INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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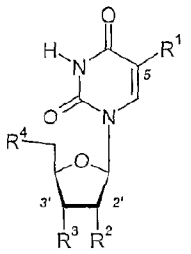
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(54) Title: URIDINE DERIVATIVES AS ANTIVIRAL DRUGS AGAINST A FLAVIVIRIDAE, ESPECIALLY HCV



(I)

(57) Abstract: The invention relates to the use of an uridine derivative of formula (I) : wherein - R^1 represents monohalogenated alkynyl or dihalogenated alkenyl; - R^2 is chosen from among hydrogen, hydroxyl, O-alkyl, O-CO alkyl and halogen; - R^3 is chosen from among hydrogen, hydroxyl, O-alkyl, O-CO alkyl, halogen, SH, S-alkyl and N_3; and - R^4 is chosen from among hydroxyl, O-alkyl, O-CO alkyl, O-phosphate, O-diphosphate, O-triphosphate and O phosphonate, as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms, for the preparation of a drug having antiviral activity against a Flaviviridae.

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URIDINE DERIVATIVES AS ANTIVIRAL DRUGS AGAINST A FLAVIVIRIDAE, ESPECIALLY HCV

The present invention relates to the use of uridine derivative(s) for the preparation of a drug having antiviral activity against a Flaviviridae, e.g. against hepatitis C virus (HCV). It also relates to new compounds having such antiviral activity, to drugs incorporating them and to a method of treating a subject (a human or an animal) with such a drug.

Hepatitis C Virus (HCV) infection remains a main public health preoccupation with 175 million people infected in the world. Currently, the best treatment available consists in the association of pegylated interferon (IFN) alpha 2b and ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). 20% of patients infected with HCV genotype 2 or 3 and 50% of patients infected with HCV genotype 1 are responders to this treatment. Therefore new treatment regimens based on more potent and specific inhibitors of HCV replication are required to improve the current antiviral strategies against chronic HCV infection.

The absence of a cellular system able to allow a complete multiplication cycle of HCV *in vitro* is a limiting factor for the search of new drugs. Recently, major knowledge has been gained about the mechanism of HCV replication. Study models have been developed such as the replicon system described in Ju-Tao Guo et al. (J. Virol. 2001, 75, 18: 8516-8523), allowing replication of HCV subgenome in cell culture.

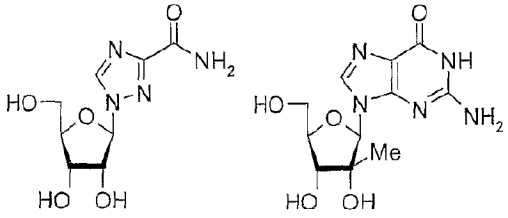
The recent developments of the replicon system has promoted the study of new inhibitors of HCV replication. The NS3 serine protease and NTPase/helicase and the RNA-dependent RNA polymerase NS5B are key enzymes for the replication of HCV. To date, several inhibitors of NS3 were discovered. The NS5B has also been studied because of its central role in viral replication (Behrens, S.E. et al. *EMBO J.*, **1996**, *15*, 12; Ferrari, E. et al. *J. Virol.*, **1999**, *73*, 1649 ; Ishii, K. et al. *Hepatology* **1999**, *29*, 1227; Lohmann, V. et al. *J. Virol.*, **1997**, *71*, 8416; Oh, J.W. et al. *J. Virol.*, **1999**, *73*, 7694; Yamashita, T. et al. *J. Biol. Chem.*, **1998**, *273*, 15479 ; Walker, M.P.; Hong, Z., *Curr. Opinion Pharmacol.* **2002**, *2*, 1). Recently Bressanelli *et al.* reported a first co-crystallization of HCV NS5B with ribonucleotides, which lead to the identification of a specific and unique GTP-binding pocket outside the active site (Bressanelli, S. et al. *J. Virol.* **2002**, *76*, 3482). Specific inhibitors of this virus-encoded RNA-dependent RNA polymerase (RdRP) may represent potent antiviral agents (De Francesco, R. et al. *Antiviral Res.* **2003**, 58, 1-16.

The pharmaceutical importance of nucleoside analogues against viral DNA polymerases such as HIV-RT, HBV and HSV polymerases, has prompted the design and synthesis of analogous viral RNA polymerase. While numerous of non-nucleoside inhibitors of NS5B-

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mediated HCV RNA replication have been reported (Chan, L. et al. *J. Med. Chem.* **2003**, *46*, 1283-1285; Wang, M. et al. *J. Biol. Chem.* **2003**, *278*, 9489-9495; Dhanak, D. et al. *J. Biol. Chem.* **2002**, *277*, 38322-38327), only a few nucleoside inhibitors have been identified so far (Carroll, S. S. et al *J. Biol. Chem.* **2003**, *278*, 11979-11984; Shim, J. et al. *Antiviral Res.* **2003**, 243-251; Eldrup, A. B. et al. *J. Med. Chem.* **2004**, 47- 2283-2295). An example of nucleoside inhibitor is the 2'-*C*-methylarabinoguanosine (2'-C-methylaraG), recently reported in WO 01/190121, which is phosphorylated in cultured, uninfected cells and orally bioavailable in primates.



1, Ribavirin

2, 2'-*C*-methyl*ara*G
Idenix Pharmaceuticals

Many nucleoside analogues substituted at the 5-position of the heterocycle, and especially in the 2'-deoxyuridine series (*e.g.* BVDU, IDU, FIAU), are known to have potent biological properties and have been developed as antiviral and anticancer agents. The 5-(2-substitutedvinyl)-2'-deoxyuridines have emerged as potent and selective inhibitors of herpes viruses (HSV-1 & HSV-2) (De Clercq, E. *Exp. Clin. Pharmacol.* **1980**, *2*, 253 ; De Clercq, E. *Biochem. Pharmacol.* **1984**, *33*, 2159). In general, 5-alkynyl-2'-deoxyuridines has been also evaluated as potential antiviral agents (De Clercq, E. et al *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947 ; De Clercq, E.et al. *J. Infect. Dis.* **1980**, *141*, 563; Kundu, N. G.; Dasgupta, S. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2657). The structure activity relationship studies seem to indicate that the type of C-5 substituents likely to confer activity are those which are electron withdrawing and conjugated to the heterocycle (Goodchild, J. et al. *J. Med. Chem.* **1983**, *26*, 1252). Recently, McGuigan *et al.* reported that analogous furanopyridine by-product in the preparation of the parent 5-alkynyl-2'-deoxyuridine displayed important potency and exclusive selectivity for varicella zooster virus (VZV) (McGuigan C. et al. *J. Med. Chem.* **1999**, *42*, 4479; McGuigan, C. et al. *J. Med. Chem.* **2000**, *43*, 4993; Srinivasan, S. et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 391; McGuigan, C.et al. *Drugs Future* **2000**, *25*, 1151; Carangio, A. et al. *Antivir. Chem. Chemother.* **2001**, *12*, 187), meanwhile imidazo[1,2-c]pyrimidin-5(6H)-one heterosubstituted nucleoside analogues were discovered by Mansour *et al.* (*Bioorg. Med. Chem. Lett.* **1997**, *7*, 303) to have anti-HBV (hepatitis B virus) activity. The chemistry involves the Pd-catalyzed coupling of arylacetylenes or terminal alkynes with 5-iodonucleosides.

Providing the art with new efficient and acceptable anti-Flaviridae, in particular anti-HCV, drugs or treatments would be of great benefit.

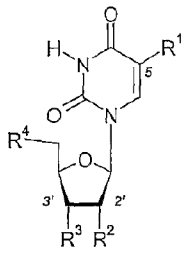
An objective of the invention is to provide the art with new treatments effective against a Flaviviridae infection, e.g. against FCV, say new treatments having a strong antiviral activity with no or acceptable side effects.

Another objective of the invention is to provide a treatment that is efficient against the major HCV genotypes, including genotypes 1, 2 and 3.

Another objective of the invention is to provide a treatment that is efficient against any HCV genotype.

These objectives are attained by the use of some uridine derivatives that will be described in details below.

A first object of the invention is the use of a uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms,
for the preparation of a drug having antiviral activity against a Flaviviridae.

In the above formula (I):

"monohalogenated alkynyl" is –C ≡C-X or –C ≡C-Ak(X), where Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;

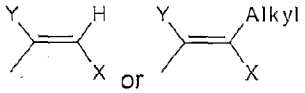
"dihalogenated alkenyl" is -C(Y)=CH(X), -C(Y)=C(X)alkyl or -C(Y)=C-Ak(X), where Y is halogen and Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;

"alkyl", unless otherwise indicated, represents a linear or branched C_1-C_{10} alkyl radical;

"halogen" is fluorine, chlorine, bromine or iodine, preferably chlorine, bromine or iodine.

The dihalogenated alkenyl may present a *Z* or *E* configuration, the *E* configuration being preferred, i.e. the two halogen atoms X and Y are not on the same side of the planar double bond.

Preferred configuration for -C(Y)=CH(X) or -C(Y)=C(X)alkyl is therefore respectively :



According to a first embodiment, a preferred uridine derivative of formula (I) useful for the preparation of a drug having antiviral activity against a Flaviviridae, presents the following characteristics:

- R^1 represents –C ≡C-X or -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen ;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -phosphate, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Preferred compounds of formula (I) are those where

- R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R^2, R^3 and R^4 being as defined above,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

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Compounds where R^2 and R^3 do not simultaneously represent hydrogen form another sub-group of even more preferred compounds.

Particularly preferred compounds for the intended above-mentioned use are those wherein

- R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl; and
- R^2 and R^3 not simultaneously being each hydrogen ; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

A most preferred uridine derivative of formula (I) is chosen from among the following compounds:

- (*E*)-5-(1-Chloro-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Diiodovinyl)-2'-deoxyuridine,
- 5-(2-Iodoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Dibromovinyl)-2'-deoxyuridine,
- 5-(2-Bromoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Chloro-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Diiodovinyl)-uridine,
- 5-(2-Iodoethynyl)-uridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Dibromovinyl)-uridine, and
- 5-(2-bromoethynyl)-uridine,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Compounds of formula (I) wherein R^4 represents -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate are deemed to represents pro-drugs of the corresponding compounds wherein R^4 represents -OH. Other pro-drugs leading to compounds wherein R^4 is -OH are also encompassed within the present invention. Such other pro-drugs include for instance esters, such as aminoacid esters, e.g. alanine esters and glycine esters, quaternary salts of phosphate, and the like.

Acids that may be used to form pharmaceutically acceptable addition salts of the compound of formula (I) are organic or inorganic acids. Such salts include for example hydrochlorides, hydrobromides, sulfates, hydrogensulfates, dihydrogene-phosphates, citrates, maleates, fumarates, trifluoroacetates, 2-naphthalenesulfonate and *para*-toluenesulfonate.

Similarly, bases that may be used to form pharmaceutically acceptable addition salts of the compound of formula (I) are organic or inorganic bases. Such salts include for example metallic salts from alkali metals, alkaline-earth metals or transition metals, such as sodium, potassium, calcium, magnesium, aluminum. Other suitable bases include ammoniac or secondary or tertiary amines (diethylamine, triethylamine, piperidine, piperazine, morpholine) or basic amino-acids, or alternatively osamines (such as meglumine), or aminoalcools (such as 3-aminobutanol and 2-aminoéthanol).

The present invention also encompasses salts that are useful for suitable separation or crystallization of the compounds of formula (I), such as salts obtained from chiral amines or acids.

Example of chiral amines include for example quinine, brucine, (*S*)-1-(benzyloxy-methyl)propylamine, (-)-ephedrine, (4*S*,5*R*)-(+)-1,2,2,3,4-tetramethyl-5-phenyl-1,3-oxazolidine, (*R*)-1-phenyl-2-*p*-tolylethylamine, (*S*)-phenylglycinol, (-)-N-methylephedrine, (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol, (*S*)-phenylglycinol, (*S*)-α-methylbenzylamine, alone or in mixtures.

Example of chiral acids include for example (+)-d-di-O-benzoyltartaric acid, (-)-l-di-O-benzoyltartaric acid, (-)-di-O,O'-p-toluyl-l-tartaric acid, (+)-di-O,O'-p-toluyl-d-tartaric acid, (*R*)-(+)-malic acid, (*S*)-(-)-malic acid, (+)-camphanic acid, (-)-camphanic acid, (+)-camphoric acid, (-)-camphoric acid, (*S*)-(+)-2-phenylpropionic acid, (*R*)-(-)-2-phenylpropionic acid, d-(-)-mandelic acid, l-(+)-mandélic acid, d-tartaric acid, l-tartaric acid, alone or mixtures.

In an embodiment, the invention more specifically relates to the use of such an uridine derivative and an efficient amount of an interferon (IFN), for the preparation of a drug having antiviral activity against a Flaviviridae. It also relates to the use of such an uridine derivative for the preparation of a drug having antiviral activity against a Flaviviridae, that is intended to be used in an recipient that is treated with an efficient amount of IFN. The recipient may have been treated recently with the IFN (for instance less than 30 days before), or received IFN at

approximatively the same time or later, for instance less than 30 days. The IFN may be chosen among those that are described *infra*.

In another embodiment, the IFN is replaced or accompanied (concomitant or successive administration) by the use of another drug such as one of those described *infra*

According to a preferred aspect, the Flaviviridae is HCV and the use of a uridine derivative of formula (I) is for the preparation of a drug having antiviral activity against HCV. There exists up to 6 HCV genotypes classified 1-6. Any of them is included in the present invention. The major genotypes are genotypes 1, 2 and 3, and a "use" according to the invention may be, for example, directed against HCV genotype 1, HCV genotype 2, HCV genotype 3, HCV genotypes 1 and 2, HCV genotypes 2 and 3, HCV genotypes 1 and 3, HCV genotypes 1, 2 and 3. The use may also be against any and all HCV genotypes, including quasispecies.

In another aspect of the invention, the Flaviviridae member may be a member of the Japanese encephalitis virus group, including Japanese encephalitis virus and West Nile Virus.

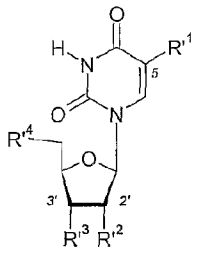
Alternatively it may be a member of the Yellow fever virus group.

Alternatively it may be a member of the Pestivirus group, such as Bovine viral diarrhea virus (BVDV-1 and/or BVDV-2), Classical swine fever virus, Border disease virus.

It may be appreciated that the recipient may be a human or an animal, depending on the Flaviviridae concerned.

Among the compounds of formula (I), 5-bromoethynyl-2'-deoxyuridine is known and reported by Eger K. *et al.* (*Tetrahedron*, **1994**, *50*, 8371-8380), whereas compounds of formula (I), wherein R^1 represents dihalogenated alkenyl are new.

Therefore, a further object of the present invention is a compound of formula (I'):



(I')

wherein

- R'^1 represents dihalogenated alkenyl;
- R'^2, R'^3 and R'^4 have the same definitions as R^2, R^3 and R^4, respectively, in the above formula (I);

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Compounds of formula (I') may be used for the preparation of a drug having an antiviral activity against a Flaviviridae.

In the above formula (I'), "dihalogenated alkenyl" has the same meaning as defined above, i.e. -C(Y)=CH(X), -C(Y)=C(X)alkyl or -C(Y)=C-Ak(X), where Y is halogen and Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;

All definitions and preferred embodiments described hereinbefore for compounds of formula (I) also apply to compounds of formula (I'), R'^1 not possibly representing however a monohalogenated alkynyl radical.

Accordingly, a preferred compound of formula (I') presents the following characteristics:

- R'^1 represents -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R'^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Preferred compounds of formula (I') are those where:

- R'^1 represents -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R'^2, R'^3 and R'^4 being as defined above,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

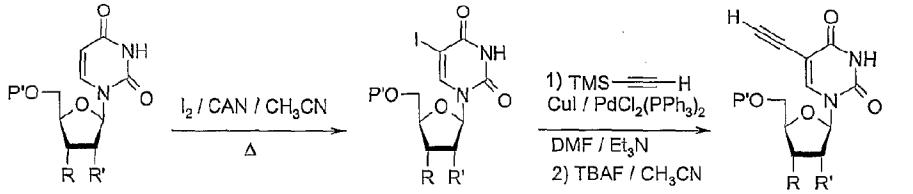
Particularly preferred compounds for the intended above-mentioned use are those wherein

- R'^1 represents -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R'^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl; and
- R'^2 and R'^3 not simultaneously being each hydrogen; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

The present invention is further related to the process for the preparation of compounds of formula (I) and formula (I').

Halogenated pyrimidine **4a-c** in Scheme 1 below are prepared by direct reaction with halogens following the procedure reported by Asakura et al. (*J. Org. Chem.*, **1990**, *55*, 4928-4933) *via* a cerium(IV)-mediated halogenation at the C-5 of uracil derivatives. Thus, treatment of the known acetylated nucleosides **3a-c**, according to a process well known by the one skilled in the art, with elemental iodine and ceric ammonium nitrate (CAN) at 80°C, gives the corresponding protected 5-iodouracil nucleosides 4a-c in excellent yields. This CAN-mediated halogenation has advantages over other available methods as mild reaction conditions are employed with short reaction times.



3a R = OPc, R' = H
3b R = R' = OP
3c R = H, R' = OP

4a R = OP, R' = H
4b R = R' = OP
4c R = H, R' = OP

5a R = OP, R' = H
5b R = R' = OP
5c R = H, R' = OP

Scheme 1

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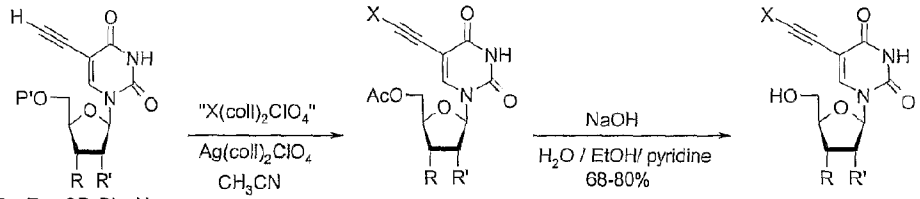
In the above scheme 1, P and P', which may be identical or different, stand for protective groups of hydroxyl groups, and are well-known to the person skilled in the art.

Preferably, protective groups P and P' are chosen from among acyl groups such as $CH_3C=O$, trityl, monomethoxytrityl, mesyl, and the like.

In scheme 1 above, protective groups P and P' each preferably an acyl group, specifically $CH_3C=O$.

The introduction of a C-5-alkynyl group is performed by a Pd(0)-mediated reaction, using the *Sonogashira conditions* (Sonogashira K., *Comprehensive Organic Synthesis*, Trost/Fleming (Eds), Pergamon Press, New York, **1991**, vol 3, p. 521;. Sonogashira K. et al.; *Tetrahedron Lett.*, **1975**, *16*, 4467; Takahashi S. et al., *Synthesis*, **1980**, 627; Ratovelomana V. et al., *Synth. Commun.*, **1981**, *11*, 917). Thus, reaction of the resulting pure acetylated 5-iodouracil **4a-c** with trimethylsilylacetylene in the presence of triethylamine (Et_3N, base), cuprous iodide (CuI, co-catalyst) and $PdCl_2(PPh_3)_2$ (catalyst) in anhydrous dimethyl formamide (DMF) at room temperature, followed by a removal of the trimethylsilyl (TMS) group with TBAF (tetrabutyl ammonium fluoride) affords the corresponding 5-ethynyluracil nucleosides **5a-c**. In most cases, it is observed that slight elevations in the reaction temperature lead to increase in the rate of coupling. In all cases, a by-product, furanopyrimidine derivatives is either isolated with a < 7% yield, or just detected by TLC; nevertheless, the using of DMF reduces the amount of this cyclic by-product; this base-catalyzed cyclization was previously reported by Bleackley *et al.* (*Tetrahedron*, **1976**, *32*, 2795) by base treatment of (E)-5-(2-bromovinyl)uracil.

The halogenation of alkynes **5a-c** is realized using halogenating agents (such as iodonium di-syn-collidine perchlorate (IDCP), N-iodosuccinimide (NIS) or chloroiodine (ICL) for iodination, bromonium di-syn-collidine perchlorate ($Br(coll)_2ClO_4$) for bromination, or, for chlorination, sulfuryl chloride, Cl_2, CCl_4, N-chlorophtalimide, dichlorine monoxide or PCl_5, in anhydrous polar solvent, for example methane nitrile (CH_3CN) according to reaction Scheme 2, where P and P' are as defined above for Scheme 1. These halogenating reagents are known to act as very reactive electrophiles (such as I^+ and Br^+, respectively).



5a R = OP, R' = H
5b R = R' = OP
5c R = H, R' = OP

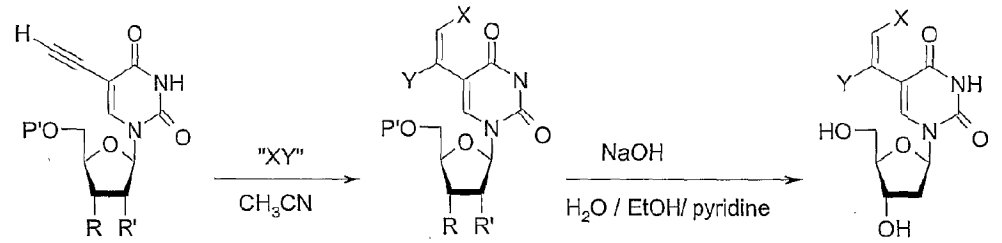
6a-c, X = I
7a-c, X = Br

12a-c, X = I
13a-c, X = Br

Scheme 2

The final deprotection of protected nucleosides **6a-c** and **7a-c** is realized under smooth basic conditions (for example 1M sodium hydroxide in a mixture of H_2O/EtOH/pyridine) when P = P' = Ac) to afford final 5-haloethynyluracil nucleosides **12a-c** and **13a-c**, respectively, in good to moderate yield.

Dihalogenation of the above 5-ethynyl nucleosides (Scheme 3) leads to hitherto unknown 5-(1,2-dihalogenated)ethenyluracil nucleosides **14a-c** to **17a-c**. Several halogenating reagents (i.e. I_2, IBr, ICl or Br_2) are used to reach the corresponding 1,2-dihaloderivatives. In all cases of halo-iodination, the formation of vicinal halo-iodoalkenes (**8a-c to 10a-c**) occurs with high anti-stereospecificity, implicating the intermediary of an iodonium ion in the reaction sequence, and a high and unique regioselectivity, implicating a predominantly Markovnikov addition. The formation of **11a-c** using Br_2 occurs also with a *E*-stereochemistry.



5a R = OP, R' = H
5b R = R' = OP
5c R = H, R' = OP

8a-c, X = Y = I
9a-c, X = I, Y = Br
10a-c, X = I, Y = Cl
11a-c, X = Y = Br

14a-c, X = Y = I
15a-c, X = I, Y = Br
16a-c, X = I, Y = Cl
17a-c, X = Y = Br

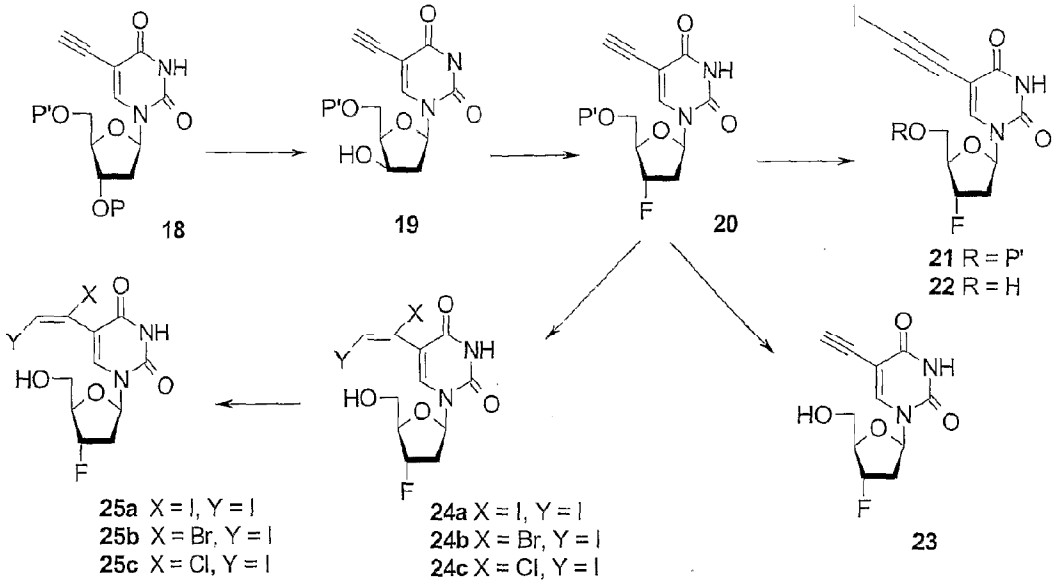
Scheme 3

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The final deprotection of protected nucleosides **8a-c** to **11a-c** is realized as previously reported (for example 1M NaOH in a mixture of H_2O/EtOH/pyridine when P = P'Ac) and final 5-(1,2-dihaloethenyl)uracil nucleosides **14a-c** (for X = Y = I), **15a-c** (for X = I, Y = Br), **16a-c** (for X = I, Y = Cl), **17a-c** (for X = Y = Br) are obtained, respectively.

All other compounds encompassed by formulae (I) and (I') are easily prepared from the above described synthetic route with easily conceivable modifications and/or adaptations well known by the one skilled in the art.

For illustrative purposes only, compounds of formula (I) or of formula (I') may be obtained according to scheme 4 below, wherein P preferably represents mesyl and P' preferably represents monomethoxytrityl.



Scheme 4

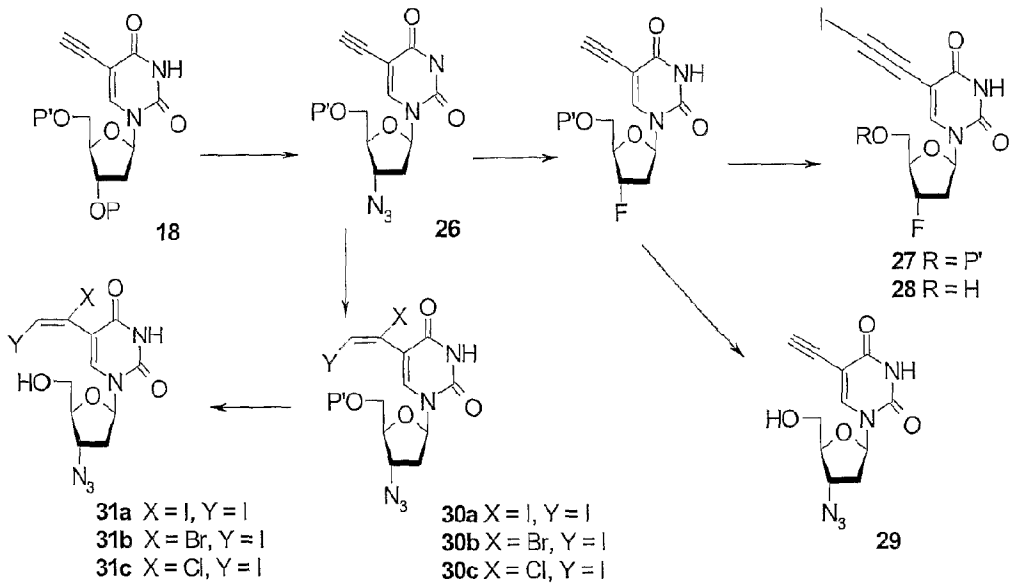
In scheme 4 above, coumpound **19** is obtained after specific deprotection, in mild basic conditions, the free resulting hydroxyl group being substituted by methods well known in the art, for example using diethylaminosulfur trifluoride, affordinf compound 21.

Compounds 21 and 22 are obtained from compound **20** under conditions similar as those described above for the preparation of compounds **12** and **13.**

Compound 23 results from the deprotection of the P' protecting group of compound 20.

Compounds **24a-c** and **25a-c** are respectively obtained using a similar process as the one disclosed above for the preparation of compounds **8-11a-c** and **14-17a-c**.

As further illustrative purpose only, compounds of formula (I) and of formula (I') wherein R^3 (and R^{13} respectively) represents N_3 may be obtained according the following scheme 5.



Scheme 5

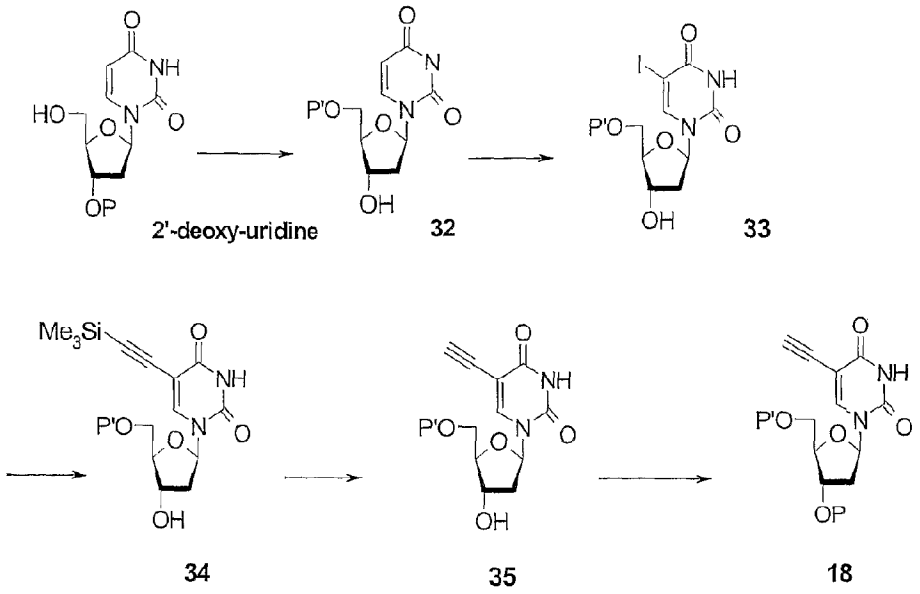
In the above scheme 5, P and P' each denote protective groups defined as defined above and advantageously P represents mesyl and P' represents monomethoxytrityl.

Azidation of compound **18** may be carried out using conventional techniques of azidation and for example using sodium azide in polar aprotic solvent, such as for example dimethylformamide under reflux, resulting in compound 26.

Compounds **27-31** are obtained through similar methods as those disclosed above for the preparation of compounds **21-25** respectively.

Compound **18** in scheme 4 and scheme 5 above may be obtained according to a process similar to the process for the preparation of compound 5 in the above scheme 1.

Alternatively, compound of formula 18 may advantageously be obtained according to the preparation process of scheme 6 below :



In scheme 6 above, P and P' are preferably different, each representing a protective group as defined above. Particularly preferred are compounds wherein P' represents monomethoxytrityl and P represents mesyl.

The introduction of the P' protective group is carried out using conventional techniques, and for example, where P' represents monomethoxytrityl using para-anisylchlorodiphenyl-methane in mild basic conditions, such as dry pyridine at reflux.

The selective introduction of protective group I is also achieved using conventional techniques, and, for example, when P represents mesyl, using methanelsulfonychloride in mild basic conditions, such as for example dry pyridine at 0° C.

In scheme **6** above, the introduction of a C-5-alkynyl group is performed as stated above in scheme 1 for the preparation of compound **5**.

Compounds **14-31 a-c** are purified, when necessary, using conventional methods known in the art.

Compounds of formulae (I) and (I') may be obtained in pure enantiomeric form and/or isomeric form, or in mixture, in all proportions, of enantiomers and/or isomers. Separations of such enantiomers and/or isomers is run according to techniques well known in the art.

The above compounds are also optionally converted into pharmaceutically acceptable addition salts with an acid or a base, and optionally into their N-oxide form, using appropriate and suitable methods as known by the one skilled in the art.

All starting materials are known and either commercially available or prepared, directly or with slight variations easily conceivable by the one skilled in the art, from one or more processes disclosed in the scientific literature, patents and patents application, the "Chemical Abstracts", on-line data bases and the Internet.

Another object of the invention is a drug or drug formulation having an antiviral activity against a Flaviviridae, in particular HCV, comprising at least one compound of formulae (I) (the active ingredient) with a pharmaceutically acceptable vehicle, carrier or excipient. "Acceptable" means that this further ingredient is compatible with the active ingredient included in the formulation and is not deleterious to the recipient thereof. The pharmaceutically acceptable vehicle, carrier or excipient are well known to the one skilled in the art. For example, for parenteral administration, it can be a 0.9 % NaCl saline solution for a phosphate buffer. The pharmaceutical acceptable vehicles, carriers or excipients also cover any compound or combination of compounds facilitating the administration of the active ingredient and/or improving preservation.

In the whole specification and Claims, the words "comprise/comprising" are synonymous with (means the same thing as) "include/including", "contain/containing", are inclusive or open-ended and do not exclude additional, unrecited elements.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal or sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. These various formulations are well known, as well as their methods of preparation. The choice of the formulation may vary depending upon the identity of the recipient, and will generally be chosen according to the best practice for a human or for the animal considered. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Formulations for oral administration may be presented as discrete units such as, for example: capsules, cachets or tablets each containing a predetermined amount of active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or an emulsion, e.g. a water-in-oil or an oil-in-water emulsion. The active ingredient may also be presented as a bolus, electuary or paste. The solid forms may optionally be coated and may be formulated so as to provide slow or controlled release of the

active ingredient. For infections of the eye or other external tissues (e.g. skin or mouth), the formulations are preferably presented as ointment or cream for topical application, containing an efficient amount of active ingredient. Formulations suitable for administration to the eye also include eye drops where the active ingredient is dissolved or suspended in a suitable carrier, such as an aqueous solvent. Formulations for rectal administration may be presented as a suppository with a suitable base. Liquid or solid carriers may be used for nasal administration. Pessaries, tampons, creams, gels, pastes, foams or spray formulations may be used for vaginal administration. Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions, suspensions or emulsions.

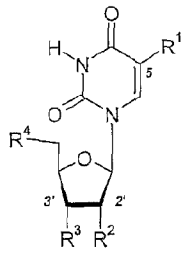
The amount of active ingredient in a single dosage form will depend upon a number of factors including the identity of the recipient and the condition to be treated. In general, however, for a human, the amount of active ingredient in a single dose form will be in the range, for example, of 1 mg to 10 g, preferably in the range of 100 mg to 5 g, most preferably in the range of 500 to 2000 mg.

For multiple dosage form, for example a cream or ointment, the concentration of active ingredient will depend upon a number of factors including the identity of the recipient and the condition to be treated. In general, however, for a human, the concentration of active ingredient in a multiple dose form will be in the range, for example, of 0.01 to 200 mg of active ingredient per g of formulation, preferably in the range of 0.1 to 100 mg/g, most preferably in the range of 1 to 50 mg/g.

In one embodiment, the drug formulation according to the invention further comprises an additional compound having an antiviral activity against a Flaviviridae or that is useful in the treatment of the infection or its symptoms. The use according to the invention thus encompasses the use of at least two different active ingredients, at least one of them being an uridine derivative as described herein.

In a first aspect, this additional compound is at least one formula (I) compound. Thus the invention formulation does comprise at least two formula (I) compounds or derivatives.

In a second aspect, the drug formulation having an antiviral activity against a Flaviviridae comprises an additional compound which is not an uridine derivative according to the invention. The drug formulation may be then represented as comprising :
(1) an uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms,

(2) an immunomodulator or another active ingredient having an antiviral activity against a Flaviviridae or being useful in treating the infection by a Flaviviridae, and

(3) a pharmaceutically acceptable vehicule, carrier or excipient.

The additional compound is advantageously an immunomodulator, especially an interferon (IFN) or a derivative of an interferon such as the so-called pegylated forms of interferon (pegylated interferon), such as any those currently used in the medical field. It may be in particular IFN-α, e.g. IFN-α 2b, such as pegylated IFN-α 2b Peg-Intron® (Schering Plough), IFN-α 2a, such as pegylated IFN-α 2a Pegasis® (Roche), Albuferon-a® (Human Genome Sciences), Multiferon® (Viragen) ; IFN-β, e.g. IFN β 1a, such as Rebif® IFN-β 1a (Serono) ; IFN-γ, e.g. IFN-γ 1b, such as IFN-γ 1b (from Interimmune Pharmaceuticals ; IFN-ω, e.g. IFN-ω from Biomedines.

Other immunomodulators may be associated to the invention compounds, such as histamine dihydrochloride (e.g. Ceplene®, Maxim Pharmaceuticals), Thymosine-a (SciClone Pharmaceuticals), Interleukines such as IL-12 and IL-10, therapeutical vaccines (e.g. based on the E1 protein), preparation for passive immunity transfer (e.g. Cicavir®, NABI).

More generally, the invention compounds may find an interest in the association to any available drug used in the treatment of the infection by a Flaviviridae, especially HCV. Thus, the drug formulation may include in addition an active principle chosen among antisens

molecules, protease inhibitors, helicase inhibitors, polymerase inhibitors, nucleoside or nucleotide analogs (chain terminators, ribonucleoside analogs, sugar modified nucleoside analogs), ribavirine or ribavirine pro-drug, inosine monophosphate dehydrogenase inhibitors.

The invention encompasses of course combinations of at least two different additional compounds with an uridine derivative according to the invention.

In a third aspect, the drug or drug formulation according to the invention comprises at least two formula (I) compounds and at least one additional compound as described above, in particular an IFN or derivative thereof.

Another object of the invention is thus a drug formulation comprising at least one formula (I) compound, at least one additional compound as described *supra*, in particular an IFN or derivative thereof, and a pharmaceutically acceptable vehicle, carrier or excipient, as described *supra*.

Another object of the invention is a method for antiviral treatment of a recipient (a human or an animal), wherein the recipient is administered with an efficient amount of a drug or drug formulation according to the invention.

In an embodiment, the method includes the administration of an efficient amount of uridine derivative(s) and an efficient amount of interferon(s) (IFN). The uridine derivative and the IFN may be in admixture, or may be separately formulated and are either co-injected after extemporaneous mixture, or administered separately to the recipient. As an alternative, the method provides for the administration of an efficient amount of uridine derivative(s), where this administration is intended to be made in a recipient that is treated with an efficient amount of IFN(s). The recipient may have been treated recently with the IFN(s) (for instance less than 30 days before), or he receives IFN(s) at approximately the same time or later, for instance less than 30 days. In another embodiment, the IFN is replaced or accompanied (concomitant or successive administration) by the administration of another drug such as one of those described *supra*. Any and all characteristics recited with respect to the use according to the invention apply to the method.

As mentioned above, the compounds or derivatives, and the formulations or compositions comprising them may be administered by any route appropriate to the condition to be treated. Suitable routes including oral, rectal, nasal, topical (including buccal or sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal,

intrathecal and epidural). It will be appreciated that the preferred route may vary with, for example, the condition of the recipient. Various suitable formulation types have been described earlier and may be used in the method.

For each of the above-indicated infectious events or indications the amount required of the active ingredient will depend upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician. In general, however, for each of these indications, a suitable, effective dose will be in the range 0.01 to 200 mg per kilogram body weight of recipient per day, preferably in the range of 2 to 100 mg, most preferably 10 to 40 mg per kilogram body weight of recipient per day. The dose may if desired be presented as two, three, four or more sub-doses administered at appropriate intervals throughout the day.

The invention is described further in details with the following description of non-limitative examples.

EXAMPLES

Commercially available chemicals and solvents are reagent grade and used as received. Dry tetrahydrofuran, pyridine and dichloromethane are obtained from distillation over calcium hydride (CaH_2) or sodium (Na), *N,N*-dimethylformamide and ethanol over barium oxide (BaO) over calcium hydride (CaH_2). Triethylamine is dried over potassium hydroxide (KOH). The reactions are monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 F_{254}, E. Merck). Compounds are visualized by UV irradiation and/or spraying with 20% sulphuric acid (H_2SO_4) in ethanol (EtOH), followed by charring at 150 °C. Column chromatography is performed on Silica Gel 60 M (0.040-0.063 mm, E. Merck). Melting points (mp) are recorded on a Büchi (Dr. Tottoli) and are uncorrected. ^1H and ^{13}C NMR spectra are recorded on a Bruker AVANCE DPX 250 Fourier Transform spectrometer at 250 MHz for ^1H and 62.9 MHz for ^{13}C, respectively, in (D)-chloroform, (D_4)-methanol and (D_6)-DMSO, shift values in ppm relative to $SiMe_4$ as internal reference, unless otherwise stated ; signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), J in Hz. $[\alpha]_D$ were performed with a Perkin-Elmer (model 41) polarimeter. UV spectra were recorded on a Beckman DU-640 spectrophotometer. Mass spectra are recorded on a Perkin-Elmer SCIEX API-300 (heated nebullizer) spectrometer. High-resolution Mass spectra (HRMS) were performed by the Centre Regional de Mesures Physiques de l'Ouest, University of Rennes 1 (France) using the FAB (Fast Atom Bombardment) or ESI (Electron Spray Ionization) mode. The nomenclature of the obtained compounds is in accordance with the IUPAC rules. The

numbering and assignment of the chemical shifts for all described compounds are related to the corresponding ribose derivatives.

Preparation of compounds of formula (I)

General procedure for iodination of acetylated nucleosides

A solution of acetylated nucleoside **3a-c** (synthetic route described by L. B. Townsend and R. S. Tipson in "Nucleic acid chemistry", Wiley Eds., 1978) (15 mmol) in dry methane nitrile (CH_3CN, 150 mL), ceric ammonium nitrate (CAN, 4.94 g, 0.6 eq.) and iodine (I_2, 2.28 g; 0.6 eq.) is refluxed until completion (typically 1 h, checked by TLC). After cooling to room temperature (rt), solvents are evaporated under reduced pressure and the dark oily residue is dissolved in ethyl acetate (AcOEt, 300 mL) and water (H_2O, 50 mL). The biphasic mixture is cooled in an ice bath and a saturated $Na_2S_2O_3$ solution is smoothly added until complete decolouration. The organic layer is washed with water (2 x 50 mL) and brine (50 mL), dried over magnesium sulfate ($MgSO_4$) and concentrated under reduced pressure. The white foam is triturated with pentane (50 mL), filtrated and dried under reduced pressure to afford pure iodinated compounds **4a-c**, respectively.

General procedure for Sonogashira cross-coupling and subsequent desilylation

Iodinated nucleoside **4a-c** (5 mmol) was dissolved in a mixture of dry dimethyl formamide (DMF; 15 mL), dry triethyl amine (Et_3N; 2.06 mL, 3 eq.) and trimethyl silyl acetylene (2.06 mL, 3 eq.). Cuprous iodide (CuI; 190 mg, 0.2 eq.) and $PdCl_2(PPh_3)_2$ (350 mg, 0.1 eq.) were then added and the reaction mixture was stirred at room temperature until completion (typically 5-20 h, checked by TLC). Solvents were evaporated under reduced pressure. The oily residue was dissolved in AcOEt (250 mL) then washed with water (5 x 40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to a dark oil. A first purification using a short path flash chromatography (eluent: methylene chloride (CH_2Cl_2) then MeOH/CH_2Cl_2 5 %) afforded the desired compound contaminated with coloured reaction co-products. Pure silylated alkynes (2 mmol), obtained after a second flash chromatography (eluent: hexanes/AcOEt 7/3 then 1/1), were dissolved in dry CH_3CN (20 mL). Tetrabutyl ammonium fluoride (TBAF) monohydrate (583 mg, 1.05 eq.) was added and the resulting solution was stirred at room temperature until completion (typically 30 min. to 2 h, checked by TLC). Solvents were evaporated under reduced pressure at room temperature and the oily residue was submitted to a flash column chromatography (eluent: hexanes/AcOEt 1/1 then AcOEt then MeOH/AcOEt 2% then 5%) to afford pure 5-ethynyl nucleosides **5a-c**, respectively.

General procedure for mono-halogenation of 5-ethynyl nucleosides

5-Ethynyl nucleoside **5a-c** (0.5 mmol) is dissolved in 5 mL dry CH_3CN and the mixture is cooled in an ice bath. 0.7 mmol (1.4 eq.) of the halogenating reagent (i.e. IDCP (iodonium di-syn-collidine perchlorate) or $Br(coll)_2ClO_4$) and 11 mg $Ag(coll)_2ClO_4$ (0.05 eq.) are added and the mixture is stirred in the dark at rt (typically 2 h-20 h, checked by TLC). The reaction mixture is cooled to 0°C then quenched by a saturated $Na_2S_2O_3$ solution (2 mL) and extracted with AcOEt (4 x 10 mL). The organic layer is washed with water (10 mL), a 1M HCl (hydrochloric acid) solution (3 x 5 mL), water (2 x 5 mL) and brine (10 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. The solid residue is purified by flash chromatography (eluent : hexanes/AcOEt, 1/1, v/v) to yield the desired mono-halogenated compound **6-7a-c**.

Example 1: **3',5'-Di-*O*-acetyl-5-(2-iodoethynyl)-2'-deoxyuridine (6a)**

The title compound is obtained according to the above described general procedures from 3',5'-Di-*O*-acetyl-2'-deoxy-5-iodouridine (4a) (see Asakura, J. et al., *J. Org. Chem.*, **1990**, *55*, 4928-4933; and Asakura, J. et al., *Tetrahedron Lett.*, **1988**, *29*, 2855-2858) or from 3',5'-di-*O*-acetyl-2'-deoxy-5-ethynyluridine (5a) (see US 5,028,596).

Yield: 93%.

mp: 175-177 (dec) °C

$[\alpha]_D^{20}$ -32 (c 0.5, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 11.68 (br s, 1H, NH), 8.02 (s, 1H, H-6), 6.12 (t, J = 7.1 Hz, 1H, H-1'), 5.20 (m, 1H, H-3'), 4.33-4.15 (m, 3H, H-4',5'), 2.55 (m, 1H, H-2'a), 2.31 (m, 1H, H-2'b), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc).

HRMS m/z 486.1982 calculated for $C_{15}H_{15}IN_2O_7Na$, found m/z 486.1986.

Example 2: **3',5'-Di-*O*-acetyl-5-(2-bromoethynyl)-2'-deoxyuridine (7a)**

According to a procedure similar to that of Example 1, the title compound is obtained as an oil.

Yield: 21%

$[\alpha]_D^{20}$ -68 (c 1.0, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 8.88 (br s, 1H, NH), 7.95 (s, 1H, H-6), 6.31 (dd, J = 7.3, 6.4 Hz, 1H, H-1'), 5.25 (m, 1H, H-3'), 4.38-4.30 (m, 3H, H-4',5'), 2.55 (m, 1H, H-2'a), 2.31 (m, 1H, H-2'b), 2.18 (s, 3H, OAc), 2.12 (s, 3H, OAc).

HRMS m/z 439.1978 calculated for $C_{15}H_{15}BrN_2O_7Na$, found m/z 439.1981.

Examples 3 to 6 below are obtained according to similar processes.

Example 3: **2',3',5'-Tri-*O*-acetyl-5-(2-iodoethynyl)-uridine (6b)**

Yield: 68%

mp: 100-102 °C

$[\alpha]_D^{20}$ -71 (c 1.0, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 9.41 (br s, 1H, NH), 7.91 (s, 1H, H-6), 6.07 (d, J = 4.6 Hz, 1H, H-1'), 5.35 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.25 (s, 3H, OAc), 2.12 (s, 2 x 3H, 2 x OAc).

HRMS m/z 544.2352 calculated for $C_{17}H_{17}IN_2O_9Na$, found m/z 544.2349.

Example 4: 2',3',5'-Tri-*O*-acetyl-5-(2-bromoethynyl)-uridine (7b)

Yield: 58% as a colorless oil

$[\alpha]_D^{20}$ -59 (c 0.4, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 9.75 (br s, 1H, NH), 7.92 (s, 1H, H-6), 6.07 (d, J = 4.4 Hz, 1H, H-1'), 5.35 (m, 2H, H-2',3'), 4.37 (m, 3H, H-4',5'), 2.22 (s, 3H, OAc), 2.12 (s, 2 x 3H, 2 x OAc).

HRMS m/z 497.2348 calculated for $C_{17}H_{17}BrN_2O_9Na$, found m/z 497.2351.

Example 5: 2',5'-Di-*O*-acetyl-5-(2-iodoethynyl)-3'-deoxyuridine (6c)

Step a): 2',5'-Di-*O*-acetyl-3'-deoxy-5-iodouridine (4c)

^1H NMR ($CDCl_3$) δ 9.53 (br s, 1H, NH), 7.93 (s, 1H, H-6), 5.82 (d, J = 1.6 Hz, 1H, H-1'), 5.30 (m, 1H, H-2'), 4.55 (m, 1H, H-4'), 4.41 (dd, J = 12.8, 2.8 Hz, 1H, H-5'a), 4.33 (dd, J = 12.8, 3.8 Hz, 1H, H-5'b), 2.31-1.95 (m, 2H, H-3'), 2.23 (s, 3H, OAc), 2.13 (s, 3H, OAc).

Step b): 2',5'-Di-*O*-acetyl-3'-deoxy-5-ethynyluridine (5c)

^1H NMR ($CDCl_3$) δ 9.8 (br s, 1H, NH), 7.88 (s, 1H, H-6), 5.78 (s, 1H, H-1'), 5.31 (d, J = 7.5 Hz, 1H, H-2'), 4.48 (m, 1H, H-4'), 4.35 (dd, J = 12.5, 1.8 Hz, 1H, H-5'a), 4.25 (dd, J = 12.5, 3.4 Hz, 1H, H-5'b), 3.1 (s, 1H, H-Csp), 2.31-1.95 (m, 2H, H-3'), 2.12 (s, 3H, OAc), 2.05 (s, 3H, OAc)

HRMS m/z 360.2968 calculated for $C_{15}H_{16}N_2O_7Na$, found m/z 360.2971.

Step c): 2',5'-Di-*O*-acetyl-5-(2-iodoethynyl)-3'-deoxyuridine (6c)

Yield: 76% as an oil

$[\alpha]_D^{20}$ -49 (c 0.8, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 11.68 (br s, 1H, NH), 7.98 (s, 1H, H-6), 5.74 (s, 1H, H-1'), 5.30 (d, J = 7.5 Hz, 1H, H-2'), 4.43 (m, 1H, H-4'), 4.28 (br s, 2H, H-5'), 2.31-1.95 (m, 2H, H-3'), 2.09 (s, 3H, OAc), 2.05 (s, 3H, OAc).

HRMS m/z 486.1982 calculated for $C_{15}H_{15}IN_2O_7Na$, found m/z 486.1986.

Example 6: 2',5'-Di-*O*-acetyl-5-(2-bromoethynyl)-3'-deoxyuridine (7c)

Yield: 25% as an oil

$[\alpha]_D^{20}$ -52 (c 0.4, $CHCl_3$)

^{1}H NMR (DMSO-d_6) δ 11.75 (br s, 1H, NH), 8.07 (s, 1H, H-6), 5.85 (s, 1H, H-1'), 5.31 (d, J = 7.5 Hz, 1H, H-2'), 4.43 (m, 1H, H-4'), 4.28 (br s, 2H, H-5'), 2.31-1.95 (m, 2H, H-3'), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc).

HRMS m/z 439.1978 calculated for $C_{15}H_{15}BrN_2O_7Na$, found m/z 439.1975.

General procedure for di-halogenation of 5-ethynyl nucleosides

5-ethynyl nucleoside **5a-c** (0.5 mmol) is dissolved in 5 mL dry CH_3CN and the mixture is cooled in an ice bath. 0.6 mmol (1.2 eq.) of a solution of the halogenating reagent (i.e. I_2, IBr, ICl or Br_2) in 1 mL dry CH_3CN is added dropwise and the mixture is stirred at 0°C until completion (typically 15 min.-2 h, checked by TLC). The reaction mixture is quenched at 0°C by a saturated $Na_2S_2O_3$ solution (2 mL) then extracted with AcOEt (3 x 10 mL). The organic layer is washed with water (2 x 5 mL) and brine (10 mL) then dried over $MgSO_4$ and concentrated *in vacuo* to yield the desired di-halogenated compounds of examples 7-18 (**8-11a-c**) in a reasonably pure form. Pure analytical samples were obtained using flash chromatography (eluent: hexanes/AcOEt, 1/1, v/v).

Example 7: **(*E*)-3',5'-Di-*O*-acetyl-5-(1,2-diiodovinyl)-2'-deoxyuridine (8a)**

94% yield; mp 76-78 °C; $[\alpha]_D^{20}$ -19 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.72 (br s, 1H, NH), 7.67 (s, 1H, H-6), 7.45 (s, 1H, =CHI), 6.36 (dd, J = 8.1, 5.6 Hz, 1H, H-1'), 5.25 (m, 1H, H-3'), 4.50-4.28 (m, 3H, H-4',5'), 2.60 (m, 1H, H-2'a), 2.30 (m, 1H, H-2'b), 2.17 (s, 3H, OAc), 2.08 (s, 3H, OAc). HRMS m/z 614.1106 calculated for $C_{15}H_{16}I_2N_2O_7Na$, found m/z 614.1110.

Example 8: **(*E*)-2',3',5'-Tri-*O*-acetyl-5-(1,2-diiodovinyl)-uridine (8b)**

98% yield; mp 83-85 °C; $[\alpha]_D^{20}$ -41 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.56 (br s, 1H, NH), 7.58 (s, 1H, H-6), 7.40 (s, 1H, =CHI), 6.15 (d, J = 4.6 Hz, 1H, H-1'), 5.36 (m, 2H, H-2',3'), 4.38 (br s, 3H, H-4',5'), 2.19 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.11 (s, 3H, OAc). HRMS m/z 672.1476 calculated for $C_{17}H_{18}I_2N_2O_9Na$, found m/z 672.1480.

Example 9: **(*E*)-2',5'-Di-*O*-acetyl-5-(1,2-diiodovinyl)-3'-deoxyuridine (8c)**

87% yield; mp 75-77 °C; $[\alpha]_D^{20}$ -23 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.38 (br s, 1H, NH), 7.64 (s, 1H, H-6), 7.39 (s, 1H, =CHI), 5.92 (d, J = 1.6 Hz, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.44 (dd, J = 12.5, 4.4 Hz, 1H, H-5'a), 4.33 (dd, 1H, H-5'b), 2.31-1.95 (m, 2H, H-3'), 2.14 (s, 3H, OAc), 2.12 (s, 3H, OAc). HRMS m/z 614.1106 calculated for $C_{15}H_{16}I_2N_2O_7Na$, found m/z 614.1101.

Example 10: **(*E*)-3',5'-Di-*O*-acetyl-5-(1-bromo-2-iodovinyl)-2'-deoxyuridine (9a)**

96% yield; mp 82-84 °C; $[\alpha]_D^{20}$ -14 (c 4.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.78 (br s, 1H, NH), 7.71 (s, 1H, H-6), 7.08 (s, 1H, =CHI), 6.25 (dd, J = 8.1, 5.6 Hz, 1H, H-1'), 5.28 (m, 1H, H-3'), 4.50-4.05 (m, 3H, H4', 5'), 2.58 (m, 1H, H-2'a), 2.20 (m, 1H, H-2'b), 2.12 (s, 3H, OAc), 1.96 (s, 3H, OAc). HRMS m/z 567.1102 calculated for $C_{15}H_{16}BrIN_2O_7Na$, found m/z 567.1107.

Example 11: **(*E*)-2',3',5'-Tri-*O*-acetyl-5-(1-bromo-2-iodovinyl)-uridine (9b)**

92% yield; mp 86-88 °C; $[\alpha]_D^{20}$ -39 (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.57 (br s, 1H, NH), 7.66 (s, 1H, H-6), 7.15 (s, 1H, =CHI), 6.15 (d, J = 4.7 Hz, 1H, H-1'), 5.38 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.18 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.13 (s, 3H, OAc). HRMS m/z 625.1469 calculated for $C_{17}H_{18}BrIN_2O_9Na$, found m/z 625.1473.

Example 12: **(*E*)-2',5'-Di-*O*-acetyl-5-(1-bromo-2-iodovinyl)-3'-deoxyuridine (9c)**

89% yield as an oil; $[\alpha]_D^{20}$ -19 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.63 (br s, 1H, NH), 7.61 (s, 1H, H-6), 7.13 (s, 1H, =CHI), 5.92 (s, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.44 (dd, J = 12.4, 2.6 Hz, 1H, H-5'a), 4.33 (dd, J = 12.4, 4.4 Hz, 1H, H-5'b), 2.31-1.95 (m, 2H, H-3'), 2.16 (s, 3H, OAc), 2.14 (s, 3H, OAc). HRMS m/z 567.1102 calculated for $C_{15}H_{16}BrIN_2O_7Na$, found m/z 567.1105.

Example 13: **(*E*)-3',5'-Di-*O*-acetyl-5-(1-chloro-2-iodovinyl)-2'-deoxyuridine (10a)**

91% yield; mp 81-83 °C; $[\alpha]_D^{20}$ -14 (c 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.28 (br s, 1H, NH), 7.75 (s, 1H, H-6), 6.91 (s, 1H, =CHI), 6.32 (m, 1H, H-1'), 5.24 (m, 1H, H-3'), 4.50-4.30 (m, 3H, H-4',5'), 2.75 (m, 1H, H-2'a), 2.18 (m, 1H, H-2'b), 2.13 (s, 2 x 3H, 2 x OAc). HRMS m/z 522.6592 calculated for $C_{15}H_{16}ClIN_2O_7Na$, found m/z 522.6597.

Example 14: **(*E*)-2',3',5'-Tri-*O*-acetyl-5-(1-chloro-2-iodovinyl)-uridine (10b)**

97% yield; mp 85-87 °C; $[\alpha]_D^{20}$ -27 (c 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.43 (br s, 1H, NH), 7.68 (s, 1H, H-6), 6.92 (s, 1H, =CHI), 6.15 (br s, 1H, H-1'), 5.36 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.17 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.12 (s, 3H, OAc). HRMS m/z 580.6962 calculated for $C_{17}H_{18}ClIN_2O_9Na$, found m/z 580.6958.

Example 15: **(*E*)-2',5'-Di-*O*-acetyl-5-(1-chloro-2-iodovinyl)-3'-deoxyuridine (10c)**

83% yield; mp 87-89 °C; $[\alpha]_D^{20}$ -13 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.75 (br s, 1H, NH), 7.74 (s, 1H, H-6), 6.90 (s, 1H, =CHI), 5.91 (d, J = 1.7 Hz, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.43 (dd, J = 12.5, 2.8 Hz, 1H, H-5'a), 4.33 (dd, J = 12.5, 4.1 Hz, 1H, H-5'b), 2.35-1.95 (m, 2H, H-3'), 2.14 (s, 2 x 3H, 2 x OAc). HRMS m/z 522.6592 calculated for $C_{15}H_{16}ClIN_2O_7Na$, found m/z 522.6593.

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Example 16: 3',5'-Di-*O*-acetyl-5-(1,2-dibromovinyl)-2'-deoxyuridine (11a)

97% yield; mp 79-81 °C; $[\alpha]_D^{20}$ -15 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.85 (br s, 1H, NH), 7.75 (s, 1H, H-6), 6.89 (s, 1H, =CHBr), 6.33 (dd, J = 8.1, 5.6 Hz, 1H, H-1'), 5.24 (m, 1H, H-3'), 4.45-4.25 (m, 3H, H-4',5'), 2.65 (m, 1H, H-2'a), 2.18 (m, 1H, H-2'b), 2.14 (s, 2 x 3H, 2 x OAc). HRMS m/z 520.1098 calculated for $C_{15}H_{16}Br_2N_2O_7Na$, found m/z 520.1099.

Example 17: (*E*)-2',3',5'-Tri-*O*-acetyl-5-(1,2-dibromovinyl)-uridine (11b)

92% yield; mp 83-85 °C; $[\alpha]_D^{20}$ -43 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.38 (br s, 1H, NH), 7.66 (s, 1H, H-6), 6.90 (s, 1H, =CHBr), 6.12 (d, J = 4.8 Hz, 1H, H-1'), 5.36 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.17 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.12 (s, 3H, OAc). HRMS m/z 578.1468 calculated for $C_{17}H_{18}Br_2N_2O_9Na$, found m/z 578.1473.

Example 18: 2',5'-Di-*O*-acetyl-5-(1,2-dibromovinyl)-3'-deoxyuridine (11c)

82% yield; mp 78-80 °C; $[\alpha]_D^{20}$ -16 (c 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.61 (br s, 1H, NH), 7.72 (s, 1H, H-6), 6.88 (s, 1H, =CHI), 5.88 (d, J = 1.5 Hz, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.43 (dd, J = 12.5, 2.8 Hz, 1H, H-5'a), 4.33 (dd, J = 12.5, 4.1 Hz, 1H, H-5'b), 2.35-1.95 (m, 2H, H-3'), 2.15 (s, 3H, OAc), 2.14 (s, 3H, OAc). HRMS m/z 520.1098 calculated for $C_{15}H_{16}Br_2N_2O_7Na$, found m/z 520.1103.

General procedure for deacetylation

Acetylated nucleoside analogue **6-11a-c** (1 mmol) is dissolved in 10 mL pyridine and 5 mL EtOH. The reaction mixture is cooled to -10°C and 5 mL of a 1M NaOH (sodium hydroxide) aqueous solution is added. The resulting solution is stirred at this temperature until completion (typically 1-4 h, checked by TLC). The reaction mixture is neutralized with Dowex then filtered through a fritted glass funnel. Solvents are evaporated *in vacuo* and the oily residue is submitted to a flash column chromatography using an appropriate eluent (typically hexanes/AcOEt 25/75 then AcOEt then MeOH/AcOEt 1%) to yield pure compounds **12-17a-c** (Examples 19-36).

Example 19: 5-(2-Iodoethynyl)-2'-deoxyuridine (12a)

68% yield; mp 135-137 °C; $[\alpha]_D^{20}$ +14 (c 0.8, MeOH); ^1H NMR (CD_3OD) δ 8.32 (s, 1H, H-6), 6.22 (t, J = 6.6 Hz, 1H, H-1'), 4.41 (m, 1H, H-3'), 3.95 (m, 1H, H-4'), 3.83 (dd, J = 12.1, 3.0 Hz, 1H, H-5'a), 3.73 (dd, J = 12.1, 3.4 Hz, 1H, H-5'b), 2.40-2.12 (m, 2H, H-2'). HRMS m/z 402.1229 calculated for $C_{11}H_{11}IN_2O_5Na$, found m/z 402.1231.

Example 20: 5-(2-Iodoethynyl)-uridine (12b)

70% yield as an oil; $[\alpha]_D^{20}$ -12 (c 0.2, MeOH); ^{1}H NMR (DMSO-*d6*) δ 11.65 (br s, 1H, NH), 8.29 (s, 1H, H-6), 5.72 (m, 1H, H-1'), 5.05-5.12 (3 x br s, 3 x OH), 4.05-3.95 (m, 2H, H-2',3'), 3.85 (m, 1H, H-4'), 3.70-355 (m, 2H, H-5'). HRMS m/z 418.1223 calculated for $C_{11}H_{11}IN_2O_6Na$, found m/z 418.1219.

Example 21: 5-(2-Iodoethynyl)-3'-deoxyuridine (12c)

66% yield as an oil; $[\alpha]_D^{20}$ +6 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 11.65 (s, 1H, NH), 8.48 (s, 1H, H-6), 5.59 (s, 1H, H-1'), 5.54 (d, J = 4.1 Hz, 1H, OH), 5.23 (t, J = 5.1 Hz, 1H, OH), 4.32 (m, 1H, H-4'), 4.21 (m, 1H, H-2'), 3.75 (m, 1H, H-5'a), 3.52 (m, 1H, H-5'b), 1.98 (m, 1H, H-3'a), 1.76 (m, 1H, H-3'b). HRMS m/z 402.1229 calculated for $C_{11}H_{11}IN_2O_5Na$, found m/z 402.1233.

Example 22: 5-(2-Bromoethynyl)-2'-deoxyuridine (13a)

80% yield as an oil; $[\alpha]_D^{20}$ +3 (c 0.3, MeOH); ^{1}H NMR (CD_3OD) δ 8.30 (s, 1H, H-6), 6.05 (t, J = 6.3 Hz, 1H, H-1'), 4.21 (m, 1H, H-3'), 3.78 (m, 1H, H-4'), 3.65-3.50 (m, 2H, H-5'), 2.15 (dd, J = 5.6, 5.0 Hz, 2H, H-2'). HRMS m/z 355.1225 calculated for $C_{11}H_{11}BrN_2O_5Na$, found m/z 355.1227.

Example 23: 5-(2-bromoethynyl)-uridine (13b)

74% yield as an oil; $[\alpha]_D^{20}$ -23 (c 0.5, MeOH); ^{1}H NMR (DMSO-*d6*) δ 11.69 (br s, 1H, NH), 8.39 (s, 1H, H-6), 5.73 (d, J = 4.7 Hz, 1H, H-1'), 5.41 (d, J = 5.3 Hz, OH), 5.24 (t, J = 4.7 Hz, OH), 5.08 (d, J = 5.3 Hz, OH), 4.10-3.91 (m, 2H, H-2',3'), 3.85 (m, 1H, H-4'), 3.75-350 (m, 2H, H-5'). HRMS m/z 371.1219 calculated for $C_{11}H_{11}BrN_2O_6Na$, found m/z 371.1224.

Example 24: 5-(2-Bromoethynyl)-3'-deoxyuridine (13c)

72% yield as an oil; $[\alpha]_D^{20}$ -29 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 11.63 (s, 1H, NH), 8.53 (s, 1H, H-6), 5.59 (s, 1H, H-1'), 5.56 (d, J = 4.1 Hz, 1H, OH), 5.26 (t, J = 5.1 Hz, 1H, OH), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.81 (m, 1H, H-5'a), 3.61 (m, 1H, H-5'b), 1.95 (m, 1H, H-3'a), 1.72 (m, 1H, H-3'b). HRMS m/z 355.1225 calculated for $C_{11}H_{11}BrN_2O_5Na$, found m/z 355.1223.

Example 25: (*E*)-5-(1,2-Diiodovinyl)-2'-deoxyuridine (14a)

72% yield; mp 103-105 °C; $[\alpha]_D^{20}$ +28 (c 0.3, MeOH); ^{1}H NMR (CD_3OD) δ 8.27 (s, 1H, H-6), 7.52 (s, 1H, =CHI), 6.28 (t, J = 6.3 Hz, 1H, H-1'), 4.43 (m, 1H, H-3'), 3.97 (m, 1H, H-4'), 3.83 (dd, J = 11.9, 3.2 Hz, 1H, H-5'a), 3.73 (m, J = 11.9, 3.4 Hz, 1H, H-5'b), 2.43-2.12 (m, 2H, H-2'). HRMS m/z 530.0353 calculated for $C_{11}H_{12}I_2N_2O_5Na$, found m/z 530.0558.

Example 26: **(*E*)-5-(1,2-Diiodovinyl)-uridine (14b)**

82% yield; mp 107-109 °C; $[\alpha]_D^{20}$ +5 (c 1.0, MeOH); ^{1}H NMR (DMSO-*d6*) δ 11.65 (br s, 1H, NH), 8.05 (s, 1H, H-6), 7.05 (s, IH, =CHI), 5.80 (d, J = 4.7 Hz, 1H, H-1'), 5.50-5.10 (3 x br s, 3 x OH), 4.12-3.95 (m, 2H, H-2',3'), 3.87 (m, 1H, H-4'), 3.75-355 (m, 2H, H-5'). HRMS m/z 546.0347 calculated for $C_{11}H_{12}I_2N_2O_6Na$, found m/z 546.0351.

Example 27: **(*E*)-5-(1,2-Diiodovinyl)-3'-deoxyuridine (14c)**

76% yield as an oil; $[\alpha]_D^{20}$ +1.0 (c 0.8, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.21 (s, 1H, H-6), 7.55 (s, 1H, =CHI), 5.61 (s, 1H, H-1'), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.81 (m, 1H, H-5'a), 3.52 (m, 1H, H-5'b), 1.97 (m, 1H, H-3'a), 1.74 (m, 1H, H-3'b). HRMS m/z 530.0553 calculated for $C_{11}H_{12}I_2N_2O_5Na$, found m/z 530.0554.

Example 28: **(*E*)-5-(1-Bromo-2-iodovinyl)-2'-deoxyuridine (15a)**

78% yield as an oil; $[\alpha]_D^{20}$ +26 (c 2.0, MeOH); ^{1}H NMR (CD_3OD) δ 8.35 (s, 1H, H-6), 7.39 (s, 1H, =CHI), 6.25 (t, J = 6.5 Hz, 1H, H-1'), 4.45 (m, 1H, H-3'), 3.94 (m, 1H, H-4'), 3.86 (dd, J = 11.9, 3.2 Hz, 1H, H-5'a), 3.72 (dd, J = 11.9, 3.4 Hz, 1H, H-5'b), 2.45-2.15 (m, 2H, H-2'). HRMS m/z 483.0349 calculated for $C_{11}H_{12}BrIN_2O_5Na$, found m/z 483.0352.

Example 29: **(*E*)-5-(1-Bromo-2-iodovinyl)-uridine (15b)**

76% yield as an oil; $[\alpha]_D^{20}$ -1 (c 0.3, MeOH); ^{1}H NMR (D_2O) δ 8.27 (s, 1H, H-6), 7.45 (s, IH, =CHI), 5.79 (d, J = 4.7 Hz, 1H, H-1'), 4.15-3.92 (m, 2H, H-2',3'), 3.88 (m, 1H, H-4'), 3.67 (dd, J = 11.8, 2.5 Hz, 1H, H-5'a), 3.56 (dd, 1H, H-5'b). HRMS m/z 499.0343 calculated for $C_{11}H_{12}BrIN_2O_6Na$, found m/z 499.0348.

Example 30: **(*E*)-5-(1-Bromo-2-iodovinyl)-3'-deoxyuridine (15c)**

68% yield as an oil; $[\alpha]_D^{20}$ +3 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.35 (s, 1H, H-6), 7.39 (s, 1H, =CHI), 5.61 (d, J = 1.3 Hz, 1H, H-1'), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.76 (dd, J = 12.2, 2.4 Hz, 1H, H-5'a), 3.52 (dd, J = 12.2, 2.8 Hz, 1H, H-5'b), 1.97 (m, 1H, H-3'a), 1.75 (m, 1H, H-3'b). HRMS m/z 483.0349 calculated for $C_{11}H_{12}BrIN_2O_5Na$, found m/z 483.0344.

Example 31: **(*E*)-5-(1-Chloro-2-iodovinyl)-2'-deoxyuridine (16a)**

71% yield; mp 109-111 °C; $[\alpha]_D^{20}$ +34 (c 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 8.38 (s, 1H, H-6), 7.06 (s, 1H, =CHI), 6.30 (t, J = 6.5 Hz, 1H, H-1'), 4.43 (ddd, J = 6.5, 3.8, 3.6 Hz, 1H, H-3'), 3.96 (ddd, J = 3.6, 3.4, 3.0 Hz, 1H, H-4'), 3.83 (dd, J = 11.9, 3.1 Hz, 1H, H-5'a), 3.73 (dd, J = 11.9, 3.4 Hz, 1H, H-5'b), 2.45-2.10 (m, 2H, H-2'). HRMS m/z 438.5839 calculated for $C_{11}H_{12}ClIN_2O_5Na$, found m/z 438.5843.

Example 32: **(*E*)-5-(1-Chloro-2-iodovinyl)-uridine (16b)**

78% yield; mp 109-111 °C; $[\alpha]_D^{20}$ +5 (c 0.4, MeOH); ^{1}H NMR (D_2O) δ 8.45 (s, 1H, H-6), 7.05 (s, IH, =CHI), 5.89 (br s, 1H, H-1'), 4.30 (br s, 2H, H-2',3'), 4.10 (m, 1H, H-4'), 3.85 (dd, J = 11.5, 2.2 Hz, 1H, H-5'a), 3.75 (dd, 1H, H-5'b). HRMS m/z 454.5833 calculated for $C_{11}H_{12}ICIN_2O_6Na$, found m/z 545.5835.

Example 33: **(*E*)-5-(1-Chloro-2-iodovinyl)-3'-deoxyuridine (16c)**

70% yield as an oil; $[\alpha]_D^{20}$ +2 (c 2.0, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.38 (s, 1H, H-6), 7.18 (s, 1H, =CHI), 5.65 (d, J = 1.2 Hz, 1H, H-1'), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.76 (dd, J = 12.3, 2.6 Hz, 1H, H-5'a), 3.52 (dd, J = 12.3, 2.8 Hz, 1H, H-5'b), 2.01 (m, 1H, H-3'a), 1.75 (m, 1H, H-3'b). HRMS m/z 438.5839 calculated for $C_{11}H_{12}ClIN_2O_5Na$, found m/z 438.5837.

Example 34: **(*E*)-5-(1,2-Dibromovinyl)-2'-deoxyuridine (17a)**

85% yield as an oil; $[\alpha]_D^{20}$ +26 (c 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 8.39 (s, 1H, H-6), 7.06 (s, 1H, =CHBr), 6.28 (t, J = 6.5 Hz, 1H, H-1'), 4.41 (m, 1H, H-3'), 3.95 (m, 1H, H-4'), 3.82 (dd, J = 11.9, 2.9 Hz, 1H, H-5'a), 3.73 (dd, J = 11.9, 3.4 Hz, 1H, H-5'b), 2.45-2.10 (m, 2H, H-2'). HRMS m/z 436.0345 calculated for $C_{11}H_{12}Br_2N_2O_5Na$, found m/z 436.0348.

Example 35: **(*E*)-5-(1,2-Dibromovinyl)-uridine (17b)**

72% yield as an oil; $[\alpha]_D^{20}$ -14 (c 0.5, MeOH); ^{1}H NMR (D_2O) δ 8.45 (s, 1H, H-6), 7.07 (s, 1H, =CHBr), 5.93 (d, J = 5.2 Hz, 1H, H-1'), 4.18 (m, 2H, H-2',3'), 4.05 (m, 1H, H-4'), 3.88 (dd, J = 12.5, 2.5 Hz, 1H, H-5'a), 3.74 (dd, J = 12.5, 2.8 Hz, 1H, H-5'b). HRMS m/z 452.0339 calculated for $C_{11}H_{12}Br_2N_2O_6Na$, found m/z 452.0342.

Example 36: **(*E*)-5-(1,2-Dibromovinyl)-3'-deoxyuridine (17c)**

74% yield as an oil; $[\alpha]_D^{20}$ +5 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.42 (s, 1H, H-6), 7.25 (s, 1H, =CHI), 5.64 (br s, 1H, H-1'), 4.35 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.78 (m, H-5'a), 3.54 (m, H-5'b), 1.95 (m, 1H, H-3'a), 1.75 (m, 1H, H-3'b). HRMS m/z 436.0345 calculated for $C_{11}H_{12}Br_2N_2O_5Na$, found m/z 436.0340.

Preparation of the key intermediate 18 (for both 3'-F and 3'-N_3 series)

1-(4-Hydroxy-5-trityloxymethyl-tetrahydro-furan-2-yl)-1H-pyrimidine-2,4-dione (32)

A solution of 2'-deoxyuridine (10.0 g, 43.9 mmol) and para-anisylchlorodiphenylmethane (16.3 g, 52.6 mmol) in dry pyridine (235 mL) is refluxed for 2 hours. After cooling at room

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temperature (rt), pyridine is evaporated under reduced pressure, then dichloromethane (400mL) is added and the solution is washed with water (50 mL x3), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5 to EtOAc/MeOH: 9/1) to give the pure protected nucleoside **32** (21.9 g, 99 %) as a white solid. The physico-chemical data of the compound are fully related with those previously published.

1-(4-Hydroxy-5-trityloxymethyltetrahydrofuran-2-yl)-5-iodo-1*H*-pyrimidine-2,4-dione(33)

A solution of **32** (21.9 g, 43.8 mmol), I_2 (17.0 g, 66.9 mmol), CAN (17.7 g, 32.3 mmol), $NaHCO_3$ (1.0 g) in dry acetonitrile (480 mL) is refluxed for 4 days. After cooling at rt, a solution of saturated Na_2SO_3 (800 mL) and EtOAc (200 mL) are added: aqueous layer is extracted with EtOAc (300 mL x2), then organic layer is washed with saturated Na_2SO_3 (300mL), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 6/4 to EtOAc) to give the pure iodinated nucleoside **33** (12.8 g, 57 %) as a white solid. The physico-chemical data of the compound are fully related with those previously published.

1-(4-Hydroxy-5-trityloxymethyl-tetrahydro-furan-2-yl)-5-trimethylsilanylethynyl-1*H*-pyrimidine-2,4-dione (34)

33 (5.00 g, 8.0mmol) is dissolved in a mixture of dry DMF (62.5 mL), dry Et_3N (3.3 mL, 24.0mmol), and trimethylsilylacetylene (3.4 mL, 24.0 mmol). CuI (300.0 mg, 1.6 mmol) and $PdCl_2(PPh_3)_2$ (563 mg) are then added and the reaction mixture is stirred at rt under argon for 16 hours. Solvents are evaporated under reduced pressure. The crude product is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5 to 2/8) to give **34** (4.10 g, 86 %) as a pale yellow solid. $[\alpha]_D^{20}$ +27.5 (c 0.5, $CHCl_3$); mp 104 °C; ^{1}H NMR ($CDCl_3$) δ : 2.08-2.33 (m, 1H, H-2'a), 2.42-2.64 (m, 1H, H-2'b), 3.20-3.52 (m, 2H, H-5'), 3.78 (s, 3H, OCH3), 4.05-4.25 (m, 1H, H-4'), 4.40-4.53 (m, 1H, H-3'), 6.31 (dd, J = 5.6 Hz, 8.1 Hz, 1H, H-1'), 6.78-7.55 (m, 14H, trityl), 8.05 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ : 41.5 (C-2'), 55.3 (OCH3), 63.7 (C-5'), 72.5 (C-3'), 85.9 (C-1'), 86.6 (C-4'), 87.3 (C), 94.9 (C), 99.9 (C), 100.7 (C), 113.5 (CH), 127.2 (CH), 128.2 (CH), 128.3 (C), 130.5 (CH), 135.1 (C), 142.8 (C-6), 144.0 (C), 144.1 (C), 149.5 (C=O), 158.8 (C), 161.5 (C);

5-Ethynyl-1-(4-hydroxy-5-trityloxymethyl-tetra hydro-furan-2-yl)-1*H*-pyrimidine-2,4-dione (35)

A solution of **34** (616.3 mg, 1.03mmol), TBAF (303.4 mg, 1.16 mmol) in dry acetonitrile (24.0mL) is stirred at rt for 2 hours. Solvent is removed under reduced pressure, the crude product is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5 to 2/8) to give **35** (516.8 mg, 95 %) as a pale yellow solid. $[\alpha]_D^{20}$ +14.5 (c 1.0, $CHCl_3$); mp 110°C ; ^1H NMR ($CDCl_3$) δ : 2.22-2.40 (m, 1H, H-2'a), 2.45-2.60 (m, 1H, H-2'b), 2.90 (s, 1H, CH alkyne), 3.41 (t, J = 3.6 Hz, 2H, H-5'), 3.81 (s, 3H, OCH3), 4.15-4.20 (m, 1H, H-4'), 4.51-4.62 (m, 1H, H-3'), 6.30 (t, J = 8.2 Hz, 1H, H-1'), 6.70-7.50 (m, 14H, trityl), 8.10 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ : 41.6 (C-2'), 55.4 (OCH3), 63.7 (C-5'), 72.4 (C-3'), 74.2 (C), 82.2 (C), 85.9 (C-1'), 86.6 (C-4'), 87.5 (C), 99.4 (C), 113.5 (CH), 127.3 (CH), 128.2 (CH), 128.3 (C), 128.4 (C), 130.5 (CH), 135.1 (C), 143.8 (C-6), 143.9 (C), 144.1 (C), 149.4 (C=O), 158.9 (C), 161.7 (C);

Methanesulfonic acid 5-(5-ethynyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-2-trityloxymethyltetrahydrofuran-3-yl ester (18)

A solution of **35** (500.0 mg, 0.95 mmol) and methanesulfonylchloride (0.73 mL, 9.50 mmol) in dry pyridine at 0°C is allowed to warm to rt and is stirred for 16 hours. After cooling at 0°C, ice, water (100 mL) and EtOAc (100 mL) are added, the aqueous layer is extracted with EtOAc (50 mL x3), the organic layers are washed with water (50 mL x3), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5) to give **18** (587.0 mg, 99 %) as an orange solid. $[\alpha]_D^{20}$ +28.5 (c 1.0, $CHCl_3$); mp 99 °C; ^1H NMR ($CDCl_3$) δ : 2.30-2.50 (m, 1H, H-2'a), 2.70-2.82 (m, 1H, H-2'b), 2.91 (s, 1H, CH alkyne), 3.02 (s, 3H, SCH_3), 3.33-3.57 (m, 2H, H-5'), 3.80 (s, 3H, OCH_3), 4.35 (se, 1H, H-4'), 5.31 (se, 1H, H-3'), 6.29 (t, J = 8.2 Hz, 1H, H-1'), 6.75-7.50 (m, 14H, trityl), 8.07 (s, 1H, H-6), 8.58 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 38.8 (SCH_3), 39.3 (C-2'), 55.4 (OCH_3), 63.0 (C-5'), 74.0 (C-3'), 79.8 (C), 82.4 (C), 84.5 (C-1'), 85.4 (C-4'), 88.0 (C), 99.9 (C), 113.6 (CH), 127.5 (CH), 128.3 (CH), 128.3 (CH), 129.2 (C), 130.5 (CH), 134.6 (C), 143.2 (C-6), 143.6 (C), 143.7 (C), 149.2 (C=O), 159.0 (C), 161.2 (C);

Example 37 : 5-(1,2-Di-iodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2.4-dione (25a)

Step a):5-Ethynyl-1-(4-hydroxy-5-trityloxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (19)

A solution of **18** (50.0 mg, 0.08 mmol) in dioxanne (2.0 mL) and aqueous 1M NaOH (168 µL, 0.16 mmol) is refluxed for 2 hours. After cooling at rt, solvents are removed in vaccuo and the crude product is submitted to a flash silica gel column chromatography (eluent:

hexanes/EtOAc: 5/5 to EtOAc) to give **19** (41.0 mg, 93 %) as a pale yellow solid. $[\alpha]_D^{20}$ –13.0 (c1.0, $CHCl_3$); mp 124 °C ; ^1H NMR ($CDCl_3$) δ: 2.08-2.25 (m, 1H, H-2'a), 2.47-2.66 (m, 1H, H-2'b), 3.07 (s, 1H, CH alkyne), 3.43-3.72 (m, 2H, H-5'), 3.79 (s, 3H, OCH_3), 4.00-4.12 (m, 1H, H-4'), 4.38-4.50 (m, 1H, H-3'), 6.15 (t, J = 6.1 Hz, 1H, H-1'), 6.80-7.55 (m, 14H, trityl), 8.15 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 41.1 (C-2'), 55.4 (OCH_3), 61.9 (C-5'), 70.9 (C-3'), 75.0 (C), 81.7 (CH alkyne), 83.4 (C-1'), 85.9 (C-4'), 87.5 (C), 98.5 (C), 113.6 (CH), 127.4 (CH), 128.2 (CH), 130.4 (CH), 134.9 (C), 143.8 (C), 143.8 (C), 145.3 (C-6), 149.5 (C=O), 159.0 (C), 161.8 (C);

Step b): 5-Ethynyl-1-(4-fluoro-5-trityloxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (**20**)

To a solution of the product Step (a) (1.26 g, 2.4 mmol) in dry dichloromethane (77.0 mL) at 0°C is added dropwise diethylaminosulfur trifluoride (0.6mL, 4.8mmol), and the reaction mixture is stirred for 15 minutes. Then a saturated $NaHCO_3$ solution (50.0 mL) is added, the aqueous layer is extracted with CH_2Cl_2 (50 mL x3), the organic layers are washed with water (50 mL), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5) to give **20** (805.0 mg, 64 %) as a pale yellow solid. $[\alpha]_D^{20}$ +12.0 (c 1.0, $CHCl_3$); mp 54 °C; ^1H NMR ($CDCl_3$) δ: 2.12-2.46 (m, 1H, H-2'a), 2.68-2.90 (m, 1H, H-2'b), 2.88 (s, 1H, CH alkyne), 3.35-3.48 (m, 2H, H-5'), 3.80 (s, 3H, OCH_3), 4.37 (d, J = 27.4 Hz, 1H, H-4'), 5.28 (dd, J = 4.6 Hz, 53.6 Hz, 1H, H-3'), 6.34 (dd, J = 5.3 Hz, 9.0 Hz, 1H, H-1'), 6.80-7.50 (m, 14H, trityl), 8.10 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 39.7 (d, J = 84.2 Hz, C-2'), 55.4 (OCH_3), 63.4 (d, J = 40.9 Hz, C-5'), 82.2 (CH alkyne), 84.8 (d, J = 101.1 Hz, C-4'), 85.7 (C-1'), 87.8 (C), 94.5 (d, J = 710.0 Hz, C-3'), 99.7 (C), 113.6 (CH), 127.4 (CH), 128.3 (CH), 128.4 (CH), 130.5 (CH), 134.6 (C), 143.4 (C-6), 143.6 (C), 143.7 (C), 149.2 (C=O), 159.0 (C x2);

General procedure for di-halogenation of 5- ethynyl compound

5-ethynyl nucleoside of example 37, Step b) (0.5 mmol) is dissolved in dry acetonitrile (5.0 mL) and the reaction mixture is cooled to an ice bath. A solution of the halogenating reagent (i.e. I_2, IBr or ICl; 0.6 mmol) in dry CH_3CN (1.0 mL) is added dropwise at 0°C and the reaction mixture is stirred until completion (typically 15 min.-2 hours, checked by TLC). The reaction mixture is quenched at 0°C by a saturated Na_2SO_3 solution (2 mL) then extracted with EtOAc (10 mL x 3). The organic layer is washed with water (5 mL x2) and brine (10 mL), then dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure

to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 8/2 to 3/7) to give the desired di-halogenated compound.

Step c): 5-(1,2-Diiodovinyl)-1-(4-fluoro-5-trityloxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (**24a**)

Prepared from compound **20** of step b) using I_2 with the typical procedure described before to give **24a** (32 %) as an orange solid. $[\alpha]_D^{20}$ +4.5 (c 1.0, $CHCl_3$); mp 58 °C; ^1H NMR ($CDCl_3$) δ: 2.05-2.35 (m, 1H, H-2'a), 2.67-2.86 (m, 1H, H-2'b), 3.43 (d, J = 3.8 Hz, 2H, H-5'), 3.81 (s, 3H, OCH_3), 4.34 (td, J = 3.5 Hz, 27.0 Hz, 1H, H-4'), 5.23 (dd, J = 4.7 Hz, 53.7 Hz, 1H, H-3'), 6.33 (dd, J = 5.0 Hz, 9.1 Hz, 1H, H-1'), 6.75-7.50 (m, 15H, CH alkene, trityl), 7.63 (s, 1H, H-6), 9.00 (se, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 39.4 (d, J = 84.2 Hz, C-2'), 55.5 (OCH_3), 63.1 (d, J = 38.5 Hz, C-5'), 84.5 (d, J = 101.0 Hz, C-4'), 85.3 (C), 85.5 (CH alkene), 87.5 (C), 87.7 (C-1'), 94.1 (d, J = 710.0 Hz, C-3'), 113.6 (CH), 118.1 (C), 127.4 (CH), 128.3 (CH), 128.4 (CH), 130.5 (CH), 134.8 (C), 139.2 (C-6), 143.7 (C), 143.8 (C), 149.5 (C=O), 158.9 (C), 159.0 (C);

Step d): 5-(1,2-Diiodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (**25a**)

Prepared from compound **24a**, using the typical procedure described before to give **25a** (51%) as a yellow solid. $[\alpha]_D^{20}$ +16.0 (c 1.0, CH_3OH); mp 112 °C; UV (MeOH) λ_{max} 232 nm, 274 nm; ^1H NMR (CD_3OD) δ : 2.13-2.47 (m, 1H, H-2'a), 2.50-2.77 (m, 1H, H-2'b), 3.80 (d, J = 2.8 Hz, 2H, H-5'), 4.32 (td, J = 2.9 Hz, 27.0 Hz, 1H, H-4'), 5.30 (dd, J = 4.6 Hz, 53.7 Hz, 1H, H-3'), 6.36 (dd, J = 5.6 Hz, 9.0 Hz, 1H, H-1'), 7.53 (s, 1H, CH alkene), 8.28 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 40.3 (d, J = 81.9 Hz, C-2'), 62.7 (d, J = 43.3 Hz, C-5'), 87.0 (C-1'), 87.3 (d, J = 96.3 Hz, C-4'), 87.3 (C), 88.1 (CH alkene), 96.0 (d, J = 698.0 Hz, C-3'), 119.2 (C), 142.2 (C-6), 151.5 (C=O), 161.8 (C=O);

Compounds of examples 38 and 39 are obtained in a similar way starting from compounds **24b** and **24c** respectively.

Example 38 : 5-(1-Bromo-2-iodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (25b).

Prepared from compound **24b**, using the typical procedure described before to give the title compound (52 %) as a pale yellow solid. $[\alpha]_D^{20}$ +13.0 (c 0.6, CH_3OH); mp 107 °C; UV (MeOH) λ_{max} 296 nm; ^1H NMR (CD_3OD) δ: 2.14-2.47 (m, 1H, H-2'a), 2.52-2.78 (m, 1H, H-2'b), 3.80 (d, J = 3.0 Hz, 2H, H-5'), 4.31 (td, J = 2.9 Hz, 27.0 Hz, 1H, H-4'), 5.30 (dd, J = 4.7 Hz, 53.7 Hz, 1H, H-3'), 6.36 (dd, J = 5.6 Hz, 9.0 Hz, 1H, H-1'), 7.30 (s, 1H, CH alkene), 8.36 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 40.3 (d,C-2'), 62.7 (d, C-5'), 83.2 (CH alkene), 87.0 (C-1'),

87.3 (d, C-4'), 87.3 (C), 96.0 (d, C-3'), 115.5 (C), 116.0 (C), 143.9 (C-6), 151.5 (C=O), 161.8 (C=O);

Example 39 :5-(1-Chloro-2-iodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (25c)

Prepared from compound **24c**, using the typical procedure described before to give the title compound (76 %) as an orange solid. $[\alpha]_D^{20}$ +17.0 (c 0.7, CH_3OH); mp 87 °C; UV (MeOH) λ_{max} 274 nm; ^1H NMR (CD_3OD) δ : 2.13-2.48 (m, 1H, H-2'a), 2.52-2.75 (m, 1H, H-2'b), 3.80 (d, J = 2.8 Hz, 2H, H-5'), 4.30 (td, J = 2.8 Hz, 26.8 Hz, 1H, H-4'), 5.30 (dd, J = 4.6 Hz, 53.5 Hz, 1H, H-3'), 6.37 (dd, J = 5.7 Hz, 8.8 Hz, 1H, H-1'), 7.06 (s, 1H, CH alkene), 8.38 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 40.2 (d, J = 84.2 Hz, C-2'), 62.7 (d, J = 43.3 Hz, C-5'), 81.1 (CH alkene), 87.0 (C-1'), 87.4 (d, J = 93.9 Hz, C-4'), 96.2 (d, J = 698.0 Hz, C-3'), 114.5 (C) , 128.9 (C), 146.0 (C-6), 151.2 (C=O), 164.2 (C=O);

Example 40 : 1-(4-Fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (22)

Step a): 1-(4-Fluoro-5-trityloxymethyl-tetrahydro-furan-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (**21**)

5-ethynyl nucleoside **20** (0.5 mmol) was dissolved in dry acetonitrile (5.0 mL) and the reaction mixture is cooled to an ice bath. A solution of the halogenating reagent (i.e. IDCP; 0.7 mmol) and $Ag(coll)_2ClO_4$ (11.0mg) are added and the reaction mixture is stirred in the dark at rt (typically 2 h-20 h, checked by TLC). The reaction mixture is quenched at 0°C by a saturated Na_2SO_3 solution (2 mL) then extracted with EtOAc (10 mL x4). The organic layer is washed with water (10 mL), a 1M HCl solution (5 mL x3), water (5 mL x2), and brine (10 mL), then dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 8/2 to 3/7) to give **21** (26 %) as yellow solid. $[\alpha]_D^{20}$ +122.0 (c 1.0, $CHCl_3$); mp 73 °C; ^1H NMR ($CDCl_3$) δ: 2.15-2.48 (m, 1H, H-2'a), 2.68-2.93 (m, 1H, H-2'b), 3.30-3.56 (m, 2H, H-5'), 3.81 (s, 3H, OCH_3), 4.38 (d, J = 27.0 Hz, 1H, H-4'), 5.32 (dd, J = 4.4 Hz, 53.4 Hz, 1H, H-3'), 6.33 (dd, J = 5.3 Hz, 9.1 Hz, 1H, H-1'), 6.75-7.50 (m, 14H, trityl), 8.01 (s, 1H, H-6), 9.20 (se, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 12.1 ($C\underline{C}I$), 39.8 (d, J = 86.6 Hz, C-2'), 55.4 ($O\underline{C}H_3$), 63.4 (d, J = 40.9 Hz, C-5'), 84.2 (C), 84.9 (d, J = 101.1 Hz, C-4'), 86.0 (C-1'), 87.8 (C), 94.5 (d, J = 707.6 Hz, C-3'), 101.0 (C), 113.6 (CH), 127.5 (CH), 127.9 (C), 128.1 (CH), 128.2 (CH), 130.4 (CH), 134.6 (C), 143.5 (C), 143.7 (C-6), 143.8 (C), 149.2 (C=O), 159.0 (C), 161.6 (C);

Step b): 1-(4-Fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (**22**)

A solution of the protected nucleoside **21** (0.3 mmol) in acetic acid 80 % (30 mL) is stirred until completion (checked by TLC, typically 18 hours). After evaporation of the solvent, the crude product was submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 2/8) to give **22** (47 %) as a yellow solid. $[\alpha]_D^{20}$ –1.5 (c 1.0, CH_3OH); mp 140°C; UV (MeOH) λ_{max} 233 nm, 298 nm; ^1H NMR (CD_3OD) δ: 2.11-2.45 (m, 1H, H-2'a), 2.46-2.75 (m, 1H, H-2'b), 3.79 (d, J = 3.2 Hz, 2H, H-5'), 4.29 (td, J = 2.9 Hz, 27.0 Hz, 1H, H-4'), 5.27 (dd, J = 4.9 Hz, 53.9 Hz, 1H, H-3'), 6.28 (dd, J = 5.5 Hz, 8.9 Hz, 1H, H-1'), 8.30 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 15.8 (C<u>C</u>I), 39.8 (d, J = 81.8 Hz, C-2'), 62.5 (d, J = 43.3 Hz, C-5'), 85.2 (C), 87.0 (C-1'), 87.3 (d, J = 96.3 Hz, C-4'), 96.0 (d, J = 700.4 Hz, C-3'), 101.5 (C) , 146.0 (C-6), 151.1 (C=O), 164.4 (C=O).

<u>Example 41:</u> 1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1,2-diiodovinyl)-1*H*-pyrimidine-2,4-dione (31a)

Step a): 1-(4-Azido-5-trityloxymethyltetrahydrofuran-2-yl)-5-ethynyl-1*H*-pyrimidine-2,4-dione (**26**)

A solution of **18** (100 mg, 0.16 mmol) and NaN_3 (35 mg, 0.54 mmol) in DMF (5 mL) is refluxed overnight. After evaporation of volatiles, the crude product is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 2/8) to give **26** (61.0 mg, 70%) as a pale yellow solid. $[\alpha]_D^{20}$ +13 (c 0.8, CH_3OH); mp 110°C; ^1H NMR ($CDCl_3$) δ : 2.35-2.46 (m, 1H, H-2'a), 2.52-2.62 (m, 1H, H-2'b), 2.89 (s, 1H, CH alkyne), 3.37-3.52 (m, 2H, H-5'), 3.82 (s, 3H, O<u>C</u>H_3), 4.00-4.04 (m, 1H, H-4'), 4.28-4.34 (m, 1H, H-3'), 6.15 (t, J = 6.1 Hz, 1H, H-1'), 6.88 (d, J = 8.9 Hz, 2H, trityl), 7.21-7.51 (m, 14H, trityl), 8.08 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 38.6 (C-2'), 55.3 (O<u>C</u>H_3), 60.4 (C-3'), 62.7 (C-5'), 82.3 (CH alkyne), 84.0 (C-4'), 85.5 (C-1'), 87.6 (C), 99.4 (C), 113.6 (CH x2), 127 .3 (CH), 128.1 (CH), 128.2 (CH), 130.4 (CH), 134.7 (C), 143.7 (C), 149.2 (C), 158.9 (C), 161.6 (C);

Step b):1-(4-Azido-5-trityloxymethyl-tetrahydro-furan-2-yl)-5-(1,2-diiodo-vinyl)-1*H*-pyrimidine-2,4-dione (**30a**)

Prepared from compound of Step a), using I_2 with the typical procedure described before for the preparation of **24a** to give **30a** (52 %) as a pale yellow solid. $[\alpha]_D^{20}$ +16 (c 1.0, CH_3OH); mp 139°C; ^1H NMR ($CDCl_3$) δ: 2.23-2.34 (m, 1H, H-2'a), 2.51-2.61 (m, 1H, H-2'b); 3.36-3.49 (m, 2H, H-5'), 3.81 (s, 3H, O<u>C</u>H_3), 3.98-4.05 (m, 1H, H-4'), 4.16-4.26 (m, 1H, H-3'), 6.16 (t, J = 6.6 Hz, 1H, H-1'), 6.87 (d, J = 8.8 Hz, 2H, trityl), 7.21-7.43 (m, 13H, trityl, CH alkene), 7.58 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 38.1 (C-2'), 55.2 (O<u>C</u>H_3), 60.4 (C-3'), 62.8 (C-5'), 83.5 (C-

4'), 85.1 (C-1'), 87.1 (C), 87.2 (CH alkene), 113.3 (CH), 117.6 (C), 127.1 (CH), 128.0 (CH), 128.1 (CH), 130.2 (CH), 135.6 (C), 139.0 (C-6), 143.5 (C), 143.6 (C), 149.1 (C=O), 158.6 (C), 158.7 (C);

Step c):1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1,2-diiodo-vinyl)-1*H*-pyrimidine-2,4-dione (**31a**)

Prepared from compound **30a** using the typical procedure described before for the preparation of **24a** to give **31a** (78%) as a pale yellow gum. $[\alpha]_D^{20}$ +17 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 225 nm, 284 nm; ^1H NMR (DMSO-d_6) δ : 2.34-2.43 (m, 2H, H-2'), 3.56-3.71 (m, 2H, H-5'), 3.85-3.90 (m, 1H, H-4'), 4.35-4.41 (m, 1H, H-3'), 5.26 (t, J = 4.9 Hz, 1H, OH), 6.09 (t, J = 6.3 Hz, 1H, H-1'), 7.61 (s, 1H, CH alkene), 8.06 (s, 1H, H-6'), 11.68 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 37.5 (C-2'), 60.4 (C-3'), 61.4 (C-5'), 85.0 (C-1', C-4'), 88.9 (C-I), 90.2 (CH alkene), 117.7 (C-5), 140.5 (C-6), 150.1 (C=O), 159.9 (C=O).

Compounds of examples 42 and 43 are obtained in a similar way, starting from compounds **30b** and **30c** respectively.

Example 42: 1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1-bromo-2-iodo-vinyl)-1H-pyrimidine-2,4-dione (31b)

Prepared from compound **30b** using the typical procedure described before to give **31b** (53%) as a pale yellow gum. $[\alpha]_D^{20}$ +11 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 229 nm, 276 nm; ^1H NMR (DMSO-d_6) δ: 2.36-2.43 (m, 2H, H-2'), 3.57-3.69 (m, 2H, H-5'); 3.86-3.91 (m, 1H, H-4'), 4.35-4.42 (m, H-3'), 5.28 (brs, 1H, OH), 6.09 (t, J = 5.9 Hz, 1H, H-1'), 7.45 (s, 1H, CH alkene), 8.18 (s, 1H, H-6'), 11.7 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 37.0 (C-2'), 60.0 (C-3'), 60.7 (C-5'), 84.6 (C-1', C-4'), 85.6 (CH alkene), 113.9 (C), 114.2 (C), 141.9 (C-6), 149.6 (C=O), 159.4 (C=O);

Example 43: 1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1-chloro-2-iodo-vinyl)-1*H*-pyrimidine-2,4-dione (31c)

Prepared from compound **30c** using the typical procedure described before to give **31c** (57%) as a pale yellow gum. $[\alpha]_D^{20}$ +28 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 214 nm, 273 nm; ^1H NMR (DMSO-d_6) δ: 2.33-2.44 (m, 2H, H-2'), 3.33-3.71 (m, 1H, H-5'), 3.86-3.91 (m, 1H, H-4'), 4.35-4.42 (m, 1H, H-3'), 5.28 (t, J = 4.9 Hz, 1H, OH), 6.09 (t, J = 6.2 Hz, 1H, H-1'), 7.23 (s, 1H, CH alkene), 8.22 (s, 1H, H-6), 11.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 37.7 (C-2'), 60.7 (C-3'), 61.3 (C-5'), 84.5 (CH), 85.2 (CH x2), 113.0 (C), 127.4 (C), 143.1 (C-6), 150.3 (C=O), 160.1 (C=O);

Example 44: 1-(4-Azido-5-hydroxymethyl-tetrahydro-furan-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (28)

Prepared from compound **26** using a similar procedure as the one disclose above for Example 40, to give the title compound 60 % as a pole yellow gum, $[\alpha]_D^{20}$ +15 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 236 nm, 295 nm; ^1H NMR (DMSO-d_6) δ : 2.24-2.34 (m, 1H, H-2'a), 2.39-2.46 (m, 1H, H-2'b), 3.54-3.72 (m, 2H, H-5'), 3.79-3.84 (m, 1H, H-4'), 4.34-4.41 (m, 1H, H-3'), 5.30 (t, *J* = 5.3 Hz, 1H, OH), 6.01 (t, *J* = 6.0 Hz, 1H, H-1'), 8.22 (s, 1H, H-6), 11.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ : 19.8 (C), 36.8 (C-2'), 59.2 (C-3'), 60.2 (C-5'), 84.3 (C-1', C-4'), 84.8 (C), 99.0 (C), 144.6 (C-6), 149.3 (C=O), 161.7 (C=O).

Biological evaluation

Antiviral and Cytotoxicity assays for HCV. Huh7 cells harbouring the subgenomic HCV replicon BM4-5 (J.T. Guo et al., J. Virol. 2001, 75 : 8516-8523) were used in this study. Cells were maintained in Dulbecco's modified Eagle's medium high glucose 4.5 g/l (LifeTechnlogies) supplemented with 10% fetal bovine serum, 1% L-glutamine, 1% penicillin and streptomycin, 1% L-Pyruvate and 500 µg/ml of geneticien (G418, Invitrogen). Geneticin was used to select cells permitting the HCV RNA replication. Cells were passaged every four days with a 1:4 ratio.

Cells were seeded in 6-wells plates at a density of 2.5 x 10^5 cells per well, sixteen hours before the beginning of treatment. Cells were treated with the molecules administered at different concentrations in complete medium that did not contain geneticin. The administration of each drug was renewed every day for three consecutive days. Ribarivin (ICN Pharmaceuticals), mycophenolic acid (MPA, Sigma), and interferon alpha-2b (IntronA®) were used in the same conditions as positive controls. The concentrations used for these drugs were respectively: 0; 0.5; 1; 2; 4; 8; 16; 32; 64; 128; 256 and 512 µM for ribavirin, 0; 2.5; 5; 10; 20; 40 µM for mycophenolic acid, and 0; 0.1; 1; 10; 100 and 1000 UI/mL for IFN alpha-2b. Total RNA was extracted at the end of treatment (24 hours after the last day of treatment) with the « Extract all » reagent (Eurobio), which is a mix of phenol and guanidium thiocyanate. Northern blot analysis was then performed using the NorthernMax™-Gly kit (Ambion), following manufacturer's instructions. Five micrograms of total RNA were denaturated in glyoxal buffer at 50°C for 30 minutes, separated by 1.1% agarose gel electrophoresis, and then transferred for 12 hours onto a charged nylon membrane (HybondN+, Amersham). Hybridization was carried out with three different [^{32}P]CTP-labelled riboprobes obtained by *in vitro* transcription (Riboprobe *in vitro* transcription system, Promega). Two probes were complementary to the NS5A region of the HCV genome of

negative polarity and positive polarity. A third probe was complementary to the beta-actin mRNA and obtained by *in vitro* transcription from a specific plasmid (pTRI beta actin human, reference 7424, Ambion). First, the blot was hybridized with the riboprobes directed against the negative strand of HCV RNA and beta-actin mRNA, respectively. After one night of hybridization at 68°C, the membrane was washed, then exposed to X-ray film and a phosphor screen (phosphorimager). This screen was then scanned and quantitative analysis was achieved using ImageQuant software. The amount of beta-actin mRNA was used as an internal loading control to standardize the amount of HCV RNA detected. The same membrane was subsequently hybridized with the negative sense riboprobe to determine the level of positive strand HCV RNA, suing the same approach.

For cell viability assays, cells were seeded in 96-well plates at a density of 12,500 cells per well. They were treated by the different molecules with the same concentrations and conditions than those used for the antiviral assays. Then, cell viability was measured by neutral red assay. Neutral red specifically colors lysosomes and its accumulation depends on cellular membrane integrity. The yield of neutral red incorporated in cells is proportional to the number of living cells. At the end of treatment, culture medium was removed; cells were washed by PBS, then coloured with neutral red at 0.005% for 3 hours at 37°C. Cells were then fixed 1 minute by formol calcium and lysed by atreatment with a vol/vol mixture of acetic acid and ethanol. After 15 minutes incubation, absorbance was read at 490nm.

Antiviral and cytotoxicity assays for BVDV. Noncytopathic-BVDV-free MDBK cells (European Collection of Animal Cell Cultures, Porton Down, U.K.) were kindly provided by Dr N. Zitzmann (Oxford University). Cells were propagated in DMEM F12 (Eurobio) supplemented with 10% horse serum (Life Technologies), 1% L-glutamin (Gibco), 1% penicillin ansd streptomycin (Gibco). The NADL cytopathic (CP) BVDV strain was obtained from ATCC: VR-504.

MDBK cells were seeded in microwell plates (96 wells) at a density of 1.10^5 cells per well, then infected with BVDV (strain NADL) (at dilution inducing 100% cytopathic effect three days post inoculation, *i.e* approximately 10 plaque forming units (pfu) per well at three days post infection) for one hour, at 37°C. After a wash with DMEM, infected cells were incubated for three days in the presence of absence of drug; each concentration of drug was added in 12 consecutive wells. The appearance of CPE was visually checked the third day post inoculation to evaluate the IC50 on BVDV (strain NADL), according to the different conditions of treatment. By definition, the IC50 is the concentration of drug that inhibits 50% of the CPE in comparison to cells inoculated but untreated presenting 100% of CPE.

Uninfected MDBK cells were grown in the absence or presence of varying concentrations of drug tested. After 3 days, toxicity was evaluated by neutral red coloration as described above.

	Compound #	Anti-HCV activity and cytotoxicity on Replicon System (+)-RNA				Cytotoxicity (CC_{50})		
		CC_{50}	IC_{50}	IC_{90}	SI	PBM	CEM	VERO
	IFNα-2b	> 1000	19	760	52			
	Ribavirin	110	170	> 512	< 1			
	MPA	7	40		< 1			
2'-deoxyribosyl moiety	12a	>182	57.1	> 239	> 3.2	7.5	15.8	> 100
	13a	>200	> 200	> 200	≥1	>100	> 100	> 100
	14a	76.7	> 161	> 263	< 1	14.7	19.5	19.5
	15a	43	> 100	> 100	< 1	13.3	0.13	6.6
	16a	213	79.8	> 207	2.7	3.2	14.8	1.4
	17a	> 200	< 200	> 200	≥1	>100	43.9	> 100
ribosyl moiety	12b	147.5	> 200	> 200	< 1	> 100	> 100	> 100
	13b	188.3	58	> 200	3.2	> 100	> 100	> 100
	14b	> 250	161.7	> 250	> 1.5	> 100	41.7	49.5
	15b	> 100	> 100	> 100	≤1	> 100	93.6	> 100
	16b	> 200	74.9	> 250	> 2.8	> 100	> 100	> 100
	17b	> 200	> 200	> 200	≤1	> 100	> 100	59.8
3'-deoxyribosyl moiety	12c	> 200	> 200	> 200	≤1	> 100	> 100	3.2
	13c	> 300	> 300	> 300	≤1	> 100	> 100	6.4
	14c	> 200	> 200	> 200	≤1	87.2	> 100	42.6
	15c	> 200	> 200	> 200	≤1	71.5	79.3	> 100
	16c	> 200	> 200	> 200	≤1	94.4	66.6	15.3
	17c	> 200	≥200	> 200	≤1	> 100	79.3	7.8

Table 1 : Evaluation of the antiviral activity and cells viability (obtained with neutral red test) against Hepatitis C Virus (HCV) replication using cell line harboring HCV subgenomic replicon, of the antiviral activity against HIV-1 in PBM cells and of the cytotoxicity against PBM, CEM and VERO cells *in vitro*. Results are expressed in *μM*, except for IFN which is expressed as International Units/ml. Selectivity Index (SI) is the ratio between CC_{50} and IC_{50}.

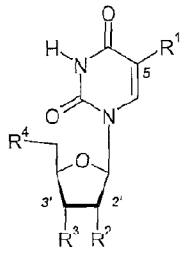
Compound #	**CC_{50} (Neutral Red)**	**EC_{50} ECP inhibition (3rd day p.i.)**	**SI**
Ribavirin	> 100	36 μM	> 2.77
12a-c, 13b, 14a-c, 15c, 16a-c	> 100	> 100	< 1

Table 2 : Neutral red testing and antiviral assay on BVDV strain NADL expressed in μM.

It should be clearly understood that the invention defined by the attached claims is not limited to the particular embodiments indicated in the above description, but encompasses the variants which depart neither from the context nor from the spirit of the present invention.

CLAIMS

1. Use of an uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms,

for the preparation of a drug having antiviral activity against a Flaviviridae.

2. The use according to claim 1, wherein the uridine derivative of formula (I) presents the following characteristics:

- R^1 represents –C≡C-X or -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen ;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -phosphate, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

3. The use according to claim 2, wherein R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or –C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.

4. The use according to claim 2, wherein

- R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine;
- R^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl;
- R^2 and R^3 not simultaneously being each hydrogen ; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as their possible tautomers, their possible pharmaceutically acceptable addition salts with an acid or a base, and their N-oxide forms

5. The use according to claim 1, wherein the uridine derivatives is chosen from among the following compounds:

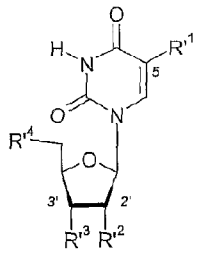
- (*E*)-5-(1-Chloro-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Diiodovinyl)-2'-deoxyuridine,
- 5-(2-Iodoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Dibromovinyl)-2'-deoxyuridine,
- 5-(2-Bromoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Chloro-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Diiodovinyl)-uridine,
- 5-(2-Iodoethynyl)-uridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Dibromovinyl)-uridine, and
- 5-(2-bromoethynyl)-uridine,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

6. The use according to any one of claims 1 to 5, wherein an uridine derivative of formula (I) as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms, and an interferon are used for the preparation of a drug having antiviral activity against a Flavividdae.

7. The use according to any one of claims 1 to 6, for the preparation of a drug having antiviral activity against hepatitis C virus (HCV).

8. A compound of formula (I') :



(I')

wherein

- R'^1 represents -C(Y)=CH(X), -C(Y)=C(X)alkyl or -C(Y)=C-Ak(X), where Y is halogen and Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;
- R'^2, R'^3 and R'^4 have the same definitions as R^2, R^3 and R^4, respectively, in the above formula (I);

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

9. The compound according to claim 8, wherein :

- R'^1 represents -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R'^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms.

10. The compound according to claim 9, wherein R^1 represents –C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.

11. The compound according to claim 9, wherein

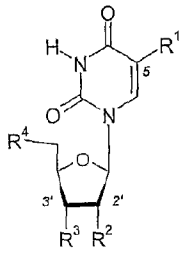
- R'^1 represents -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R'^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl; and

- R'^2 and R'^3 not simultaneously being each hydrogen; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms.

12. A drug formulation having an antiviral activity against a Flaviviridae comprising

(1) an uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms,.

(2) an immunomodulator or another active ingredient having an antiviral activity against a Flaviviridae, and

(3) a pharmaceutically acceptable vehicule, carrier or excipient.

13. The drug formulation according to claim 12, wherein ingredient (2) comprises an interferon.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003882

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A61K31/70 A61P31/12

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)
A61K

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 practical, search terms used)
EPO-Internal, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GOODCHILD ET AL: "Structural requirements of olefinic 5 substituted deoyuridines for antiherpes activity" J.MED.CHEM, vol. 26, 1983, pages 1252-1257, XP002329924 cited in the application compound 5	8-11
A	CLERCQ: "HAMAO UMEZAWA MEMORILA AWARD LECTURE" INTERN.J.ANTIMICROB AGENTS, vol. 18, 2001, - 2001 pages 309-328, XP002329925 paragraph [02.5]	1-12

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[X] Further documents are listed in the continuation of Box C. [ ] 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
"E" earlier document but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"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
"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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2006	25/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cattell, James

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003882

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MENDIRATTA ET AL: "Structure Activity Study on Antiviral 5-vinylpyrimidine Nucleoside Analogs Using Wiener's Topological Index" J.CHEM.INF.COMPUT.SCI, vol. 34, 1994, - 1994 pages 867-871, XP002371658 compound 30 -----	8-11

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WO 02/08241 A2

(54) Title: PRODRUGS OF PHOSPHONATE NUCLEOTIDE ANALOGUES AND METHODS FOR SELECTING AND MAKING SAME

(57) Abstract: A novel method is provided for screening prodrugs of methoxyphosphonate nucleotide analogues to identify prodrugs selectively targeting desired tissues with antiviral or antitumor activity. This method has led to the identification of novel mixed ester-amidates of PMPA for retroviral or hepadnaviral therapy, including compounds of structure (5a) having substituent groups as defined herein. Compositions of these novel compounds in pharmaceutically acceptable excipients and their use in therapy and prophylaxis are provided. Also provided is an improved method for the use of magnesium alkoxide for the preparation of starting materials and compounds for use herein.

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Prodrugs of Phosphonate Nucleotide Analogues and Methods for Selecting and Making Same

This application relates to prodrugs of methoxyphosphonate nucleotide analogues. In particular it relates to improved methods for making and identifying such prodrugs.

Many methoxyphosphonate nucleotide analogues are known. In general, such compounds have the structure A-$OCH_2P(O)(OR)_2$ where A is the residue of a nucleoside analogue and R independently is hydrogen or various protecting or prodrug functionalities. See U.S. Patent Nos. 5,663,159, 5,977,061 and 5,798,340, Oliyai et al, "Pharmaceutical Research" 16(11):1687-1693 (1999), Stella et al., "J. Med. Chem." 23(12):1275-1282 (1980), Aarons, L., Boddy, A. and Petrak, K. (1989) *Novel Drug Delivery and Its Therapeutic Application* (Prescott, L. F. and Nimmo, W. S., ed.), pp. 121–126; Bundgaard, H. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 70–74 and 79-92; Banerjee, P. K. and Amidon, G. L. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 118-121; Notari, R. E. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 135-156; Stella, V. J. and Himmelstein, K. J. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 177-198; Jones, G. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 199-241; Connors, T. A. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 291–316. All literature and patent citations herein are expressly incorporated by reference.

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Summary of the Invention

Prodrugs of methoxyphosphonate nucleotide analogues intended for antiviral or antitumor therapy, while known, traditionally have been selected for their systemic effect. For example, such prodrugs have been selected for enhanced bioavailability, i.e., ability to be absorbed from the gastrointestinal tract and converted rapidly to parent drug to ensure that the parent drug is available to all tissues. However, applicants now have found that it is possible to select prodrugs that become enriched at therapeutic sites, as illustrated by the studies described herein where the analogues are enriched at localized focal sites of HIV infection. The objective of this invention is, among other advantages, to produce less toxicity to bystander tissues and greater potency of the parental drug in tissues which are the targets of therapy with the parent methoxyphosphonate nucleotide analogue.

Accordingly, pursuant to these observations, a screening method is provided for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue;

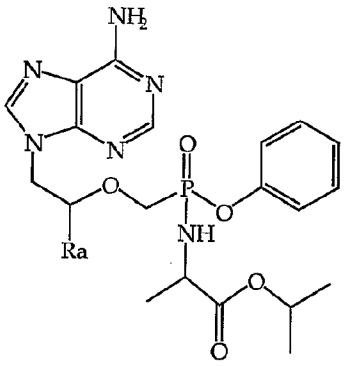
(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and

(d) determining the relative antiviral activity conferred by the prodrug in the tissues in step (c).

In preferred embodiments, the target tissue are sites where HIV is actively replicated and/or which serve as an HIV reservoir, and the non-target tissue is an intact animal. Unexpectedly, we found that selecting lymphoid tissue as the target tissue for the practice of this method for HIV led to identification of prodrugs that enhance the delivery of active drug to such tissues.

A preferred compound of this invention, which has been identified by this method has the structure (1),

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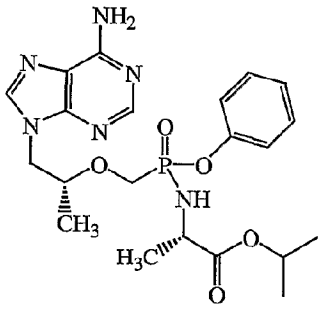


(1)

where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

A preferred compound of this invention has the structure (2)



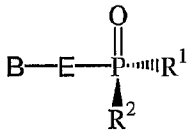
(2)

and its enriched diasteromers, salts, free base and solvates.

In addition, we unexpectedly found that the chirality of substituents on the phosphorous atom and/or the amidate substituent are influential in the enrichment observed in the practice of this invention. Thus, in another embodiment of this

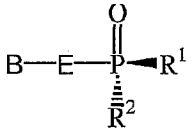
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invention, we provide diastereomerically enriched compounds of this invention having the structure (3)



(3)

which are substantially free of the diastereomer (4)



(4)

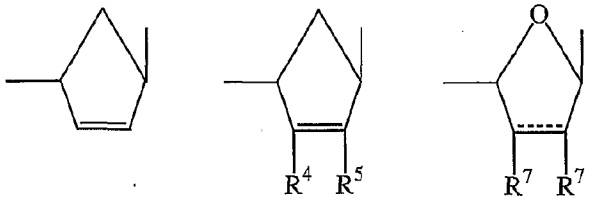
wherein

R^1 is an oxyester which is hydrolyzable *in vivo*, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $-(CH_2)2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2F)CH_2-$, $-CH(CH_2OH)CH_2-$, $-CH(CH=CH_2)CH_2-$, $-CH(C\equiv CH)CH_2-$, $-CH(CH_2N_3)CH_2-$,



$-CH(R^6)OCH(R^{6'})-$, $-CH(R^9)CH_2O-$ or $-CH(R^8)O-$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

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R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form -O- or $-CH_2-$;

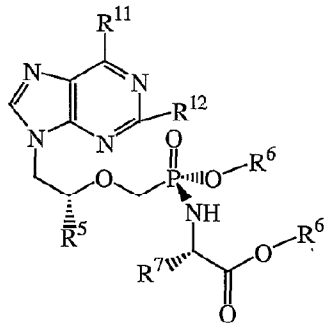
R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

R^9 is H, hydroxymethyl or acyloxymethyl;

and their salts, free base, and solvates.

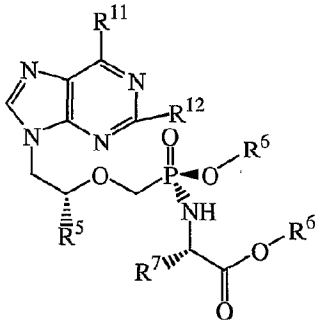
The diastereomers of structure (3) are designated the (S) isomers at the phosphorus chiral center.

Preferred embodiments of this invention are the diastereomerically enriched compounds having the structure (5a)



(5a)

which is substantially free of diastereomer (5b)



(5b)

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wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

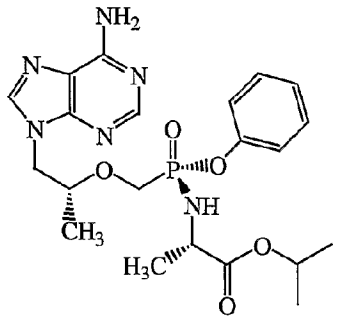
R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

and its salts, tautomers, free base and solvates.

A preferred embodiment of this invention is the compound of structure (6), 9-[(*R*)-2-[[(*S*)-[[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine, also designated herein GS-7340

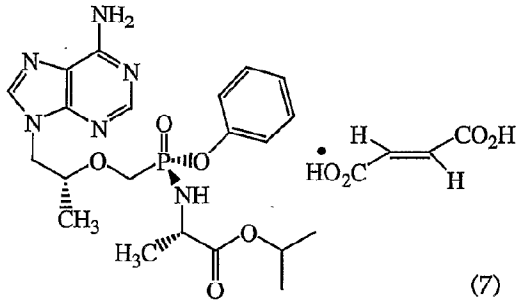


(6)

Another preferred embodiment of this invention is the fumarate salt of structure (5) (structure (7)), 9-[(*R*)-2-[[(*S*)-[[(*S*)-1-

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(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine fumarate (1:1), also designated herein GS-7340-2



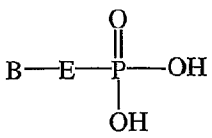
(7)

The compounds of structures (1)-(7) optionally are formulated into compositions containing pharmaceutically acceptable excipients. Such compositions are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.

In a further embodiment, a method is provided for the facile manufacture of 9-[2-(phosphonomethoxy)propyl]adenine (hereinafter "PMPA" or 9-[2-(phosphonomethoxy)ethyl] adenine (hereinafter "PMEA") using magnesium alkoxide, which comprises combining 9-(2-hydroxypropyl)adenine or 9-(2-hydroxyethyl)adenine, protected *p*-toluenesulfonyloxymethylphosphonate and magnesium alkoxide, and recovering PMPA or PMEA, respectively.

Detailed Description of the Invention

The methoxyphosphonate nucleotide analogue parent drugs for use in this screening method are compounds having the structure A-$OH_2P(O)(OH)_2$ wherein A is the residue of a nucleoside analogue. These compounds are known per se and are not part of this invention. More particularly, the parent compounds comprise a heterocyclic base B and an aglycon E, in general having the structure



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wherein the group B is defined below and group E is defined above. Examples are described in U.S. Patent Nos. 4,659,825, 4,808,716, 4,724,233, 5,142,051, 5,130,427, 5,650,510, 5,663,159, 5,302,585, 5,476,938, 5,696,263, 5,744,600, 5,688,778, 5,386,030, 5,733,896, 5,352,786, and 5,798,340, and EP 821,690 and 654,037.

The prodrugs for use in the screening method of this invention are covalently modified analogues of the parent methoxyphosphonate nucleotide analogues described in the preceding paragraph. In general, the phosphorus atom of the parent drug is the preferred site for prodrug modification, but other sites are found on the heterocyclic base B or the aglycon E. Many such prodrugs are already known. Primarily, they are esters or amidates of the phosphorus atom, but also include substitutions on the base and aglycon. None of these modifications per se is part of this invention and none are to be considered limiting on the scope of the invention herein.

The phosphorus atom of the methoxyphosphonate nucleotide analogues contains two valences for covalent modification such as amidation or esterification (unless one phosphoryl hydroxyl is esterified to an aglycon E hydroxyl substituent, whereupon only one phosphorus valence is free for substitution). The esters typically are aryloxy. The amidates ordinarily are naturally occurring monoamino acids having free carboxyl group(s) esterified with an alkyl or aryl group, usually phenyl, cycloalkyl, or t-, n- or s- alkyl groups. Suitable prodrugs for use in the screening method of this invention are disclosed for example in U.S. Patent No. 5,798,340. However, any prodrug which is potentially believed to be capable of being converted *in vivo* within target tissue cells to the free methoxyphosphonate nucleotide analogue parent drug, e.g., whether by hydrolysis, oxidation, or other covalent transformation resulting from exposure to biological tissues, is suitable for use in the method of this invention. Such prodrugs may not be known at this time but are identified in the future and thus become suitable candidates available for testing in the method of this invention. Since the prodrugs are simply candidates for screening in the methods their structures are not relevant to practicing or enabling the screening method, although of course their structures ultimately are dispositive of whether or not a prodrug will be shown to be selective in the assay.

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The pro-moieties bound to the parent drug may be the same or different. However, each prodrug to be used in the screening assay will differ structurally from the other prodrugs to be tested. Distinct, i.e. structurally different, prodrugs generally are selected on the basis of either their stereochemistry or their covalent structure, or these features are varied in combination. Each prodrug tested, however, desirably is structurally and stereochemically substantially pure, else the output of the screening assay will be less useful. It is of course within the scope of this invention to test only a single prodrug in an individual embodiment of the method of this invention, although typically then one would compare the results with prior studies with other prodrugs.

We have found that the stereochemistry of the prodrugs is capable of influencing the enrichment in target tissues. Chiral sites are at the phosphorus atom and are also found in its substituents. For example, amino acid used in preparing amidates may be D or L forms, and the phosphonate esters or the amino acid esters can contain chiral centers as well. Chiral sites also are found on the nucleoside analogue portion of the molecules, but these typically are already dictated by the stereochemistry of the parent drug and will not be varied as part of the screen. For example the R isomer of PMPA is preferred as it is more active than the corresponding S isomer. Typically these diasteromers or enantiomers will be chirally enriched if not pure at each site so that the results of the screen will be more meaningful. As noted, distinctiveness of stereoisomers is conferred by enriching or purifying the stereoisomer (typically this will be a diastereomer rather than an enantiomer in the case of most methoxyphosphonate nucleotide analogues) free of other stereoisomers at the chiral center in question, so that each test compound is substantially homogeneous. By substantially homogeneous or chirally enriched, we mean that the desired stereoisomer constitutes greater than about 60% by weight of the compound, ordinarily greater than about 80% and preferably greater than about 95%.

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Novel Screening Method

Once at least one candidate prodrug has been selected, the remaining steps of the screening method of this invention are used to identify a prodrug possessing the required selectivity for the target tissue. Most conveniently the prodrugs are labeled with a detectable group, e.g. radiolabeled, in order to facilitate detection later in tissues or cells. However, a label is not required since other suitable assays for the prodrug or its metabolites (including the parent drug) can also be employed. These assays could include mass spectrometry, HPLC, bioassays or immunoassays for instance. The assay may detect the prodrug and any one or more of its metabolites, but preferably the assay is conducted to detect only the generation of the parent drug. This is based on the assumption (which may not be warranted in all cases) that the degree and rate of conversion of prodrug to antivirally active parent diphosphate is the same across all tissues tested. Otherwise, one can test for the diphosphate.

The target tissue preferably will be lymphoid tissue when screening for prodrugs useful in the treatment of HIV infection. Lymphoid tissue will be known to the artisan and includes CD4 cells, lymphocytes, lymph nodes, macrophages and macrophage-like cells including monocytes such as peripheral blood monocytic cells (PBMCs) and glial cells. Lymphoid tissue also includes non-lymphoid tissues that are enriched in lymphoid tissues or cells, e.g. lung, skin and spleen. Other targets for other antiviral drugs of course will be the primary sites of replication or latency for the particular virus concerned, e.g., liver for hepatitis and peripheral nerves for HSV. Similarly, target tissues for tumors will in fact be the tumors themselves. These tissues are all well-known to the artisan and would not require undue experimentation to select. When screening for antiviral compounds, target tissue can be infected by the virus.

Non-target tissues or cells also are screened as part of the method herein. Any number or identity of such tissues or cells can be employed in this regard. In general, tissues for which the parent drug is expected to be toxic will be used as non-target tissues. The selection of a non-target tissue is entirely dependent upon

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the nature of the prodrug and the activity of the parent. For example, non-hepatic tissues would be selected for prodrugs against hepatitis, and untransformed cells of the same tissue as the tumor will suffice for the antitumor-selective prodrug screen.

It should be noted that the method of this invention is distinct from studies typically undertaken to determine oral bioavailability of prodrugs. In oral bioavailability studies, the objective is to identify a prodrug which passes into the systemic circulation substantially converted to parent drug. In the present invention, the objective is to find prodrugs that are not metabolized in the gastrointestinal tract or circulation. Thus, target tissues to be evaluated in the method of this invention generally do not include the small intestines or, if the intestines are included, then the tissues also include additional tissues other than the small intestines.

The target and non-target tissues used in the screening method of this invention typically will be in an intact living animal. Prodrugs containing esters are more desirably tested in dogs, monkeys or other animals than rodents; mice and rat plasma contains high circulating levels of esterases that may produce a misleading result if the desired therapeutic subject is a human or higher mammal.

It is not necessary to practice this method with intact animals. It also is within the scope of this invention to employ perfused organs, *in vitro* culture of organs (e.g. skin grafts) or cell lines maintained in various forms of cell culture, e.g. roller bottles or zero gravity suspension systems. For example, MT-2 cells can be used as a target tissue for selecting HIV prodrugs. Thus, the term "tissue" shall not be construed to require organized cellular structures, or the structures of tissues as they may be found in nature, although such would be preferred. Rather, the term "tissue" shall be construed to be synonymous with cells of a particular source, origin or differentiation stage.

The target and non-target tissue may in fact be the same tissue, but the tissues will be in different biological status. For example, the method herein could be used to select for prodrugs that confer activity in virally-infected tissue (target tissue) but which remain substantially inactive in virally-uninfected cells (corresponding non-target tissue). The same strategy would be employed to select

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prophylactic prodrugs, i.e., prodrugs metabolized to antivirally active forms incidental to viral infection but which remain substantially unmetabolized in uninfected cells. Similarly, prodrugs could be screened in transformed cells and the untransformed counterpart tissue. This would be particularly useful in comparative testing to select prodrugs for the treatment of hematological malignancies, e.g. leukemias.

Without being limited by any particular theory of operation, tissue selective prodrugs are thought to be selectively taken up by target cells and/or selectively metabolized within the cell, as compared to other tissues or cells. The unique advantage of the methoxyphosphonate prodrugs herein is that their metabolism to the dianion at physiological pH ensures that they will be unable to diffuse back out of the cell. They therefore remain effective for lengthy periods of time and are maintained at elevated intracellular concentrations, thereby exhibiting increased potency. The mechanisms for enhanced activity in the target tissue are believed to include enhanced uptake by the target cells, enhanced intracellular retention, or both mechanisms working together. However, the manner in which selectivity or enhanced delivery occurs in the target tissue is not important. It also is not important that all of the metabolic conversion of the prodrug to the parent compound occurs within the target tissue. Only the final drug activity-conferring conversion need occur in the target tissue; metabolism in other tissues may provide intermediates finally converted to antiviral forms in the target tissue.

The degree of selectivity or enhanced delivery that is desired will vary with the parent compound and the manner in which it is measured (% dose distribution or parent drug concentration). In general, if the parent drug already possess a generous therapeutic window, a low degree of selectivity may be sufficient for the desired prodrug. On the other hand, toxic compounds may require more extensive screening to identify selective prodrugs. The relative expense of the method of this invention can be reduced by screening only in the target tissue and tissues against which the parent compound is known to be relatively toxic, e.g. for PMEA, which is nephrotoxic at higher doses, the primary focus will be on kidney and lymphoid tissues.

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The step of determining the relative antiviral activity of a prodrug in the selected tissues ordinarily is accomplished by assaying target and non-target tissues for the relative presence or activity of a metabolite of the prodrug, which metabolite is known to have, or is converted to, a metabolite having antiviral or antitumor activity. Thus, typically one would determine the relative amount of the parent drug in the tissues over substantially the same time course in order to identify prodrugs that are preferentially metabolized in the target tissue to an antivirally or antitumor active metabolite or precursor thereof which in the target tissue ultimately produces the active metabolite. In the case of antiviral compounds, the active metabolite is the diphosphate of the phosphonate parent compounds. It is this metabolite that is incorporated into the viral nucleic acid, thereby truncating the elongating nucleic acid strand and halting viral replication. Metabolites of the prodrug can be anabolic metabolites, catabolic metabolites, or the product of anabolism and catabolism together. The manner in which the metabolite is produced is not important in the practice of the method of this invention.

The method of this invention is not limited to assaying a metabolite which per se possesses antiviral or antitumor activity. Instead, one can assay inactive precursors of the active metabolites. Precursors of the antivirally active diphosphate metabolite include the monophosphate of the parent drug, monophosphates of other metabolites of the parent drug (e.g., an intermediate modification of a substituent on the heterocyclic base), the parent itself and metabolites generated by the cell in converting the prodrug to the parent prior to phosphorylation. The precursor structures may vary considerably as they are the result of cellular metabolism. However, this information is already known or could be readily determined by one skilled in the art.

If the prodrug being assayed does not exhibit antitumor or antiviral activity per se then adjustments to the raw assay results may be required. For example, if the intracellular processing of the inactive metabolite to an active metabolite occurs at different rates among the tissues being tested, the raw assay results with the inactive metabolite would need to be adjusted to take account of the differences

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among the cell types because the relevant parameter is the generation of activity in the target tissue, not accumulation of inactive metabolites. However, determining the proper adjustments would be within the ordinary skill. Thus, when step (d) of the method herein calls for determining the activity, activity can be either measured directly or extrapolated. It does not mean that the method herein is limited to only assaying intermediates that are active per se. For instance, the absence or decline of the prodrug in the test tissues also could be assayed. Step (d) only requires assessment of the activity conferred by the prodrug as it interacts with the tissue concerned, and this may be based on extrapolation or other indirect measurement.

Step (d) of the method of this invention calls for determining the "relative" activity of the prodrug. It will be understood that this does not require that each and every assay or series of assays necessarily must also contain runs with the selected non-target tissue. On the contrary, it is within the scope of this invention to employ historical controls of the non-target tissue or tissues, or algorithms representing results to be expected from such non-target tissues, in order to provide the benchmark non-target activity.

The results obtained in step (d) are then used optimally to select or identify a prodrug which produces greater antiviral activity in the target tissue than in the non-target tissue. It is this prodrug that is selected for further development.

It will be appreciated that some preassessment of prodrug candidates can be undertaken before the practice of the method of this invention. For example, the prodrug will need to be capable of passing largely unmetabolized through the gastrointestinal tract, it will need to be substantially stable in blood, and it should be able to permeate cells at least to some degree. In most cases it also will need to complete a first pass of the hepatic circulation without substantial metabolism. Such prestudies are optional, and are well-known to those skilled in the art.

The same reasoning as is described above for antiviral activity is applicable to antitumor prodrugs of methoxyphosphonate nucleotide analogues as well. These include, for example, prodrugs of PMEG, the guanyl analogue of PMEA. In

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this case, cytotoxic phosphonates such as PMEG are worthwhile candidates to pursue as their cytotoxicity in fact confers their antitumor activity.

A compound identified by this novel screening method then can be entered into a traditional preclinical or clinical program to confirm that the desired objectives have been met. Typically, a prodrug is considered to be selective if the activity or concentration of parent drug in the target tissue (% dose distribution) is greater than 2x, and preferably 5x, that of the parent compound in non-target tissue. Alternatively, a prodrug candidate can be compared against a benchmark prodrug. In this case, selectivity is relative rather than absolute. Selective prodrugs will be those resulting in greater than about 10x concentration or activity in the target tissue as compared with the prototype, although the degree of selectivity is a matter of discretion.

Novel Method for Preparation of Starting Materials or Intermediates

Also included herein is an improved method for manufacture of preferred starting materials (parent drugs) of this invention, PMEA and (*R*)-PMPA. Typically, this method comprises reacting 9-(2-hydroxypropyl)adenine (HPA) or 9-(2-hydroxyethyl)adenine (HEA) with a magnesium alkoxide, thereafter adding the protected aglycon synthon *p*-toluene-sulfonyloxymethylphosphonate (tosylate) to the reaction mixture, and recovering PMPA or PMEA, respectively.

Preferably, HPA is the enriched or isolated R enantiomer. If a chiral HPA mixture is used, R-PMPA can be isolated from the chiral PMPA mixture after the synthesis is completed.

Typically the tosylate is protected by lower alkyl groups, but other suitable groups will be apparent to the artisan. It may be convenient to employ the tosylate presubstituted with the prodrug phosphonate substituents which are capable of acting as protecting groups in the tosylation reaction, thereby allowing one to bypass the deprotection step and directly recover prodrug or an intermediate therefore.

The alkyl group of the magnesium alkoxide is not critical and can be any C_1-C_6 branched or normal alkyl, but is preferably t-butyl (for PMPA) or isopropyl (for

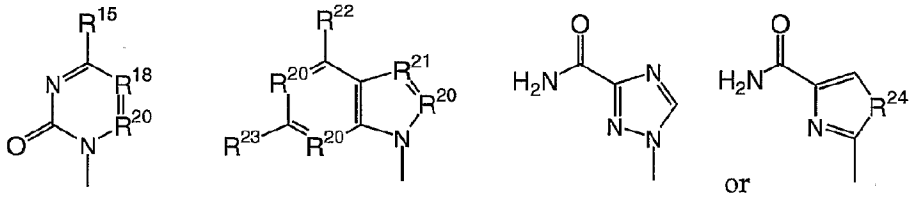
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PMEA). The reaction conditions also are not critical, but preferably comprise heating the reaction mixture at about 70-75°C with stirring or other moderate agitation.

If there is no interest in retaining the phosphonate substituents, the product is deprotected (usually with bromotrimethylsilane where the tosylate protecting group is alkyl), and the product then recovered by crystallization or other conventional method as will be apparent to the artisan.

Heterocyclic Base

In the compounds of this invention depicted in structures (3) and (4), the heterocyclic base B is selected from the structures



or

wherein

R^{15} is H, OH, F, Cl, Br, I, OR^{16}, SH, SR^{16}, NH_2, or NHR^{17};

R^{16} is C_1-C_6 alkyl or C_2-C_6 alkenyl including CH_3, CH_2CH_3, CH_2CCH, CH_2CHCH_2 and C_3H_7;

R^{17} is C_1-C_6 alkyl or C_2-C_6 alkenyl including CH_3, CH_2CH_3, CH_2CCH, CH_2CHCH_2, and C_3H_7;

R^{18} is N, CF, CCl, CBr, CI, CR^{19}, CSR^{19}, or COR^{19};

R^{19} is H, C_1-C_9 alkyl, C_2-C_9 alkenyl, C_2 - C_9 alkynyl, C_1-C_9 alkyl-C_1-C_9 alkoxy, or C_7-C_9 aryl-alkyl unsubstituted or substituted by OH, F, Cl, Br or I, R^{19} therefore including -CH_3, -CH_2CH_3, -$CHCH_2$, -CHCHBr, -CH_2CH_2Cl, -CH_2CH_2F, -CH_2CCH, -CH_2CHCH_2, -C_3H_7, -CH_2OH, -CH_2OCH_3, -$CH_2OC_2H_5$, -CH_2OCCH, -$CH_2OCH_2CHCH_2$, -$CH_2C_3H_7$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$,

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-$CH_2CH_2OC_2H_5$, -CH_2CH_2OCCH, -$CH_2CH_2OCH_2CHCH_2$, and -$CH_2CH_2OC_3H_7$;

R^{20} is N or CH;

R^{21} is N, CH, CCN, CCF_3, CC≡CH or $CC(O)NH_2$;

R^{22} is H, OH, NH_2, SH, SCH_3, SCH_2CH_3, SCH_2CCH, SCH_2CHCH_2, SC_3H_7, $NH(CH_3)$, $N(CH_3)_2$, $NH(CH_2CH_3)$, $N(CH_2CH_3)_2$, $NH(CH_2CCH)$, $NH(CH_2CHCH_2)$, $NH(C_3H_7)$, halogen (F, Cl, Br or I) or X wherein X is $-(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein each m is independently 0-2, n is 0-1, and

R^{10} independently is

H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_{15} arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 heterocycloalkyl,

C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by –O-,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

or one of the foregoing R^{10} groups which is substituted with 1 to 3 halo, CN or N_3; but optionally at least one R^{10} group is not H;

R^{23} is H, OH, F, Cl, Br, I, SCH_3, SCH_2CH_3, SCH_2CCH, SCH_2CHCH_2, SC_3H_7, OR^{16}, NH_2, NHR^{17} or R^{22}; and

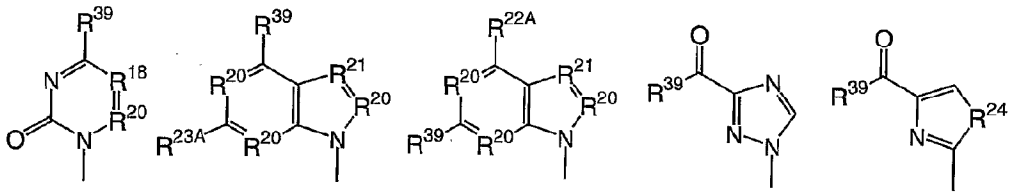
R^{24} is O, S or Se.

B also includes both protected and unprotected heterocyclic bases, particularly purine and pyrimidine bases. Protecting groups for exocyclic amines and other labile groups are known (Greene et al. "Protective Groups in Organic Synthesis") and include N-benzoyl, isobutyryl, 4,4'-dimethoxytrityl (DMT) and the

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like. The selection of protecting group will be apparent to the ordinary artisan and will depend upon the nature of the labile group and the chemistry which the protecting group is expected to encounter, e.g. acidic, basic, oxidative, reductive or other conditions. Exemplary protected species are N^4-benzoylcytosine, N^6-benzoyladenine, N^2-isobutyrylguanine and the like.

Protected bases have the formulas Xa.1, XIa.1, XIb.1, XIIa.1 or XIIIa.1



(Xa.1) (XIa.1) (XIb.1) (XIIa.1) (XIIIa.1)

wherein R^{18}, R^{20}, R^{21}, R^{24} have the meanings previously defined; R^{22A} is R^{39} or R^{22} provided that R^{22} is not NH_2; R^{23A} is R^{39} or R^{23} provided that R^{23} is not NH_2; R^{39} is NHR^{40}, $NHC(O)R^{36}$ or $CR^{41}N(R^{38})_2$ wherein R^{36} is C_1-C_{19} alkyl, C_1-C_{19} alkenyl, C_3-C_{10} aryl, adamantoyl, alkylanyl, or C_3-C_{10} aryl substituted with 1 or 2 atoms or groups selected from halogen, methyl, ethyl, methoxy, ethoxy, hydroxy and cyano; R^{38} is C_1-C_{10} alkyl, or both R^{38} together are 1-morpholino, 1-piperidine or 1-pyrrolidine; R^{40} is C_1-C_{1a} alkyl, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, octyl and decanyl; and R^{41} is hydrogen or CH_3.

For bases of structures XIa.1 and XIb.1, if R^{39} is present at R^{22A} or R^{23A}, both R^{39} groups on the same base will generally be the same. Exemplary R^{36} are phenyl, phenyl substituted with one of the foregoing R^{36} aryl substituents, $-C_{10}H_{15}$ (where $C_{10}H_{15}$ is 2-adamantoyl), $-CH_2-C_6H_5$, $-C_6H_5$, $-CH(CH_3)_2$, $-CH_2CH_3$, methyl, butyl, t-butyl, heptanyl, nonanyl, undecanyl, or undecenyl.

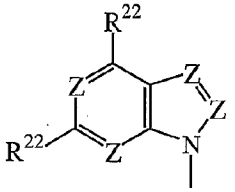
Specific bases include hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza

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derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

Preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-dezazadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B′ is a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(C_1-C_3-alkyl)cytosinyl.

Preferred B groups have the formula



wherein

R^{22} independently is halo, oxygen, NH_2, X or H, but optionally at least one R^{22} is X;

X is $-(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein m is 0-2, n is 0-1, and

R^{10} independently is

H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_{15} arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 heterocycloalkyl,

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C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by –O-,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

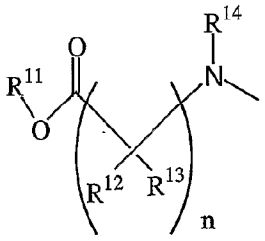
or one of the foregoing R^{10} groups is substituted with 1 to 3 halo, CN or N3; but optionally at least one R^{10} group is not H; and

Z is N or CH, provided that the heterocyclic nucleus varies from purine by no more than one Z.

E groups represent the aglycons employed in the methoxyphosphonate nucleotide analogues. Preferably, the E group is $-CH(CH_3)CH_2-$ or $-CH_2CH_2-$. Also, it is preferred that the side groups at chiral centers in the aglycon be substantially solely in the (*R*) configuration (except for hydroxymethyl, which is the enriched (*S*) enantiomer).

R^1 is an *in vivo* hydrolyzable oxyester having the structure $-OR^{35}$ or $-OR^6$ wherein R^{35} is defined in column 64, line 49 of U.S. Patent No. 5,798,340, herein incorporated by reference, and R^6 is defined above. Preferably R^1 is aryloxy, ordinarily unsubstituted or para-substituted (as defined in R^6) phenoxy.

R^2 is an amino acid residue, optionally provided that any carboxy group linked by less than about 5 atoms to the amidate N is esterified. R^2 typically has the structure



(8)

wherein

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n is 1 or 2;

R^{11} is R^6 or H; preferably R^6 = C_3-C_9 alkyl; C_3-C_9 alkyl substituted independently with OH, halogen, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, O or N; or C_3-C_6arylalkyl which is independently substituted with OH, halogen, O or N;

R^{12} independently is H or C_1-C_9 alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; C_3-C_6aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; or C_3-C_9 aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen;

R^{13} independently is C(O)-OR^{11}; amino; amide; guanidinyl; imidazolyl; indolyl; sulfoxide; phosphoryl; C_1-C_3 alkylamino; C_1-C_3 alkyldiamino; C_1-C_6 alkenylamino; hydroxy; thiol; C_1-C_3 alkoxy; C_1-C_3 alkthiol; $(CH_2)_nCOOR^{11}$; C_1-C_6 alkyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; C_2-C_6 alkenyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and C_6-C_{12} aryl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and

R^{14} is H or C_1-C_9 alkyl or C_1-C_9 alkyl independently substituted with OH, halogen, $COOR^{11}$, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, $COOR^{11}$, O or N; or C_3-C_6 arylalkyl which is independently substituted with OH, halogen, $COOR^{11}$, O or N.

Preferably, R^{11} is C_1-C_6 alkyl, most preferably isopropyl, R^{13} is the side chain of a naturally occurring amino acid, n = 1, R^{12} is H and R^{14} is H. In the compound of structure (2), the invention includes metabolites in which the phenoxy and isopropyl esters have been hydrolyzed to -OH. Similarly, the de-esterified enriched phosphonoamidate metabolites of compounds (5a), 5(b) and (6) are included within the scope of this invention.

Aryl and "O" or "N" substitution are defined in column 16, lines 42-58, of

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United States Patent No. 5,798,340.

Typically, the amino acids are in the natural or *l* amino acids. Suitable specific examples are set forth in U. S. Patent No. 5,798,340, for instance Table 4 and col. 8-10 therein.

Alkyl as used herein, unless stated to the contrary, is a normal, secondary, tertiary or cyclic hydrocarbon. Unless stated to the contrary alkyl is C_1-C_{12}. Examples are -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$), -$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_2CH_3$, -$CH(CH_2CH_3)_2$, -$C(CH_3)_2CH_2CH_3$), -$CH(CH_3)CH(CH_3)_2$, -$CH_2CH_2CH(CH_3)_2$), -$CH_2CH(CH_3)CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_2CH_2CH_3$, -$CH(CH_2CH_3)(CH_2CH_2CH_3)$, -$C(CH_3)_2CH_2CH_2CH_3$, -$CH(CH_3)CH(CH_3)CH_2CH_3$, -$CH(CH_3)CH_2CH(CH_3)_2$, -$C(CH_3)(CH_2CH_3)_2$, -$CH(CH_2CH_3)CH(CH_3)_2$, -$C(CH_3)_2CH(CH_3)_2$, and -$CH(CH_3)C(CH_3)_3$. Alkenyl and alkynyl are defined in the same fashion, but contain at least one double or triple bond, respectively.

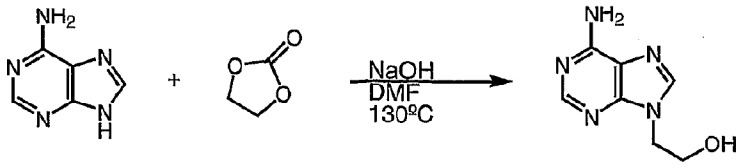
Where enol or keto groups are disclosed, the corresponding tautomers are to be construed as taught as well.

The prodrug compounds of this invention are provided in the form of free base or the various salts enumerated in U. S. Patent No. 5,798,340, and are formulated with pharmaceutically acceptable excipients or solvating diluents for use as pharmaceutical products also as set forth in U. S. Patent No. 5,798,340. These prodrugs have the antiviral and utilities already established for the parent drugs (see U. S. Patent 5,798,340 and other citations relating to the methoxyphosphonate nucleotide analogues). It will be understood that the diastereomer of structure (4) at least is useful as an intermediate in the chemical production of the parent drug by hydrolysis *in vitro*, regardless of its relatively unselective character as revealed in the studies herein.

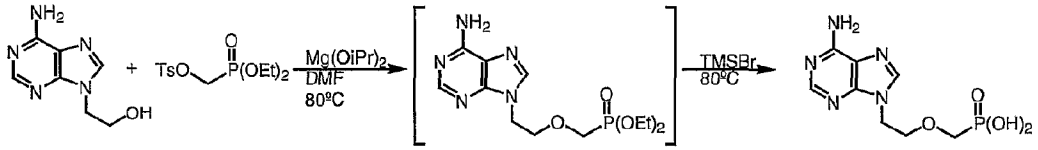
The invention will be more fully understood by reference to the following examples:

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Example 1a



Adenine to PMEA using Magnesium Isopropoxide. To a suspension of adenine (16.8g, 0.124 mol) in DMF (41.9 ml) was added ethylene carbonate (12.1g, 0.137 mol) and sodium hydroxide (.100g, 0.0025 mol). The mixture was heated at 130°C overnight. The reaction was cooled to below 50°C and toluene (62.1 ml) was added. The slurry was further cooled to 5°C for 2 hours, filtered, and rinsed with toluene (2x). The wet solid was dried *in vacuo* at 65°C to yield 20.0g (90%) of 9-(2-hydroxyethyl)adenine as an off-white solid. Mp: 238-240°C.

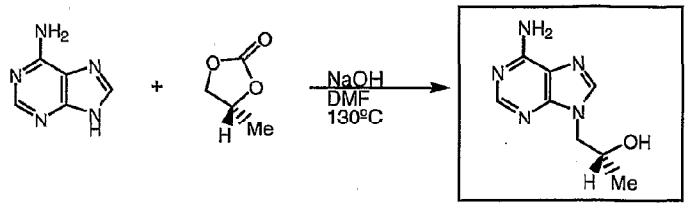


9-(2-Hydroxyethyl)adenine (HEA) (20.0g, 0.112 mol) was suspended in DMF (125 ml) and heated to 80°C. Magnesium isopropoxide (11.2g, 0.0784 mol) , or alternatively magnesium t-butoxide, was added to the mixture followed by diethyl *p*-toluenesulfonyloxymethylphosphonate (66.0g, 0.162 mol) over one hour. The mixture was stirred at 80°C for 7 hours. 30 ml of volatiles were removed via vacuum distillation and the reaction was recharged with 30 ml of fresh DMF. After cooling to room temperature, bromotrimethylsilane (69.6g, 0.450 mol) was added and the mixture heated to 80°C for 6 hours. The reaction was concentrated to yield a thick gum. The gum was dissolved into 360 ml water, extracted with 120 ml dichloromethane, adjusted to pH 3.2 with sodium hydroxide, and the resulting slurry stirred at room temperature overnight. The slurry was cooled to 4°C for one hour. The solids were isolated by filtration, washed with water (2x), and dried *in*

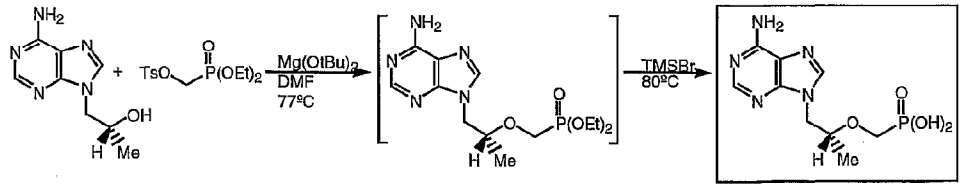
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vacuo at 56°C to yield 20g (65.4%) of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as a white solid. Mp: > 200°C dec. ^{1}H NMR (D_2O) • 3.49 (t, 2H); 3.94 (t, 2H); 4.39 (t, 2H); 8.13 (s, 1H); 8.22 (s, 1H).

Example 1b



Adenine to PMPA using Magnesium t-Butoxide. To a suspension of adenine (40g, 0.296 mol) in DMF (41.9 ml) was added *(R)*-propylene carbonate (34.5g, 0.338 mol) and sodium hydroxide (.480g, 0.012 mol). The mixture was heated at 130°C overnight. The reaction was cooled to 100°C and toluene (138 ml) was added followed by methanesulfonic acid (4.7g, 0.049 mol) while maintaining the reaction temperature between 100-110°C. Additional toluene (114 ml) was added to create a homogeneous solution. The solution was cooled to 3°C over 7 hours and then held at 3°C for one hour. The resulting solid was isolated by filtration and rinsed with acetone (2x). The wet solid was dried *in vacuo* at 80°C to yield 42.6g (75%) of *(R)*-9-[2-(hydroxy)propyl]adenine (HPA) as an off-white solid. Mp: 188-190°C.



(R)-9-[2-(hydroxy)propyl]adenine (HPA) (20.0g, 0.104 mol) was suspended in DMF (44.5 ml) and heated to 65°C. Magnesium t-butoxide (14.2g, 0.083 mol), or alternatively magnesium isopropoxide, was added to the mixture over one hour followed by diethyl *p*-toluenesulfonyloxymethylphosphonate (66.0g, 0.205 mol)

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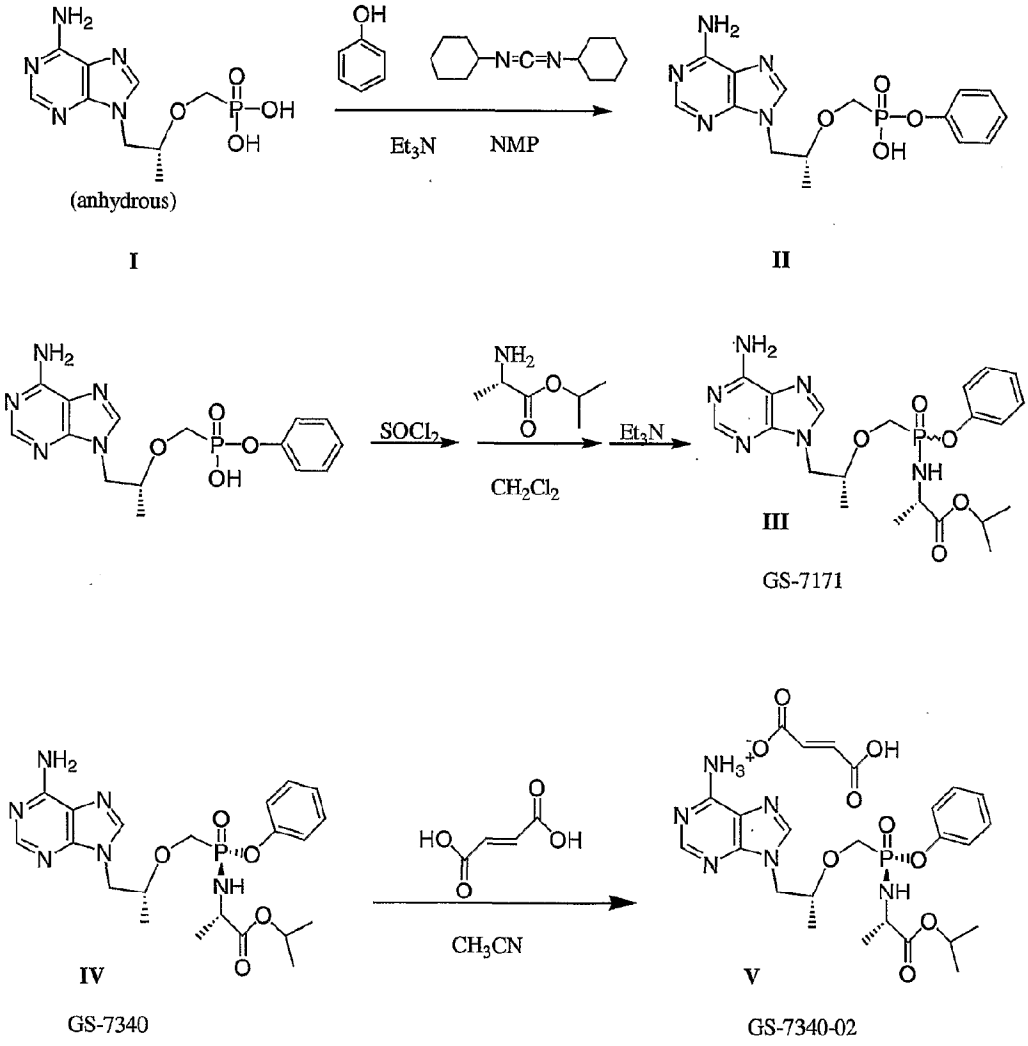
over two hours while the temperature was kept at 78°C. The mixture was stirred at 75°C for 4 hours. After cooling to below 50°C, bromotrimethylsilane (73.9g, 0.478 mol) was added and the mixture heated to 77°C for 3 hours. When complete, the reaction was heated to 80°C and volatiles were removed via atmospheric distillation. The residue was dissolved into water (120 ml) at 50°C and then extracted with ethyl acetate (101 ml). The pH of the aqueous phase was adjusted to pH 1.1 with sodium hydroxide, seeded with authentic *(R)*-PMPA, and the pH of the aqueous layer was readjusted to pH 2.1 with sodium hydroxide. The resulting slurry was stirred at room temperature overnight. The slurry was cooled to 4°C for three hours. The solid was isolated by filtration, washed with water (60 ml), and dried *in vacuo* at 50°C to yield 18.9g (63.5%) of crude*(R)*-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as an off-white solid.

The crude*(R)*-9-[2-(phosphonomethoxy)propyl]adenine was heated at reflux in water (255 ml) until all solids dissolved. The solution was cooled to room temperature over 4 hours. The resulting slurry was cooled at 4°C for three hours. The solid was isolated by filtration, washed with water (56 ml) and acetone (56 ml), and dried *in vacuo* at 50°C to yield 15.0g (50.4%) of *(R)*-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as a white solid. Mp: 278-280°C.

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Example 2
Preparation of GS-7171 (III)

Scheme 1



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A glass-lined reactor was charged with anhydrous PMPA, (I) (14.6 kg, 50.8 mol), phenol (9.6 kg, 102 mol), and 1-methyl-2-pyrrolidinone (39 kg). The mixture was heated to 85°C and triethylamine (6.3 kg, 62.3 mol) added. A solution of 1,3-dicyclohexylcarbodiimide (17.1 kg, 82.9 mol) in 1-methyl-2-pyrrolidinone (1.6 kg) was then added over 6 hours at 100°C. Heating was continued for 16 hours. The reaction was cooled to 45°C, water (29 kg) added, and cooled to 25°C. Solids were removed from the reaction by filtration and rinsed with water (15.3 kg). The combined filtrate and rinse was concentrated to a tan slurry under reduced pressure, water (24.6 kg) added, and adjusted to pH = 11 with NaOH (25% in water). Fines were removed by filtration through diatomaceous earth (2 kg) followed by a water (4.4 kg) rinse. The combined filtrate and rinse was extracted with ethyl acetate (28 kg). The aqueous solution was adjusted to pH = 3.1 with HCl (37% in water) (4 kg). Crude II was isolated by filtration and washed with methanol (12.7 kg). The crude II wet cake was slurried in methanol (58 kg). Solids were isolated by filtration, washed with methanol (8.5 kg), and dried under reduced pressure to yield 9.33 kg II as a white powder: ^{1}H NMR (D_2O) δ 1.2 (d, 3H), 3.45 (q, 2H), 3.7 (q, 2H), 4 (m, 2H), 4.2 (q, 2H), 4.35 (dd, 2H), 6.6 (d, 2H), 7 (t, 1H), 7.15 (t, 2H), 8.15 (s, 1H), 8.2 (s, 1H); ^{31}P NMR (D_2O) δ 15.0 (decoupled).

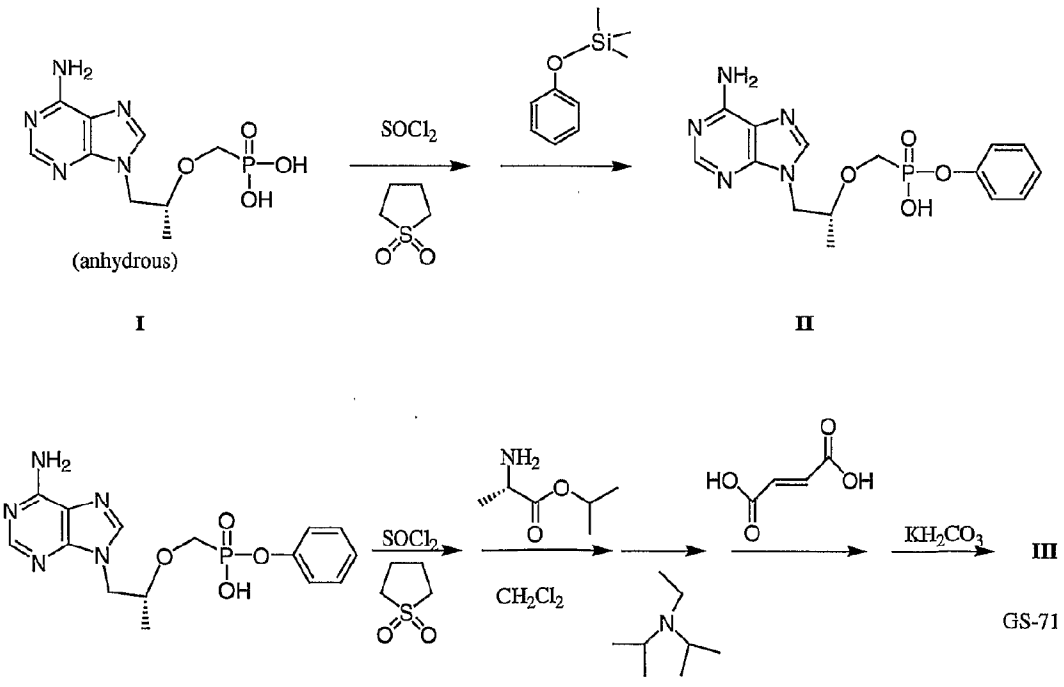
GS-7171 (III). (Scheme 1) A glass-lined reactor was charged with monophenyl PMPA, (II), (9.12 kg, 25.1 mol) and acetonitrile (30.7 kg). Thionyl chloride (6.57 kg, 56.7 mol) was added below 50°C. The mixture was heated at 75°C until solids dissolved. Reaction temperature was increased to 80°C and volatiles (11.4 kg) collected by atmospheric distillation under nitrogen. The pot residue was cooled to 25°C, dichloromethane (41 kg) added, and cooled to –29°C. A solution of (L)-alanine isopropyl ester (7.1 kg, 54.4 mol) in dichloromethane (36 kg) was added over 60 minutes at –18°C followed by triethylamine (7.66 kg, 75.7 mol) over 30 minutes at –18 to –11°C. The reaction mixture was warmed to room temperature and washed five times with sodium dihydrogenphosphate solution (10% in water, 15.7 kg each wash). The organic solution was dried with anhydrous sodium sulfate (18.2 kg), filtered, rinsed with dichloromethane (28 kg), and concentrated to an oil

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under reduced pressure. Acetone (20 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetone (18.8 kg) was charged to the resulting oil. Half the product solution was purified by chromatography over a 38 x 38 cm bed of 22 kg silica gel 60, 230 to 400 mesh. The column was eluted with 480 kg acetone. The purification was repeated on the second half of the oil using fresh silica gel and acetone. Clean product bearing fractions were concentrated under reduced pressure to an oil. Acetonitrile (19.6 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetonitrile (66.4 kg) was charged and the solution chilled to 0 to –5°C for 16 hours. Solids were removed by filtration and the filtrate concentrated under reduced pressure to 5.6 kg III as a dark oil: ^{1}H NMR ($CDCl_3$) δ 1.1 (m 12H), 3.7 (m, 1H), 4.0 (m, 5H), 4.2 (m, 1H), 5.0 (m, 1H), 6.2 (s, 2H), 7.05 (m, 5H), 8.0 (s, 1H), 8.25 (d, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0, 22.5 (decoupled).

Alternate Method for GS-7171(III)

Scheme 2



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Monophenyl PMPA (II). A round-bottom flask with reflux condenser and nitrogen inlet was placed in a 70°C oil bath. The flask was charged with anhydrous PMPA (I) (19.2 g, 67 mmol), *N,N*-dimethylformamide (0.29 g, 3.3 mmol), and tetramethylene sulfone (40 mL). Thionyl chloride (14.2 g, 119 mmol) was added over 4 hours. Heating was increased to 100°C over the same time. A homogeneous solution resulted. Phenoxytrimethylsilane (11.7 g, 70 mmol) was added to the solution over 5 minutes. Heating in the 100°C oil bath continued for two hours more. The reaction was poured into rapidly stirring acetone (400 mL) with cooling at 0°C. Solids were isolated by filtration, dried under reduced pressure, and dissolved in methanol (75 mL). The solution pH was adjusted to 3.0 with potassium hydroxide solution (45% aq.) with cooling in ice/water. The resulting solids were isolated by filtration, rinsed with methanol, and dried under reduced pressure to 20.4 g II (Scheme 2) as a white powder.

GS-7171 (III). Monophenyl PMPA (II) (3 g, 8.3 mmol), tetramethylene sulfone (5 mL), and *N,N*-dimethylformamide (1 drop) were combined in a round bottom flask in a 40°C oil bath. Thionyl chloride (1.96 g, 16.5 mmol) was added. After 20 minutes the clear solution was removed from heat, diluted with dichloromethane (10 ml), and added to a solution of (L)-alanine isopropyl ester (5g, 33 mmol) and diisopropylethylamine (5.33 g, 41 mmol) in dichloromethane (20 mL) at -10°C. The reaction mixture was warmed to room temperature and washed three times with sodium dihydrogenphosphate solution (10% aq., 10 mL each wash). The organic solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to a oil. The oil was combined with fumaric acid (0.77g, 6.6 mmol) and acetonitrile (40 mL) and heated to reflux to give a homogeneous solution. The solution was cooled in an ice bath and solids isolated by filtration. The solid GS-7171 fumarate salt was dried under reduced pressure to 3.7 g. The salt (3.16 g, 5.3 mmol) was suspended in dichloromethane (30 mL) and stirred with potassium carbonate solution (5 mL, 2.5 M in water) until the solid dissolved. The organic layer was isolated, then washed with water (5 mL), dried over anhydrous

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sodium sulfate, and concentrated under reduced pressure to afford 2.4 g **III** as a tan foam.

Example 3

A. Diastereomer Separation by Batch Elution Chromatography

The diastereomers of GS-7171 (**III**) were resolved by batch elution chromatography using a commercially available Chiralpak AS, 20 μm, 21 x 250 mm semi-preparative HPLC column with a Chiralpak AS, 20 μm, 21 x 50 mm guard column. Chiralpak® AS is a proprietary packing material manufactured by Diacel and sold in North America by Chiral Technologies, Inc. (U. S. Patent Nos. 5,202,433, RE 35,919, 5,434,298, 5,434,299 and 5,498,752). Chiralpak AS is a chiral stationary phase (CSP) comprised of amylosetris[(*S*)-α-methylbenzyl carbamate] coated onto a silica gel support.

The GS-7171 diastereomeric mixture was dissolved in mobile phase, and approximately 1 g aliquots of GS-7171 were pumped onto the chromatographic system. The undesired diastereomer, designated GS-7339, was the first major broad (approx. 15 min. duration) peak to elute from the column. When the GS-7339 peak had finished eluting, the mobile phase was immediately switched to 100% methyl alcohol, which caused the desired diastereomer, designated GS-7340 (**IV**), to elute as a sharp peak from the column with the methyl alcohol solvent front. The methyl alcohol was used to reduce the over-all cycle time. After the first couple of injections, both diastereomers were collected as a single large fractions containing one of the purified diastereomers (>99.0% single diastereomer). The mobile phase solvents were removed *in vacuo* to yield the purified diastereomer as a friable foam.

About 95% of the starting GS-7171 mass was recovered in the two diastereomer fractions. The GS-7340 fraction comprised about 50% of the total recovered mass.

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The chromatographic conditions were as follows:

Mobile Phase(Initial)	: GS-7171 – Acetonitrile : Isopropyl Alcohol (90:10)
(Final)	: 100% Methyl Alcohol
Flow	: 10 mL/minute
Run Time	: About 45 minute
Detection	: UV at 275 nm
Temperature	: Ambient
Elution Profile	: GS-7339 (diastereomer B)
	: GS-7340 (diastereomer A; (IV))

B. Diastereomer Separation of GS-7171 by SMB Chromatography

For a general description of simulated moving bed (SMB) chromatography, see Strube et al., "Organic Process Research and Development" 2:305-319 (1998).

GS-7340 (IV). GS-7171 **(III)**, 2.8 kg, was purified by simulated moving bed chromatography over 10 cm by 5 cm beds of packing (Chiral Technologies Inc., 20 micron Chiralpak AS coated on silica gel) (1.2 kg). The columns were eluted with 30% methanol in acetonitrile. Product bearing fractions were concentrated to a solution of **IV** in acetonitrile (2.48 kg). The solution solidified to a crystalline mass wet with acetonitrile on standing. The crystalline mass was dried under reduced pressure to a tan crystalline powder, 1.301 kg **IV**, 98.7% diastereomeric purity: mp 117 – 120°C; ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 4.0 (m, 5H), 4.2 (dd, 1H), 5.0 (m, 1H), 6.05 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0 (decoupled).

C. Diastereomer Separation by C18 RP-HPLC

GS-7171 (III) was chromatographed by reverse phase HPLC to separate the diastereomers using the following summary protocol.

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Chromatographic column:	Phenomenex Luna™ C18(2), 5 µm, 100 Å pore size, (Phenomenex, Torrance, CA), or equivalent
Guard column:	Pellicular C18 (Alltech, Deerfield, IL), or equivalent
Mobile Phase:	A — 0.02% (85%) H_3PO_4 in water : acetonitrile (95:5) B — 0.02% (85%) H_3PO_4 in water : acetonitrile (50:50)

Mobile Phase Gradient:

Time	% Mobile Phase A	% Mobile Phase B
0	100	0
5	100	0
7	70	30
32	70	30
40	0	100
50	0	100

Run Time:	50 minutes
Equilibration Delay:	10 min at 100% mobile phase A
Flow Rate:	1.2 mL/min
Temperature:	Ambient
Detection:	UV at 260 nm
Sample Solution:	20 mM sodium phosphate buffer, pH 6
Retention Times:	GS-7339, about 25 minutes
	GS-7340, about 27 minutes

D. Diastereomer Separation by Crystallization

GS-7340 (IV). A solution of GS-7171 (**III**) in acetonitrile was concentrated to an amber foam (14.9g) under reduced pressure. The foam was dissolved in acetonitrile (20 mL) and seeded with a crystal of **IV**. The mixture was stirred overnight, cooled to 5°C, and solids isolated by filtration. The solids were dried to 2.3 g **IV** as white crystals, 98% diastereomeric purity (^{31}P NMR): ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 3.95 (m, 2H), 4.05 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 6.4 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 19.5 (decoupled). X-ray crystal analysis of a single crystal selected from this product yielded the following data:

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Crystal Color, Habit	colorless, column
Crystal Diminsions	0.25 X 0.12 X 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 8.352(1) Å b = 15.574(2) Å c = 18.253(2) Å V = 2374.2(5) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.333 g/cm^3
F_{000}	1008.00
μ(MoKα)	1.60 cm^{-1}

Example 4

Preparation of Fumarate Salt of GS-7340

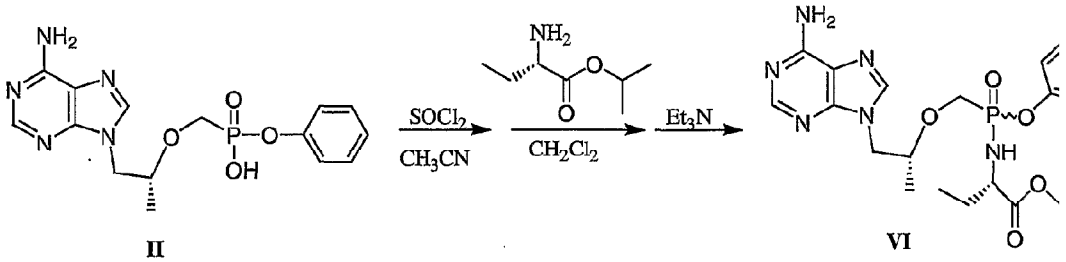
GS-7340-02 (V). (Scheme 1) A glass-lined reactor was charged with GS-7340 (IV), (1.294 kg, 2.71 mol), fumaric acid (284 g, 2.44 mol), and acetonitrile (24.6 kg). The mixture was heated to reflux to dissolve the solids, filtered while hot and cooled to 5°C for 16 hours. The product was isolated by filtration, rinsed with acetonitrile (9.2 kg), and dried to 1329 g (V) as a white powder: mp 119.7 - 121.1°C; $[\alpha]_D^{20}$ –41.7° (*c* 1.0, acetic acid).

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Example 5

Preparation of **GS-7120 (VI)**

Scheme 3



II **VI**

GS-7120

A 5 L round bottom flask was charged with monophenyl PMPA, (II), (200 g, 0.55 mol) and acetonitrile (0.629 kg). Thionyl chloride (0.144 kg, 1.21 mol) was added below 27°C. The mixture was heated at 70°C until solids dissolved. Volatiles (0.45 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25°C, dichloromethane (1.6 kg) was added and the mixture was cooled to –20°C. A solution of (L)-α aminobutyric acid ethyl ester (0.144 kg, 1.1 mol) in dichloromethane (1.33 kg) was added over 18 minutes at –20 to -10°C followed by triethylamine (0.17 kg, 1.65 mol) over 15 minutes at –8 to –15°C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.3 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.5 kg) and filtered. The solids were rinsed with dichloromethane (0.6 kg) and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was purified by chromatography over a 15 x 13 cm bed of 1.2 kg silica gel 60, 230 to 400 mesh. The column was eluted with a gradient of dichloromethane and methanol. Product bearing fractions were concentrated under reduced pressure to afford 211 g **VI** (Scheme 3) as a tan foam.

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Example 5a

Diastereomer Separation of **GS-7120** by Batch Elution Chromatography

The diastereomeric mixture was purified using the conditions described for GS-7171 in Example 3A except for the following:

Mobile Phase	(Initial)	: GS-7120 – Acetonitrile : Isopropyl Alcohol (98:2)
	(Final)	: 100% Methyl Alcohol
Elution Profile		: GS-7341 (diastereomer B)
		: GS-7342 (diastereomer A)

Example 6

Diastereomer Separation of **GS-7120** by Crystallization

A 1 L round bottom flask was charged with monophenyl PMPA, (**II**), (50 g, 0.137 mol) and acetonitrile (0.2 L). Thionyl chloride (0.036 kg, 0.303 mol) was added with a 10°C exotherm. The mixture was heated to reflux until solids dissolved. Volatiles (0.1 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25°C, dichloromethane (0.2 kg) was added, and the mixture was cooled to –20°C. A solution of (L)-α aminobutyric acid ethyl ester (0.036 kg, 0.275 mol) in dichloromethane (0.67 kg) was added over 30 minutes at –20 to -8°C followed by triethylamine (0.042 kg, 0.41 mol) over 10 minutes at up to –6°C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.075 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.1 kg) and filtered. The solids were rinsed with ethyl acetate (0.25 L, and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was diluted with ethyl acetate (0.25 L), seeded, stirred overnight, and chilled to – 15°C. The solids were isolated by filtration and dried under reduced pressure to afford 17.7 g of GS-7342 (Table 5) as a tan powder: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.3 (m, 6H), 1.7, (m, 2H),

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3.7 (m, 2H), 4.1(m, 6H), 4.4 (dd, 1H), 5.8 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.4 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21 (decoupled).

Example 7

Diastereomer Separation of GS-7097

The diastereomeric mixture was purified using the conditions described for GS-7171 (Example 3A) except for the following:

Mobile Phase	(Initial)	: GS-7120 – Acetonitrile : Isopropyl Alcohol (95:5)
	(Final)	: 100% Methyl Alcohol
Elution Profile		: GS-7115 (diastereomer B)
		: GS-7114 (diastereomer A)

Example 8

Alternative Procedure for Preparation of GS-7097

GS-7097: Phenyl PMPA, Ethyl L-Alanyl Amidate. Phenyl PMPA (15.0 g, 41.3 mmol), L-alanine ethyl ester hydrochloride (12.6 g, 83 mmol) and triethylamine (11.5 mL, 83 mmol) were slurried together in 500 mL pyridine under dry N_2. This suspension was combined with a solution of triphenylphosphine (37.9 g, 145 mmol), Aldrithiol 2 (2,2'-dipyridyl disulfide) (31.8 g, 145 mmol), and 120 mL pyridine. The mixture was heated at an internal temperature of 57°C for 15 hours. The complete reaction was concentrated under vacuum to a yellow paste, 100 g. The paste was purified by column chromatography over a 25 x 11 cm bed of 1.1 kg silica gel 60, 230 to 400 mesh. The column was eluted with 8 liters of 2% methanol in dichloromethane followed by a linear gradient over a course of 26 liters eluent up to a final composition of 13% methanol. Clean product bearing fractions were concentrated to yield 12.4 g crude (5), 65% theory. This material was contaminated with about 15% (weight) triethylamine hydrochloride by ^1H NMR. The contamination was removed by dissolving the product in 350 mL ethyl acetate, extracting with 20 mL water, drying the organic solution over anhydrous sodium

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sulfate, and concentrating to yield 11.1 g pure GS-7097 as a white solid, 58% yield. The process also is employed to synthesize the diastereomeric mixture of GS-7003a and GS-7003b (the phenylalanyl amidate) and the mixture GS-7119 and GS-7335 (the glycyl amidate). These diastereomers are separated using a batch elution procedure such as shown in Example 3A, 6 and 7.

Example 9

In Vitro Studies of Prodrug Diastereomers

The *in vitro* anti-HIV-1 activity and cytotoxicity in MT-2 cells and stability in human plasma and MT-2 cell extracts of GS-7340 (freebase) and tenofovir disoproxil fumarate (TDF), are shown in Table 1. GS-7340 shows a 10-fold increase in antiviral activity relative to TDF and a 200-fold increase in plasma stability. This greater plasma stability is expected to result in higher circulating levels of GS-7340 than TDF after oral administration.

Table 1. *In Vitro* Activity and Stability

	HIV-1 Activity	Cytotoxicity	Stability T 1/2 (min)		
	$IC_{50\mu M}$	$CC_{50\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0.005	> 40	90.0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	--	--	--

In order to estimate the relative intracellular PMPA resulting from the intracellular metabolism of TDF as compared to that from GS-7340, both prodrugs and PMPA were radiolabeled and spiked into intact human whole blood at equimolar concentrations. After 1 hour, plasma, red blood cells (RBCs) and peripheral blood mononuclear cells (PBMCs) were isolated and analyzed by HPLC with radiometric detection. The results are shown in Table 2.

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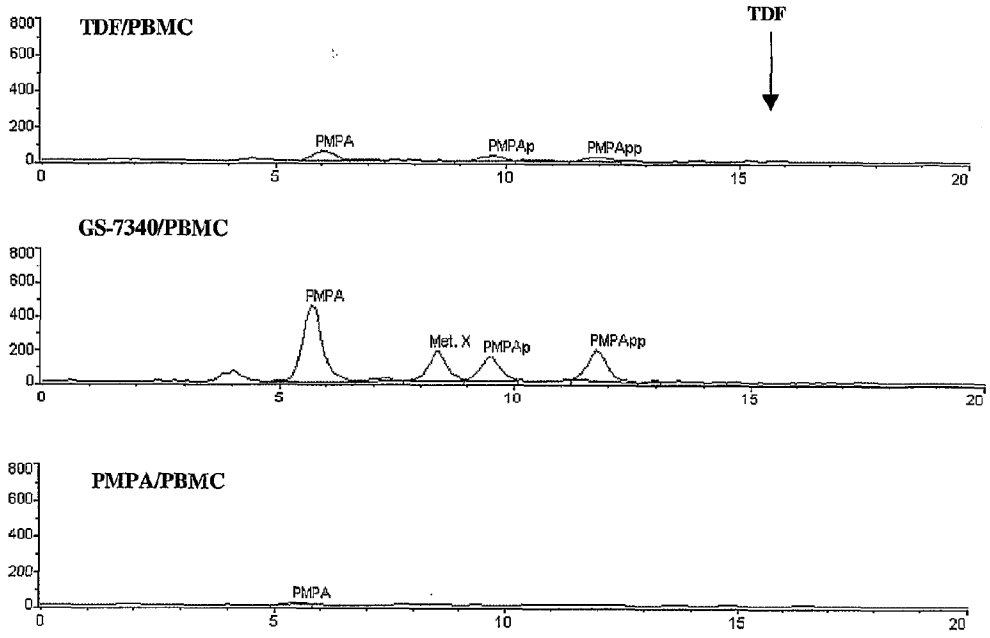
After 1 hour, GS-7340 results in 10x and 30x the total intracellular concentration of PMPA species in PBMCs as compared to TDF and PMPA, respectively. In plasma after 1 hour, 84% of the radioactivity is due to intact GS-7340, whereas no TDF is detected at 1 hour. Since no intact TDF is detected in plasma, the 10x difference at 1 hour between TDF and GS-7340 is the minimum difference expected *in vivo*. The HPLC chromatogram for all three compounds in PBMCs is shown in Figure 1.

Table 2. PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340 (60 µg-eq)	Plasma/FP	43.0	1	-	-	2	13	84
	PBMC	1.25	45	16	21	18	-	-
	RBC/FP	12.6	8	-	-	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331 (TDF) (60 µg-eq)	Plasma/FP	48.1	11	-	-	89	-	
	PBMC	0.133	50	25	18	7	-	
	RBC/FP	10.5	93	7.0	-	-	-	
			PMPA	PMPAp	PMPApp			
PMPA (60 µg-eq)	Plasma/FP	55.7	100	-	-			
	PBMC	0.033	86	14	-			
	RBC/FP	3.72	74	10	16			

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Figure 1. HPLC/C-14 Traces of PBMC Extracts from Human Blood Incubated for 1 h at 37°C with TDF, GS-7340 or PMPA.



Met. X and Met Y (metabolites X and Y) are shown in Table 5. Lower case "p" designates phosphorylation. These results were obtained after 1 hour in human blood. With increasing time, the *in vitro* differences are expected to increase, since 84% of GS-7340 is still intact in plasma after one hour. Because intact GS-7340 is present in plasma after oral administration, the relative clinical efficacy should be related to the IC_{50} values seen *in vitro*.

In Table 3 below, IC_{50} values of tenofovir, TDF, GS-7340, several nucleosides and the protease inhibitor nelfinivir are listed. As shown, nelfinavir and GS-7340 are 2-3 orders of magnitude more potent than all other nucleotides or nucleosides.

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Table 3. *In Vitro* Anti-HIV-1 Activities of Antiretroviral Compounds

Compound	IC_{50} (μM)
Adefovir (PMEA)	13.4 ± 4.2^1
Tenofovir (PMPA)	6.3 ± 3.3^1
AZT	0.17 ± 0.08^1
3TC	1.8 ± 0.25^1
d4T	8 ± 2.5^1
Nelfinavir	0.006 ± 0.002^1
TDF	0.05
GS 7340	0.005

1. A. S. Mulato and J. M. Cherrington, *Antiviral Research* **36**, 91 (1997)

Additional studies of the *in vitro* cell culture anti-HIV-1 activity and CC_{50} of separated diastereomers of this invention were conducted and the results tabulated below.

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Table 4. Effect of Diastereomer

Compound	Diastereomer	IC_{50} (μM)	Fold change	A/B activity	CC_{50} (μM)
PMPA	-	5	1x	-	6000
Ala-methylester	Mixture 1:1	0.025	200x	20x	80
GS-6957a	A	0.0075	670x		
GS-6957b		0.15	33x		
Phe-methylester	Mixture 1:1	0.03	170x	10x	60
GS-7003a	A	0.01	500x		
GS-7003b	B	0.1	50x		
Gly-ethylester	Mixture 1:1	0.5	10x	20x	
GS-7119	A	0.05	100x		>100
GS-7335	B	1.0	5x		
Ala-isopropyl	Mixture 1:1	0.01	500x	12x	
GS-7340	A	0.005	1,000x		40
GS-7339	B	0.06	83x		>100
ABA-ethyl	Mixture 1:1	0.008	625x	7.5x	>100
GS-7342	A	0.004	1,250x		
GS-7341	B	0.03	170x		
Ala-ethyl	Mixture 1:1	0.02	250x	10x	60
GS- 7114	A	0.005	1,000x		
GS- 7115	B	0.05	100x		

Assay reference: Arimilli, MN, et al., (1997) Synthesis, *in vitro* biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Antiviral Chemistry and Chemotherapy 8(6):557-564.

"Phe-methylester" is the methylphenylalaninyl monoamidate, phenyl monoester of tenofovir; "gly-methylester" is the methylglycyl monoamidate, phenyl monoester of tenofovir.

In each instance above, isomer A is believed to have the same absolute stereochemistry as GS-7340 (S), and isomer B is believed to have the same absolute stereochemistry that of GS-7339.

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The *in vitro* metabolism and stability of separated diastereomers were determined in PLCE, MT-2 extract and human plasma. A biological sample listed below, 80 μL, was transferred into a screw-capped centrifuge tube and incubated at 37°C for 5 min. A solution containing 0.2 mg/mL of the test compound in a suitable buffer, 20 μL, was added to the biological sample and mixed. The reaction mixture, 20 μL, was immediately sampled and mixed with 60 μL of methanol containing 0.015 mg/mL of 2-hydroxymethylnaphthalene as an internal standard for HPLC analysis. The sample was taken as the time-zero sample. Then, at specific time points, the reaction mixture, 20 μL, was sampled and mixed with 60 μL of methanol containing the internal standard. The mixture thus obtained was centrifuged at 15,000 G for 5 min and the supernatant was analyzed with HPLC under the conditions described below.

The biological samples evaluated are as follows.

(1) PLCE (porcine liver carboxyesterase from Sigma, 160 u/mg protein, 21 mg protein/mL) diluted 20 fold with PBS (phosphated-buffered saline).

(2) MT-2 cell extract was prepared from MT-2 cells according to the published procedure [A. Pompon, I. Lefebvre, J.-L. Imbach, S. Kahn, and D. Farquhar, "Antiviral Chemistry & Chemotherapy", 5:91–98 (1994)] except for using HEPES buffer described below as the medium.

(3) Human plasma (pooled normal human plasma from George King Biomedical Systems, Inc.)

The buffer systems used in the studies are as follows.

In the study for PLCE, the test compound was dissolved in PBS. PBS (phosphate-buffered saline, Sigma) contains 0.01 M phosphate, 0.0027 M potassium chloride, and 0.137 M sodium chloride. pH 7.4 at 37°C.

In the study for MT-2 cell extracts, the test compound was dissolved in HEPES buffer. HEPES buffer contains 0.010 M HEPES, 0.05 M potassium chloride, 0.005 M magnesium chloride, and 0.005 M *dl*-dithiothreitol. pH 7.4 at 37°C.

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In the study for human plasma, the test compound was dissolved in TBS. TBS (tris-buffered saline, Sigma) contains 0.05 M Tris, 0.0027 M potassium chloride, and 0.138 M sodium chloride. pH 7.5 at 37°C.

The HPLC analysis was carried out under the following conditions.

Column:	Zorbax R_X-C8, 4.6 x 250 mm, 5 µ (MAC-MOD Analytical, Inc. Chadds Ford, PA)
Detection:	UV at 260 nm
Flow Rate:	1.0 mL/min
Run Time:	30 min
Injection Volume:	20 µL
Column Temperature:	Ambient temperature

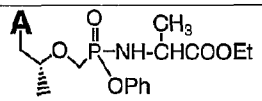
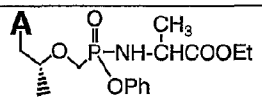
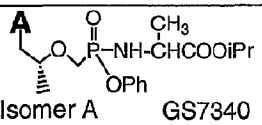
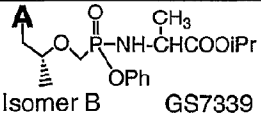
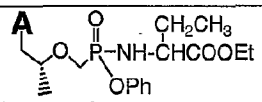
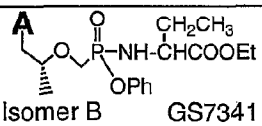
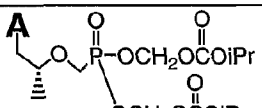
Mobile Phase A:	50 mM potassium phosphate (pH 6.0)/CH_3CN = 95/5 (v/v)
Mobile Phase B:	50 mM Potassium phosphate (pH 6.0)/CH_3CN = 50/50 (v/v)

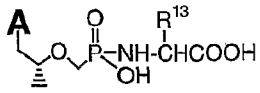
Gradient Run:	0 min	100% Mobile Phase A
	25 min	100% Mobile Phase B
	30 min	100% Mobile Phase B

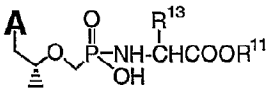
The results are shown below in Table 5 (also including selected IC_{50} data from Table 4).

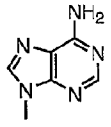
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Table 5. In Vitro Metabolism of Isomers A and B of PMPA monoamidate at 37°C

No.	PMPA monoamidate structure	HIV IC_{50} (μM)	PLCE hydrolysis rate and product	MT-2 extract hydrolysis rate and product	Human Plasma Stability (HP)
1	 Isomer A GS7114	0.005	$t_{1/2}$ = 2.9 min Met. X & PMPA	$t_{1/2}$ = 2.9 min Met. X & PMPA	$t_{1/2}$ = 148 min Met. Y
2	 Isomer B GS7115	0.05	$t_{1/2}$ = 8.0 min Met. X & PMPA	$t_{1/2}$ = 150.6 min Met. X & PMPA	$t_{1/2}$ = 495 min Met. Y
3	 Isomer A GS7340	0.005	$t_{1/2}$ = 3.3 min Met. X & PMPA	$t_{1/2}$ = 28.3 min Met. X & PMPA	$t_{1/2}$ = 90.0 min Met. Y
4	 Isomer B GS7339	0.06	$t_{1/2}$ = 10.1 min Met. X & PMPA	$t_{1/2}$ > 1000 min	$t_{1/2}$ = 231 min Met. Y
5	 Isomer A GS7342	0.004	$t_{1/2}$ = 3.9 min Met. X	$t_{1/2}$ = 49.2 min Met. X & PMPA	$t_{1/2}$ = 103 min Met. Y
6	 Isomer B GS7341	0.03	$t_{1/2}$ = 11.3 min Met. X	$t_{1/2}$ > 1000 min	$t_{1/2}$ = 257 min Met. Y
7	 GS4331	0.05	$t_{1/2}$ < 0.14 min MonoPOC PMPA	$t_{1/2}$ = 70.7 min monoPOC PMPA	$t_{1/2}$ = 0.41 min monoPOC PMPA

Met. X: 

Met. Y: 

A = 

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Example 10

Plasma and PBMC Exposures Following Oral Administration Of Prodrug Diastereomers to Beagle Dogs

The pharmacokinetics of GS 7340 were studied in dogs after oral administration of a 10 mg-eq/kg dose.

Formulations. The prodrugs were formulated as solutions in 50 mM citric acid within 0.5 hour prior to dose. All compounds used in the studies were synthesized by Gilead Sciences. The following lots were used:

GSI	Amidate Amino acid	AA Ester	Diastereoisomer	Lot Number
GS-7340-2	Alanine	i-Propyl	Isomer A	1504-187-19
GS-7339	Alanine	i-Propyl	Isomer B	1509-185-31
GS7114	Alanine	Ethyl	Isomer A	1509-181-26
GS7115	Alanine	Ethyl	Isomer B	1509-181-22
GS7119	Glycine	Ethyl	Isomer A	1428-163-28
GS7342	α-Aminobutyric Acid	Ethyl	Isomer A	1509-191-12
GS7341	α-Aminobutyric Acid	Ethyl	Isomer B	1509-191-7

Dose Administration and Sample Collection. The in-life phase of this study was conducted in accordance with the recommendations of the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health publication 86-23) and was approved by an Institutional Animal Care and Use Committee. Fasted male beagle dogs (10 ± 2 kg) were used for the studies. Each drug was administered as a single dose by oral gavage (1.5–2 ml/kg). The dose was 10 mg-equivalent of PMPA/kg. For PBMCs, blood samples were collected at 0 (pre-dose), 2, 8, and 24 h post-dose. For plasma, blood samples were collected at 0 (pre-dose), 5, 15, and 30 min, and 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose. Blood (1.0 ml) was processed immediately for plasma by centrifugation at 2,000 rpm for 10 min. Plasma samples were frozen and maintained at 70°C until analyzed.

Peripheral Blood Mononuclear Cell (PBMC) preparation. Whole blood (8 ml) drawn at specified time points was mixed in equal proportion with phosphate buffered saline (PBS), layered onto 15 ml of Ficoll-Paque solution (Pharmacia Biotech,) and centrifuged at 400 x g for 40 min. PBMC layer was removed and

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washed once with PBS. Formed PMBC pellet was reconstituted in 0.5 ml of PBS, cells were resuspended, counted using hemocytometer and maintained at 70°C until analyzed. The number of cells multiplied by the mean single-cell volume was used in calculation of intracellular concentrations. A reported value of 200 femtoliters/cell was used as the resting PBMC volume (B. L. Robins, R.V. Srinivas, C. Kim, N. Bischofberger, and A. Fridland, Antimicrob. Agents Chemother. 42, 612 (1998).

Determination of PMPA and Prodrugs in plasma and PBMCs. The concentration of PMPA in dog plasma samples was determined by derivatizing PMPA with chloroacetaldehyde to yield a highly fluorescent N^1, N^6-ethenoadenine derivative (L. Naesens, J. Balzarini, and E. De Clercq, Clin. Chem. 38, 480 (1992). Briefly, plasma (100 µl) was mixed with 200 µl acetonitrile to precipitate protein. Samples were then evaporated to dryness under reduced pressure at room temperature. Dried samples were reconstituted in 200 µl derivatization cocktail (0.34% chloroacetaldehyde in 100 mM sodium acetate, pH 4.5), vortexed, and centrifuged. Supernatant was then transferred to a clean screw-cap tube and incubated at 95°C for 40 min. Derivatized samples were then evaporated to dryness and reconstituted in 100 µl of water for HPLC analysis.

Before intracellular PMPA could be determined by HPLC, the large amounts of adenine related ribonucleotides present in the PBMC extracts had to be removed by selective oxidation. We used a modified procedure of Tanaka et al (K. Tanaka, A. Yoshioka, S. Tanaka, and Y. Wataya, Anal. Biochem., 139, 35 (1984). Briefly, PBMC samples were mixed 1:2 with methanol and evaporated to dryness under reduced pressure. The dried samples were derivatized as described in the plasma assay. The derivatized samples were mixed with 20 µL of 1M rhamnose and 30 µL of 0.1M sodium periodate and incubated at 37°C for 5 min. Following incubation, 40 µL of 4M methylamine and 20 µL of 0.5M inosine were added. After incubation at 37°C for 30 min, samples were evaporated to dryness under reduced pressure and reconstituted in water for HPLC analysis.

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No intact prodrug was detected in any PBMC samples. For plasma samples potentially containing intact prodrugs, experiments were performed to verify that no further conversion to PMPA occurred during derivatization. Prodrug standards were added to drug-free plasma and derivatized as described. There were no detectable levels of PMPA present in any of the plasma samples, and the projected % of conversion was less than 1%.

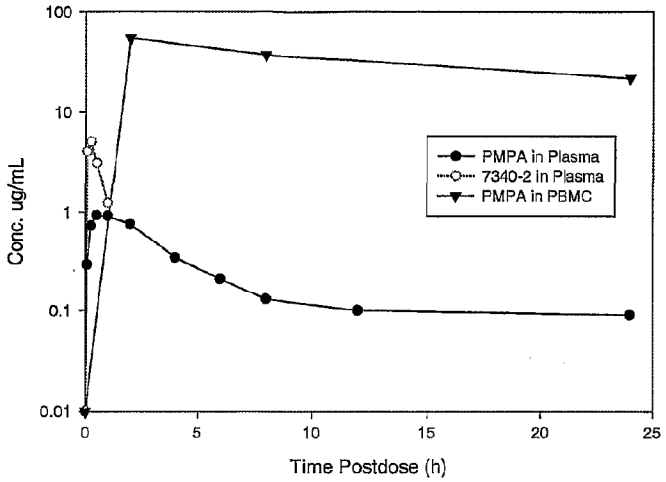
The HPLC system was comprised of a P4000 solvent delivery system with AS3000 autoinjector and F2000 fluorescence detector (Thermo Separation, San Jose, CA). The column was an Inertsil ODS-2 column (4.6 × 150 mm). The mobile phases used were: A, 5% acetonitrile in 25 mM potassium phosphate buffer with 5 mM tetrabutyl ammonium bromide (TBABr), pH 6.0; B, 60% acetonitrile in 25 mM potassium phosphate buffer with 5 mM TBABr, pH 6.0. The flow rate was 2 ml/min and the column temperature was maintained at 35°C by a column oven. The gradient profile was 90% A/10% B for 10 min for PMPA and 65%A/35%B for 10 min for the prodrug. Detection was by fluorescence with excitation at 236 nm and emission at 420 nm, and the injection volume was 10 µl. Data was acquired and stored by a laboratory data acquisition system (PeakPro, Beckman, Allendale, NJ).

Pharmacokinetic Calculations. PMPA and prodrug exposures were expressed as areas under concentration curves in plasma or PBMC from zero to 24 hours (AUC). The AUC values were calculated using the trapezoidal rule.

Plasma and PBMC Concentrations. The results of this study is shown in Figures 2 and 3. Figure 2 shows the time course of GS 7340-2 metabolism summary of plasma and PBMC exposures following oral administration of pure diastereoisomers of the PMPA prodrugs.

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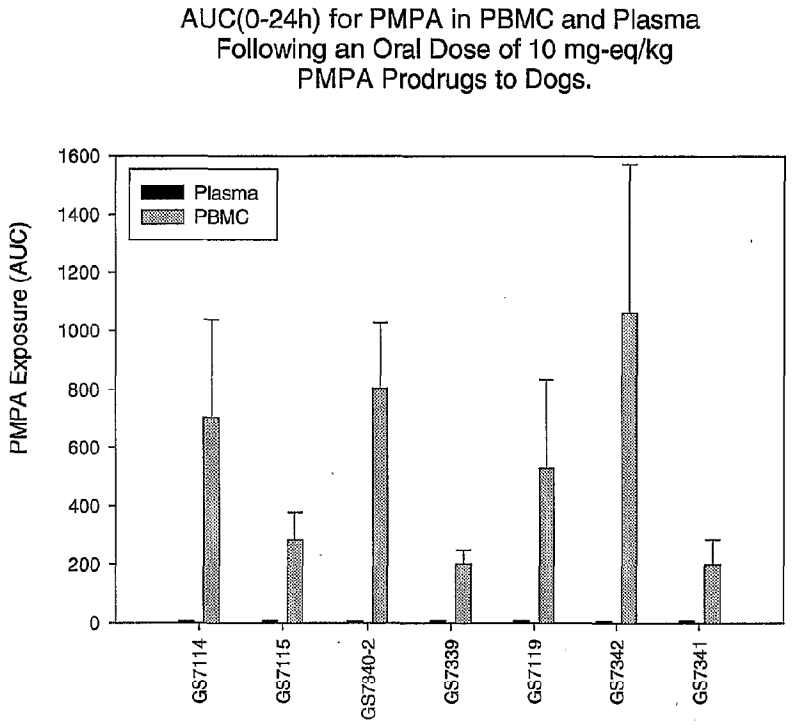
Figure 2. PMPA and Prodrug Concentration in Plasma and PBMCs Following Oral Administration of GS 7340-2 to Dogs at 10 mg-eq/kg.



The bar graph in Figure 2 shows the AUC (0-24h) for tenofovir in dog PBMCs and plasma after administration of PMPA s.c., TDF and amidate ester prodrugs. All of the amidate prodrugs exhibited increases in PBMC exposure. For example, GS 7340 results in a ~21-fold increase in PBMC exposure as compared to PMPA s.c. and TDF; and a 6.25-fold and 1.29-fold decrease in plasma exposure, respectively.

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Figure 3. Depicts Tenofovir Exposure in PBMCs and Plasma Upon Administration of 10 mg-eq/kg in dogs



These data establish *in vivo* that GS 7340 can be delivered orally, minimizes systemic exposure to PMPA and greatly enhances the intracellular concentration of PMPA in the cells primarily responsible for HIV replication.

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Table 6

PMPA Exposure in PBMC and Plasma from Oral Prodrugs of PMPA in Dogs

GS#	Moiety	PMPA AUC in Plasma			PMPA AUC in PBMC			Prodrug in Plasma	PBMC/Plasma Exposure Ratio
		Mean	StDev	N	Mean	StDev	N		
GS-7114	Mono-Ala-Et-A	5.8	0.9	2	706	331	5	YES	122
GS-7115	Mono-Ala-Et-B	6.6	1.5	2	284	94	5	YES	43
GS-7340-2	Mono-Ala-iPr-A	5.0	1.1	5	805	222	5	YES	161
GS-7339	Mono-Ala-iPr-A	6.4	1.3	2	200	57	5	YES	31
GS-7119	Mono-Gly-Et-A	6.11	1.86	2	530	304	5	YES	87
GS-7342	Mono-ABA-Et-A	4.6	1.2	2	1060	511	5	YES	230
GS7341	Mono-ABA-Et-B	5.8	1.4	2	199	86	5	YES	34

Example 11

Biodistribution of GS-7340

As part of the preclinical characterization of GS-7340, its biodistribution in dogs was determined. The tissue distribution of GS-7340 (isopropyl alaninyl monoamidate, phenyl monoester of tenofovir) was examined following oral administration to beagle dogs. Two male animals were dosed orally with ^{14}C=GS-7340 (8.85 mg-equiv. of PMPA/kg, 33.2 μCi/kg; the 8-carbon of adenine is labeled) in an aqueous solution (50 mM citric acid, pH 2.2). Plasma and peripheral blood mononuclear cells (PBMCs) were obtained over the 24-hr period. Urine and feces were cage collected over 24 hr. At 24 h after the dose, the animals were sacrificed and tissues removed for analysis. Total radioactivity in tissues was determined by oxidation and liquid scintillation counting.

The biodistribution of PMPA after 24 hours after a single oral dose of radiolabelled GS 7340 is shown in Table 4 along with the data from a previous study with TDF (GS-4331). In the case of TDF, the prodrug concentration in the plasma is below the level of assay detection, and the main species observed in plasma is the parent drug. Levels of PMPA in the lymphatic tissues, bone marrow, and skeletal muscle are increased 10-fold after administration of GS-7340.

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Accumulation in lymphatic tissues is consistent with the data observed from the PBMC analyses, since these tissues are composed primarily of lymphocytes. Likewise, accumulation in bone marrow is probably due to the high percentage of lymphocytes (70%) in this tissue.

Table 7. Excretion and Tissue Distribution of Radiolabelled GS-7340 in Dogs (Mean, N=2) Following an Oral Dose at 10 mg-eq. PMPA/kg.

Tissue/Fluid	GS-4331		GS-7340		Tissue Conc. Ratio of GS 7340 to GS-4331
	% Dose	Conc. (ug-eq/g)	% Dose	Conc. (ug-eq/g)	
Liver	12.40	38.30	16.45	52.94	1.4
Kidney	4.58	87.90	3.78	80.21	0.9
Lungs	0.03	0.53	0.34	4.33	8.2
Iliac Lymph Nodes	0.00	0.51	0.01	5.42	10.6
Axillary Lymph Nodes	0.00	0.37	0.01	5.54	14.8
Inguinal Lymph Nodes	0.00	0.28	0.00	4.12	15.0
Mesenteric Lymph Nodes	0.00	1.20	0.04	6.88	5.7
Thyroid Gland	0.00	0.30	0.00	4.78	15.8
Pituitary Gland	0.00	0.23	0.00	1.80	7.8
Salivary Gland (L+R)	0.00	0.45	0.03	5.54	12.3
Adrenal Gland	0.00	1.90	0.00	3.47	1.8
Spleen	0.00	0.63	0.17	8.13	12.8
Pancreas	0.00	0.57	0.01	3.51	6.2
Prostate	0.00	0.23	0.00	2.14	9.1
Testes (L+R)	0.02	1.95	0.02	2.01	1.0
Skeletal Muscle	0.00	0.11	0.01	1.12	10.1
Heart	0.03	0.46	0.15	1.97	4.3
Femoral Bone	0.00	0.08	0.00	0.28	3.5
Bone Marrow	0.00	0.20	0.00	2.05	10.2
Skin	0.00	0.13	0.00	0.95	7.2
Abdominal fat	0.00	0.16	0.00	0.90	5.8
Eye (L+R)	0.00	0.06	0.00	0.23	3.7
Brain	0.00	<LOD	0.00	<LOD	n.d.
Cerebrospinal Fluid	0.00	<LOD	0.00	0.00	n.d.
Spinal Cord	0.00	<LOD	0.00	0.04	n.d.
Stomach	0.11	1.92	0.26	2.68	1.4
Jejunum	1.34	3.01	0.79	4.16	1.4
Duodenum	0.49	4.96	0.44	8.77	1.8
Ileum	0.01	0.50	0.16	4.61	9.2
Large Intestine	1.63	5.97	2.65	47.20	7.9
Gall bladder	0.00	3.58	0.04	25.02	7.0
Bile	0.00	9.63	0.22	40.48	4.2
Feces	40.96	n.d.	0.19	n.d.	n.a.
Total GI Tract Contents	5.61	n.d.	21.64	n.d.	n.a.
Urine	23.72	n.d.	14.73	n.d.	n.a.
Plasma at 24 h	0.00	0.20	0.00	0.20	1.0
Plasma at 0.25 h	n.a.	3.68	n.a.	3.48	0.9
PBMC*	0.00	n.d.	0.00	63.20	n.d.
Whole Blood	0.00	0.85	0.16	0.20	0.2
Total Recovery	81.10		68.96		

* Calculated using typical recovery of 15 x 10^6 cells total, and mean PBMC volume of 0.2 picoliters/cell

n.s. = no sample, n.a. = not applicable, n.d. = not determined.

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CLAIMS:

1. A screening method for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue;

(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and

(d) determining the relative activity conferred by the prodrug in the tissues in step (c).

2. The method of claim 1 wherein the activity is antiviral activity or antitumor activity.

3. The method of claim 2 wherein the activity is antiviral activity.

4. The method of claim 3 wherein the activity is anti-HIV or anti-HBV activity.

5. The method of claim 1 wherein the prodrug is a prodrug of PMPA or PMEA.

6. The method of claim 5 wherein the prodrug is a phosphonoamidate, phosphonoester or mixed phosphonoamidate/phosphonoester.

7. The method of claim 6 wherein the amidate is an amino acid amidate.

8. The method of claim 6 wherein the ester is an aryl ester.

9. The method of claim 1 further comprising selecting a prodrug having a relative activity in the target tissue that is greater than 10 times that of the non-target tissue.

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10. The method of claim 1 wherein the target and non-target tissue are in an animal, the prodrug is administered to the animal and the relative activity is determined by analysis of the animal tissues after administration of the prodrug.

11. The method of claim 1 wherein activity in the target and non-target tissues is determined by assaying the amount of at least one metabolite of the prodrug in the tissues.

12. The method of claim 12 wherein the metabolite is the parental drug.

13. The method of claim 12 wherein the metabolite is the diphosphate of the parental drug.

14. The method of claim 1 wherein the target tissue is virally infected tissue and the non-target tissue is the same tissue which is not virally infected.

15. The method of claim 1 wherein the target tissue is lymphoid tissue and the activity is anti-HIV activity.

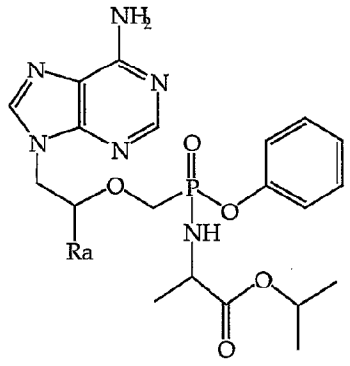
16. The method of claim 1 wherein the target tissue is liver and the activity is anti-HBV activity.

17. The method of claim 1 wherein the target tissue is hematological and the activity is antitumor activity.

18. The method of claim 1 wherein the target tissue is malignant and the non-target tissue is the same tissue but non-malignant.

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19. A compound having the structure (1)

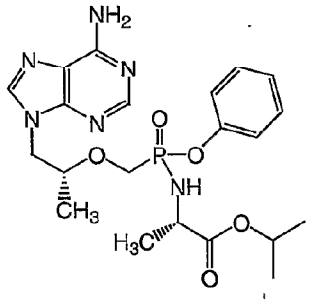


(1)

where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

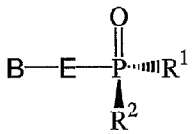
20. A compound having the structure (2)



(2)

and its enriched diasteromers, salts, free base and solvates.

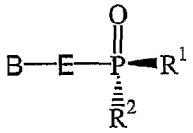
21. A diastereomerically enriched compound having the structure (3)



(3)

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which is substantially free of the diastereomer (4)



(4)

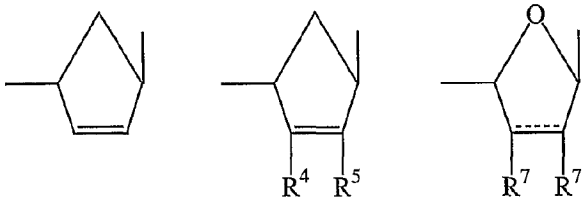
wherein

R^1 is an oxyester which is hydrolyzable *in vivo*, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $-(CH_2)_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2F)CH_2-$, $-CH(CH_2OH)CH_2-$, $-CH(CH{=}CH_2)CH_2-$, $-CH(C{\equiv}CH)CH_2-$, $-CH(CH_2N_3)CH_2-$,



$-CH(R^6)OCH(R^{6'})-$, $-CH(R^9)CH_2O-$ or $-CH(R^8)O-$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form -O- or $-CH_2-$;

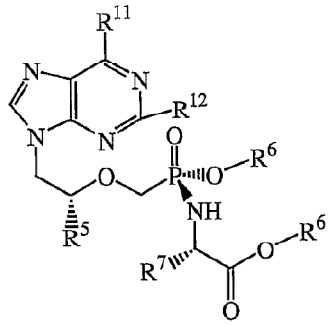
Gilead Exhibit 2024
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R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

R^9 is H, hydroxymethyl or acyloxymethyl;

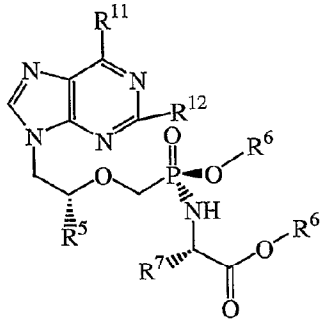
and their salts, free base, and solvates.

22. A diastereomerically enriched compound having the structure (5a)



(5a)

which is substantially free of diastereomer (5b)



(5b)

wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy,

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alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

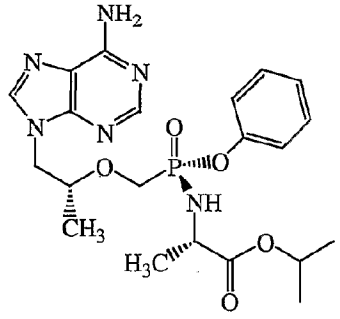
R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

and it salts, tautomers, free base and solvates.

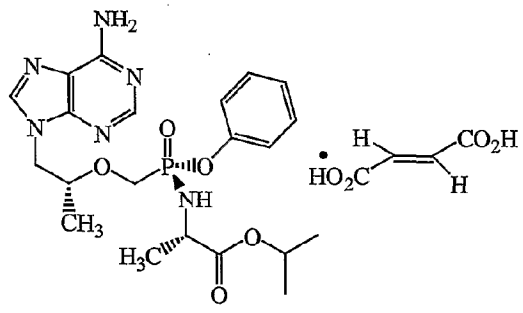
23. A compound of structure (6)



(6)

and its salts and solvates.

24. A compound of structure (7)



(7)

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PGR2023-00046 - Page 00936

25. A composition comprising a compound of any of claims 19-24 and a pharmaceutically effective excipient.

26. The composition of claim 25 wherein the excipient is a gel.

27. The composition of claim 25 which is suitable for topical administration.

28. A method for antiviral therapy or prophylaxis comprising administering a compound of any of claims 19-24 in a therapeutically or prophylactically effective amount to a subject in need of such therapy or prophylaxis.

29. A method for use of magnesium alkoxide comprising reacting 9-(2-hydroxypropyl)adenine (HPA) or 9-(2-hydroxyethyl)adenine (HEA), magnesium alkoxide, and protected *p*-toluenesulfonyloxymethylphosphonate.

30. The method of claim 29 further comprising recovering PMPA or PMEA, respectively.

31. The method of claim 29 wherein the phosphonate of the *p*-toluenesulfonyloxymethylphosphonate is protected by ethyl ester.

32. The method of claim 29 wherein the alkoxide is a C_1-C_6 alkoxide.

33. The method of claim 32 wherein the alkoxide is t-butyl or isopropyl oxide.

Gilead Exhibit 2024
PGR2023-00046 - Page 00937

Electronic Acknowledgement Receipt

EFS ID:	17636400
Application Number:	14057675
International Application Number:	
Confirmation Number:	4233
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.4
Receipt Date:	12-DEC-2013
Filing Date:	18-OCT-2013
Time Stamp:	09:48:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	039560538004_IDSTransmittal_2013-12-12.pdf	54629 10176ec2a5686a169f6cd14ac1b3fbc5df53adf4	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	03956053800-4-IDS-SB08.PDF	612798 92334a9d0804e3c0d84a3e82a1a4b11b9915b9bc	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Foreign Reference	FOR1_WO2006067606.pdf	4412294 c645bc379280a837af8e697bdb1cl54a06f741803	no	46
Warnings:					
Information:					
4	Foreign Reference	FOR2_WO2002008241.pdf	4724247 ef1e0cbf57eb04f9e7f57efd8ae48dbe8415fc39	no	59
Warnings:					
Information:					
5	Non Patent Literature	NPL1_McGuigan_FEBS_1994.pdf	608235 319e31172ebab86ceb10ce60f095ab0f6fcd6084	no	4
Warnings:					
Information:					
6	Non Patent Literature	NPL2_Cahard_MiniRev_2004.pdf	552500 50ab309fc6f92e48f0394af5bbafab0223383e9c	no	12
Warnings:					
Information:					
		Total Files Size (in bytes):	10964703		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

03956.053800.4 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/057,675	)	
	:	Examiner: PATRICK T. LEWIS
First Named Inventor:	)	
	:	Group Art Unit: 1621
JINFA DU	)	
	:	Confirmation No.: 4233
Filed: October 18, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	December 12, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the documents listed on the attached PTO/SB/08a Form. It is respectfully requested that this information be considered by the Examiner and that a copy of the attached PTO/SB/08a form be returned indicating that such information has been considered.

In accordance with 37 C.F.R. §1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether these references are, or are considered to be, material to patentability.

Pursuant to 37 C.F.R. § 1.97(b), it is believed that no fees are due in connection with this submission. However, should the U.S. Patent and Trademark Office determine that fees are due, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-3939.

Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

03956.053800.4 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/057,675	)	
	:	Examiner: PATRICK T. LEWIS
First Named Inventor:	)	
	:	Group Art Unit: 1621
JINFA DU	)	
	:	Confirmation No.: 4233
Filed: October 18, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	December 13, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the following U.S. Application, which is electronically viewable:

Appln. No.	Filing Date	Group Art Unit	Examiner's Initials
13/956,195	July 31, 2013	1629	

It is respectfully requested that the above information be considered by the Examiner and that a copy of this document be returned indicating that such information has been considered.

In accordance with 37 C.F.R. §1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether this references is, or is considered to be, material to patentability.

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Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

Electronic Acknowledgement Receipt

EFS ID:	17650501
Application Number:	14057675
International Application Number:	
Confirmation Number:	4233
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.4
Receipt Date:	13-DEC-2013
Filing Date:	18-OCT-2013
Time Stamp:	10:31:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	03956053800-4IDSTransmittal.pdf	54994 32b3489c8c41db5ad650f1b49be3f923564d30fb	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	54994

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

104538 7590 12/20/2013
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

EXAMINER	
LEWIS, PATRICK T	
ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 12/20/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/057,675	10/18/2013	Jinfa Du	03956.053800.4	4233

TITLE OF INVENTION: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/20/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Gilead Exhibit 2024
PGR2023-00046 - Page 00947

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

104538 7590 12/20/2013
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/057,675	10/18/2013	Jinfa Du	03956.053800.4	4233

TITLE OF INVENTION: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/20/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1672	514-051000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Gilead Exhibit 2024
PGR2023-00046 - Page 00948

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/057,675	10/18/2013	Jinfa Du	03956.053800.4	4233

104538 7590 12/20/2013
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 12/20/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notices of Allowance and Fee(s) Due mailed between October 1, 2013 and December 31, 2013

(Addendum to PTOL-85)

If the "Notice of Allowance and Fee(s) Due" has a mailing date on or after October 1, 2013 and before January 1, 2014, the following information is applicable to this application.

If the issue fee is being timely paid on or after January 1, 2014, the amount due is the issue fee and publication fee in effect January 1, 2014. On January 1, 2014, the issue fees set forth in 37 CFR 1.18 decrease significantly and the publication fee set forth in 37 CFR 1.18(d)(1) decreases to $0.

If an issue fee or publication fee has been previously paid in this application, applicant is not entitled to a refund of the difference between the amount paid and the amount in effect on January 1, 2014.

Notice of Allowability	Application No. 14/057,675	Applicant(s) DU ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *4 and 5*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10292013 (6); 12062013; 12122013
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/PATRICK LEWIS/
Primary Examiner, Art Unit 1621

Gilead Exhibit 2024
PGR2023-00046 - Page 00952

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14057675	DU ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	2	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621	12/16/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14057675	DU ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
514	51

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	43	49	50		

INTERNATIONAL CLASSIFICATION					
CLAIMED					**NON-CLAIMED**
A	0	1	N	43 / 04 (2006.01.01)	
A	6	1	K	31 / 70 (2006.01.01)	

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	2	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621	12/16/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14057675	DU ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

☒ **Claims renumbered in the same order as presented by applicant** ☐ **CPA** ☐ **T.D.** ☐ **R.1.47**

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1														
	2														
	3														
	4														
	5														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 2	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621 (Primary Examiner)	12/16/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

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BIB DATA SHEET

CONFIRMATION NO. 4233

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/057,675	10/18/2013 RULE	514	1621	03956.053800.4

APPLICANTS

Gilead Pharmasset LLC, Foster City, CA, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

Jinfa Du, Redwood City, CA;
Dhanapalan Nagarathnam, Bethany, CT;
Michael Joseph Sofia, Doylestown, PA;
Peiyuan Wang, Totowa, NJ;

**** CONTINUING DATA ***************************

This application is a CON of 13/609,614 09/11/2012 PAT 8580765
which is a CON of 13/099,671 05/03/2011 PAT 8334270
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

11/04/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /PATRICK T LEWIS/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	0	2	1

ADDRESS

Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104
UNITED STATES

TITLE

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
5500	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14057675
Filing Date	2013-10-18
First Named Inventor	Jinfa Du
Art Unit	1623
Examiner Name	Not yet assigned
Attorney Docket Number	03956.053800.4

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8334270	B2	2012-12-18	Sofia et al.	
	2	8173621	B2	2012-05-08	Du et al.	
	3	8551973	B2	2013-10-08	Bao et al.	
	4	7754699	B2	2010-07-13	Chun et al.	
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100081628	A1	2010-04-01	Du et al.	
	2	20100279973	A1	2010-11-04	Chun et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (12/08/2013)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Not yet assigned
	Attorney Docket Number	03956.053800.4

	3	20110015146	A1	2011-01-20	Sofia et al.	
	4	20100298257	A1	2010-11-25	Ross et al.	
	5	20110251152	A1	2011-10-13	Ross et al.	
	6	20100286083	A1	2010-11-11	Bao et al.	
	7	20120107278	A1	2012-05-03	Berrey et al.	
	8	20110245484	A1	2011-10-10	Ross et al.	
	9	20130029929	A1	2013-01-31	Sofia et al.	
	10	20130137654	A1	2013-05-30	Ross et al.	
	11	20130165401	A1	2013-06-27	Ross et al.	
	12	20130165644	A1	2013-06-27	Ross et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Not yet assigned
	Attorney Docket Number	03956.053800.4

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2006/050161	WO	A2	2006-05-11	BIOCRYST PHARMACEUTICALS, INC.		☐
	2	2007/095269	WO	A2	2007-08-23	MERCK & CO., INC.		☐
	3	2006/116557	WO	A1	2006-11-02	GENELABS TECHNOLOGIES, INC.		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	GUDMUNDSSON, Kristjan S., et al., "Phosphoramidate Protides of Carbocyclic 2',3'-Dideoxy-2',3'-Didehydro-7-Deazaadenosine with Potent Activity Against HIV and HBV," Nucleosides, Nucleotides & Nucleic Acids (2004) 23(12): 1929-1937.	☐
	2	SIDDIQUI, Adam Q., et al., "The Presence of Substituents on the Aryl Moiety of the Aryl Phosphoramidate Derivatives of d4T Enhances Anti-HIV Efficacy in Cell Culture: A Structure-Activity Relationship," J. Med. Chem. (1999) 42:393-399.	☐
	3	DUMEZ, Darin, et al., "Large-Scale Synthesis and Formulation of GMP-Grade Stampidine, a New Anti-HIV Agent," Arzneim.-Forsch./Drug Res. (2006) 56(2a):136–151.	☐
	4	GUDMUNDSSON, Kristjan S., et al., "Phosphoramidate Protides of 2',3'-Dideoxy-3'-fluoroadenosine and Related Nucleosides with Potent Activity Against HIV and HBV," Nucleosides, Nucleotides & Nucleic Acids (2003) 22 (10):1953-1961.	☐
	5	NAKAYAMA, Kensaku, et al., "A Highly Enantioselective Synthesis of Phosphate Triesters," J. Am. Chem. Soc. (1990) 112:6936-6942.	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (12/08/2013)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	1623
	Examiner Name	Not yet assigned
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	6	WOZNIAK, Lucyna A., et al., "The stereospecific synthesis of P-chiral biophosphates and their analogues by the Stec reaction," Chem. Soc. Rev. (2003) 32:158-169.	☐
	7	UCHIYAMA, Mamoru, et al., "O-Selective Phosphorylation of Nucleosides without N-Protection," J. Org. Chem. (1993) 58:373-379.	☐
	8	Written Opinion of the International Searching Authority issued in International Application No. PCT/US2004/012472 (7 pages) (Nov. 30, 2005)	☐
	9	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2004/012472 (8 pages) (Dec. 1, 2005)	☐
	10	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2005/025916 (5 pages) (Jan. 23, 2007)	☐
	11	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2005/032406 (4 pages) (Mar. 10, 2009)	☐
	12	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/EP2006/069060 (7 pages) (Nov. 5, 2008)	☐
	13	Written Opinion of the International Searching Authority issued in the International Application No. PCT/US/2008/058183 (16 pages) (Apr. 1, 2010)	☐
	14	International Search Report issued in International Application No. PCT/US2009/046619 (4 pages) (Sept. 23, 2010)	☐
	15	Partial International Search Report issued in International Application No. PCT/US2009/069475 (7 pages) (Mar. 5, 2010)	☐
	16	International Search Report and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2009/069475 (21 pages) (May 10, 2010)	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Not yet assigned
	Attorney Docket Number	03956.053800.4

	17	Invitation to Pay Additional Fees & Partial International Search Report issued in International Application No. PCT/US2010/035641 (10 pages) (July 23, 2010)	☐
	18	International Search Report and Written Opinion of the International Searching Authority issued in PCT/US2010/035641 (23 pages) (Nov. 20, 2011)	☐
	19	MURAKAMI, E., et al., "The Mechanism of Action of beta-D-2'-Deoxy-2'-fluoro-2'-C-methylcytidine Involves a Second Metabolic Pathway Leading to beta-D-2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-Triphosphate, a Potent Inhibitor of the HCV RNA-Dependent RNA Polymerase," 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland (September 2007)	☐
	20	GILLESPIE, S., et al., "Stereoselective Inhibition of Cholesterol Esterase by Enantiomeric Phosphonates," Phosphorous, Sulfur and Silicon, 1997, 122: 205-208	☐
	21	U.S. Application No. 12/553,483, Non-Final Office Action Rejection, mailed 12/17/2009	☐
	22	U.S. Application No. 12/240,342, Non-Final Office Action Rejection, mailed 10/01/2009	☐
	23	U.S Application No. 12/142,554, Non-Final Office Action Rejection, mailed 10/01/2009	☐
	24	U.S. Application No. 12/142,536, Non-Final Office Action Rejection, mailed 10/02/2009	☐
	25	U.S. Application No. 11/854,218, Non-Final Office Action Rejection, mailed 10/01/2009	☐
	26	U.S. Application No. 11/635,898, Non-Final Office Action Rejection, mailed 07/28/2009	☐
	27	U.S. Application No. 11/353,597, Final Office Action Rejection, mailed 12/02/2008	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (12/08/2013)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Not yet assigned
	Attorney Docket Number	03956.053800.4

	28	U.S Application No. 11/353,597, Non-Final Office Action Rejection, mailed 07/17/2008	☐
	29	U.S Application No. 11/353,597, Non-Final Office Action Rejection, mailed 10/02/2007	☐
	30	U.S. Application No. 11/225,425, Final Office Action Rejection, mailed 02/18/2010	☐
	31	Response to non-final Office Action dated October 1, 2009 for U.S. Application No. 12/142,554	☐
	32	U.S. Application No. 11/225,425, Non-Final Office Action Rejection, mailed 07/07/2009	☐
	33	U.S. Application No. 11/225,425, Non-Final Office Action Rejection, mailed 11/13/2008	☐
	34	U.S. Application No. 10/828,753, Non-Final Office Action Rejection, mailed 03/30/2007	☐
	35	U.S Application No. 10/828,753, Final Office Action Rejection, mailed 02/26/2008	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (12/08/2013)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (12/08/2013)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Not yet assigned
	Attorney Docket Number	03956.053800.4

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Leila Marcovici/	Date (YYYY-MM-DD)	2013-10-23
Name/Print	Leila Marcovici	Registration Number	66,066

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Application Number	14057675
Filing Date	2013-10-18
First Named Inventor	Jinfa Du
Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	03956.053800.4

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7202224	B2	2007-04-10	Eldrup et al.	
	2	7390791	B2	2008-06-24	Becker et al.	
	3	7879815	B2	2011-02-01	MacCoss et al.	
	4	7964580	B2	2011-06-21	Sofia et al.	
	5	8148349	B2	2012-04-03	Meppen et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020198173	A1	2002-12-26	Schinazi et al.	

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	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

	2	20020058635	A1	2002-05-16	Averett	
	3	20010034440	A1	2001-10-25	Shepard et al.	
	4	20100137576	A1	2010-06-03	Stec et al.	
	5	20100152128	A1	2010-06-17	Attenni et al.	
	6	20100173863	A1	2010-07-08	Schinazi et al.	
	7	20100227801	A1	2010-09-09	Hopkins et al.	
	8	20100316594	A1	2010-12-16	Sommadossi et al.	
	9	20110124592	A1	2011-05-26	McGuigan et al.	
	10	20060122146	A1	2006-06-08	Chun et al.	
	11	20060199738	A1	2006-09-07	Otsubo et al.	
	12	20070197463	A1	2007-08-23	Chun et al.	

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	Art Unit	1623
	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

	13	20080070861	A1	2008-03-20	Clark	
	14	20080253995	A1	2008-10-16	Clark	
	15	20090004135	A1	2009-01-01	Clark	
	16	20090036666	A1	2009-02-05	Clark	
	17	20100081628	A1	2010-04-01	Du et al.	
	18	20100048917	A1	2010-02-25	Wang et al.	
	19	20100286083	A1	2010-11-11	Bao et al.	
	20	20110015146	A1	2011-01-20	Sofia et al.	
	21	20100279973	A1	2010-11-04	Chun et al.	
	22	20110257122	A1	2011-10-20	Sofia et al.	

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	Art Unit	1623
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	02/32414	WO	A2	2002-04-25	SCHERRING CORPORATION		☐

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Examiner Signature	/Patrick Lewis/ (12/08/2013)	Date Considered	

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Signature	/Leila Marcovici/	Date (YYYY-MM-DD)	2013-10-23
Name/Print	Leila Marcovici	Registration Number	66066

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PGR2023-00046 - Page 00970

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     (FILE 'HOME' ENTERED AT 22:24:13 ON 08 DEC 2013)

     FILE 'REGISTRY' ENTERED AT 22:24:26 ON 08 DEC 2013
L1             STRUCTURE UPLOADED
L2           6 S L1 SSS SAM
L3         111 S L1 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 22:24:58 ON 08 DEC 2013
L4          95 S L3
L5          91 S L4 AND (HEPATITIS C OR HCV)
L6           0 S L5 AND NSRA
L7          28 S L5 AND NS5A
L8          18 S L5 AND NS5A INHIBITOR
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
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Application Number	14057675
Filing Date	2013-10-18
First Named Inventor	DU, Jinfa
Art Unit	1621
Examiner Name	LEWIS, Patrick T.
Attorney Docket Number	03956.053800.4

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1	2006/067606	WO	A1	2006-06-29	INSERM, CNRS		☐
	2	2002/008241	WO	A2	2002-01-31	GILEAD SCIENCES, INC.		☐

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	Attorney Docket Number	03956.053800.4

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	MCGUIGAN, CHRISTOPHER, et al., Certain Phosphoramidate Derivatives of Dideoxy Uridine (ddU) Are Active Against HIV and Successfully By-pass Thymidine Kinase, FEBS Letters (1994), 351, 11-14.	☐
	2	CAHARD, DOMINIQUE, et al., Aryloxy Phosphoramidate Triesters as Pro-Tides, Mini-Reviews in Medicinal Chemistry (2004), 4, 371-381.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (12/16/2013)	Date Considered	

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	Filing Date	2013-10-18
	First Named Inventor	DU, Jinfa
	Art Unit	1621
	Examiner Name	LEWIS, Patrick T.
	Attorney Docket Number	03956.053800.4

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Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-12-12
Name/Print	Alicia A. Russo	Registration Number	46,192

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14057675	DU ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1621

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/16/2013								
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14057675	DU ET AL.
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	PATRICK LEWIS	1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	12/16/2013	/PL/

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	43, 49, 50, 51	12/16/2013	/PL/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14057675
Filing Date	2013-10-18
First Named Inventor	Jinfa Du
Art Unit	1623
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Attorney Docket Number	03956.053800.4

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

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	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

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	2	6132763	A	2000-10-17	Fisher	
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	1	2004/106356	WO	A1	2004-12-09	UNIV. SYDDANSK		☐
	2	2005/002626	WO	A2	2005-01-13	GILEAD SCIENCES INC.		☐
	3	2005/003147	WO	A2	2005-01-13	PHARMASSET LTD.		☐
	4	2005/007810	WO	A2	2005-01-27	GRINSTAFF MARK W		☐
	5	2005/009418	WO	A2	2005-02-03	IDENIX CAYMAN LTD CENTRE NAT DE LA RECH SCIENT		☐
	6	2005/012327	WO	A2	2005-02-10	UNIV. COLLEGE CARDIFF CONSULTANTS LTD.		☐
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	10	2005/037214	WO	A2	2005-04-28	INTERMUNE INC.		☐
	11	2005/067900	WO	A2	2005-07-28	ACHILLION PHARMACEUTICALS INC.		☐
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	21	2006/020082	WO	A1	2006-02-23	SQUIBB BRISTOL MYERS CO.		☐
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	43	2007/015824	WO	A2	2007-02-08	INTERMUNE INC.		☐
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	48	2007/070556	WO	A2	2007-06-21	GENELABS TECH INC.		☐
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	1	Mitchell et al., "Bioreversible Protection for the Phospho Group: Bioactivation of the Di(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Phosphoesters of Methylphosphonate and Phosphonoacetate," J. Chem. Soc. Perkin. Trans. 1, pages 2345 - 2353 (1992)	☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (12/08/2013)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

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	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

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	32	International Search Report issued in International Application No. PCT/US2005/025916 mailed June 15, 2006 (2 pages)	☐
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	Examiner Name	Unassigned
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EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (12/08/2013)	Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Leila Marcovici/	Date (YYYY-MM-DD)	2013-10-23
Name/Print	Leila Marcovici	Registration Number	66066

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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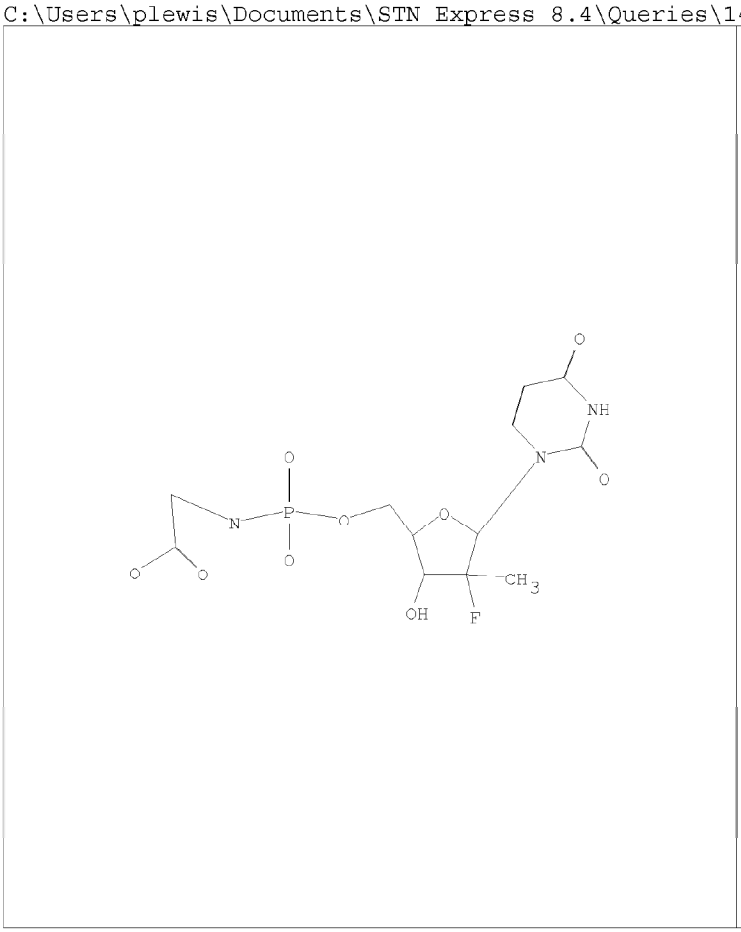
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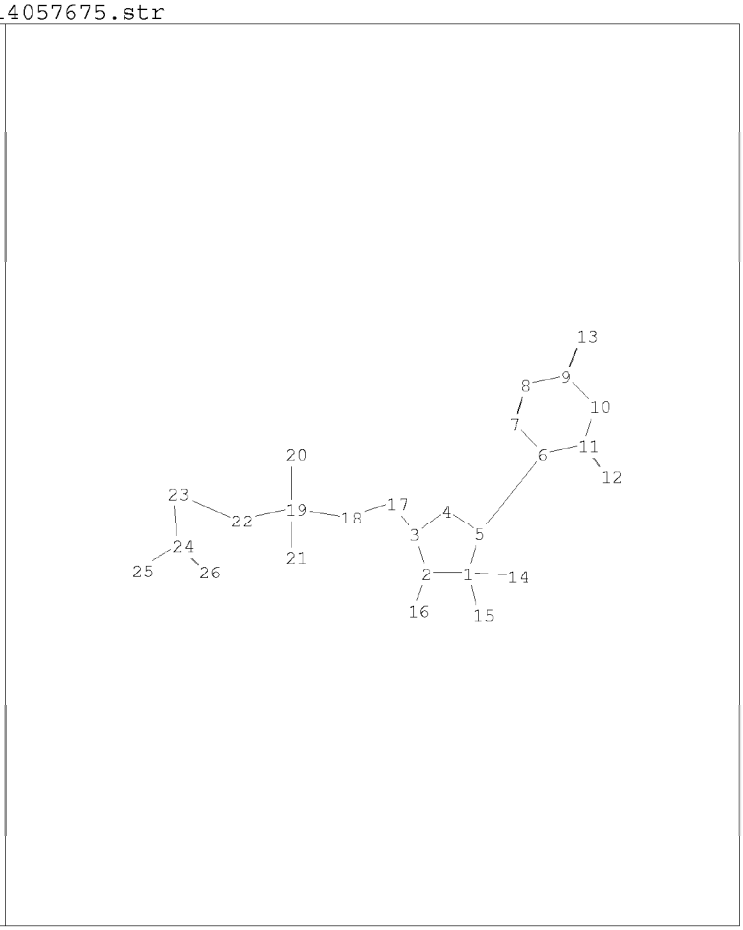
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
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	First Named Inventor	DU, Jinfa
	Art Unit	1621
	Examiner Name	LEWIS, Patrick T.
	Attorney Docket Number	03956.053800.4

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8580765	B2	2013-11-12	SOFIA,Michael Joseph	
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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20120245335	A1	2012-09-27	CLARK, Jeremy	
	2	20130109647	A1	2013-05-02	BERREY, Miriam Michelle	
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	Attorney Docket Number	03956.053800.4

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	1	Yuodka et al., Bioorganicheskaya Khimiya, 2(11), 1513-1519 (1976) (translated from Russian).	☐

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-12-06
Name/Print	Alicia A. Russo	Registration Number	46,192

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Filing Date	2013-10-18
First Named Inventor	Jinfa Du
Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	03956.053800.4

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	12	03/006490	WO	A1	2003-01-23	VERTEX PHARMA., INC.		☐
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	15	03/026589	WO	A2	2003-04-03	IDENIX CAYMAN LTD CENTRE NAT DE LA RECH SCIENT		☐
	16	03/037895	WO	A1	2003-05-08	GLAXO GROUP LTD.		☐
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	43	2004/046331	WO	A2	2004-06-03	IDENIX CAYMAN LTD.		☐
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	Attorney Docket Number	03956.053800.4

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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	23	Eisenberg et al., "Metabolism of GS-7340, A Novel Phenyl Monophosphoramidate Intracellular Prodrug of PMPA, In Blood," Nucleosides, Nucleotides & Nucleic Acids, Vol. 20, No. 4 - 7, pages 1091 - 1098 (2001)	☐
	24	Lee et al., "Selective Intracellular Activation of a Novel Prodrug of the Human Immunodeficiency Virus reverse Transcriptase Inhibitor Tenofovir Leads to Preferential Distribution and Accumulation in Lymphatic Tissue," Antimicrobial Agents and Chemotherapy, Vol. 49, No. 5, pages 1898 - 1906 (2005)	☐
	25	McGuigan et al., "Synthesis, anti-human immunodeficiency virus activity and esterase lability of some novel carboxylic ester-modified phosphoramidate derivatives of stavudine (d4T)," Antiviral Chemistry & Chemotherapy, Vol. 9, pages 473 - 479 (1998)	☐
	26	Murakami et al., "The Mechanism of Action of beta-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine Involves a Second Metabolic Pathway Leading to beta-D-2'-Deoxy-2'-Fluoro-2'-C-Methyluridine 5'-Triphosphate, a Potent Inhibitor of the Hepatitis C Virus RNA-Dependent RNA Polymerase," Antimicrobial Agents and Chemotherapy, Vol. 52, No. 2, pages 458 - 464 (2008)	☐
	27	Murakami et al., "Mechanism of Activation of beta-D-2' -Deoxy-2'-Fluoro-2'-C-Methylcytidine and Inhibition of hepatitis C Virus NS5B RNA Polymerase," Antimicrobial Agents and Chemotherapy, Vol. 51, No. 2, pages 503 - 509 (February 2007)	☐
	28	Ray et al., "Intracellular Metabolism of the Nucleotide Prodrugs GS-9131, a Potent Anti-Human Immunodeficiency Virus Agent," Antimicrobial Agents and Chemotherapy, Vol. 52, No. 2, pages 648 - 654 (2008)	☐
	29	Stuyver et al., "Inhibition of the Subgenomic Hepatitis C Virus Replicon in Huh-7 Cells by 2'-Deoxy-2'-Fluorocytidine," Antimicrobial Agents and Chemotherapy, Vol. 48, No. 2, pages 651 - 654 (2004)	☐
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (12/08/2013)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

EXAMINER SIGNATURE			
Examiner Signature	/Patrick Lewis/ (12/08/2013)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (12/08/2013)

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	Filing Date	2013-10-18
	First Named Inventor	Jinfa Du
	Art Unit	1623
	Examiner Name	Unassigned
	Attorney Docket Number	03956.053800.4

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Leila Marcovici/	Date (YYYY-MM-DD)	2013-10-23
Name/Print	Leila Marcovici	Registration Number	66066

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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Gilead Exhibit 2024
PGR2023-00046 - Page 001047

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	DU, Jinfa
	Art Unit	1621
	Examiner Name	LEWIS, Patrick T.
	Attorney Docket Number	03956.053800.4

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	1	20130310551	A1	2013-11-21	BRUCE S. ROSS, ET AL.	
	2	20130288997	A1	2013-10-31	BRUCE S. ROSS, ET AL.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	DU, Jinfa
	Art Unit	1621
	Examiner Name	LEWIS, Patrick T.
	Attorney Docket Number	03956.053800.4

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	U.S. Patent Application No. 14/013,237, as filed Aug. 29, 2013	☐
	2	Claims of U.S. Patent Application No. 14/013,237 as amended Aug. 30, 2013	☐
	3	U.S. Patent Application No. 13/956,195, as filed July 31, 2013	☐
	4	Claims of U.S. Patent Application No. 13/956,195 as amended Oct. 21, 2013	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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	Art Unit	1621
	Examiner Name	LEWIS, Patrick T.
	Attorney Docket Number	03956.053800.4

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☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

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Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2014-01-15
Name/Print	Alicia A. Russo	Registration Number	46,192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	17918491
Application Number:	14057675
International Application Number:	
Confirmation Number:	4233
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.4
Receipt Date:	15-JAN-2014
Filing Date:	18-OCT-2013
Time Stamp:	13:26:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	03956053800-4RequesttoConsiderIDS.pdf	88236 2d9521626c591a9eb13a988d92b920d15108285c	no	3
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	PH3080PC5TRK1_SB08a.pdf	612504 2c87e6851350f15ba9711e23e4b7cbcc0b044b6d	no	4

Warnings:	
Information:	
Total Files Size (in bytes):	700740

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

03956.053800.4 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/057,675	)	
	:	Examiner: PATRICK T. LEWIS
First Named Inventor:	)	
	:	Group Art Unit: 1621
JINFA DU	)	
	:	Confirmation No.: 4233
Filed: October 18, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	
	:	
	)	January 15, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST TO CONSIDER
CORRECTED INFORMATION DISCLOSURE STATEMENT

Sir:

The Applicant respectfully requests consideration of the corrected Information Disclosure statement submitted herewith.

Information Disclosure Statements (IDSs) submitted on October 23, 2013 and December 13, 2013 were not initialed and returned. These IDSs listed unpublished co-pending applications. During a telephone call between the Examiner and the Applicant's attorney, Erin Austin, it was discussed that the same had not been initialed and returned because the co-pending applications had not been listed using a Form PTO/SB/08a. The Examiner requested that the Applicant submit a Form PTO/SB/08a listing the previously-cited co-pending applications.

The Applicant submits herewith a corrected IDS consisting of the previously-cited co-pending applications listed on a Form PTO/SB/08a. Previously-cited U.S. Application Nos. 13/936,448, filed July 8, 2013 and 13/925,078, filed June 24, 2013 correspond to U.S. Patent Application Pub. Nos. 2013-0310551 A1 and 2013-0288997 A1, respectively.

During the telephone call between the Examiner and the Applicant's attorney, Erin Austin, the Examiner kindly stated he would indicate the references had been considered if a Form PTO/SB/08a were submitted. The Applicant thanks the Examiner for his courtesy and respectfully requests consideration of the same.

Pursuant to MPEP § 609.04(a)(II)(C) and the *Waiver of the Copy Requirement in 37 CFR 1.98 for Cited Pending U.S. Patent Applications*, 1287 O.G. 163 (Oct. 19, 2004), copies of cited pending unpublished U.S. applications are not submitted herewith because they are stored in the Image File Wrapper (IFW) system.

As no fee was due in connection with the IDSs submitted on October 23, 2013 or December 13, 2013, the Applicant believes that no fee is due in connection with this paper. However, should the U.S. Patent and Trademark Office determine that fees are due, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-3939.

Gilead Exhibit 2024
PGR2023-00046 - Page 001055

Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/057,675	10/18/2013	Jinfa Du	03956.053800.4	4233

104538 7590 01/28/2014
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1672	

MAIL DATE	DELIVERY MODE
01/28/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Gilead Exhibit 2024
PGR2023-00046 - Page 001057

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
14/057,675	18 October, 2013	DU ET AL.	03956.053800.4

Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

EXAMINER	
PATRICK LEWIS	
ART UNIT	PAPER
1672	20140117

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Attached is an initialed, signed copy of the IDS submitted on 1/15/2014.

/PATRICK LEWIS/
Primary Examiner, Art Unit 1672

PTO-90C (Rev.04-03)

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Examiner Name	LEWIS, Patrick T.
Attorney Docket Number	03956.053800.4

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	1	20130310551	A1	2013-11-21	BRUCE S. ROSS, ET AL.	
	2	20130288997	A1	2013-10-31	BRUCE S. ROSS, ET AL.	

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	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	DU, Jinfa
	Art Unit	1621
	Examiner Name	LEWIS, Patrick T.
	Attorney Docket Number	03956.053800.4

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	U.S. Patent Application No. 14/013,237, as filed Aug. 29, 2013	☐
	2	Claims of U.S. Patent Application No. 14/013,237 as amended Aug. 30, 2013	☐
	3	U.S. Patent Application No. 13/956,195, as filed July 31, 2013	☐
	4	Claims of U.S. Patent Application No. 13/956,195 as amended Oct. 21, 2013	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (01/17/2014)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (01/17/2014)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14057675
	Filing Date	2013-10-18
	First Named Inventor	DU, Jinfa
	Art Unit	1621
	Examiner Name	LEWIS, Patrick T.
	Attorney Docket Number	03956.053800.4

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2014-01-15
Name/Print	Alicia A. Russo	Registration Number	46,192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Gilead Exhibit 2024
PGR2023-00046 - Page 001062

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/057,675	10/18/2013	Jinfa Du	03956.053800.4

CONFIRMATION NO. 4233

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

PUBLICATION NOTICE

OC000000066624556

Title:NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Publication No.US-2014-0045783-A1
Publication Date:02/13/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Gilead Exhibit 2024
PGR2023-00046 - Page 001063

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

104538 7590 12/20/2013
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/057,675	10/18/2013	Jinfa Du	03956.053800.4	4233

TITLE OF INVENTION: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/20/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1672	514-051000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Fitzpatrick, Cella, Harper & Scinto
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Gilead Pharmasset LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Foster City, CA 94404

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-3939 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Alicia A. Russo/ Date March 6, 2014
Typed or printed name Alicia A. Russo Registration No. 46,192

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Gilead Exhibit 2024
PGR2023-00046 - Page 001064

Electronic Patent Application Fee Transmittal

Application Number:	14057675
Filing Date:	18-Oct-2013
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Filer:	Erin Julia Daida Austin/Maria Miglio
Attorney Docket Number:	03956.053800.4
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	18386251
Application Number:	14057675
International Application Number:	
Confirmation Number:	4233
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.4
Receipt Date:	06-MAR-2014
Filing Date:	18-OCT-2013
Time Stamp:	11:42:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	12486
Deposit Account	503939
Authorized User	NGUY, DAVID
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	03956053800-4-IssueFeeFINAL.pdf	143659 c26fd3f7588926f59336c2035340bf5e4475ee3c	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30236 7930204934ccd1ecb9bfb4398b5da15a9e7344145	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	173895		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/057,675	10/18/2013	Jinfa Du	03956.053800.4	4233

104538 7590 03/15/2014
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1672	

MAIL DATE	DELIVERY MODE
03/15/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Gilead Exhibit 2024
PGR2023-00046 - Page 001069

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 14057675
Applicant : Du
Filing Date : 10/18/2013
Date Mailed : 03/15/2014

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Kam Sin/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 14057675

IDENTIFICATION OF APPLICATION DEFICIENCIES

[X] Applicant must provide legible text for the following item(s).

- [X] Specification filed 10/18/2013, page(s) 116-638; see other.
- [ ] Claims filed , claim(s) .
- [ ] Oath/declaration filed .
- [X] Other: all tables numbered 43 appear to have an overprint in the right side of the table with either a "5" or "10".

[ ] Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.

[ ] The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.

[ ] Applicant must provide an Abstract of the Disclosure.

[ ] Applicant has submitted a DECLARATION (37 CFR 1.63) FOR A UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76) (e.g., form PTO/SB/01A). The Application Data Sheet, however, is not present with the filed application. Applicant must submit an Application Data Sheet or file a new oath or declaration (e.g., PTO/SB/01) executed by the inventors and containing the information required in 37 CFR 1.63.

[ ] Applicant must provide an executed declaration.

[ ] Applicant must provide the missing page(s) of the oath/declaration or Application Data Sheet filed

[ ] Applicant must provide a declaration signed by inventor(s) .

[ ] The oath/declaration filed shows non-initialed and/or non-dated alterations. Applicant must file a new oath/declaration in compliance with 37 CFR 1.67(a).

[ ] Applicant(s) in the latest-filed oath/declaration or Application Data Sheet (ADS) did not show the inventor's residence at all, or did not show both a city and state in the U.S. inventor's residence, or did not show both a city and country in the non-U.S. inventor's residence. Applicant must supply an oath/declaration or Application Data Sheet (ADS) that shows each U.S. inventor's city and state of residence and each non-U.S. inventor's city and country of residence.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/057,675	10/18/2013	Jinfa Du	03956.053800.4	4233

104538 7590 03/15/2014
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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1672	

MAIL DATE	DELIVERY MODE
03/15/2014	PAPER

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The time period for reply, if any, is set in the attached communication.

Gilead Exhibit 2024
PGR2023-00046 - Page 001072

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
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Application No. : 14057675
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See attachment(s).

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/Kam Sin/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 14057675

IDENTIFICATION OF APPLICATION DEFICIENCIES

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- [ ] Claims filed , claim(s) .
- [ ] Oath/declaration filed .
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[ ] Applicant must provide an Abstract of the Disclosure.

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[ ] Applicant must provide an executed declaration.

[ ] Applicant must provide the missing page(s) of the oath/declaration or Application Data Sheet filed

[ ] Applicant must provide a declaration signed by inventor(s) .

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[ ] Applicant(s) in the latest-filed oath/declaration or Application Data Sheet (ADS) did not show the inventor's residence at all, or did not show both a city and state in the U.S. inventor's residence, or did not show both a city and country in the non-U.S. inventor's residence. Applicant must supply an oath/declaration or Application Data Sheet (ADS) that shows each U.S. inventor's city and state of residence and each non-U.S. inventor's city and country of residence.

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Cross-Reference to Related Applications

This application is a continuation application of U.S. Patent Application No. 13/609,614, filed September 11, 2012, which is a continuation of U.S. Patent Application No. 13/099,671, filed May 3, 2011, which issued as U.S. Patent No. 8,334,270 on December 18, 2012, which is a continuation of U.S. Patent Application No. 12/053,015, filed March 21, 2008, which issued as U.S. Patent No. 7,964,580 on June 21, 2011, which claims the benefit of U.S. Provisional Application No. 60/982,309, filed October 24, 2007, and U.S. Provisional Application No. 60/909,315, filed March 30, 2007. The entire contents of the aforementioned applications are incorporated herein by reference in their entirety.

Incorporation of Sequence Listing

The Sequence Listing filed on October 10, 2012 (in U.S. Patent Application No. 13/609,614, filed September 11, 2012), created on September 30, 2012, named 039560538002_ST25.txt, having a size in bytes of 1,091 B, is hereby incorporated by reference herein in its entirety.

Field of Invention

The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals. The

invention provides novel chemical compounds, and the use of these compounds alone or in combination with other antiviral agents for treating HCV infection.

Background

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their offspring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection.

The HCV virion is an enveloped positive-strand RNA virus with a single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the

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structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. Therefore, NS5B polymerase is considered to be an essential component in the HCV replication complex (K. Ishi, et al, *Heptology*, 1999, 29: 1227-1235; V. Lohmann, et al., *Virology*, 1998, 249: 108-118). Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of HCV-specific antiviral therapies.

HCV belongs to a much larger family of viruses that share many common features.

Flaviviridae Viruses

The Flaviviridae family of viruses comprises at least three distinct genera: *pestiviruses*, which cause disease in cattle and pigs; *flavivruses*, which are the primary cause of diseases such as dengue fever and yellow fever; and *hepaciviruses*, whose sole member is HCV. The flavivirus genus includes more than 68 members separated into groups on the basis of serological relatedness (Calisher et al., *J. Gen. Virol*, 1993,70,37-43). Clinical symptoms vary and include fever, encephalitis and hemorrhagic fever (*Fields Virology*, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, 1996, Chapter 31, 931-959). Flaviviruses of global

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concern that are associated with human disease include the Dengue Hemorrhagic Fever viruses (DHF), yellow fever virus, shock syndrome and Japanese encephalitis virus (Halstead, S. B., *Rev. Infect. Dis.*, 1984, 6, 251-264; Halstead, S. B., *Science*, 239:476-481, 1988; Monath, T. P., *New Eng. J. Med*, 1988, 319, 64 1-643).

The pestivirus genus includes bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, also called hog cholera virus) and border disease virus (BDV) of sheep (Moennig, V. et al. *Adv. Vir. Res.* 1992, 41, 53-98). Pestivirus infections of domesticated livestock (cattle, pigs and sheep) cause significant economic losses worldwide. BVDV causes mucosal disease in cattle and is of significant economic importance to the livestock industry (Meyers, G. and Thiel, H.J., Advances in Virus Research, 1996, 47, 53-118; Moennig V., et al, Adv. Vir. Res. 1992, 41, 53-98). Human pestiviruses have not been as extensively characterized as the animal pestiviruses. However, serological surveys indicate considerable pestivirus exposure in humans.

Pestiviruses and hepaciviruses are closely related virus groups within the Flaviviridae family. Other closely related viruses in this family include the GB virus A, GB virus A-like agents, GB virus-B and GB virus-C (also called hepatitis G virus, HGV). The hepacivirus group (hepatitis C virus; HCV) consists of a number of closely related but genotypically distinguishable viruses that infect humans. There are at least 6 HCV genotypes and more than 50 subtypes. Due to the similarities between pestiviruses and hepaciviruses, combined with the poor ability of hepaciviruses to grow efficiently in cell culture, bovine viral diarrhea virus (BVDV) is often used as a surrogate to study the HCV virus.

The genetic organization of pestiviruses and hepaciviruses is very similar. These positive stranded RNA viruses possess a single large open reading frame (ORF) encoding all the viral proteins necessary for virus replication. These proteins are expressed as a polyprotein that is co- and post-translationally processed by both cellular and virus-encoded proteinases to yield the mature viral proteins. The viral proteins responsible for the replication of the viral genome RNA are located within approximately the carboxy-terminal. Two-thirds of the ORF are termed nonstructural (NS) proteins. The genetic organization and polyprotein processing of the nonstructural protein portion of the ORF for pestiviruses and hepaciviruses is very similar. For both the pestiviruses and hepaciviruses, the mature nonstructural (NS) proteins, in sequential order from the amino-terminus of the nonstructural protein coding region to the carboxy-terminus of the ORF, consist of p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

The NS proteins of pestiviruses and hepaciviruses share sequence domains that are characteristic of specific protein functions. For example, the NS3 proteins of viruses in both groups possess amino acid sequence motifs characteristic of serine proteinases and of helicases (Gorbalenya et al., *Nature,* 1988, 333, 22; Bazan and Fletterick *Virology* , 1989,171,637-639; Gorbalenya et al., *Nucleic Acid Res.,*1989, 17, 3889-3897). Similarly, the NS5B proteins of pestiviruses and hepaciviruses have the motifs characteristic of RNA-directed RNA polymerases (Koonin, E.V. and Dolja, V.V., *Crir. Rev. Biochem. Molec. Biol.* 1993, 28, 375-430).

The actual roles and functions of the NS proteins of pestiviruses and hepaciviruses in the lifecycle of the viruses are directly analogous. In both cases, the NS3 serine proteinase is responsible for all proteolytic processing of polyprotein precursors

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downstream of its position in the ORF (Wiskerchen and Collett, *Virology*, 1991, 184, 341-350; Bartenschlager et al., *J. Virol.* 1993, 67, 3835-3844; Eckart et al. *Biochem. Biophys. Res. Comm.* 1993,192, 399-406; Grakoui et al., *J. Virol.* 1993, 67, 2832-2843; Grakoui et al., *Proc. Natl. Acad Sci. USA* 1993, 90, 10583-10587; Hijikata et al., *J. Virol.* 1993, 67, 4665-4675; Tome et al., *J. Virol.*, 1993, 67, 4017-4026). The NS4A protein, in both cases, acts as a cofactor with the NS3 serine protease (Bartenschlager et al., *J. Virol.* 1994, 68, 5045-5055; Failla et al., *J. Virol.* 1994, 68, 3753-3760; Xu et al., *J. Virol.*, 1997, 71:53 12-5322). The NS3 protein of both viruses also functions as a helicase (Kim et al., *Biochem. Biophys. Res. Comm.*, 1995, 215, 160-166; Jin and Peterson, *Arch. Biochem. Biophys.*, 1995, 323, 47-53; Warrener and Collett, *J. Virol.* 1995, 69,1720-1726). Finally, the NS5B proteins of pestiviruses and hepaciviruses have the predicted RNA-directed RNA polymerases activity (Behrens et al., EMBO, 1996, 15, 12-22; Lechmann et al., *J. Virol.*, 1997, 71, 8416-8428; Yuan et al., *Biochem. Biophys. Res. Comm.* 1997, 232, 231-235; Hagedorn, PCT WO 97/12033; Zhong et al, *J. Virol.,* 1998, 72, 9365-9369).

Currently, there are limited treatment options for individuals infected with hepatitis C virus. The current approved therapeutic option is the use of immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin. This therapy is limited in its clinical effectiveness and only 50% of treated patients respond to therapy. Therefore, there is significant need for more effective and novel therapies to address the unmet medical need posed by HCV infection.

A number of potential molecular targets for drug development of direct acting antivirals as anti -HCV therapeutics have now been identified including, but not limited

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to, the NS2-NS3 autoprotease, the N3 protease, the N3 helicase and the NS5B polymerase. The RNA-dependent RNA polymerase is absolutely essential for replication of the single-stranded, positive sense, RNA genome and this enzyme has elicited significant interest among medicinal chemists.

Inhibitors of HCV NS5B as potential therapies for HCV infection have been reviewed: Tan, S.-L., et al., *Nature Rev. Drug Discov.*, 2002, 1, 867-881; Walker, M.P. et al., *Exp. Opin. Investigational Drugs*, 2003, 12, 1269-1280; Ni, Z-J., et al., *Current Opinion in Drug Discovery and Development*, 2004, 7, 446-459; Beaulieu, P. L., et al., *Current Opinion in Investigational Drugs*, 2004, 5, 838-850; Wu, J., et al., *Current Drug Targets-Infectious Disorders*, 2003, 3, 207-219; Griffith, R.C., et al, *Annual Reports in Medicinal Chemistry*, 2004, 39, 223-237; Carrol, S., et al., *Infectious Disorders-Drug Targets*, 2006, 6, 17-29. The potential for the emergence of resistant HCV strains and the need to identify agents with broad genotype coverage supports the need for continuing efforts to identify novel and more effective nucleosides as HCV NS5B inhibitors.

Nucleoside inhibitors of NS5B polymerase can act either as a non-natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted *in vivo* to a triphosphate to compete for the polymerase nucleotide binding site. This conversion to the triphosphate is commonly mediated by cellular kinases which imparts additional structural requirements on a potential nucleoside polymerase inhibitor. Unfortunately, this limits the direct evaluation of nucleosides as inhibitors of HCV replication to cell-based assays capable of *in situ* phosphorylation.

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In some cases, the biological activity of a nucleoside is hampered by its poor substrate characteristics for one or more of the kinases needed to convert it to the active triphosphate form. Formation of the monophosphate by a nucleoside kinase is generally viewed as the rate limiting step of the three phosphorylation events. To circumvent the need for the initial phosphorylation step in the metabolism of a nucleoside to the active triphosphate analog, the preparation of stable phosphate prodrugs has been reported. Nucleoside phosphoramidate prodrugs have been shown to be precursors of the active nucleoside triphosphate and to inhibit viral replication when administered to viral infected whole cells (McGuigan, C., et al., *J. Med. Chem.*, 1996, 39, 1748-1753; Valette, G., et al., *J. Med. Chem.*, 1996, 39, 1981-1990; Balzarini, J., et al., *Proc. National Acad Sci USA*, 1996, 93, 7295-7299; Siddiqui, A. Q., et al., *J. Med. Chem.*, 1999, 42, 4122-4128; Eisenberg, E. J., et al., *Nucleosides, Nucleotides and Nucleic Acids*, 2001, 20, 1091-1098; Lee, W.A., et al., *Antimicrobial Agents and Chemotherapy*, 2005, 49, 1898); US 2006/0241064; and WO 2007/095269.

Also limiting the utility of nucleosides as viable therapeutic agents is their sometimes poor physicochemical and pharmacokinetic properties. These poor properties can limit the intestinal absorption of an agent and limit uptake into the target tissue or cell. To improve on their properties prodrugs of nucleosides have been employed. It has been demonstrated that preparation of nucleoside phosphoramidates improves the systemic absorption of a nucleoside and furthermore, the phosphoramidate moiety of these "pronucleotides" is masked with neutral lipophilic groups to obtain a suitable partition coefficient to optimize uptake and transport into the cell dramatically enhancing the intracellular concentration of the nucleoside monophosphate analog relative to

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