di- and triphosphates using well established methods. Furthermore, as discussed above
 15 prodrugs of mono-, di- and triphosphates can be prepared in order to optimise the biological efficacy of these phosphorylated compounds. Methods for preparing such prodrugs are well known in the art (see Wagner, C.R., *et al. Med. Res. Rev.*, **2000**, 20, 417-451).

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Scheme 3

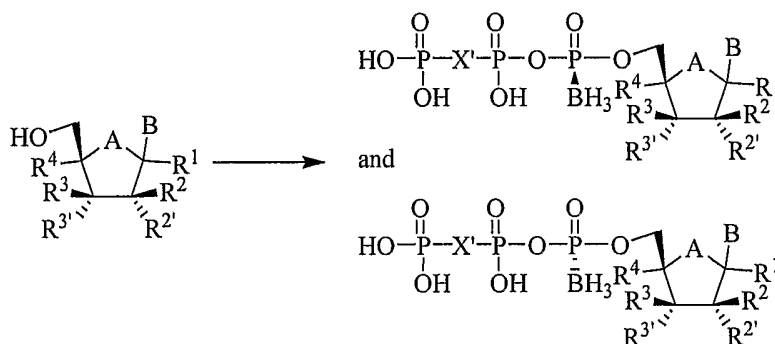


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In Scheme 3, preferably A is O, CH₂ or optionally protected N; R¹, R², R^{2'}, R³, R^{3'}, R⁴ are each independently H, halogen, alkyl, O-alkyl, OH, optionally protected O, or methyl and B is as described herein.

- 5 As discussed earlier an alternative to the use of phosphates is the use of phosphate mimics and their prodrugs. One such phosphate mimic is shown below and this can be prepared using appropriately protected nucleosides and known conditions.

Scheme 4



10

In Scheme 4, preferably A is O, CH₂ or optionally protected N; R¹, R², R^{2'}, R³, R^{3'}, R⁴ are each independently H, halogen, alkyl, O-alkyl, OH, optionally protected O, methyl or F; X' is O, S, NH, CF₂, CHF, CClH, CBr₂ or CHBr; B is as described herein.

15

The bicyclic compounds of the present invention may be tested for biological activity using well known procedures.

Antiviral assays are conducted according to published, widely used protocols. In order to obtain the therapeutic index, compound-induced cytotoxicity to host cells is also measured in parallel with antiviral activities. To determine the mode of action of antiviral nucleosides the corresponding nucleoside triphosphates are subject to enzyme-based assays for the inhibition of viral polymerases according to known protocols (Ranjith-Kumar *et al. J. Virol.* **2001**, 75, 8615; Dhanak *et al. J. Biol. Chem.* **2002**, 277, 38322-38327). Some compounds of the present invention showed K_i values of less than 1 μM against HCV NS5B.

25

- Since the replicon RNA replication mimics the replication of HCV RNA in infected hepatocytes, compounds that have the inhibitory effects in replicon assays are potentially useful as anti-HCV drugs. The HCV replicon-containing cell lines (Randall and Rice, *Current Opinion in Infectious Diseases* **2001**, 14, 743) are used for the identification of potential anti-HCV compounds. Among them is a widely used subgenomic replicon system developed by Lohmann *et al.* (*Science* **1999**, 285, 110; *J. General Virol.* **2000**, 81, 1631; *J. Virol.* **2001**, 75, 1437, **2002**, 76, 4008). Some compounds of the present invention showed potent anti-HCV activity with EC₅₀ values of low μ M.
- Widely used protocols developed by Korba *et al.* (*Antiviral Res.* **1992**, 19, 55), and Pai *et al.* (*Antimicrobial Agents Chemother.* **1996**, 40, 380) are useful for the determination of *in vitro* anti-HBV activity.
- Anti-HIV assays can be conducted according to the protocols developed by Schinazi *et al.* (*Antimicrobial Agents Chemother.* **1990**, 34, 1061; **1992**, 36, 2423; **1993**, 37, 875) or other widely used protocols (Kimpton *et al.* *J. Virol.* **1992**, 66, 2232; Chan *et al.* *J. Med. Chem.* **2001**, 44, 1866).
- Preferred nucleoside triphosphates of the present invention may act as potent inhibitors of the non-structural position 5B (NS5B) which is HCV's RNA-dependent RNA polymerase. Accordingly, such compounds are preferably suited to treat and/or prevent HCV. Also, as the preferred novel compounds of the present invention are expected to exhibit novel profiles of activity they may provide the artisan with an alternative to treating viruses which display drug resistance to conventional drugs. Other advantages which may be exhibited by the preferred novel compounds of the present invention include:
- reduced toxicity and tolerability relative to existing therapies and those in development; and/or
 - improved pharmacokinetic properties.

- 45 -

Accordingly, nucleosides, nucleotide, nucleotide mimics and/or their prodrugs of the present invention may be useful for the inhibition of a variety of enzymes including, but not limited to, DNA or RNA polymerases, helicases, ribonucleotide reductases, protein kinases, and telomerases and for the modulation of G-proteins, P2 purinergic receptors and
5 the allosteric sites of a variety of enzymes. Preferably, the novel nucleosides, nucleotides, nucleotide mimics and/or prodrugs of the present invention are used to treat viral infections caused by the RNV viruses of the group Flaviviridae and, in particular, HCV.

The novel nucleosides, nucleotides, nucleotide mimics and/or their prodrugs of the present
10 invention are useful for the treatment of infectious diseases caused by infectious agents such as parasites, bacteria and fungi.

Also, the novel nucleosides, nucleotide mimics and/or their prodrugs that display potent cytotoxicities to fast-dividing cancerous cells may be useful for the treatment of
15 proliferative disorders, including, but not limited to, lung cancer, liver cancer, prostate cancer, colon cancer, breast cancer, ovarian cancer, melanoma, and leukemia.

As the ligands of P2 receptors and G-proteins as well as the inhibitors of protein kinases, the novel nucleosides, nucleotides, nucleotide mimics and/or their prodrugs of the present
20 invention may also be useful for the treatment of a wide range of other diseases and disorders such as inflammatory diseases, autoimmune diseases, Type 2 diabetes, and cardiovascular diseases.

In order to overcome drug resistance, combination therapies are widely used in the
25 treatment of infectious diseases and proliferative disorders. The nucleosides, nucleotides, nucleotide mimics and/or their prodrugs of the present invention may be therapeutically administered as a single drug, or alternatively may be administered in combination with one or more other active chemical entities to form a combination therapy. The other active chemical entities may be a small molecule, a polypeptide, or a polynucleotide.

30

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For instance, compounds of this invention may be particularly useful when used in combination with other agents known to exert an antiviral effect. For example, combination with immunomodulatory/antiviral agents such as interferons, interferon derivatives and other large or small molecules known to modulate host immune responses may be beneficial. Similarly, combinations of compounds of this invention with IMPDH

5 inhibitors (e.g. ribavirin), antiviral nucleosides, antiviral non-nucleosides (e.g. polymerase inhibitors, protease inhibitors) could augment the activity of the bicyclic nucleosides when administered alone.

10 The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to prepare and use the compounds disclosed and claimed herein.

All references mentioned herein are incorporated herein by reference in their entirety.

15

The abbreviations that may be used herein, including the Schemes and experimental section are as follows unless indicated otherwise:

	Bu:	n-butyl
20	Bn	benzyl
	Bz:	benzoyl
	DCM:	dichloromethane
	DIEA:	diisopropylethylamine
	DMF:	dimethylformamide
25	Et:	ethyl
	EtOAc:	ethyl acetate
	Me:	methyl
	MeOH:	methyl alcohol
	MS:	mass spectrometry
30	NMR:	nuclear magnetic resonance
	Ph:	phenyl

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HPLC: high performance liquid chromatography

TEA: triethylamine

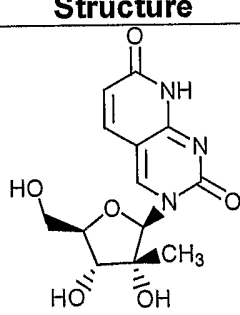
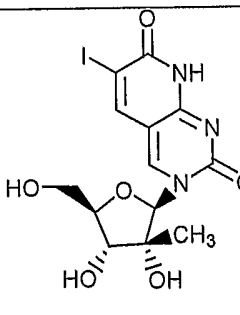
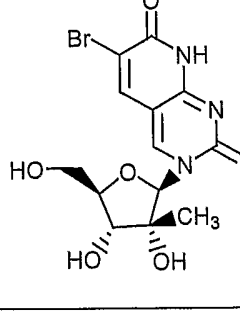
TFA: trifluoroacetic acid

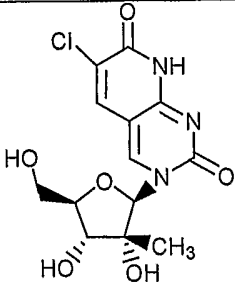
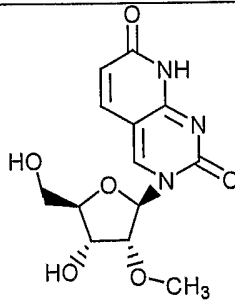
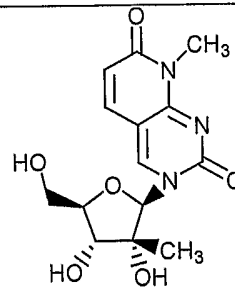
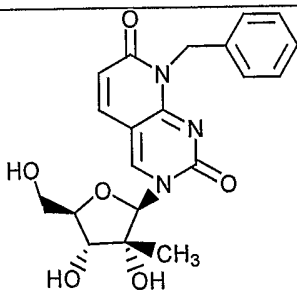
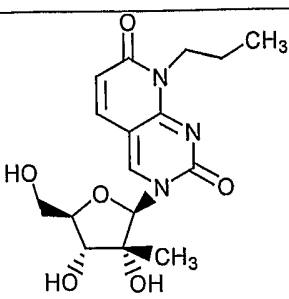
THF: tetrahydrofuran

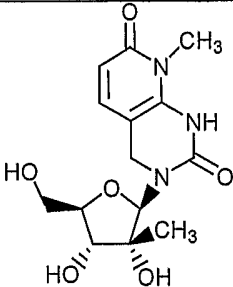
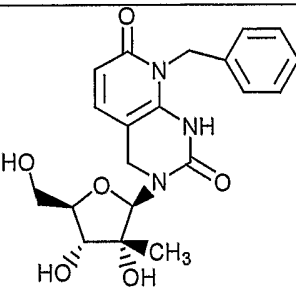
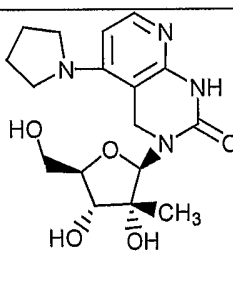
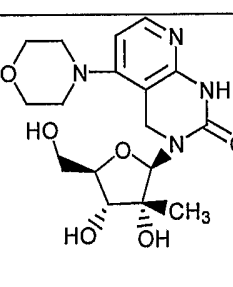
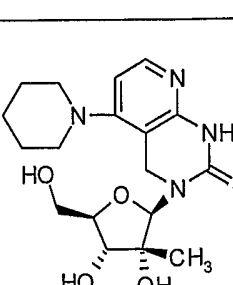
5

The following Examples are offered to illustrate but not to limit the invention.

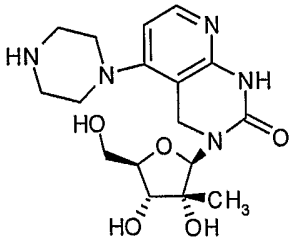
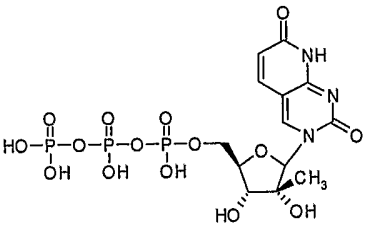
ExamplesSynthesis10 Table 1

Example	Structure	Molec Formula	MWt
1		$C_{13}H_{15}N_3O_6$	309.28
2		$C_{13}H_{14}IN_3O_6$	435.17
3		$C_{13}H_{14}BrN_3O_6$	388.17

Example	Structure	Molec Formula	MWt
4		$C_{13} H_{14} Cl N_3 O_6$	343.72
5		$C_{13} H_{15} N_3 O_6$	309.28
6		$C_{14} H_{17} N_3 O_6$	323.30
7		$C_{20} H_{21} N_3 O_6$	399.40
8		$C_{16} H_{21} N_3 O_6$	351.36

Example	Structure	Molec Formula	MWt
9		$C_{14} H_{19} N_3 O_6$	325.32
10		$C_{20} H_{23} N_3 O_6$	401.42
11		$C_{17} H_{24} N_4 O_5$	364.40
12		$C_{17} H_{24} N_4 O_6$	380.40
13		$C_{18} H_{26} N_4 O_5$	378.43

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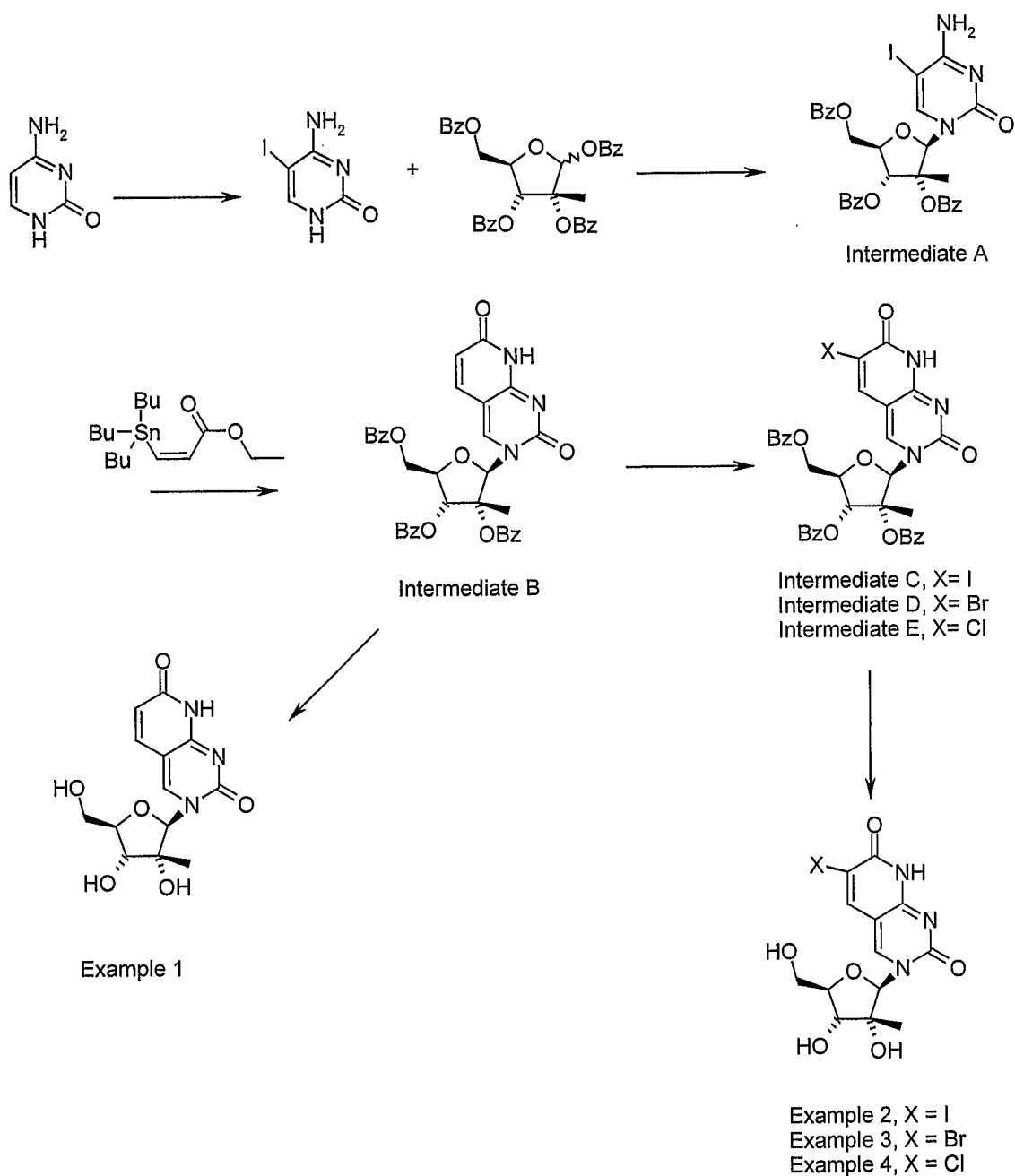
Example	Structure	Molec Formula	MWt
14		C ₁₇ H ₂₅ N ₅ O ₅	379.41
15		C ₁₃ H ₁₈ N ₃ O ₁₅ P ₃	549.21

Experimental Data

¹H and ³¹P NMR spectra were recorded on either a Bruker Avance DRX 400, AC 200 or
5 AM 300 spectrometer. Spectra were recorded in CDCl₃, d₆-acetone, CD₃OD or d₆-DMSO using the residual solvent peak as a reference. Chemical shifts are reported on the δ scale in parts per million (ppm) using the following conventions to assign the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet) and prefixed b (broad). Mass spectra (ESI) were recorded on a Finnigan LCQ Advantage spectrometer. All microwave
10 reactions were carried out in a CEM Discover microwave reactor. Flash and radial chromatography was performed on 40-63μm silica gel 60 (Merck No. 9385). Preparative HPLC was carried out using a Gilson 322 pump with a Gilson 215 liquid handler and a HP1100 PDA detector. HPLC systems employed Phenomenex C8(2) columns using either acetonitrile or acetonitrile containing 0.06% TFA in water or water containing 0.1% TFA.
15 Alternatively, a Phenomenex C18 column was used with acetonitrile and aqueous 1M triethylammonium acetate (primarily for phosphate nucleotides).

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Scheme 5



Intermediate A

5

N,O-Bis(trimethylsilyl)acetamide (7.17mL) was added to 5-iodocytidine (2.32g) in dry acetonitrile (15mL) and the mixture was heated under argon at 80°C for 30mins. A suspension of commercially available 1,2,3,5-tetra-O-benzoyl-2-C-methyl- α/β -D-

- 52 -

ribofuranose (5.16g) in dry acetonitrile (40mL) was added and the mixture heated for 1h. SnCl₄ (1.71mL) was added cautiously and heating continued for 2hrs. The reaction was cooled to ambient temperature, poured into an ice cold solution of saturated aqueous sodium bicarbonate and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried and evaporated in-vacuo. The residue was purified by flash chromatography on silica eluting with 3%MeOH/DCM. The product was obtained as a gum (3.36g). MS m/z ([M+H]⁺) 695.7; ([2M+H]⁺) 1390.8.

Intermediate B

10

A degassed solution of intermediate A (1.39g) and (Z)-ethyl-3-(tributylstannyl) propenoate (1.56g) was stirred in dry DMF under argon for 10mins. CuI (76mg) and PdCl₂(PPh₃)₂ (140mg) were added and the mixture heated at 70°C under argon for 16hrs. The reaction was cooled to ambient temperature, diluted with water (100mL) and filtered. The residue was washed with water, dissolved in EtOAc and washed again with water. The organic solution was dried (MgSO₄) and the solvent evaporated in-vacuo to provide a brown gum. The aqueous mother liquor was also extracted with EtOAc (x2) and the combined organics dried (MgSO₄), and evaporated in-vacuo. The combined crude extracts were purified by radial chromatography on silica eluting with 3%-5% MeOH/DCM to give the required product as an oil, which, on trituration with ether afforded a yellow crystalline solid (70mg). MS m/z ([2M+H]⁺) 1243.5. Further product was available from the mother-liquor.

20

Preparation of Intermediates C, D, E

25 Preparation of Intermediate C is an example of the general method.

A mixture of Intermediate B (125mg) and N-iodosuccinimide (90.6mg) in dry acetonitrile (1.50mL) was heated in a microwave reactor at 120°C for 30mins (initial power 200W). The solution was evaporated in-vacuo, dissolved in EtOAc and washed with 10% sodium metabisulphite, brine, and evaporated in-vacuo. The crude material was purified by radial

30

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chromatography on silica eluting with 3% MeOH/DCM to yield the required product (120mg). MS m/z ($[2M+H]^+$) 1494.3.

Similarly for Intermediates D and E.

5

Intermediate D

Intermediate B (62mg) yielded intermediate D (45mg). MS m/z ($[2M+H]^+$) 1400.6, 1401.6, 1403.6.

10

Intermediate E

Intermediate B (62mg) yielded 62mg intermediate D. MS m/z ($[2M+H]^+$) 1310.6, 1311.7, 1313.7.

15

Preparation of Examples 1-4

Preparation of Example 1 is an example of the general method.

20 Example 1

Intermediate B (60mg) was suspended in dry methanol (1mL) under argon. A freshly prepared solution of 1M sodium methoxide in methanol (0.5mL) was added and the reaction stirred for 18hrs. Evaporation of the solvent in-vacuo with minimal heating and purification by radial chromatography on silica eluting with 20%MeOH/DCM yielded the required compound as a crystalline solid.

25

MS m/z ($[M+H]^+$) 309.9. 1H NMR ($CD_3OD + D_2O$) δ 9.24 (s, 1H), 7.61 (d, 1H), 6.23 (d, 1H), 6.11 (s, 1H), 4.08-4.00 (m, 2H), 3.93-3.83 (m, 2H), 1.12 (s, 3H).

30

Similarly for Examples 2 and 3.

Example 2

Intermediate C (12mg) yielded Example 2 (1.70mg)

5

MS m/z ($[M+H]^+$) 435.7, ($[2M+H]^+$) 870.4. 1H NMR (CD_3OD) δ 9.26 (s, 1H), 8.18 (s, 1H), 6.10 (s, 1H), 4.07-4.00 (m, 2H), 3.95-3.82 (m, 2H), 1.12 (s, 3H).

Example 3

10

Intermediate D (21mg) yielded Example 3 (4.1mg)

MS m/z ($[M+H]^+$) 387.7, 389.7. 1H NMR (CD_3OD) δ 9.28 (s, 1H), 7.95 (s, 1H), 6.10 (s, 1H), 4.07-3.99 (m, 2H), 3.89-3.82 (m, 2H), 1.12 (s, 3H).

15

Example 4

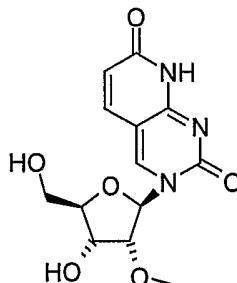
Intermediate E (28mg) was stirred with 7M NH_3 in MeOH at ambient temperature for 18h. The reaction was evaporated to dryness in-vacuo, dissolved in water (2mL) and washed with DCM (x3) and EtOAc. The aqueous phase was evaporated and the residue triturated with ether to yield the required compound as a yellow solid (12mg).

20

MS m/z ($[M+H]^+$) 343.7, 345.7; ($[2M+H]^+$) 686.6, 688.6. 1H NMR (CD_3OD) δ 9.34 (s, 1H), 7.73 (s, 1H), 6.11 (s, 1H), 4.07-3.99 (m, 2H), 3.90-3.82 (m, 2H), 1.12 (s, 3H).

25

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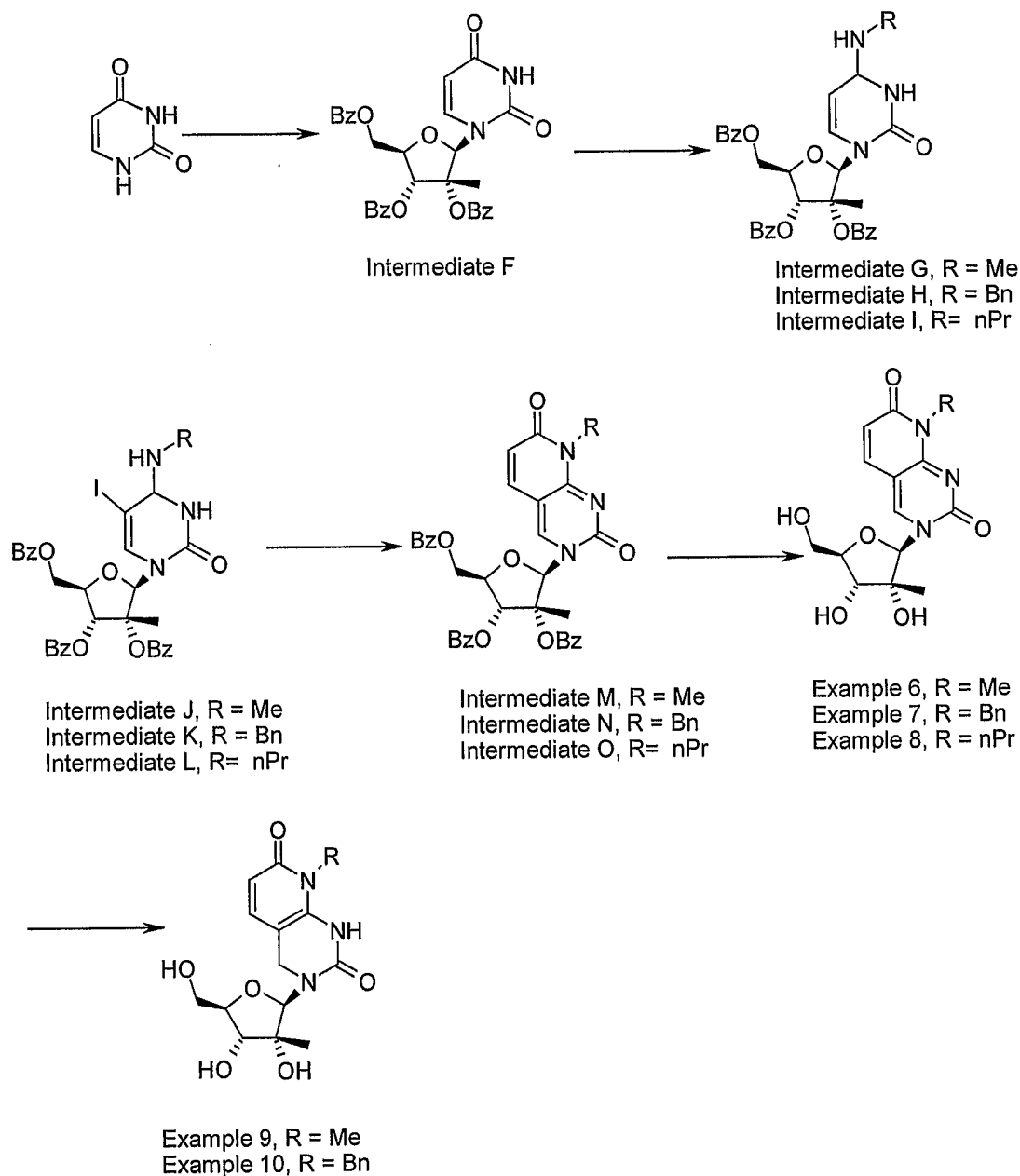
Example 5

Example 5 (10.5mg) was prepared directly from commercially available 5-iodo-2'-*O*-methylcytidine using the method described for intermediate B in scheme 1.

MS m/z ($[M+H]^+$) 309.8; ($[2M+H]^+$) 618.6, ($[2M+Na]^+$) 640.8. 1H NMR ($CD_3OD + D_2O$) δ 9.23 (s, 1H), 7.64 (d, 1H), 6.27 (d, 1H), 5.95 (s, 1H), 4.21-4.17 (m, 1H) 4.06-4.02 (m, 2H), 3.95-3.73 (m, 2H), 3.64 (s, 3H).

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Scheme 6



5 Intermediate F

N,O-Bis(trimethylsilyl)acetamide (6.45mL) and uracil (0.986g) in dry acetonitrile (20mL) were heated under argon at 80°C for 30mins. A suspension of commercially available

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1,2,3,5-tetra-O-benzoyl-2-C-methyl-alpha/beta-D-ribofuranose in dry acetonitrile (80mL) was added and heating continued for 1hr. SnCl₄ was added was added cautiously and heating continued for 5 hrs. The reaction was cooled to ambient temperature, poured into an ice cold solution of saturated sodium bicarbonate (100mL) and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated in-vacuo to provide crude product as a frothy white gum (4.7g) which was used in subsequent reactions without further purification. MS m/z ([M+H]⁺) 571, ([2M+Na]⁺) 1163.

10 Intermediate G

1,2,4-triazole (207mg) was dissolved in dry acetonitrile (5mL) under argon, cooled to 0°C and treated with POCl₃ (75μL). After 5mins, triethylamine (0.60mL) was added and stirring continued for 1h at ambient temperature before addition of Intermediate F in dry acetonitrile (5mL). The reaction was diluted with EtOAc after 90mins and washed successively with saturated NaHCO₃ and brine (each x3). The organic layer was dried (MgSO₄) and evaporated in-vacuo to provide the crude triazole intermediate as a yellow gum (127mg). This gum was suspended in MeOH (5mL) and 2M MeNH₂ in MeOH (0.20mL) added followed by vigorous stirring for 20mins. After this time, volatile materials were evaporated in-vacuo and the residue purified by radial chromatography on silica eluting with 2% MeOH/DCM to give the required product as a gum (46mg). MS m/z ([M+H]⁺) 583.9, ([2M+H]⁺) 1166.9.

Intermediate H

25

The crude triazole intermediate (621mg) was prepared using the method described for intermediate G. This gum was suspended in dry ethanol (10mL) before addition of benzylamine (164μl). After stirring for 1hr at ambient temperature the solvent was removed in-vacuo and the residue purified by radial chromatography on silica eluting with 3%-5% MeOH/DCM to give the required product as an oil (424mg). MS m/z ([M+H]⁺) 660.4, 661.4.

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Intermediate I

The crude triazole intermediate (249mg) was prepared using the method described for
5 intermediate G. This gum was suspended in dry methanol (5mL) before addition of *N*-
propylamine (49 μ l). After stirring for 30mins at ambient temperature the solvent was
removed in-vacuo and the residue purified by radial chromatography on silica eluting with
3% MeOH/DCM to give the required product as gum (45mg). MS m/z ($[M+H]^+$) 612.4,
613.4.

10

Intermediates J, K and L were prepared by the general method described previously for
Intermediate C.

Intermediate J

15

Intermediate G (200mg) yielded Intermediate J (87mg)

MS m/z ($[M+H]^+$) 709.7.

20 **Intermediate K**

Intermediate H (188mg) yielded Intermediate K (110mg).

MS m/z ($[M+H]^+$) 785.9.

25

Intermediate L

Intermediate I (130mg) yielded Intermediate L (106mg).

30 MS m/z ($[M+H]^+$) 738.2

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Intermediates M, N and O were prepared by the general method described previously for Intermediate B.

Intermediate M

5

A degassed solution of intermediate J (100mg) and (*Z*)-ethyl-3-(tributylstannyl) propenoate (110mg) was stirred in dry DMF under argon for 10mins. CuI (5.5mg) and PdCl₂(PPh₃)₂ (10mg) were added and the mixture heated at 70°C under argon for 16hr. The solvent was evaporated in-vacuo and the residue partitioned between EtOAc and water. The aqueous
10 phase was further extracted with EtOAc (x2) and the combined organic extracts dried (MgSO₄) and evaporated in-vacuo. The crude product was purified by radial chromatography on silica eluting with 3%MeOH/DCM to provide a yellow gum (56mg). MS m/z ([M+H]⁺) 635.8, ([2M+H]⁺) 1270.7.

15 Intermediate N

Intermediate K (120mg) yielded Intermediate N (19mg).

MS m/z ([M+H]⁺) 711.7, ([2M+H]⁺) 1422.5.

20

Intermediate O

Intermediate L (105mg) yielded Intermediate O (19mg).

25 MS m/z ([M+H]⁺) 663.9, ([2M+H]⁺) 1326.9.

Example 6

Intermediate M (36mg) was stirred with 7M NH₃ in MeOH (3mL) at ambient temperature
30 for 4hrs. The reaction was evaporated to dryness in-vacuo and the residue purified by

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radial chromatography on silica eluting with DCM/MeOH/25%NH₃ 90:9:1 to yield the required compound as a yellow solid (6mg).

MS m/z ([M+H]⁺) 323.8. 1H ¹H NMR (CD₃OD) δ 9.28 (s, 1H), 7.51 (d, 1H), 6.33 (d, 1H),
5 6.12 (s, 1H), 4.08-3.99 (m, 2H), 3.91-3.86 (m, 2H), 3.53 (s, 3H), 1.12 (s, 3H).

Similarly for Examples 7 and 8.

Example 7

10

Intermediate N (19mg) yielded Example 7 (3.9mg).

MS m/z ([M+H]⁺) 399.9. 1H ¹H NMR (CD₃OD) δ 9.30 (s,1H), 7.54 (d, 1H), 7.40-7.35 (m,
2H), 7.26-7.17 (m, 3H), 6.36 (d, 1H), 6.12 (s, 1H), 5.44 (s, 1H), 4.07-3.99 (m, 2H), 3.91-
15 3.81 (m, 2H), 1.12 (s, 3H).

Example 8

Intermediate O (38mg) yielded Example 8 (8.0mg).

20

MS m/z ([M+H]⁺) 351.8. 1H ¹H NMR (CD₃OD) δ 9.30 (s,1H), 7.50 (d, 1H), 6.32 (d, 1H),
6.12 (s, 1H), 4.21-4.16 (m, 2H), 4.08-3.99 (m, 2H), 3.91-3.83 (m, 2H), 1.74-1.61 (m, 2H),
1.12 (s, 3H), 0.93 (t, 3H).

25 Example 9

Example 6 (20mg) was dissolved in methanol (3mL) and NH₄Cl (10mg) in water (0.2mL) was added followed by NaBH₄ (10mg). After 10mins the reaction was evaporated to dryness in-vacuo and the residue dissolved in water (3mL) and washed with DCM. The
30 aqueous extract was then purified by preparative HPLC to afford the product as an oil (4.23mg).

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MS m/z ($[M+H]^+$) 326.0. 1H NMR (CD_3OD) δ 7.26 (d, 1H), 6.10 (d, 1H), 5.84 (s, 1H), 4.60 (d, 1H), 3.98 (d, 1H), 3.92-3.68 (m, 4H), 3.50 (s, 3H), 1.22 (s, 3H).

5 Similarly for Example 10.

Example 10

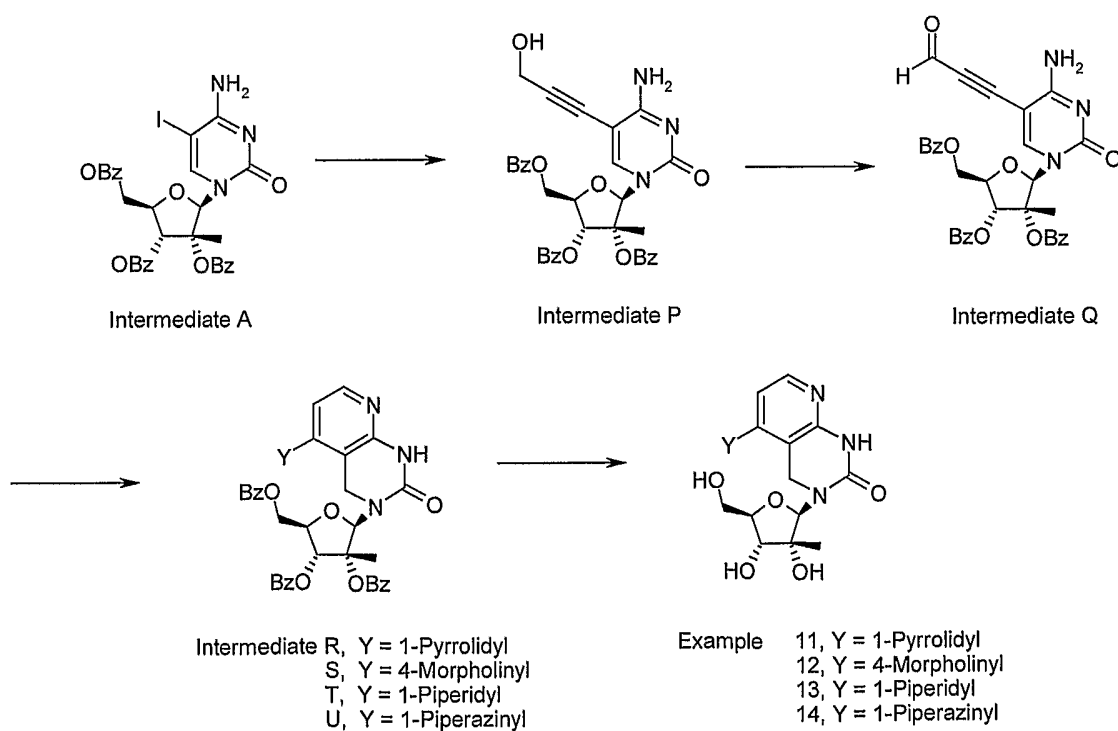
Example 7 (20mg) yielded Example 10 (7.0mg).

10

MS m/z ($[M+H]^+$) 402.0. 1H NMR (CD_3OD) δ 7.28-7.18 (m, 6H), 6.08 (d, 1H), 5.75 (s, 1H), 5.45 (d, 1H), 5.38 (d, 1H), 4.62 (d, 1H), 4.01 (d, 1H), 3.93-3.89 (m, 1H), 3.80-3.68 (m, 3H), 1.19 (s, 3H).

15

Scheme 7



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Intermediate P

A degassed solution of intermediate A (695mg) and propargyl alcohol (175 μ l) was stirred in dry DMF (7mL) under argon. CuI (38mg) and PdCl₂(PPh₃)₂ (70mg) were added
5 followed by TEA (278 μ l) and the mixture stirred at ambient temperature for 18hrs. The solvent was evaporated in-vacuo and the residue partitioned between EtOAc and water. The organic layer was washed with water, dried (MgSO₄) and evaporated in-vacuo. The crude product was purified by radial chromatography on silica eluting with DCM then 5-10% MeOH/DCM to provide a gum (257mg). MS m/z ([M+H]⁺) 624.0, ([2M+H]⁺)
10 1247.1.

Intermediate Q

Intermediate P (248mg) was suspended in DCM (10mL) and treated with Dess-Martin
15 periodinane (338mg) at ambient temperature. The reaction was diluted with DCM after 2hrs and washed with saturated aqueous NaHCO₃. The organic phase was evaporated in-vacuo and the residue purified by radial chromatography on silica eluting with 5-10% MeOH/DCM to provide the product as a gum (263mg). MS m/z ([M+H]⁺) 621.8, ([2M+H]⁺) 1242.9.

20

Intermediate R

Intermediate Q (30mg) and pyrrolidine (14mg) in acetonitrile (0.5mL) were heated in a microwave reactor at 70°C for 10mins (initial power 200W). The solvent was evaporated
25 in-vacuo and the residue dissolved in EtOAc, washed with water then 1M HCl. The organic layer was washed with water, dried (MgSO₄) and evaporated in-vacuo to yield crude cyclised product (28mg) used in the next step without further purification. The material was dissolved in MeOH (2mL) and NaBH₃CN (13mg) was added. After 1hr the solvent was evaporated in-vacuo and the residue dissolved in EtOAc. The organic layer
30 was washed successively with saturated aqueous NaHCO₃ and water, dried (MgSO₄) and

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evaporated in-vacuo. The residue was purified by radial chromatography on silica eluting with 5%MeOH/DCM to yield the product as a gum (17mg). MS m/z ($[M+H]^+$) 677.2.

Intermediates S, T and U were prepared by the general method described for Intermediate R using the appropriate amine and substituting $NaBH_4$ for $NaBH_3CN$.

Intermediate S

Intermediate Q (40mg) yielded Intermediate S (21mg).

10

MS m/z ($[M+H]^+$) 693.1.

Intermediate T

15 Intermediate Q (62mg) yielded Intermediate T (42mg).

MS m/z ($[M+H]^+$) 691.2, ($[2M+H]^+$) 1381.0

Intermediate U

20

Intermediate Q (62mg) yielded Intermediate U (28mg).

MS m/z ($[M+H]^+$) 692.1.

25 Example 11

Intermediate R (10mg) was stirred with 7M NH_3 in MeOH (1mL) at ambient temperature for 18hrs. The reaction was evaporated to dryness in-vacuo and the residue dissolved in water and washed with DCM. The aqueous layer was then subjected directly to preparative HPLC. This process afforded the target compound as an oil (1.3mg).

30

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MS m/z ($[M+H]^+$) 365.1, ($[2M+H]^+$) 728.8.

1H 1H NMR (CD_3OD) δ 7.69 (d, 1H), 6.34 (d, 1H), 5.92 (s, 1H), 5.20 (d, 1H), 4.31 (d, 1H), 3.98-3.90 (m, 1H), 3.80-3.65 (m, 3H), 3.50-3.35 (m, 4H), 1.98-1.90 (m, 4H), 1.20 (s, 3H).

The general method for Example 11 was applied to the preparation of Examples 12-14.

Example 12

10

Intermediate S (20mg) yielded compound 12 (2.4mg) after purification by preparative HPLC.

MS m/z ($[M+H]^+$) 381.1, ($[2M+Na]^+$) 782.8.

15

1H 1H NMR (CD_3OD) δ 7.97 (d, 1H), 6.68 (d, 1H), 5.96 (s, 1H), 4.48 (d, 1H), 4.12 (d, 1H), 3.96-3.71 (m, 8H), 3.27-2.87 (m, 4H), 1.12 (s, 3H).

Example 13

20

Intermediate T (42mg) yielded 4.27mg compound 13 (4.3mg) after purification by preparative HPLC.

MS m/z ($[M+H]^+$) 379.2, ($[2M+H]^+$) 756.9.

25

1H 1H NMR (CD_3OD) δ 7.93 (d, 1H), 6.65 (d, 1H), 5.97 (s, 1H), 4.42 (d, 1H), 4.07 (d, 1H), 3.93 (d, 1H), 3.82-3.71 (m, 3H), 3.04-2.87 (m, 4H), 1.86-1.60 (m, 6H), 1.13 (s, 3H).

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Example 14

Intermediate U (27mg) yielded compound 14 (2.1mg) after purification by preparative HPLC.

5

MS m/z ($[M+H]^+$) 380.1, ($[2M+Na]^+$) 780.8.

1H NMR (CD_3OD) δ 8.08 (d, 1H), 6.69 (d, 1H), 5.96, (s, 1H), 4.51 (d, 1H), 4.10 (d, 1H), 3.94-3.51 (m, 6H), 3.27-2.87 (m, 6H), 1.14 (s, 3H).

10

Example 15

Example 1 (31mg) was dried overnight under high vacuum over P_2O_5 and then stirred with trimethyl phosphate (1.7mL) at ambient temperature with oven-dried molecular sieves (4Å) for 16hrs under argon. The reaction was cooled to 0°C, $POCl_3$ (31 μ l) added and stirring continued for 2 hours before addition of Bu_3N (72ul) followed by acetonitrile (0.5mL) and tributylammonium pyrophosphate (190mg). After a further 2hrs at 0°C the reaction was quenched by pouring into ice-cold 1M triethylammonium bicarbonate buffer (10mL, pH 8.5) and the aqueous layer washed with Et_2O (3x10mL). The aqueous material was then lyophilised to give a white solid which was purified by preparative HPLC to afford the product (1.67mg).

15

20

MS m/z ($[M-H]^-$) 547.6, ($[M+3TEA+H]^+$) 852.5.

^{31}P NMR (D_2O) δ - 8.14 (m, 1P), -10.69 (m, 1P), -21.65 (m, 1P).

25

Biological Data***In vitro* anti-HCV dose-response and cytotoxicity****HCV Replicon Assay**

30 The antiviral activity of test compounds were assayed in the stably HCV RNA-replicating cell line, AVA5, derived by transfection of the human hepatoblastoma cell line, Huh7

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(Blight, *et al.*, 2000, *Sci.* 290:1972). Concentrations of compounds were added to dividing cultures once daily for three days and intracellular HCV RNA levels and cytotoxicity assessed 24 hours after the last dose of compound.

5 Intracellular HCV RNA levels were measured using standard blot hybridization techniques using triplicate cultures and levels of β -actin RNA were used to normalize HCV RNA levels in each sample. Cytotoxicity was measured using an established neutral red dye uptake assay (*B. E. Korba and J. L. Gerin. 1992. Antivir. Res. 19, 55-70*) and the 50% effective antiviral concentrations (EC_{50}) and cytotoxic concentrations (CC_{50}) were
10 calculated using a computer program for curve fitting.

Examples such as 1-14 were typically active in the replicon assay in the range 1 to >1000 μ M and cytotoxic in the range 30 to >100 μ M.

15 ***HCV Polymerase inhibition assay***

HCV 3'UTR RNA template was synthesized, gel purified and quantified by spectrophotometry. The kinetic constant, K_m , was determined for the RNA template and for each GTP, CTP, ATP and UTP using a non-linear least square fit of initial rates as a
20 function of substrate concentration assuming Michaelis-Menten kinetics.

Standard RdRp assays consisted of 30nM RNA template and 25nM HCV NS5b Δ 21 (genotype 1b) (Replizyme Ltd) in a 50 μ L reaction mixture containing 20mM Tris-HCl, 5mM MgCl₂, 3mM DTT, 0.05% BSA, 22nM GTP, 600nM ATP, 15nM CTP, 30nM UTP
25 and 3nM [α -³³P]GTP. Elongation reactions were initiated by the addition of NTPs and proceeded for 30 mins at 25°C. Reactions were quenched by the addition of 0.2 M EDTA and product formation was collected by filtration through Multiscreen plates (Millipore). Quantification of product formation was performed using TopCount (Perkin Elmer).

30 The inhibitor concentration at which the enzyme catalyzed rate is reduced by half (IC_{50}) was determined using a computer program for curve fitting

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Examples such as 15 were typically inhibitory of NS5b in the range 100 to >1000 μ M.

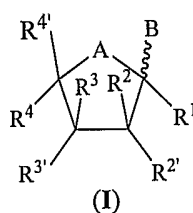
The reference to any prior art in this specification is not, and should not be taken as, an
5 acknowledgment or any form of suggestion that that prior art forms part of the common
general knowledge.

Throughout this specification and the claims which follow, unless the context requires
otherwise, the word "comprise", and variations such as "comprises" and "comprising", will
10 be understood to imply the inclusion of a stated integer or step or group of integers or steps
but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS:

1. A method for the treatment of a microbial infection comprising administering an effective amount of a compound of the formula (I) which may be a D- or L-nucleoside or
 5 nucleotide, or a pharmaceutically acceptable salt thereof,



wherein:

- 10 A is O, S, CH₂, CHF, CF₂ or NR;

R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, halogen, OH, N₃, CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl,
 15 optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkyloxy, optionally substituted alkenyloxy, optionally substituted alkynoxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted arylalkoxy, optionally substituted
 20 heterocycloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkoxy, optionally substituted cycloalkenoxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted
 25 oxyacylimino, optionally substituted aminothioacyl, optionally substituted thioacylamino, optionally substituted aminosulfinyl, optionally substituted aminosulfonyl, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacyloxy, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally

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substituted phosphorylamino, optionally substituted sulfinyl, optionally substituted sulfonyl, optionally substituted sulfinylamino, optionally substituted sulfonylamino, optionally substituted oxysulfinylamino, and optionally substituted oxysulfonylamino, or R² and R^{2'} together or R³ and R^{3'} together represents =O, =S, or =L-Y' where L is N, CH,
 5 CF, CCl or CBr and Y' is H, halogen, N₃, methyl, ethyl or CN;

R⁴ is -CY₂SH, -CY₂OH, -CY₂NH₂, or -L'-R⁵;

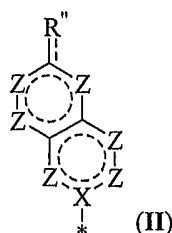
L' is selected from the group consisting of -CY₂-, -CY₂CY₂-, -CY₂OCY₂-, -CY₂SCY₂- and
 10 -CY₂NHCY₂-;

each Y is independently selected from the group consisting of H, F, Cl, Br, OR, C₁-C₆alkyl, C₂-C₆alkenyl and C₂-C₆alkynyl, wherein C₁-C₆alkyl, C₂-C₆alkenyl, and C₂-C₆alkynyl may be optionally substituted with one or more groups selected from F, Cl, Br,
 15 OH, COOH, COOCH₃, SH, SCH₃, NH₂, NHCH₃, N(CH₃)₂, CN, NO₂, C(O)NH₂, C(O)NHCH₃, N₃, C(S)NH₂, OCH₃, and OCH₂CH₃;

R⁵ is selected from the group consisting of OR, NR₂, monophosphate, diphosphate, and triphosphate, or a mono, di or triphosphate mimic;
 20

each R is independently selected from the group consisting of H, CF₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heteroaryl, optionally substituted
 25 heterocyclyl, and optionally substituted arylalkyl;

B is selected from a group of formula (II)



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wherein, if Z is a participant in a π bond (double bond), Z is independently selected from N or C-G; or, if Z is not a participant in a π bond (double bond), Z is independently selected from O, S, Se, NR, NOR, NNR₂, CO, CS, CNR, SO, S(O)₂, SeO, Se(O)₂ or C(G)₂; each G
5 is independently selected from the group consisting of H, halogen, OR, SR, NR₂, NROR, N₃, COOR, CN, CONR₂, C(S)NR₂, C(=NR)NR₂, and R; and

where any two adjacent Z are not both selected from O, S, and Se, or not both selected from CO, CS, CNR, SO, S(O)₂, SeO, and Se(O)₂;

wherein, if X is a participant in a π bond (double bond), X is C; or if X is not a participant
10 in a π bond (double bond), X is CR or N;

wherein, if R" is a participant in a π bond (double bond), R" is O, S, Se, NR, NOR or NNR₂; or if R" is not a participant in a π bond (double bond), R" is OR, SR, F, Cl, R, or SeR; and

dashed lines (---) indicate a possible π or double bond;

15

optionally in combination with one or more antiviral, antibacterial, or antiproliferative agents.

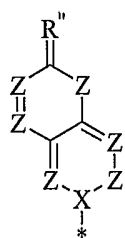
2. A method according to claim 1 for the treatment of a microbial infection which is a
20 viral infection.

3. A method according to claim 2 wherein the viral infection is caused by an RNA virus.

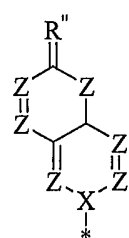
25 4. A method according to claim 3 wherein the viral infection is caused by an RNA virus of the group Flaviviridae.

5. A method according to claim 4 wherein the virus is the hepatitis C virus.

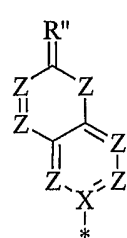
30 6. A method according to any one of claims 1 to 5, wherein the compound of formula (I) has a base structure B selected from the following formulae (XI) to (XXI)



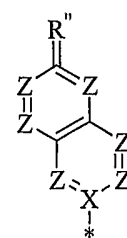
(XI)



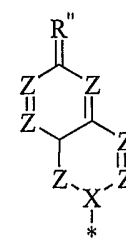
(XII)



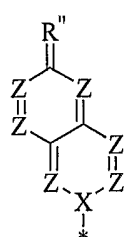
(XIII)



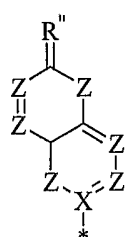
(XIV)



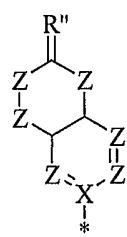
(XV)



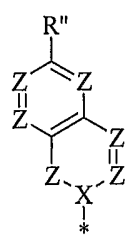
(XVI)



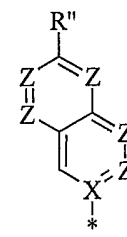
(XVII)



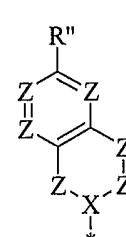
(XVIII)



(XIX)



(XX)



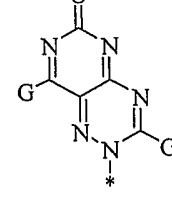
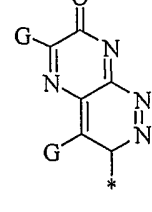
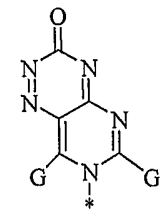
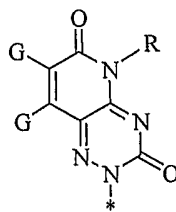
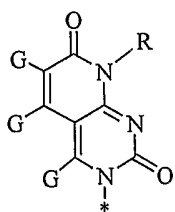
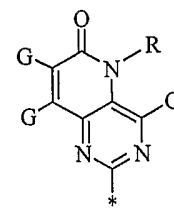
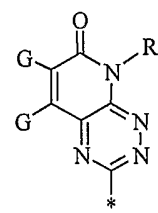
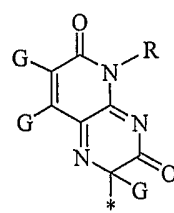
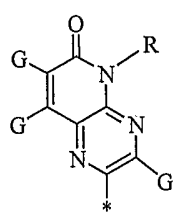
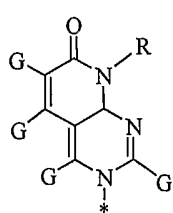
(XXI)

5 wherein Z, X and R'' are as defined in claim 1.

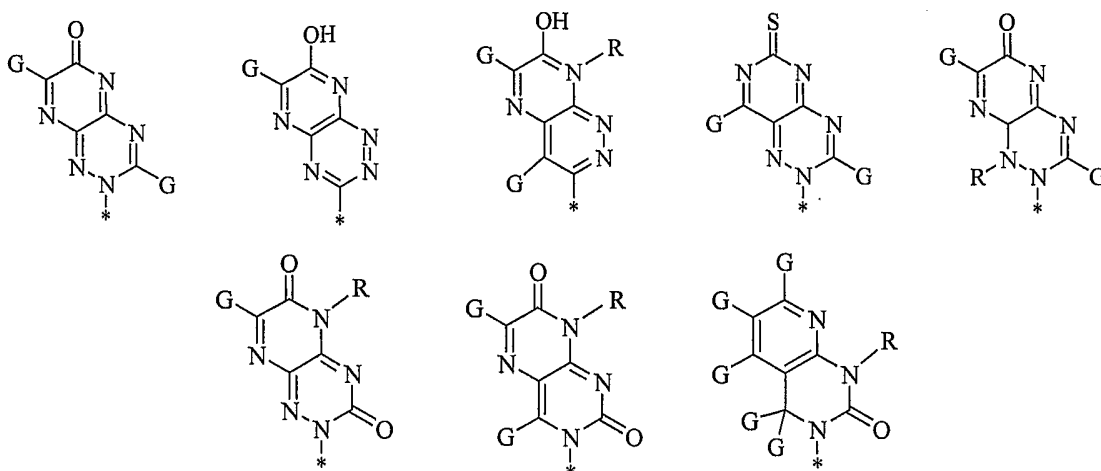
7. A method according to claim 6, wherein X is N.

8. A method according to any one of claims 1 to 5, wherein the compound of formula

10 (I) has a base structure B selected from the following:



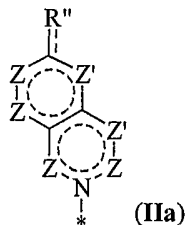
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wherein G and R are as defined in claim 1.

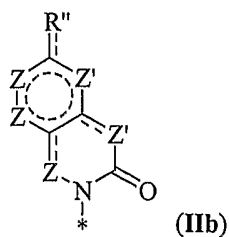
5

9. A method according to any one of claims 1 to 5, wherein the compound of formula (I) has a base structure B represented by formula **IIa**:



10 wherein each Z' is independently N (if a participant in a π bond) or NR (if not a participant in a π bond), and R'', R and Z are as defined in claim 1.

10. A method according to any one of claims 1 to 5, wherein the compound of formula (I) has a base structure B represented by the formula **IIb**:

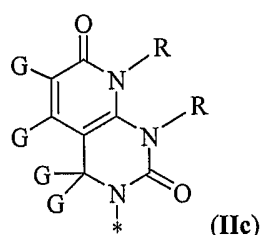


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wherein each Z' is independently N (if a participant in a π bond) or NR (if not a participant in a π bond), and each Z is independently CG (if a participant in a π bond) or $>C(G)_2$ (if not a participant in a π bond), wherein R" and G are as defined in claim 1.

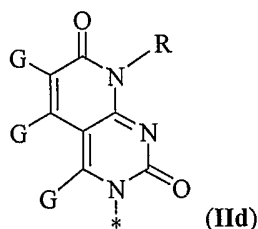
- 5 11. A method according to any one of claims 1 to 5, wherein the compound of formula (I) has a base structure B represented by formula **IIc**:



wherein R and G are as defined in claim 1.

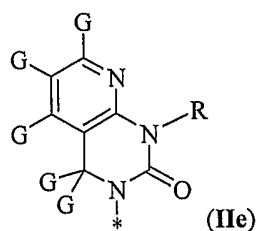
10

12. A method according to any one of claims 1 to 5, wherein the compound of formula (I) has a base structure B represented by the formula **IIId**:



- 15 wherein R and G are as defined in claim 1.

13. A method according to any one of claims 1 to 5, wherein the compound of formula (I) has a base structure B represented by the formula **IIe**:

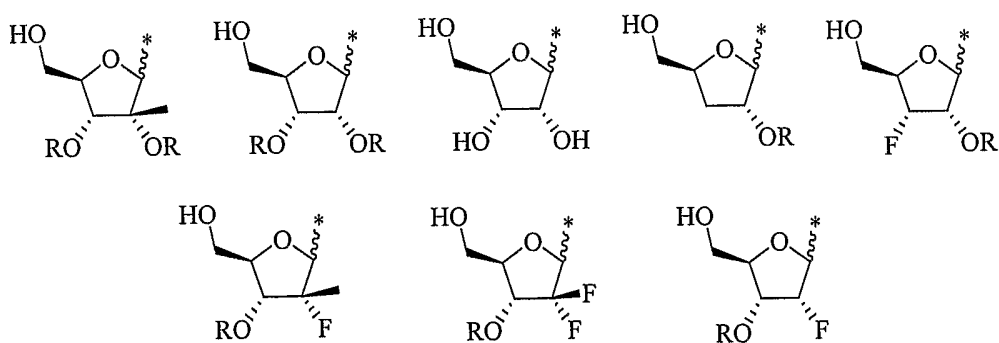


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wherein R and G are as defined in claim 1.

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14. A method according to any one of claims 1 to 13, wherein at least one of R² and R^{2'} of the compound of formula (I) is methyl, hydroxyl or F.
- 5 15. A method according to any one of claims 1 to 13, wherein L' of the compound of formula (I) is -CH₂-.
16. A method according to any one of claims 1 to 13, wherein R⁴ of the compound of formula (I) is selected from -CH₂-OH, -CF₂OH, -CCl₂-OH, -C(CH₃)(CH₃)₂OH, -
 10 CH(CH₃)OH, -CH₂-CH₂-P(O)(OH)₂, -CH₂-CH₂-P(O)(OH)₂, -CH₂SP(O)(OH)₂, -CH₂SH, -CF₂SH, and -CH₂-O-P(O)(OPh)(NHCH(CH₃)(CO₂Me)).
17. A method according to claim 16, wherein R⁴ is -CH₂-OH.
- 15 18. A method according to any one of claims 1 to 13, wherein the sugar moiety of the compound of formula (I) is selected from the following formulae:

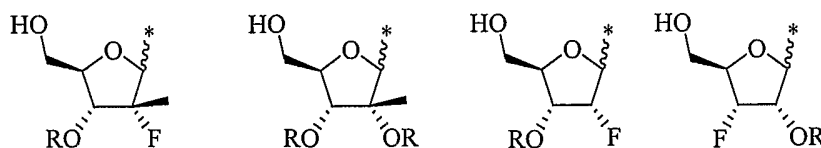


- 20 or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 1.

19. A method according to any one of claims 1 to 13, wherein the sugar moiety of the compound of formula (I) is selected from the following formulae:

25

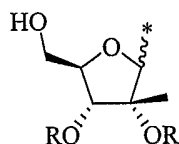
- 75 -



or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 1.

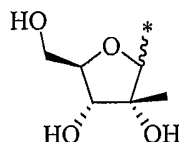
5

20. A method according to any one of claims 1 to 13, wherein the sugar moiety of the compound of formula (I) is represented by the formula:



10 or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 1.

21. A method according to any one of claims 1 to 13, wherein the sugar moiety of the compound of formula (I) is represented by the formula:

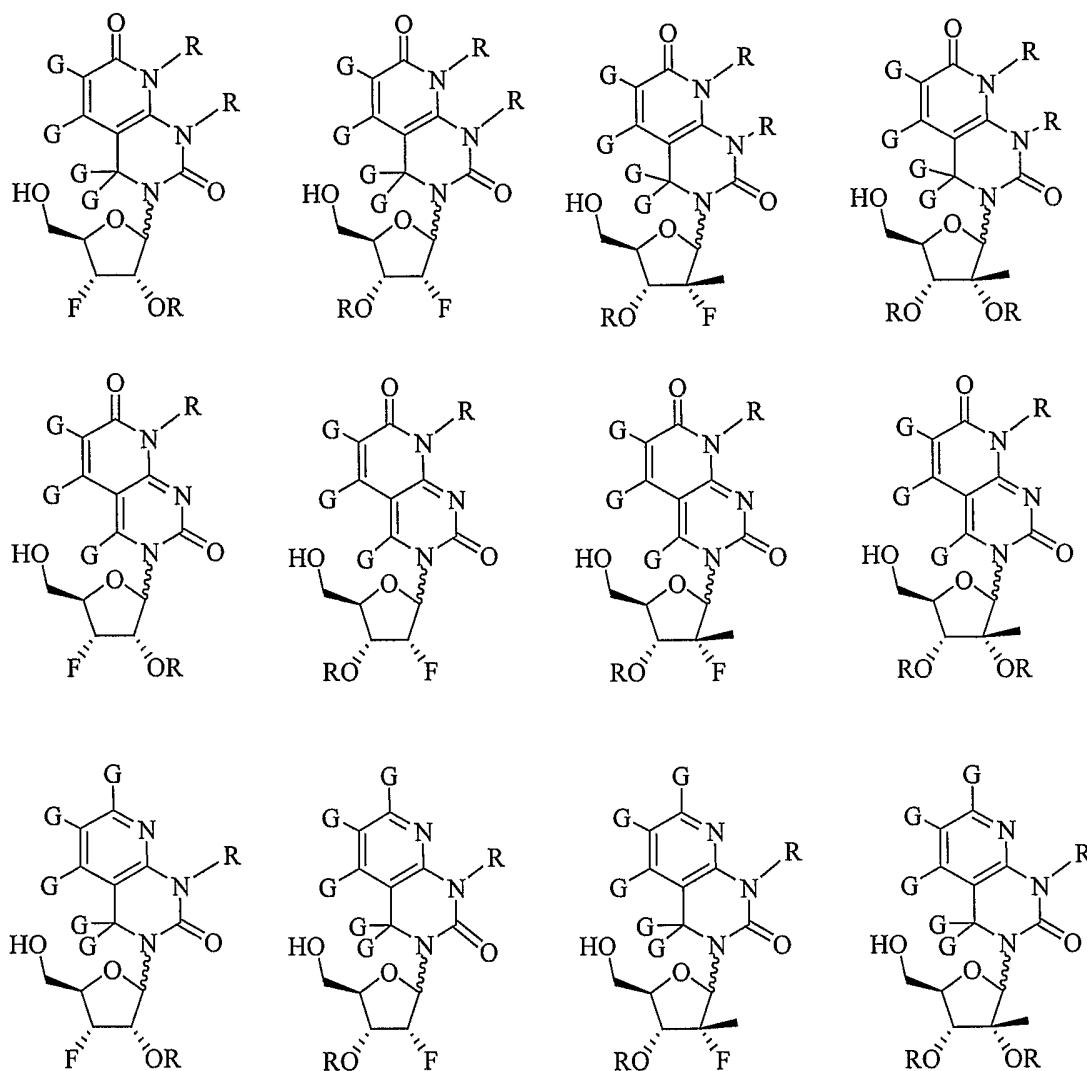


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or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

20 22. A method according to any one of claims 1 to 5, wherein the compound of formula (I) is selected from

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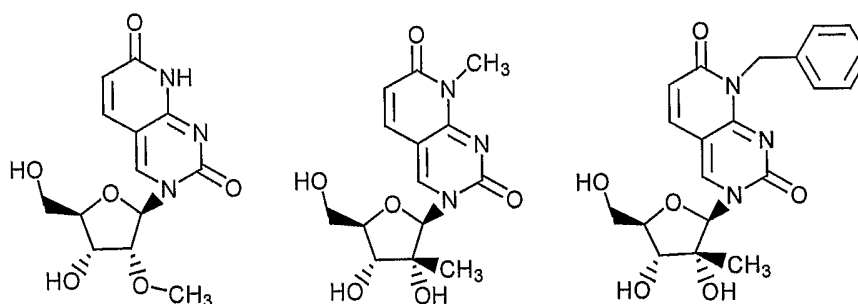
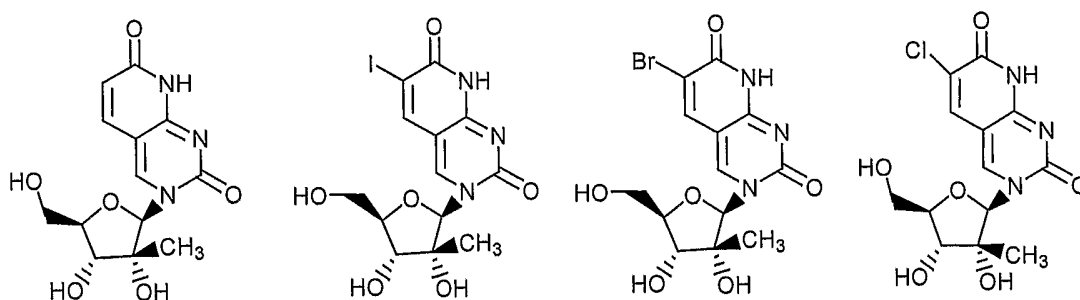
wherein:

- each R on the sugar moiety is independently selected from H, optionally substituted alkyl,
 5 optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl,
 optionally substituted acyl and optionally substituted arylalkyl;
 each R on the base moiety is independently selected from H, optionally substituted alkyl,
 optionally substituted aryl, optionally substituted heteroaryl, optionally substituted
 heterocyclyl, and optionally substituted arylalkyl;
 10 each G is independently selected from H, halogen, CF₃, optionally substituted alkyl,
 optionally substituted aryl, optionally substituted heteroaryl, optionally substituted
 heterocyclyl, and optionally substituted arylalkyl; and

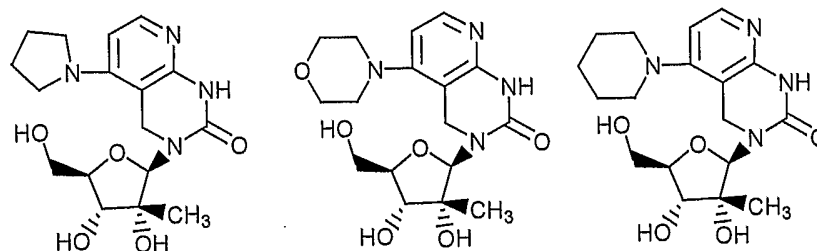
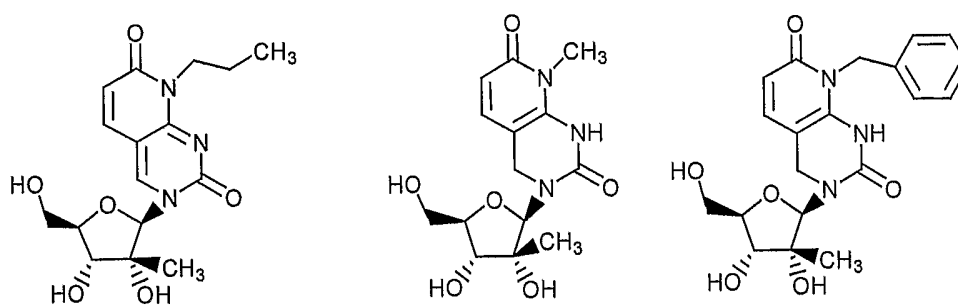
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C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

23. A method according to any one of claims 1 to 5, wherein the compound of formula 5 (I) is selected from

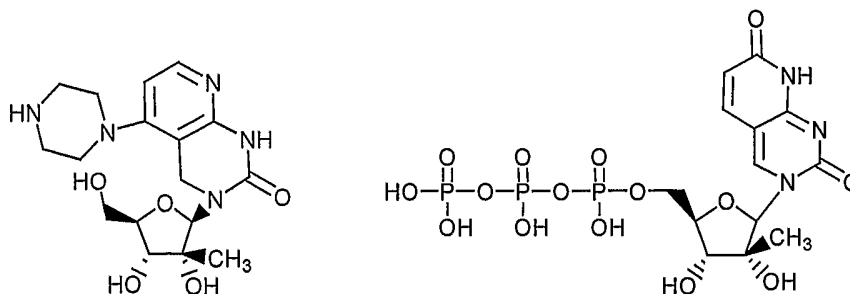


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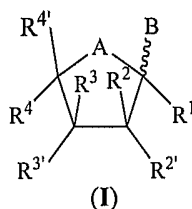


24. A method according to any one of claims 1 to 23 which includes the administration of a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with one or more antiviral agents.

25. A method according to claim 24, wherein the antiviral agents are selected from interferons and interferon derivatives, IMPDH inhibitors, antiviral nucleosides, polymerase inhibitors and protease inhibitors.

10

26. Use of a compound of formula (I) which may be a D- or L-nucleoside or nucleotide, or a salt thereof;



wherein:

15 A is O, S, CH₂, CHF, CF₂ or NR;

R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, halogen, OH, N₃, CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkyloxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted arylalkoxy, optionally substituted

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heterocycloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkoxy, optionally substituted cycloalkenoxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted oxyacylimino, optionally substituted aminothioacyl, optionally substituted thioacylamino, optionally substituted aminosulfinyl, optionally substituted aminosulfonyl, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacyloxy, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted phosphorylamino, optionally substituted sulfinyl, optionally substituted sulfonyl, optionally substituted sulfinylamino, optionally substituted sulfonylamino, optionally substituted oxysulfinylamino, and optionally substituted oxysulfonylamino, or R^2 and R^2 together or R^3 and R^3 together represents =O, =S, or =L-Y' where L is N, CH, CF, CCl or CBr and Y' is H, halogen, N_3 , methyl, ethyl or CN;

15

R^4 is $-CY_2SH$, $-CY_2OH$, $-CY_2NH_2$, or $-L^1-R^5$;

L^1 is selected from the group consisting of $-CY_2-$, $-CY_2CY_2-$, $-CY_2OCY_2-$, $-CY_2SCY_2-$ and $-CY_2NHCY_2-$;

20

each Y is independently selected from the group consisting of H, F, Cl, Br, OR, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl may be optionally substituted with one or more groups selected from F, Cl, Br, OH, COOH, COOCH₃, SH, SCH₃, NH₂, NHCH₃, N(CH₃)₂, CN, NO₂, C(O)NH₂, C(O)NHCH₃, N_3 , C(S)NH₂, OCH₃, and OCH₂CH₃;

25

R^5 is selected from the group consisting of OR, NR₂, monophosphate, diphosphate, and triphosphate, or a mono, di or triphosphate mimic;

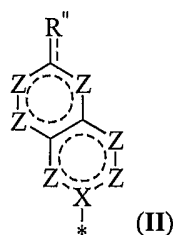
each R is independently selected from the group consisting of H, CF₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally

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substituted aryl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl;

- 5 B is selected from a group of formula (II)



wherein, if Z is a participant in a π bond (double bond), Z is independently selected from N or C-G; or, if Z is not a participant in a π bond (double bond), Z is independently selected
 10 from O, S, Se, NR, NOR, NNR₂, CO, CS, CNR, SO, S(O)₂, SeO, Se(O)₂ or C(G)₂, wherein each G is independently selected from the group consisting of H, halogen, OR, SR, NR₂, NROR, N₃, COOR, CN, CONR₂, C(S)NR₂, C(=NR)NR₂, and R; and

where any two adjacent Z are not both selected from O, S, and Se, or not both selected from CO, CS, CNR, SO, S(O)₂, SeO, and Se(O)₂;

15 wherein, if X is a participant in a π bond (double bond), X is C; or if X is not a participant in a π bond (double bond), X is CR or N;

wherein, if R'' is a participant in a π bond (double bond), R'' is O, S, Se, NR, NOR or NNR₂; or if R'' is not a participant in a π bond (double bond), R'' is OR, SR, F, Cl, R, or SeR; and

20 dashed lines (---) indicate a possible π or double bond;

in the manufacture of a medicament for the treatment of a microbial infection.

27. Use according to claim 26 for the treatment of a microbial infection which is a viral
 25 infection.

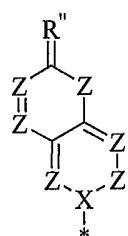
28. Use according to claim 27 wherein the viral infection is caused by an RNA virus.

29. Use according to claim 27 wherein the viral infection is caused by an RNA virus of the group Flaviviridae.

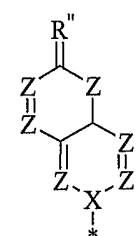
30. Use according to claim 29 wherein the virus is the hepatitis C virus.

5

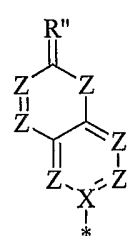
31. A use according to any one of claims 26 to 30, wherein the compound of formula (I) has a base structure B selected from the following formulae (XI) to (XXI)



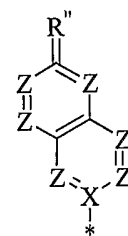
(XI)



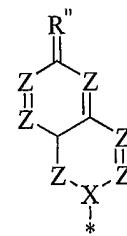
(XII)



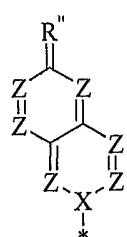
(XIII)



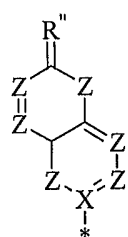
(XIV)



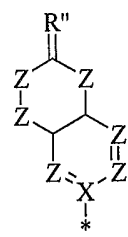
(XV)



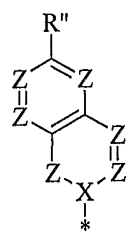
(XVI)



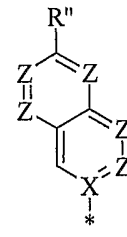
(XVII)



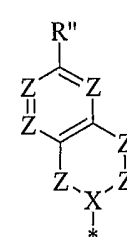
(XVIII)



(XIX)



(XX)



(XXI)

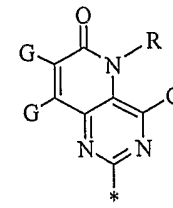
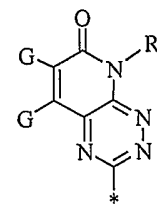
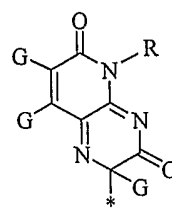
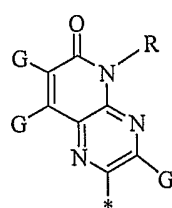
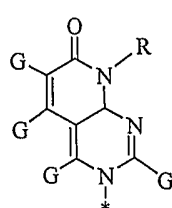
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wherein Z, X and R'' are as defined in claim 26.

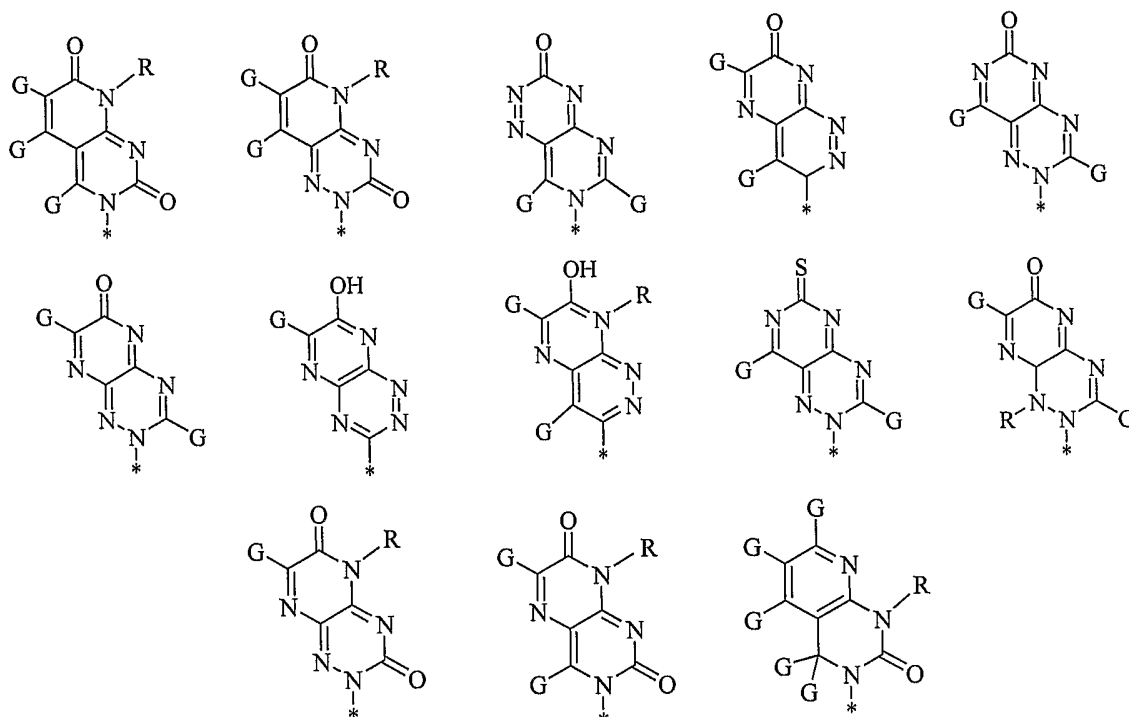
32. A use according to claim 31, wherein X is N.

15

33. A use according to any one of claims 26 to 30, wherein the compound of formula (I) has a base structure B selected from the following:

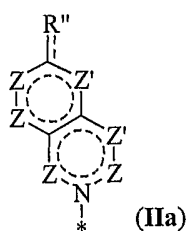


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5 wherein G and R are as defined in claim 26.

34. A use according to any one of claims 26 to 30, wherein the compound of formula (I) has a base structure B represented by formula **IIa**:



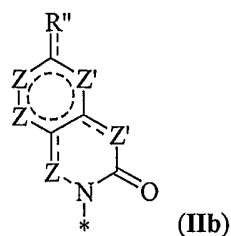
10

wherein each Z' is independently N (if a participant in a π bond) or NR (if not a participant in a π bond), and R'', R and Z are as defined in claim 26.

35. A use according to any one of claims 26 to 30, wherein the compound of formula (I) has a base structure B represented by the formula **IIb**:

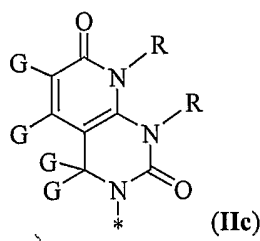
15

- 83 -



wherein each Z' is independently N (if a participant in a π bond) or NR (if not a participant in a π bond), and each Z is independently CG (if a participant in a π bond) or $>C(G)_2$ (if not a participant in a π bond), and wherein R'' and G are as defined in claim 26.

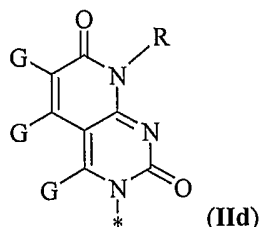
36. A use according to any one of claims 26 to 30, wherein the compound of formula **(I)** has a base structure B represented by formula **IIc**:



10

wherein R and G are as defined in claim 26.

37. A use according to any one of claims 26 to 30, wherein the compound of formula **(I)** has a base structure B represented by the formula **IIId**:

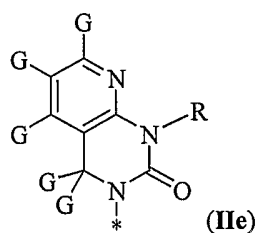


15

wherein R and G are as defined in claim 26.

38. A use according to any one of claims 26 to 30, wherein the compound of formula **(I)** has a base structure B represented by the formula **IIe**:

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wherein R and G are as defined in claim 26.

5 39. A use according to any one of claims 26 to 38, wherein at least one of R² and R^{2'} of the compound of formula (I) is methyl, hydroxyl or F.

40. A use according to any one of claims 26 to 38, wherein L' of the compound of formula (I) is -CH₂-.

10

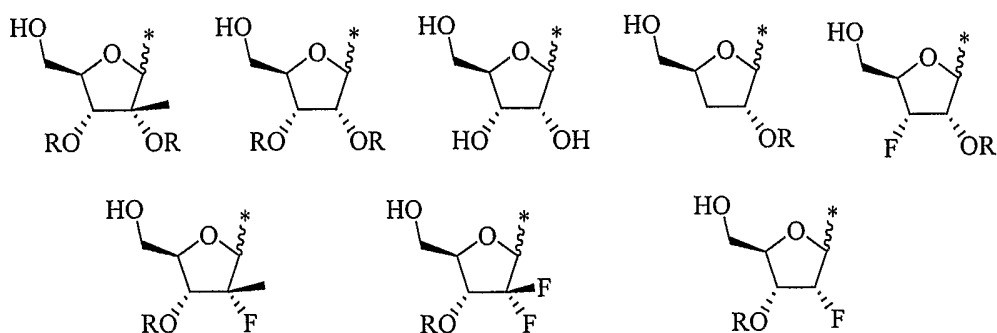
41. A use according to any one of claims 26 to 38, wherein R⁴ of the compound of formula (I) is selected from -CH₂-OH, -CF₂OH, -CCl₂-OH, -C(CH₃)(CH₃)₃OH, -CH(CH₃)OH, -CH₂-CH₂-P(O)(OH)₂, -CH₂-CH₂-P(O)(OH)₂, -CH₂SP(O)(OH)₂, -CH₂SH, -CF₂SH, and -CH₂-O-P(O)(OPh)(NHCH(CH₃))(CO₂Me).

15

42. A use according to claim 41, wherein R⁴ is -CH₂-OH.

43. A use according to any one of claims 26 to 38, wherein the sugar moiety of the compound of formula (I) is selected from the following formulae:

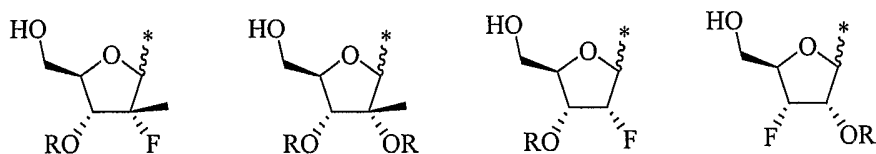
20



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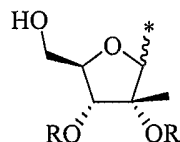
or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 26.

44. A use according to any one of claims 26 to 38, wherein the sugar moiety of the compound of formula (I) is selected from the following formulae:



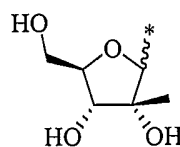
or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 26.

45. A use according to any one of claims 26 to 38, wherein the sugar moiety of the compound of formula (I) is represented by the formula:



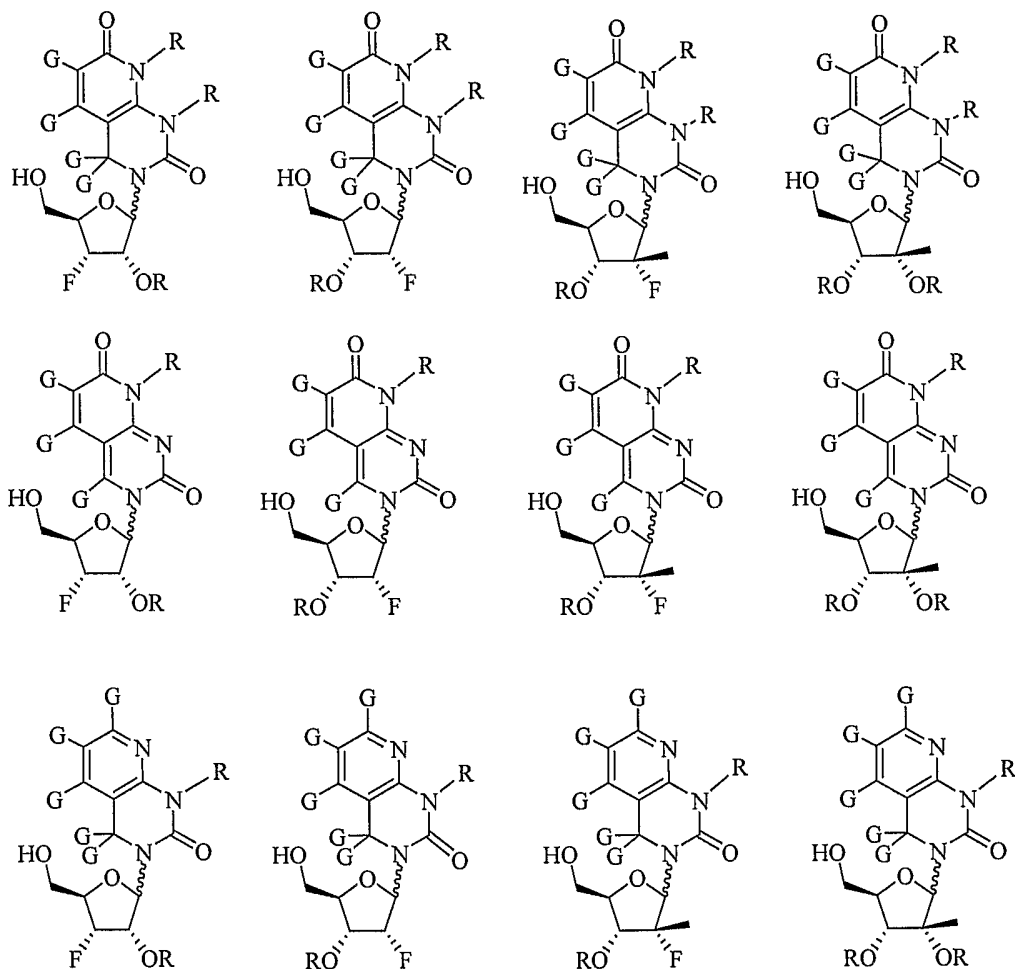
or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 26.

46. A use according to any one of claims 26 to 38, wherein the sugar moiety of the compound of formula (I) is represented by the formula:



or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

47. A use according to any one of claims 26 to 30, wherein the compound of formula (I) is selected from:



5

wherein:

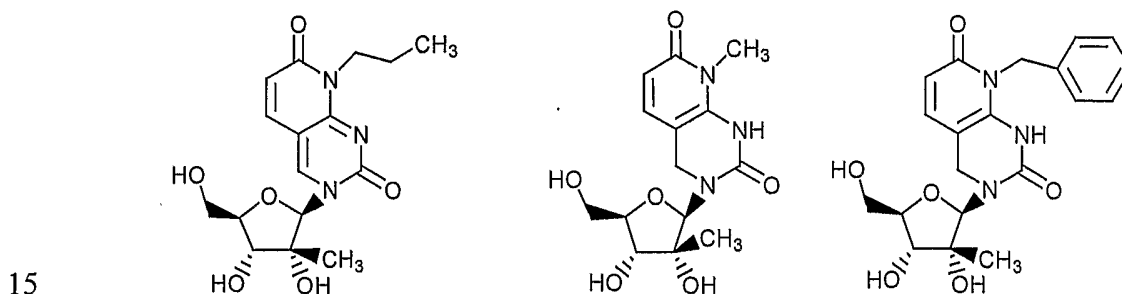
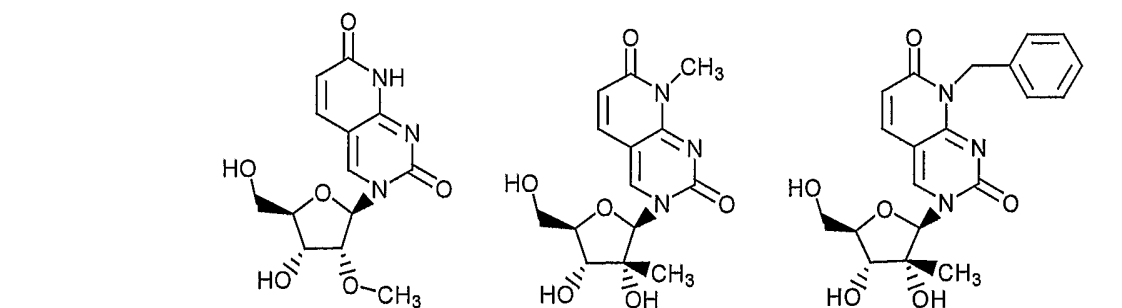
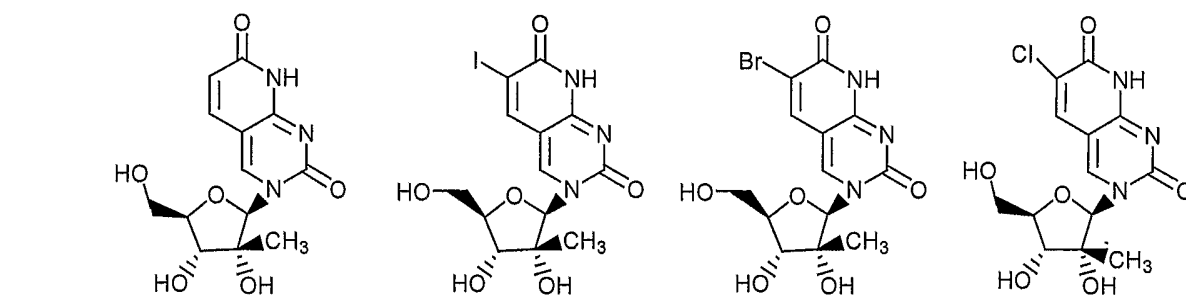
- each R on the sugar moiety is independently selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl and optionally substituted arylalkyl;
- 10 each R on the base moiety is independently selected from H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl;

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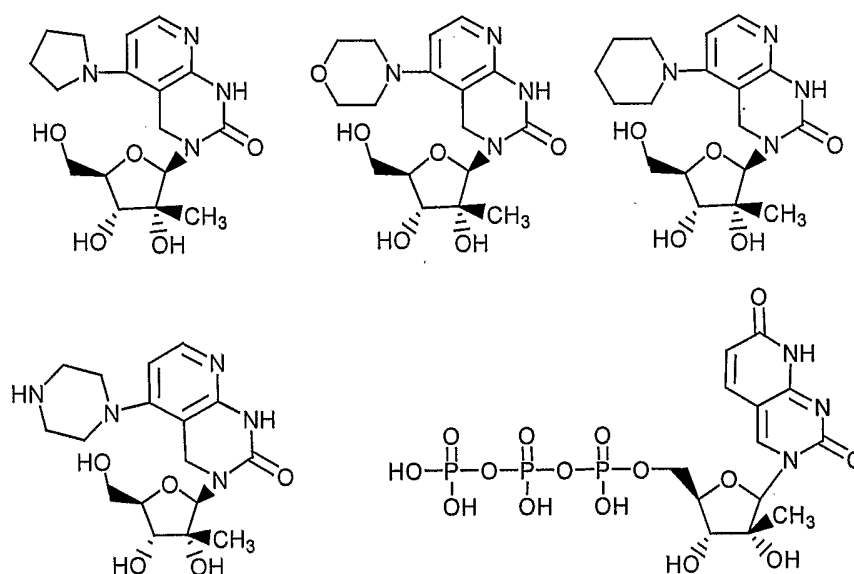
each G is independently selected from H, halogen, CF₃, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl; and

C-5 monophosphate, diphosphate and hiphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

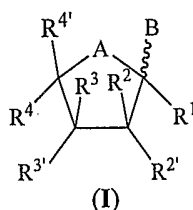
48. A use according to any one of claims 26 to 30, wherein the compound of formula (I) is selected from



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- 5 49. A compound of the formula (I) which may be a D- or L-nucleoside or nucleotide, or a salt thereof;



wherein:

A is O, S, CH₂, CHF, CF₂ or NR;

10

- R¹, R², R^{2'}, R³, R^{3'}, and R⁴ are independently selected from the group consisting of H, halogen, OH, N₃, CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted
- 15 heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkyloxy, optionally substituted alkenyloxy, optionally substituted alkynoxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted arylalkoxy, optionally substituted heterocycloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkoxy,
- 20 optionally substituted cycloalkenoxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino,

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optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted oxyacylimino, optionally substituted aminothioacyl, optionally substituted thioacylamino, optionally substituted aminosulfinyl, optionally substituted aminosulfonyl, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacyloxy, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted phosphorylamino, optionally substituted sulfinyl, optionally substituted sulfonyl, optionally substituted sulfinylamino, optionally substituted sulfonylamino, optionally substituted oxysulfinylamino, and optionally substituted oxysulfonylamino, or
10 R^2 and $R^{2'}$ together or R^3 and $R^{3'}$ together represents =O, =S, or =L-Y' where L is N, CH, CF, CCl or CBr and Y' is H, halogen, N_3 , methyl, ethyl or CN;

R^4 is $-CY_2SH$, $-CY_2OH$, $-CY_2NH_2$, or $-L^1-R^5$;

15 L^1 is selected from the group consisting of $-CY_2-$, $-CY_2CY_2-$, $-CY_2OCY_2-$, $-CY_2SCY_2-$ and $-CY_2NHCY_2-$;

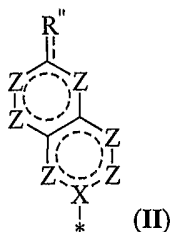
each Y is independently selected from the group consisting of H, F, Cl, Br, OR, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl may be optionally substituted with one or more groups selected from F, Cl, Br, OH, COOH, COOCH₃, SH, SCH₃, NH₂, NHCH₃, N(CH₃)₂, CN, NO₂, C(O)NH₂, C(O)NHCH₃, N_3 , C(S)NH₂, OCH₃, and OCH₂CH₃;

R^5 is selected from the group consisting of OR, NR₂, monophosphate, diphosphate, and triphosphate, or a mono, di or triphosphate mimic;

each R is independently selected from the group consisting of H, CF₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted arylalkyl;

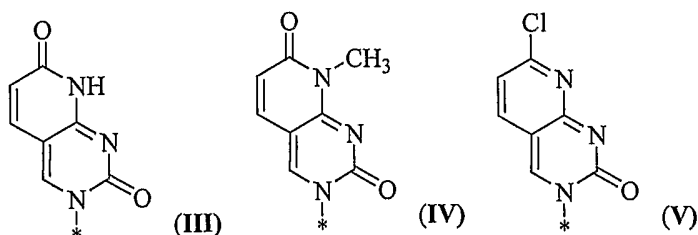
- 90 -

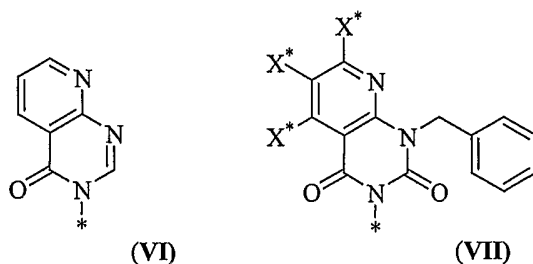
B is a group of formula (II)



wherein, if Z is a participant in a π bond (double bond), Z is independently selected from N
 5 or C-G; or, if Z is not a participant in a π bond (double bond), Z is independently selected
 from O, S, Se, NR, NOR, NNR₂, CO, CS, CNR, SO, S(O)₂, SeO, Se(O)₂ or C(G)₂, wherein
 each G is independently selected from the group consisting of H, halogen, OR, SR, NR₂,
 NROR, N₃, COOR, CN, CONR₂, C(S)NR₂, C(=NR)NR₂, and R; and
 where any two adjacent Z are not both selected from O, S, and Se, or not both selected
 10 from CO, CS, CNR, SO, S(O)₂, SeO, and Se(O)₂;
 wherein, if X is a participant in a π bond (double bond), X is C; or if X is not a participant
 in a π bond (double bond), X is CR or N;
 wherein, if R'' is a participant in a π bond (double bond), R'' is O, S, Se, NR, NOR, and
 NNR₂; or if R'' is not a participant in a π bond (double bond), R'' is OR, SR, F, Cl, R, or
 15 SeR;
 dashed lines (---) indicate a possible π or double bond; and

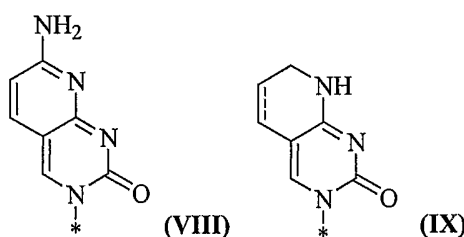
wherein when R^{2'}, R^{3'}, and R⁵ are OH or OC(O)CH₃, L' is CH₂, A is O, and R¹, R², R³ and
 R⁴ are H, B is not the group of formula (III), formula (IV), formula (V), formula (VI), or
 20 formula (VII)





(where each X* is H or one of X* is CH₃ and the other two X* are H);
when B is a group of formula (III), formula (VIII), or formula (IX)

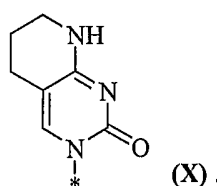
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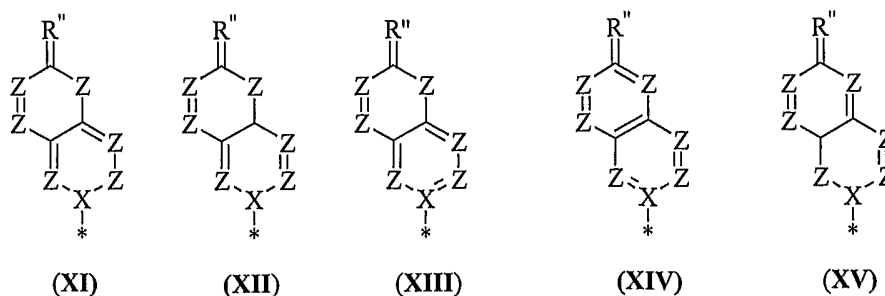
R² and R^{2'} are not both H;

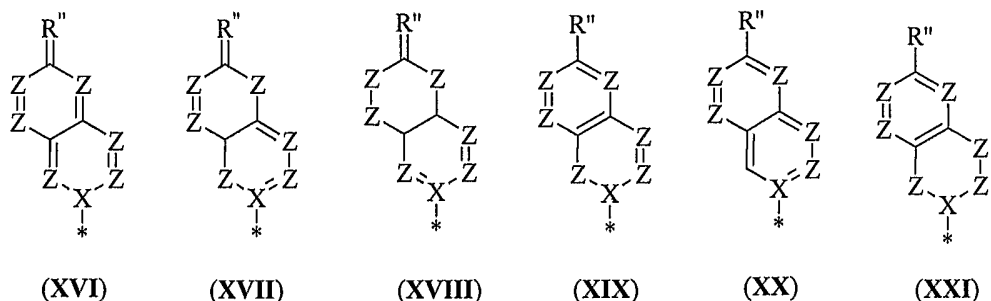
when R², R^{3'} and R⁵ are OH, L' is CH₂, A is O and R¹, R², R³ and R⁴ are H, B is not the group of formula (IV); and

- 10 when R^{2'} is F, R^{3'} is OH, R⁵ is triphosphate, L' is CH₂, A is O, and R¹, R², R³ and R⁴ are H, B is not a group of formula (X)



50. A compound according to claim 49, or a salt thereof, wherein the base structure B
15 is selected from the following formulae (XI) to (XXI)





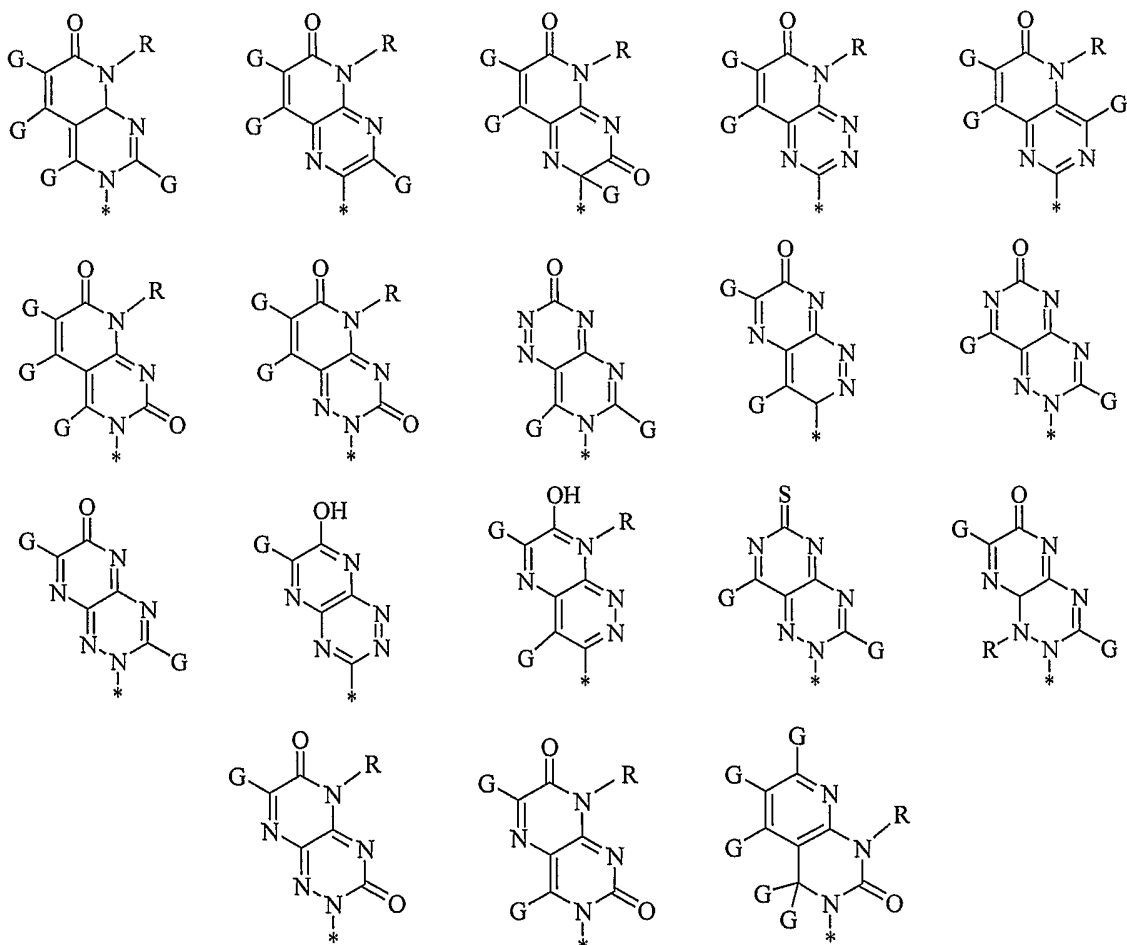
wherein Z, X and R'' are as defined in claim 49.

5

51. A compound according to claim 49 or claim 50, or a salt thereof, wherein X is N.

52. A compound according to claim 49, or a salt thereof, wherein the base structure B is selected from the following:

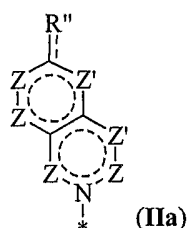
10



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wherein G and R are as defined in claim 49.

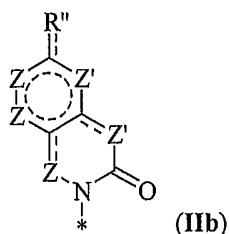
53. A compound according to claim 49, or a salt thereof, wherein the base structure B
5 is represented by formula **IIa**:



wherein each Z' is independently N (if a participant in a π bond) or NR (if not a participant in a π bond), and R'', R and Z are as defined in claim 49.

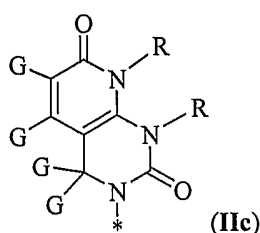
10

54. A compound according to claim 49, or a salt thereof, wherein the base structure B
is represented by the formula **IIb**:



- 15 wherein each Z' is independently N (if a participant in a π bond) or NR (if not a participant in a π bond), and each Z is independently CG (if a participant in a π bond) or $>C(G)_2$ (if not a participant in a π bond), and wherein R'' and G is as defined in claim 49.

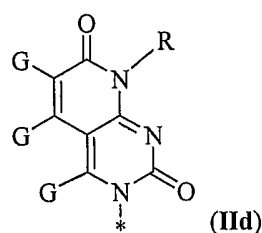
55. A compound according to claim 49, or a salt thereof, wherein the base structure B
20 is represented by formula **IIc**:



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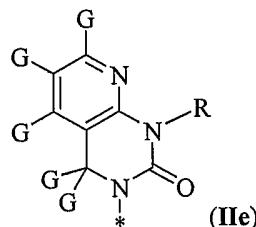
wherein R and G are as defined in claim 49.

56. A compound according to claim 49, or a salt thereof, wherein the base structure B
5 is represented by the formula **IIId**:



wherein R and G are as defined in claim 49.

- 10 57. A compound according to claim 49, or a salt thereof, wherein the base structure B
is represented by the formula **IIe**:



wherein R and G are as defined in claim 49.

15

58. A compound according to any one of claims 49 to 57, or a salt thereof, wherein R^1 , R^2 , R^2' , R^3 , R^3' , and R^4 are independently selected from the group consisting of H, halogen, OH, N_3 , CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkyloxy, optionally substituted acyloxy, optionally substituted oxyacyl, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted acylamino, optionally substituted thio, or
- 20

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R^2 and $R^{2'}$ together or R^3 and $R^{3'}$ together represents =O, =S, or =L-Y' where L is N, CH, CF, CCl or CBr and Y' is H, halogen, N_3 , methyl, ethyl or CN.

59. A compound according to any one of claims 49 to 57, or a salt thereof, wherein R^1 ,
5 R^2 , $R^{2'}$, R^3 , $R^{3'}$, and R^4 are independently selected from the group consisting of H, F, Cl,
Br, I, OH, SH, NH_2 , NHOH, $NHNH_2$, N_3 , COOH, CN, $CONH_2$, $C(S)NH_2$, COOR, R, OR,
SR, SSR, NHR, and NR_2 wherein at least one of R^2 or $R^{2'}$ is a substituent other than H, and
wherein R is selected from the group consisting of optionally substituted alkyl, optionally
substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally
10 substituted acyl, and optionally substituted arylalkyl.

60. A compound according to any one of claims 49 to 59, or a salt thereof, wherein at
least one of R^2 and $R^{2'}$ is methyl, hydroxyl or F.

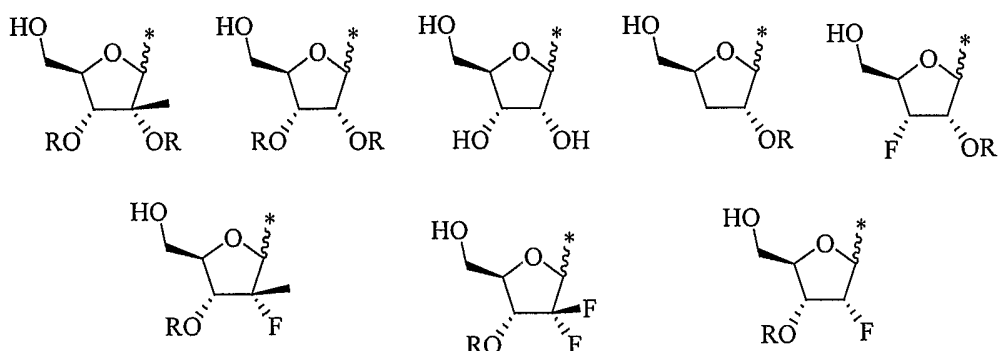
15 61. A compound according to any one of claims 49 to 60, or a salt thereof, wherein L'
is $-CH_2-$.

62. A compound according to any one of claims 49 to 60, or salt thereof, wherein R^4 is
selected from $-CH_2-OH$, $-CF_2OH$, $-CCl_2-OH$, $-C(CH_3)(CH_3)_3OH$, $-CH(CH_3)OH$, $-CH_2-$
20 $CH_2-P(O)(OH)_2$, $-CH_2-CH_2-P(O)(OH)_2$, $-CH_2SP(O)(OH)_2$, $-CH_2SH$, $-CF_2SH$, and $-CH_2-O-$
 $P(O)(OPh)(NHCH(CH_3)(CO_2Me))$.

63. A compound according to claim 62 or a salt thereof wherein R^4 is $-CH_2-OH$.

25 64. A compound according to any one of claims 49 to 57, or salt thereof, wherein the
sugar moiety is selected from the following formulae:

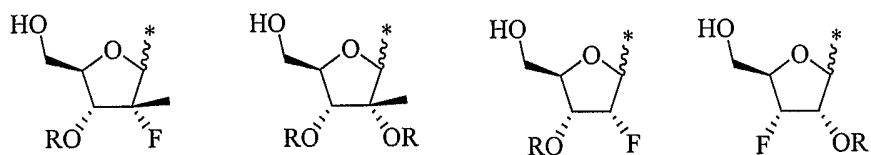
- 96 -



or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 49.

5

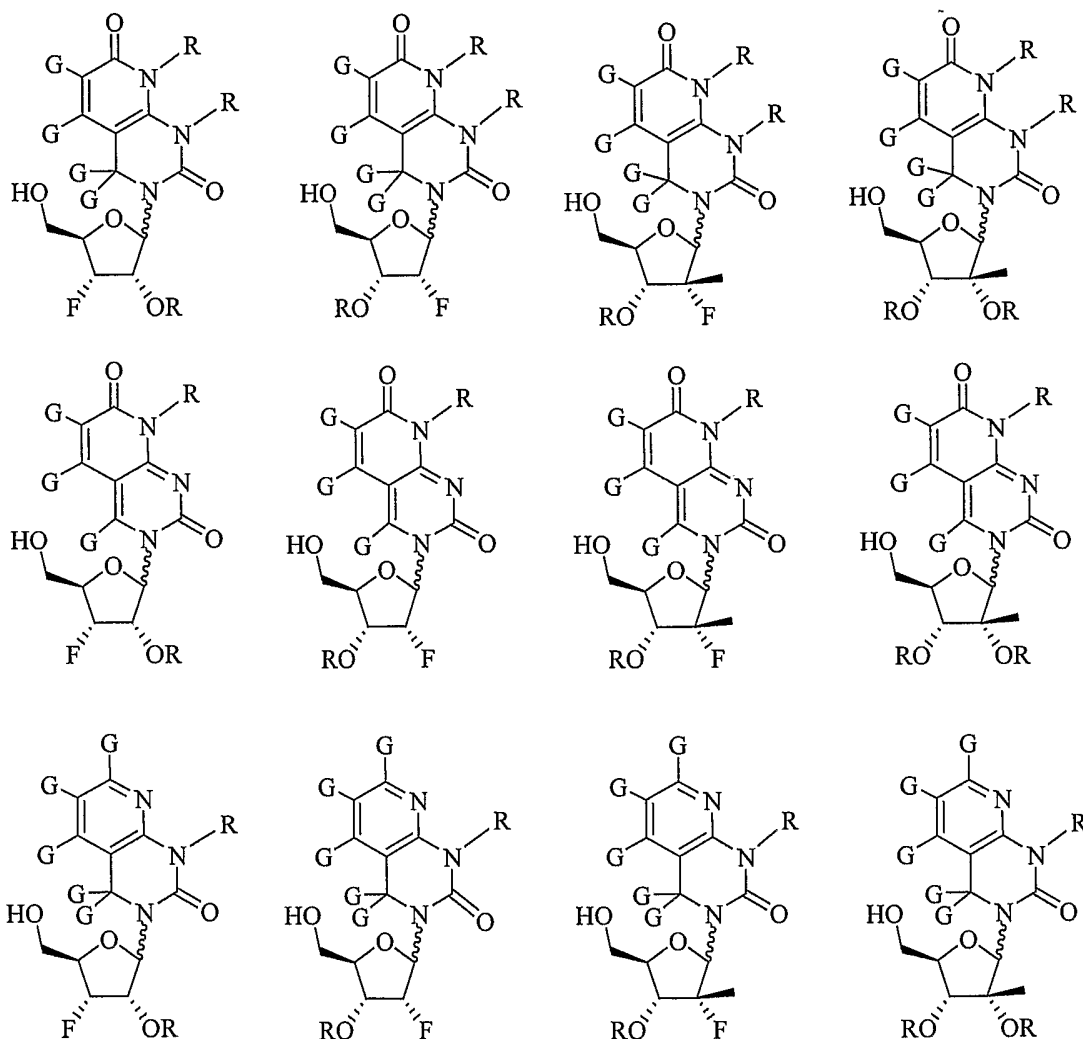
65. A compound according to any one of claims 49 to 57, or salt thereof, wherein the sugar moiety is selected from the following formulae:



10 or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics, wherein R is as defined in claim 49.

66. A compound of formula (I) selected from the following formulae, or a salt thereof,:

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wherein:

each R on the sugar moiety is independently selected from H, optionally substituted alkyl,
 5 optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl,
 optionally substituted acyl and optionally substituted arylalkyl;

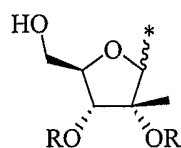
each R on the base moiety is independently selected from H, optionally substituted alkyl,
 optionally substituted aryl, optionally substituted heteroaryl, optionally substituted
 heterocyclyl, and optionally substituted arylalkyl;

10 each G is independently selected from H, halogen, CF₃, optionally substituted alkyl,
 optionally substituted aryl, optionally substituted heteroaryl, optionally substituted
 heterocyclyl, and optionally substituted arylalkyl; and

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C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di or triphosphate mimics.

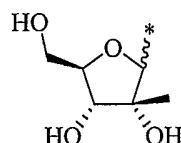
67. A compound according to any one of claims 49 to 57, or a salt thereof, wherein the
5 sugar moiety is represented by the formula:



or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di
or triphosphate mimics, wherein R is as defined in claim 49.

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68. A compound according to any one of claims 49 to 57, or a salt thereof, wherein the
sugar moiety is represented by the formula:

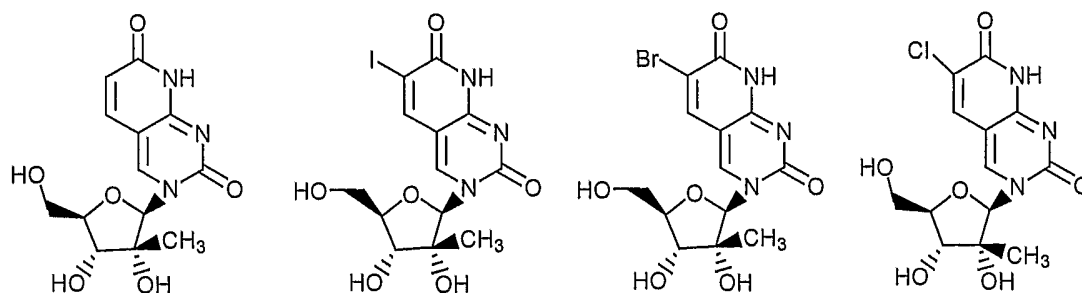


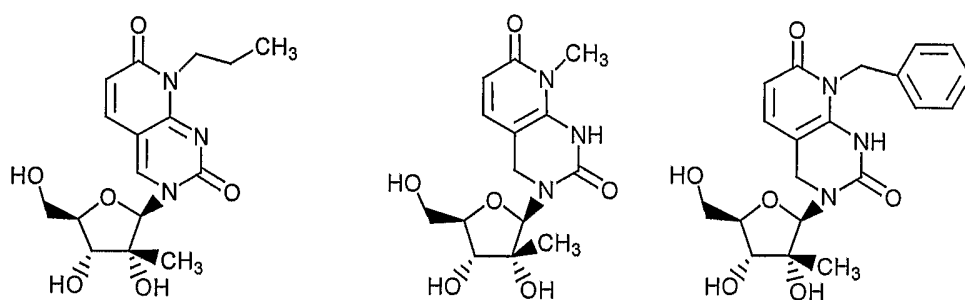
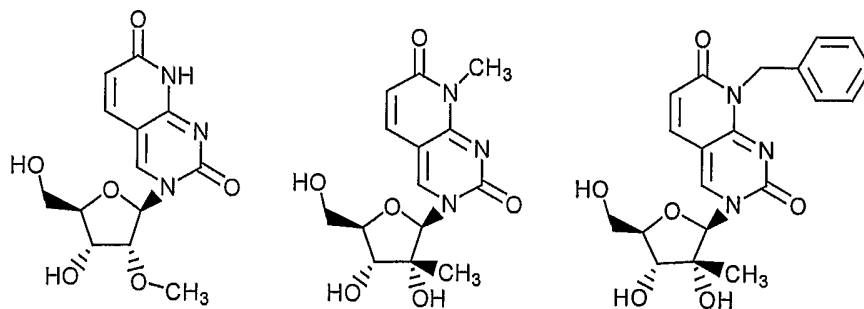
15 or C-5 monophosphate, diphosphate and triphosphate derivatives thereof, or C-5 mono, di
or triphosphate mimics.

69. A compound according to any one of claims 49 to 68, or a salt thereof, which is a β
anomer.

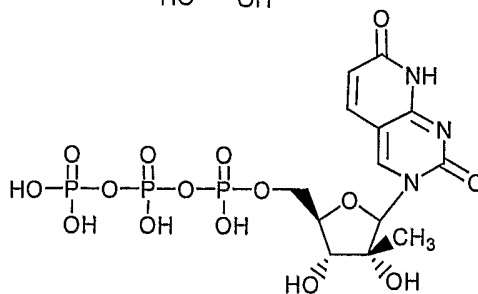
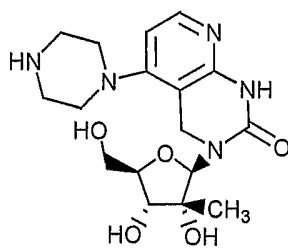
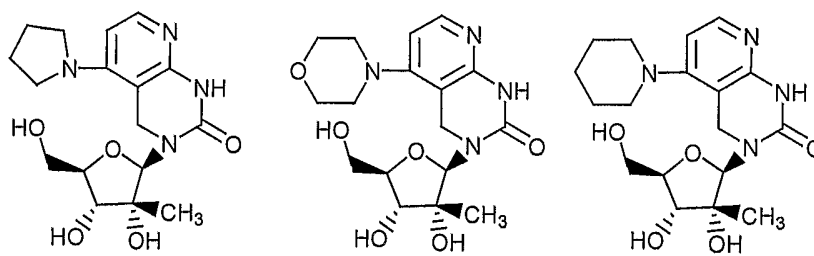
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70. A compound according to claim 49, or a salt thereof, selected from





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71. A pharmaceutical composition comprising a compound according to any one of claims 49 to 70, or a salt thereof, and at least one pharmaceutically acceptable carrier or diluent.

5 72. A pharmaceutical composition according to claim 71 for use in the treatment of a viral infection.

73. A pharmaceutical composition according to claim 72, wherein the virus is the hepatitis C virus.

10

74. A pharmaceutical composition according to claim 71 further comprising one or more antiviral or antibacterial agents.

15 75. A pharmaceutical composition according to claim 74, wherein the antiviral agents are selected from the group selected from interferon and interferon derivatives, IMPDH inhibitors, antiviral nucleosides, polymerase inhibitors and protease inhibitors.

76. A pharmaceutical composition according to claim 75, wherein the composition comprises interferon or ribavirin.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2006/000303

A. CLASSIFICATION OF SUBJECT MATTER		
Int. Cl. 8		
<i>C07D 405/14</i> (2006.01)	<i>A61P 31/04</i> (2006.01)	<i>A61P 31/14</i> (2006.01)
<i>A61K 31/706</i> (2006.01)	<i>A61P 31/06</i> (2006.01)	<i>C07F 9/06</i> (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
Electronic databases searched: see below		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CA, WPIDS searched using a structure search of claim 6 on STN		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAKO, M., "Product Class 19: pyridopyrimidines", Science of synthesis, Vol. 16, pp. 1155-1267 (2004) See entire document.	49-71
X	RAJEEV, K. et al, "5,6-diaminocytidine, a versatile synthon for pyrimidine-based bicyclic nucleosides", Organic Letters, Vol. 2, No. 23, pp. 3595-8 (2000) See scheme 1, compounds 5-6, 8-11 and p. 3595 left column l. 4-6 inter alia.	49-71
X	SAYED AHMED, A., "Syntheses of some uridine and cytidine derivatives", Egypt. J. of Pharm. Sci., Vol. 37, No. 1-6, pp. 303-11 (1996) See p. 305 inter alia.	49-71
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 08 May 2006		Date of mailing of the international search report 17 MAY 2006
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustrialia.gov.au Facsimile No. (02) 6285 3929		Authorized officer G. THOMPSON Telephone No : (02) 6283 2240

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2006/000303

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAWKINS, M. et al, "Fluorescence properties of pteridine nucleoside analogs as monomers and incorporated into oligonucleotides", Analytical biochemistry, Vol. 244, pp. 86-95 1997) See Fig. 1 inter alia.	49-71
X	WHALE, R. et al, "The synthesis of 5-substituted-2,4-dimethoxypyrimidines and some related nucleoside analogues" Nucleosides & Nucleotides, Vol. 11, No. 7, pp. 1425-42 (1992) See first paragraph p. 1425; compound 9, bottom p. 1427 and p. 1436 inter alia.	49-71
X	MAKISHIMA, M. et al, "Induction of differentiation of human myeloid leukemia HL-60 cells by novel pyrimidine nucleoside analogs", Biochimia et biophysica, acta, Vol. 1094, No. 1, pp. 1-7 (1991) See abstract and Groups B-D in Figs. 1, 3 inter alia.	49-71
X	ITOH, T. et al, "Improved procedures for the syntheses of pyrido- and pyrrolo[2,3-d]pyrimidines, and ribosides thereof", Chem. Pharm. Bull., Vol. 37, No. 12, pp. 3184-3190 (1989) See Fig. 1 inter alia.	49-71
X	LUTZ, H. et al, "Synthesis and properties of 2,2'-anhydro-n-3-lumazine nucleosides", Carbohydrate Research, Vol. 130, pp. 179-94 (1984) See compounds 8-21, 39-40 (page 180) inter alia.	49-71
X	BERGSTROM, D. et al, "Pyrido[2,3-d]pyrimidine nucleosides. Synthesis via cyclization of C-5-substituted cytidines", J. Org. Chem., Vol. 47, No. 11, pp. 2174-8 (1982) See compounds 10-11 in scheme 1, p. 2175 inter alia.	49-71

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2006/000303

C (Continuation)		DOCUMENTS CONSIDERED TO BE RELEVANT
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GOYA, P. et al, "Über die ribosiderierung des 5,6-dihydro-6-oxolumazins und seines 1,3-dimethyl-derivates", Chem. Ber., Vol. 114, No. 2, pp. 699-706 (1981) See compounds 4-7 (p. 700) inter alia.	49-71
X	GOYA, P. et al, "Synthese, eigenschaften and reaktivitat von lumazin-5-oxidribosiden", Chem. Ber., Vol. 114, No. 2, pp. 707-15 (1981) See compounds 1-22 (p. 708) inter alia.	49-71
X	RITZMANN, G. et al, "Über die synthese des 7-oxo-8-beta-D-ribofuranosyl-7,8-dihydrolumazins und seines 6-methyl-derivates", Chem. Ber., Vol. 113, No. 4, pp. 1535-48 (1980) See compounds 14-34 (p. 1537) inter alia.	49-71
X	RITZMANN, G. et al, "Über die ribosiderierung des 7-oxo-7,8-dihydrolumazins und seines 6-methyl- and 6-phenyl-derivates", Chem. Ber., Vol. 113, No. 4, pp. 1524-34 (1980) See compounds 11-28 (p. 1525) inter alia.	49-71
X	SOUTHON, I. et al, "Synthese und eigenschaften von 2-thiolumazin-nucleosiden", Chem. Ber., Vol. 111, No. 7, pp. 2571-85 (1978) See compounds 6-11 (p. 2572) inter alia.	49-71
X	IENAGA, K. et al, "Über die synthese des 6,7-diphenyl-3-(beta-D-ribofuranosyl)lumazins auf direktem wege und mit hilfe einer photolabilen N-8-schutzgruppe", Chem. Ber., Vol. 111, No. 7, pp. 2586-93 (1978) See compounds 6-9 (p. 2588) inter alia.	49-71

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2006/000303

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IENAGA, K. et al, "Eine neue umwandlung von N-heterocyclischen diribosiden in monoriboside", Chem. Ber., Vol. 110, No. 10, pp. 3456-9 (1977) See compounds 1, 3, 5-6, 9-12 (p. 3457) inter alia.	49-71
X	IENAGA, K. et al, "Synthese und eigenschaften von alloxazine-nucleosiden", Chem. Ber., Vol. 110, No. 10, pp. 3449-55 (1977) See compounds 6-15 (p. 3450) inter alia.	49-71
X	HUTZENLAUB, w. et al, "Synthese and struktur von 6,7-diphenyllumazin-arabinofuranosiden", Chem. Ber., Vol. 109, no. 9, pp. 3217-27 (1976) See compounds 6-19 (p. 3219) inter alia.	49-71
X	EISTETTER, K. et al, "Nucleosid-synthesen in der pterin-reihe", Chem. Ber., Vol. 109, No. 9, pp. 3208-16 (1976) See compounds 11-15 (p. 3209) inter alia.	49-71
X	KOBAYASHI, K. et al, "Synthese, eigenschaften und chemisches verhalten von 1(3)-methyl-6,7-diphenyl-3(1)-(beta-D-ribofuranosyl)lumazin-derivaten", Chem. Ber., Vol. 109, No. 9, pp. 3194-207 (1976) See compounds 5-10 (p. 3195), compound 16 (p. 3197) inter alia.	49-71
X	JOCHIMS, J. et al, "Syn- and anti-isomere pentofurano-nucleoside", Chem. Ber. Vol. 106, No. 9, pp. 2975-81 (1973) See compounds 4-6 (p. 2977) inter alia.	49-71

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2006/000303

C (Continuation)		DOCUMENTS CONSIDERED TO BE RELEVANT
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RITZMANN, G. et al, "Synthese und eigenschaften von lumazin-nucleosiden – strukturanaloga des uridins and thymidins", Chem. Ber., Vol. 106, No. 5, pp. 1401-17 (1973) See compounds 10-33 (p. 1403) inter alia.	49-71
X	RITZMANN, G. et al, "Synthesis of lumazine and isopterin N-1-beta-D-ribofuranosides and -(2-deoxyribofuranosides) – structural analogs of uridine, cytidine and thymidine", Angew. Chem. Internat. Edit., Vol. 10, No. 12, pp. 932-4 (1971) See compounds 15-26 inter alia.	49-71
X	RITZMANN, G. et al, "Verbesserte synthesen von lumazinnucleosiden", Liebigs Ann. Chem., pp. 1217-34 (1977) See compounds 20-48 (pp. 1219-1221) inter alia.	49-71
X	US 4 965 350 A (INOUE, H. et al) 23 October 1990 See abstract, claim 1 inter alia.	49-71
X	Derwent Abstract Accession No. 2004-460728/43, Class B02, WO 2004/048376 A1 (Genetic Lab Co. Ltd.) 10 June 2004	49-71
X	Derwent Abstract Accession No. 2005-105281/12, Class B04 D16 (B03), JP 2005015395 A (Dokuritsu Gyosei Hojin Kagaku Gijutsu Sh) 20 January 2005	49-71
X	Derwent Abstract Accession No. 89-284127/98, Class B02, JP 1143895 A (Meiji Seika Kaisha) 6 June 1989	49-71

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2006/000303

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
US 4 965 350	DE 3 686 150 EP 0 235 301
JP 7 025 788	WO 87 01373
WO 2004 048376	JP 2004 175708
JP 2005 015395	NO FAMILY
JP 01143895	NO FAMILY

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX