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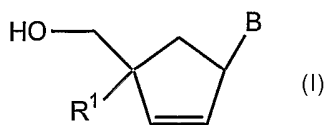
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(54) Title: 4'-SUBSTITUTED CARBOVIR-AND ABACAVIR-DERIVATIVES AS WELL AS RELATED COMPOUNDS WITH HIV AND HCV ANTIVIRAL ACTIVITY



(57) Abstract: The application relates to compounds with activity against infectious viruses. Accordingly, in one embodiment the invention provides a compound of the invention which is a compound of Formula I: (I) wherein: B is adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosines, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O<sup>6</sup>-methylguanine, N<sup>6</sup>-methyladenine, O<sup>4</sup>-methylthymine, 5,6-dihydrothymine, 5,6-dihydrocycil, 4-methylindole, triazole, or pyrazolo[3,4-d]pyrimidine; and B is optionally substituted with one or more alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy, or halo; and R<sup>1</sup> is alkyl, alkenyl, alkynyl, cyano, azido, or fluoromethyl; or a pharmaceutically acceptable salt or solvate thereof.



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4'-SUBSTITUTED CARBOVIR-AND ABACAVIR-DERIVATIVES AS WELL AS RELATED COMPOUNDS WITH HIV AND HCV ANTIVIRAL ACTIVITY

### PRIORITY OF INVENTION

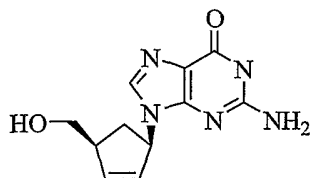
This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial Number 60/532,256, filed 22 December 2003. The entirety of this Provisional Application is incorporated herein by reference.

### FIELD OF THE INVENTION

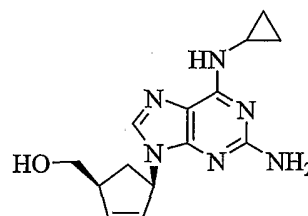
The invention relates generally to 4'-substituted nucleoside derivatives with antiviral activity.

### BACKGROUND OF THE INVENTION

Carbovir (EP 00,434,450 and EP 00,349,242) along with abacavir are well known anti-HIV carbocyclic nucleosides. Abacavir is the most potent nucleoside reverse transcriptase inhibitor (NRTI) developed to date. An average reduction in viral load of more than 1.4 log<sub>10</sub> RNA copies/ml is observed after a short course of abacavir monotherapy.



Carbovir



Abacavir

Dideoxynucleotide use such as dideoxycytidine (ddC) and of didehydrodideoxythymidine (d4T) is limited by associated painful sensory-motor peripheral neuropathy. Dideoxyinosine also shares this complication as well as causing acute pancreatitis, and hepatotoxicity in some cases (Maag, H. et al., *J. Med. Chem.*, **1992**, 35, 1440). Yet another concern about this class of compounds has been the emergence of resistant HIV strains in patients undergoing treatment with nucleosides. For instance the ddI-resistant strains were also shown to be resistant to ddC. In another study, clinical HIV isolates

resistant to AZT displayed marked resistance to d4T. It appears, then, that some cross resistance is inevitable among this class of similar nucleoside structures. Therefore, an important criterion for the design of any new nucleoside drug would be a distinct dissimilarity of structure to the current family of  
5 dideoxynucleosides.

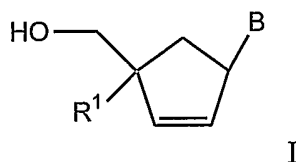
Substitution at the 4' position of nucleosides has been reported to exert potent antiviral activity against HIV-1 as demonstrated by 4'-azido-2'-deoxythymidine (4'-AZT) (Maag, H. et al., *J. Med. Chem.*, **1992**, 35, 1440). In addition, 4'-ethynyl nucleoside analogs have been shown to be active against a  
10 wide spectrum of HIV viruses, specifically against HIV-1<sub>M184V</sub> and HIV-1<sub>M184I</sub> (Kodama, E. I. et al., *Antimicrob. Agents Chemother.*, **2001**, 1539). Recently, Haraguchi et al. reported the preparation of 4'-substituted d4T analogs. They demonstrated that contrary to the previous reports, the 3'-hydroxy group is not necessary for the 4'-substituted nucleosides to be active against HIV (Haraguchi,  
15 K. et al., *Bioorg. Med. Chem. Lett.*, **2003**, 13, 3775).

There is currently a need for therapeutic antiviral agents having unique structural characteristics. Additionally, there is a need for antiviral agents with improved pharmacological properties, *e.g.*, drugs having improved antiviral activity and pharmacokinetic properties, including improved oral bioavailability,  
20 greater potency and extended effective half-life *in vivo*.

### SUMMARY OF THE INVENTION

The invention relates to compounds with activity against infectious viruses. Accordingly, in one embodiment the invention provides a compound of the invention which is a compound of Formula I:

25



wherein:

B is adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, 5 pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, *O*<sup>6</sup>-methylguanine, *N*<sup>6</sup>-methyladenine, *O*<sup>4</sup>-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, triazole, or pyrazolo[3,4-d]pyrimidine; and B is optionally substituted with one or more alkyl, alkenyl, alkynyl, cycloalkyl, 10 (cycloalkyl)alkyl, hydroxy, or halo; and

*R*<sup>1</sup> is alkyl, alkenyl, alkynyl, cyano, azido, or fluoromethyl; or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the invention also provides a pharmaceutical composition, comprising an effective amount of a compound of Formula I, or a 15 pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

In one embodiment, the invention also provides a pharmaceutical composition, comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof; a pharmaceutically 20 acceptable excipient; and a therapeutically effective amount of another therapeutic agent.

In one embodiment, the invention also provides a pharmaceutical composition, comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof; a pharmaceutically 25 acceptable excipient; and a therapeutically effective amount of an AIDS treatment agent selected from an HIV inhibitor agent, an anti-infective agent, and an immunomodulator.

In one embodiment, the invention also provides a pharmaceutical composition, comprising an effective amount of a compound of Formula I, or a 30 pharmaceutically acceptable salt or solvate thereof; a pharmaceutically

acceptable excipient; and a therapeutically effective amount of an HIV-protease inhibitor.

In one embodiment, the invention also provides a pharmaceutical composition, comprising an effective amount of a compound of Formula I, or a  
5 pharmaceutically acceptable salt or solvate thereof; a pharmaceutically acceptable excipient; and a therapeutically effective amount of a reverse transcriptase inhibitor.

In one embodiment, the invention also provides a pharmaceutical composition, comprising an effective amount of a compound of Formula I, or a  
10 pharmaceutically acceptable salt or solvate thereof; a pharmaceutically acceptable excipient; and a therapeutically effective amount of a non-nucleoside reverse transcriptase inhibitor.

In one embodiment, the invention also provides a pharmaceutical composition, comprising an effective amount of a compound of Formula I, or a  
15 pharmaceutically acceptable salt or solvate thereof; a pharmaceutically acceptable excipient; and a therapeutically effective amount of an HIV integrase inhibitor.

In one embodiment, the invention also provides a method of inhibiting a  
20 viral infection in an animal (e.g. a mammal), comprising administering an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to the animal.

In one embodiment, the invention also provides a method for the treatment or prevention of the symptoms or effects of a viral infection in an  
25 animal, comprising administering an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to the animal.

In one embodiment, the invention also provides a method of inhibiting an HCV infection in an animal, comprising administering an effective amount of

a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to the animal.

In one embodiment, the invention also provides a method for the treatment or prevention of the symptoms or effects of HCV infection in an  
5 infected animal, comprising administering an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to the animal.

In one embodiment, the invention also provides a method of inhibiting a viral enzyme, comprising contacting a sample suspected of containing viral  
10 infected cells or tissues with a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the invention also provides a method of inhibiting RNA-dependent RNA polymerase in an animal, comprising administering an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to the animal.

15 In one embodiment, the invention also provides a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, for use in medical therapy (preferably for use in treating a viral infection in an animal).

In one embodiment, the invention also provides the use of a compound of  
20 Formula I, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for inhibiting a viral infection in an animal (e.g. a mammal).

In one embodiment, the invention also provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to prepare a  
25 medicament useful for the treatment or prevention of the symptoms or effects of a viral infection in an animal.

In one embodiment, the invention also provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for inhibiting an HCV infection in an animal.

In one embodiment, the invention also provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof to prepare a medicament useful for the treatment or prevention of the symptoms or effects of HCV infection in an infected animal.

5 In one embodiment, the invention also provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for inhibiting an RNA-dependent RNA polymerase in an animal.

10 In one embodiment, the invention also provides a process for making a pharmaceutical composition comprising combining a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

15 In one embodiment, the invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of the invention are useful to prepare other compounds of the invention.

20 In one embodiment, the invention also provides a process for making a pharmaceutical composition comprising combining a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

#### **DETAILED DESCRIPTION OF EXEMPLARY CLAIMS**

Reference will now be made in detail to certain claims of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated claims, 25 it will be understood that they are not intended to limit the invention to those claims. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

## DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When tradenames are used herein, applicants intend to independently  
5 include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, *i.e.* active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed  
10 chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a  
15 whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking  
20 chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be  
25 biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to  
30 as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively



than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after  
5 deprotection, *e.g.*, alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts  
10 derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and  $NX_4^+$  (wherein X is  $C_1-C_4$  alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic  
15 acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as  $Na^+$  and  $NX_4^+$  (wherein  
20 X is independently selected from H or a  $C_1-C_4$  alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the  
25 preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

“Alkyl” is  $C_1-C_{18}$  hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me,  $-CH_3$ ), ethyl (Et,  $-CH_2CH_3$ ), 1-  
30 propyl (n-Pr, n-propyl,  $-CH_2CH_2CH_3$ ), 2-propyl (i-Pr, i-propyl,  $-CH(CH_3)_2$ ), 1-butyl (n-Bu, n-butyl,  $-CH_2CH_2CH_2CH_3$ ), 2-methyl-1-propyl (i-Bu, i-butyl,  $-CH_2CH(CH_3)_2$ ), 2-butyl (s-Bu, s-butyl,  $-CH(CH_3)CH_2CH_3$ ), 2-methyl-2-

propyl (t-Bu, t-butyl,  $-C(CH_3)_3$ ), 1-pentyl (n-pentyl,  $-CH_2CH_2CH_2CH_2CH_3$ ),  
 2-pentyl ( $-CH(CH_3)CH_2CH_2CH_3$ ), 3-pentyl ( $-CH(CH_2CH_3)_2$ ), 2-methyl-2-  
 butyl ( $-C(CH_3)_2CH_2CH_3$ ), 3-methyl-2-butyl ( $-CH(CH_3)CH(CH_3)_2$ ), 3-methyl-  
 1-butyl ( $-CH_2CH_2CH(CH_3)_2$ ), 2-methyl-1-butyl ( $-CH_2CH(CH_3)CH_2CH_3$ ), 1-  
 5 hexyl ( $-CH_2CH_2CH_2CH_2CH_2CH_3$ ), 2-hexyl ( $-CH(CH_3)CH_2CH_2CH_2CH_3$ ), 3-  
 hexyl ( $-CH(CH_2CH_3)(CH_2CH_2CH_3)$ ), 2-methyl-2-pentyl ( $-$   
 $C(CH_3)_2CH_2CH_2CH_3$ ), 3-methyl-2-pentyl ( $-CH(CH_3)CH(CH_3)CH_2CH_3$ ), 4-  
 methyl-2-pentyl ( $-CH(CH_3)CH_2CH(CH_3)_2$ ), 3-methyl-3-pentyl ( $-$   
 $C(CH_3)(CH_2CH_3)_2$ ), 2-methyl-3-pentyl ( $-CH(CH_2CH_3)CH(CH_3)_2$ ), 2,3-  
 10 dimethyl-2-butyl ( $-C(CH_3)_2CH(CH_3)_2$ ), 3,3-dimethyl-2-butyl ( $-$   
 $CH(CH_3)C(CH_3)_3$ ).

“Alkenyl” is C<sub>2</sub>-C<sub>18</sub> hydrocarbon containing normal, secondary, tertiary  
 or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon,  
 $sp^2$  double bond. Examples include, but are not limited to, ethylene or vinyl  
 15 ( $-CH=CH_2$ ), allyl ( $-CH_2CH=CH_2$ ), cyclopentenyl ( $-C_5H_7$ ), and 5-hexenyl ( $-CH_2$   
 $CH_2CH_2CH_2CH=CH_2$ ).

“Alkynyl” is C<sub>2</sub>-C<sub>18</sub> hydrocarbon containing normal, secondary, tertiary  
 or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon,  
 $sp$  triple bond. Examples include, but are not limited to, acetylenic ( $-C\equiv CH$ ) and  
 20 propargyl ( $-CH_2C\equiv CH$ ),

“Alkylene” refers to a saturated, branched or straight chain or cyclic  
 hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical  
 centers derived by the removal of two hydrogen atoms from the same or two  
 different carbon atoms of a parent alkane. Typical alkylene radicals include, but  
 25 are not limited to, methylene ( $-CH_2-$ ), 1,2-ethyl ( $-CH_2CH_2-$ ), 1,3-propyl  
 ( $-CH_2CH_2CH_2-$ ), 1,4-butyl ( $-CH_2CH_2CH_2CH_2-$ ), and the like.

“Alkenylene” refers to an unsaturated, branched or straight chain or cyclic  
 hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical  
 centers derived by the removal of two hydrogen atoms from the same or two  
 30 different carbon atoms of a parent alkene. Typical alkenylene radicals include, but  
 are not limited to, 1,2-ethylene ( $-CH=CH-$ ).

“Alkynylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH<sub>2</sub>C≡C-), and 4-pentynyl (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C≡CH-).

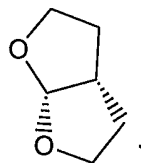
“Aryl” means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

“Arylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp<sup>3</sup> carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, *e.g.*, the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

“Substituted alkyl”, “substituted aryl”, and “substituted arylalkyl” mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R, -O<sup>-</sup>, -OR, -SR, -S<sup>-</sup>, -NR<sub>2</sub>, -NR<sub>3</sub>, =NR, -CX<sub>3</sub>, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO<sub>2</sub>, =N<sub>2</sub>, -N<sub>3</sub>, NC(=O)R, -C(=O)R, -C(=O)NRR, -S(=O)<sub>2</sub>O<sup>-</sup>, -S(=O)<sub>2</sub>OH, -S(=O)<sub>2</sub>R, -OS(=O)<sub>2</sub>OR, -S(=O)<sub>2</sub>NR, -S(=O)R, -OP(=O)O<sub>2</sub>RR, -P(=O)O<sub>2</sub>RR, -P(=O)(O<sup>-</sup>)<sub>2</sub>, -P(=O)(OH)<sub>2</sub>, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, -C(O)O<sup>-</sup>, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

“Heterocycle” as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs” (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention “heterocycle” includes a “carbocycle” as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S).

10           Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, 15 piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranlyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, 20 isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazoliny, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl,  $\beta$ -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, 25 imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperazinyl, indoliny, isoindoliny, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, isatinoyl, and bis-tetrahydrofuranlyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidione, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidione, pyrrole, pyrrolidone, 2-pyrroline, 3-pyrroline, imidazole, imidazolidone, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or  $\beta$ -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetidyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

“Carbocycle” refers to a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical  
5 chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling  
10 points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

15 The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow  
20 S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the  
25 prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical  
30 structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50

mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

## 5 Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during  
10 synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the  
15 synthesis. The PG groups do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the  
20 intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-  
25 forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

30 A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley &

Sons, Inc., New York, 1991, ISBN 0-471-62301-6) (“Greene”). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like. Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385.

#### Specific Embodiments of the Invention

Specific values described for radicals, substituents, and ranges, as well as specific embodiments of the invention described herein, are for illustration only; they do not exclude other defined values or other values within defined ranges.

For a compound of Formula I, in one specific embodiment, C<sub>1</sub>-C<sub>8</sub> substituted alkyl, C<sub>1</sub>-C<sub>8</sub> substituted alkenyl, C<sub>1</sub>-C<sub>8</sub> substituted alkynyl, C<sub>6</sub>-C<sub>20</sub> substituted aryl, and C<sub>2</sub>-C<sub>20</sub> substituted heterocycle are independently substituted with one or more substituents selected from F, Cl, Br, I, OH, -NH<sub>2</sub>, -NH<sub>3</sub><sup>+</sup>, -NHR, -NR<sub>2</sub>, -NR<sub>3</sub><sup>+</sup>, C<sub>1</sub>-C<sub>8</sub> alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C<sub>1</sub>-C<sub>8</sub> alkylsulfonate, C<sub>1</sub>-C<sub>8</sub> alkylamino, 4-dialkylaminopyridinium, C<sub>1</sub>-C<sub>8</sub> alkylhydroxyl, C<sub>1</sub>-C<sub>8</sub> alkylthiol, -SO<sub>2</sub>R, -SO<sub>2</sub>Ar, -SOAr, -SAr, -SO<sub>2</sub>NR<sub>2</sub>, -SOR, -CO<sub>2</sub>R, -C(=O)NR<sub>2</sub>, 5-7 membered ring lactam, 5-7 membered ring lactone, -CN, -N<sub>3</sub>, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>8</sub> trifluoroalkyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>3</sub>-C<sub>12</sub> carbocycle, C<sub>6</sub>-C<sub>20</sub> aryl, C<sub>2</sub>-C<sub>20</sub> heterocycle, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety.

For a compound of Formula I, in one specific embodiment, “protecting group” is selected from a carboxyl ester, a carboxamide, an aryl ether, an alkyl ether, a trialkylsilyl ether, a sulfonic acid ester, a carbonate, and a carbamate.



### Antiviral Compounds

The compounds of the invention include those with antiviral activity.

Typically, compounds of the invention have a molecular weight of from  
5 about 200 amu to about 10,000 amu; in a specific embodiment of the invention,  
compounds have a molecular weight of less than about 5000 amu; in another  
specific embodiment of the invention, compounds have a molecular weight of  
less than about 2500 amu; in another specific embodiment of the invention,  
compounds have a molecular weight of less than about 1000 amu; in another  
10 specific embodiment of the invention, compounds have a molecular weight of  
less than about 800 amu; in another specific embodiment of the invention,  
compounds have a molecular weight of less than about 600 amu; and in another  
specific embodiment of the invention, compounds have a molecular weight of  
less than about 400 amu and a molecular weight of greater than about 200 amu.

15 The compounds of the invention also typically have a logD(polarity) less  
than about 5. In one embodiment the invention provides compounds having a  
logD less than about 4; in another one embodiment the invention provides  
compounds having a logD less than about 3; in another one embodiment the  
invention provides compounds having a logD greater than about -5; in another  
20 one embodiment the invention provides compounds having a logD greater than  
about -3; and in another one embodiment the invention provides compounds  
having a logD greater than about 0 and less than about 3.

Selected substituents within the compounds of the invention are present  
25 to a recursive degree. In this context, "recursive substituent" means that a  
substituent may recite another instance of itself. Because of the recursive nature  
of such substituents, theoretically, a large number may be present in any given  
claim. For example,  $R^x$  contains a  $R^y$  substituent.  $R^y$  can be  $R^2$ , which in turn  
can be  $R^3$ . If  $R^3$  is selected to be  $R^{3c}$ , then a second instance of  $R^x$  can be  
30 selected. One of ordinary skill in the art of medicinal chemistry understands that  
the total number of such substituents is reasonably limited by the desired  
properties of the compound intended. Such properties include, by of example

and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Whenever a compound described herein is substituted with more than  
5 one of the same designated group, it will be understood that the groups may be the same or different, *i.e.*, each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

### Stereoisomers

10 The compounds of the invention may have chiral centers. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from  
15 the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-  
20 known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, *e.g.*, acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

25 The compounds of the invention can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms  
30 are within the scope of the invention.

### Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example,  $\text{Na}^+$ ,  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{+2}$  and  $\text{Mg}^{+2}$ . Such salts may include  
5 those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a  
10 compound of this invention. Examples of metal salts which are prepared in this way are salts containing  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$ . A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic  
15 and inorganic acids, *e.g.*,  $\text{HCl}$ ,  $\text{HBr}$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{PO}_4$  or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the  
20 parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or  
25 a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

### Methods of Inhibition of Viral Infections

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Compositions of the invention may act as inhibitors of viral infections, or as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of a cell having a unique geometry. Compositions binding a cell may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of viruses. Accordingly, the invention relates to methods of detecting viruses in a sample or subject suspected of containing a virus, comprising the steps of: treating such a sample or subject with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as an tumor virus. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated.

- 5 Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

#### Screens for Antiviral Compounds

- 10 Compositions of the invention are screened for antiviral activity by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibitory activity *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro*  $K_i$  (inhibitory constants) of less than about  $5 \times 10^{-6}$  M, typically less than about  $1 \times 10^{-7}$  M and preferably  
15 less than about  $5 \times 10^{-8}$  M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here.

#### Pharmaceutical Formulations

- 20 The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of  
25 Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

- 30 While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The

formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other  
5 ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. 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.  
10 Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with  
15 liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or  
20 granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a  
25 suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and  
30 optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For administration to the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in  
5 increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

10 If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which  
15 enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise  
20 merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the  
25 so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween<sup>®</sup> 60, Span<sup>®</sup> 80, cetostearyl alcohol, benzyl  
30 alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a

non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl  
5 palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

10           Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When  
15 used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more  
20 agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium  
25 carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by  
30 known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action



over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example  
5 calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions.  
10 Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*,  
15 polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl  
20 p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a  
25 thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for  
30 preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and

suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain

approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For  
5 example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500  $\mu\text{g}$  of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier,  
10 especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose  
15 and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

20 Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the  
25 alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of viral infections as described below.

30 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing

in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

#### Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

#### Combination Therapy

Active ingredients of the invention can also be used in combination with other therapeutic agents (i.e. active ingredients). Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating a viral infection the compositions of the invention can be combined with other therapeutic agents that are effective to treat a viral infection (such as other antiviral agents) or they can be combined with other therapeutic agents that are effective to ameliorate symptoms associated with a viral infection.

It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, *e.g.*, in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

#### 20 Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (*e.g.*, C<sup>14</sup> or H<sup>3</sup>) compound of the invention, administering it parenterally in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30

seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in  
5 conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no antiviral  
10 activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon  
15 incubation for 1 hour at 37 °C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

## 20 Antiviral Activity and Cytotoxicity

The antiviral activity and cytotoxicity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured in a cell culture assay using the following general protocol.

### 25 Antiviral Cell Culture Assay

The assay is based on quantification of the antiviral effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested inhibitors. The compound-induced cell death is determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfohenyl)-2H-tetrazolium-5-carboxanilide  
30 (XTT) which is converted only by intact cells into a product with specific absorption

characteristics as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR (1989) *J Natl Cancer Inst* 81, 577.

Assay protocol for determination of EC50:

1. Maintain MT2 cells in RPMI-1640 medium supplemented with 5% fetal  
5 bovine serum and antibiotics.
2. Infect the cells with the viral agent for 3 hours at 37 °C using the virus  
inoculum corresponding to a multiplicity of infection equal to 0.01.
3. Distribute the infected cells into a 96-well plate (20,000 cells in 100 µl/well)  
and add various concentrations of the tested inhibitor in triplicate (100  
10 µl/well in culture media). Include untreated infected and untreated mock-  
infected control cells.
4. Incubate the cells for 5 days at 37 °C.
5. Prepare a compound solution (6 ml per assay plate) at a concentration of  
2mg/ml in a phosphate-buffered saline pH 7.4. Heat the solution in water-  
15 bath for 5 min at 55 °C. Add 50 µl of N-methylphenazonium methasulfate (5  
µg/ml) per 6 ml of XTT solution.
6. Remove 100 µl media from each well on the assay plate.
7. Add 100 µl of the XTT substrate solution per well and incubate at 37 °C for  
45 to 60 min in a CO<sub>2</sub> incubator.
- 20 8. Add 20 µl of 2% Triton X-100 per well to inactivate the virus.
9. Read the absorbance at 450 nm with subtracting off the background  
absorbance at 650 nm.
10. Plot the percentage absorbance relative to untreated control and estimate the  
EC50 value as drug concentration resulting in a 50% protection of the  
25 infected cells.

Cytotoxicity Cell Culture Assay (Determination of CC50):

The cytotoxicity of a compound of the invention can be determined using the following general protocol. The assay is based on the evaluation of cytotoxic  
30 effect of tested compounds using a metabolic substrate.



*Assay protocol for determination of CC50:*

1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100  $\mu$ l media per well)  
5 and add various concentrations of the tested compound in triplicate (100  $\mu$ l/well). Include untreated control.
3. Incubate the cells for 5 days at 37 °C.
4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2mg/ml in a phosphate-buffered saline pH 7.4. Heat the solution in a water-  
10 bath at 55°C for 5 min. Add 50  $\mu$ l of N-methylphenazonium methasulfate (5  $\mu$ g/ml) per 6 ml of XTT solution.
5. Remove 100  $\mu$ l media from each well on the assay plate and add 100  $\mu$ l of the XTT substrate solution per well. Incubate at 37 °C for 45 to 60 min in a CO<sub>2</sub> incubator.
- 15 6. Add 20  $\mu$ l of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the  
20 CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compounds of the  
25 invention. The compounds are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol.  
30 3, Louis S. Hegeudus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as

March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

5           A number of exemplary methods for the preparation of the compounds of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

          Generally, the reaction conditions such as temperature, reaction time,  
10   solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically  
15   consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

          Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20 °C), although for metal hydride  
20   reductions frequently the temperature is reduced to 0 °C to -100 °C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

          Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled  
25   condensations reduced temperatures (0 °C to -100 °C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

          Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments)  
30   are common in the art and will be applied when applicable.

### Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

5           The terms “treated”, “treating”, “treatment”, and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that “treating  
10   compound one with compound two” is synonymous with “allowing compound one to react with compound two”, “contacting compound one with compound two”, “reacting compound one with compound two”, and other expressions common in the art of organic synthesis for reasonably indicating that compound one was “treated”, “reacted”, “allowed to react”, etc., with compound two. For  
15   example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100 °C to 250 °C, typically -78 °C to 150 °C, more typically -78 °C to 100 °C, still more typically 0 °C to 100 °C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air  
20   for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for “treating” in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus  
25   reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

          Modifications of each of the exemplary schemes and in the examples (hereafter “exemplary schemes”) leads to various analogs of the specific exemplary materials produce. The above-cited citations describing suitable  
30   methods of organic synthesis are applicable to such modifications.

          In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired

products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography.

5 Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash  
10 chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion  
15 exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of  
20 the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

25 A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic  
30 mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods,

(2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

5 Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine,  $\alpha$ -methyl- $\beta$ -phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional  
10 crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with  
15 one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis  
20 to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl chloroformate in the presence of base, or Mosher ester,  $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two  
25 atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two  
30 enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other

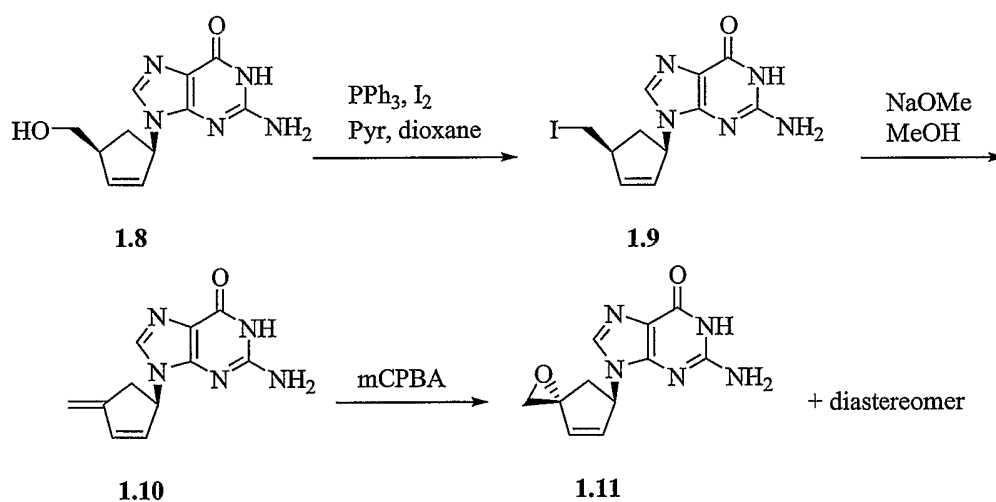
chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

### Examples General Section

A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples hereinbelow. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods. Certain compounds of the invention can be used as intermediates for the preparation of other compounds of the invention.

The invention will now be illustrated by the following non-limiting Examples.

#### Example 1. Preparation of a Representative Compound of the Invention



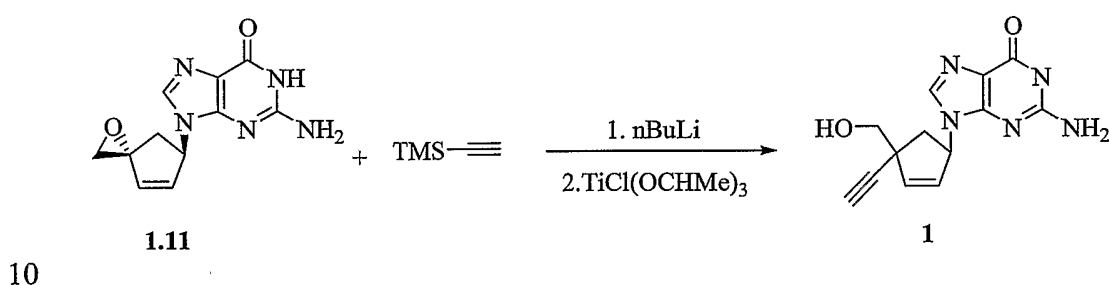
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The intermediate epoxide **1.11** can be prepared as follows. Selective iodination of carbovir **1.8** (Crimmins, M. T. et al., *J. Org. Chem.*, **1996**, *61*, 4192) at the 5'-position using triphenylphosphine, iodine, and either pyridine or imidazole in dioxane (Maag, H. et al., *J. Med. Chem.*, **1992**, *35*, 1440) provides compound **1.9**. Dehydrohalogenation of 5'-halonucleosides has been well-

20

described (Ueda, T. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press; New York, 1988; 83). Use of sodium methoxide provides product **1.10**. Epoxidation of the exocyclic olefin using *m*-chloroperbenzoic acid or Corey's reagent (dimethylsulfoxonium methylide) (Gololobov, Y. G. et al., *Tetrahedron*, **1997**, *43*, 12, 2609) proceeds without stereoselection to provide a mixture of two diastereomeric epoxides **1.11**.

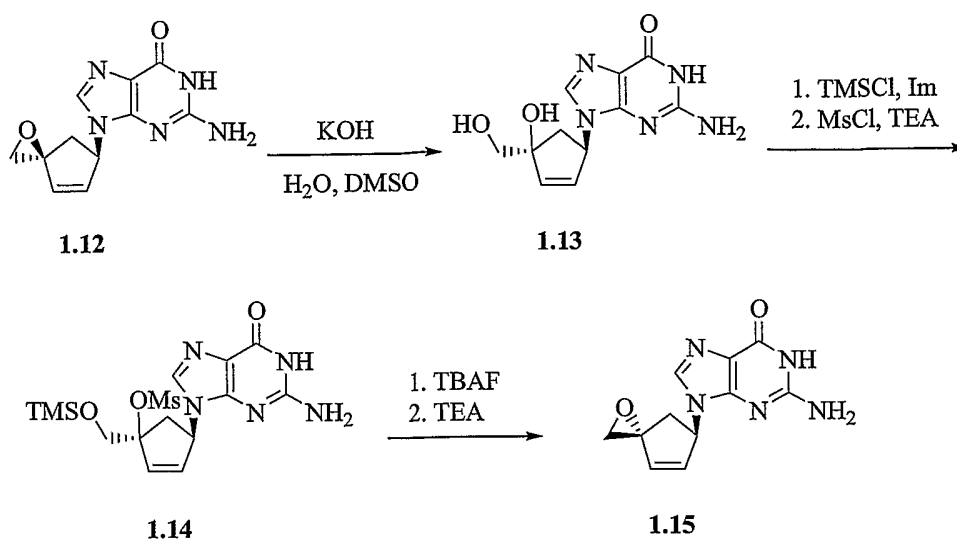
A representative compound of the invention **1** can be prepared from the epoxides **1.11** as illustrated below.



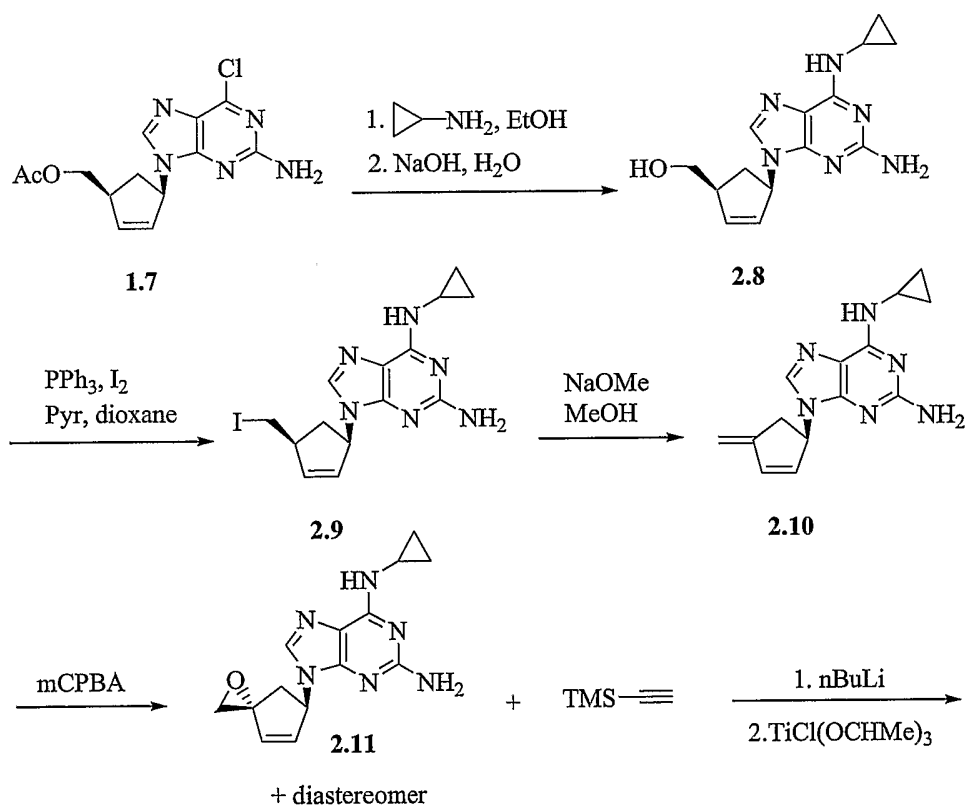
The mixture of diastereomers can be opened using ethynyl-trimethylsilane in the presence of titanium acetylide at the more highly substituted carbon atom exclusively as reported by Krause, N. et al., *Chem. Ber.*, **1988**, *121*, 7, 1315 to provide the desired product **1**.

15           Compound **1.12** from the epoxidation reaction can readily be converted to the related diastereomer using the four step sequence illustrated below. The epoxide **1.12** is opened using basic condition such as sodium hydroxide in water and DMSO (Lepage, O. et al., *J. Org. Chem.*, **2003**, *68*, 6, 2183) to provide a diol. The primary alcohol is then protected with a silyl group and the 3' alcohol is converted into a leaving group (such as a mesylate). Release of the silyl group followed by exposure of the primary alcohol to base leads to ring closure to form the diastereomer **1.15**.

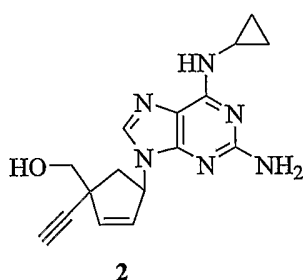
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**Example 2. Preparation of a Representative Compound of the Invention**







Abacavir **2.8** can be prepared from compound **1.7** as described by Crimmins, M. T. et al., *J. Org. Chem.*, **1996**, *61*, 4192. Selective iodination at  
5 the 5'-position using triphenylphosphine, iodine, and either pyridine or imidazole in dioxane (Maag, H. et al., *J. Med. Chem.*, **1992**, *35*, 1440) provides compound **2.9**. Dehydrohalogenation of 5'-halonucleosides has been well-described (Ueda, T. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press; New York, 1988; 83). Use of sodium methoxide  
10 proceeds to generate compound **2.10**. Epoxidation of the exocyclic olefin of **2.10** proceeds without a stereoselection to provide a mixture of two diastereomers. Such reactions may be performed using *m*-chloroperbenzoic acid or Corey's reagent (dimethylsulfoxonium methylide) (Gololobov, Y. G. et al., *Tetrahedron*, **1997**, *43*, 12, 2609). The mixture of diastereomers can be opened  
15 using ethynyl-trimethyl-silane in the presence of titanium acetylide at the more highly substituted carbon atom exclusively as reported by Krause, N. et al., *Chem. Ber.*, **1988**, *121*, 7, 1315 to provide the desired product **2**.

The same reaction scheme can be used to prepare 4' cyano and azido analogs of carbovir and abacavir. In order to prepare the 4' ethylene analog, a  
20 reduction of the acetylene to ethylene can be performed (for an example see Shinjiro, S., et al., *Org. Lett.*, **2003**, *5*, 11, 1891).

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The  
25 invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is

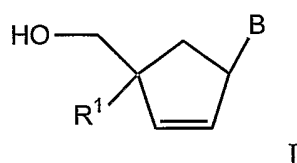
apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

### Claims

What is claimed is:

1. A compound of Formula I:

5



wherein:

B is adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-  
 10 deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine,  
 nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-  
 diaminopurine, hypoxanthine, pseudouridine, pseudocytosine,  
 pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine,  
 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, *O*<sup>6</sup>-methylguanine,  
 15 *N*<sup>6</sup>-methyladenine, *O*<sup>4</sup>-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-  
 methylindole, triazole, or pyrazolo[3,4-d]pyrimidine; and B is optionally  
 substituted with one or more alkyl, alkenyl, alkynyl, cycloalkyl,  
 (cycloalkyl)alkyl, hydroxy, or halo; and

R<sup>1</sup> is alkyl, alkenyl, alkynyl, cyano, azido, or fluoromethyl;  
 20 or a pharmaceutically acceptable salt or solvate thereof.

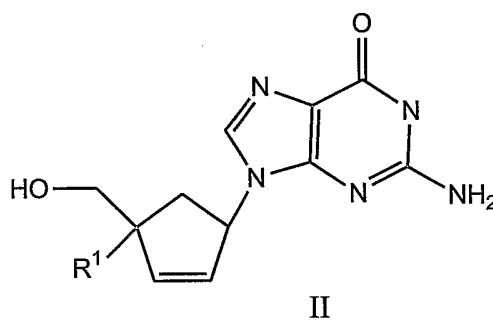
2. The compound of claim 1 wherein B is adenine, guanine, cytosine, uracil,  
 or thymine; which B is optionally substituted with one or more alkyl, alkenyl,  
 25 alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy, or halo.

3. The compound of claim 1 wherein B is 7-deazaadenine, 7-deazaguanine,  
 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole,  
 nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine,  
 30 hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-

propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, *O*<sup>6</sup>-methylguanine, *N*<sup>6</sup>-methyladenine, *O*<sup>4</sup>-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, triazole, or pyrazolo[3,4-d]pyrimidine; and B is optionally substituted with one  
5 or more alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy, or halo

4. The compound of claim 1 wherein B is adenine, guanine, cytosine, uracil, or thymine.

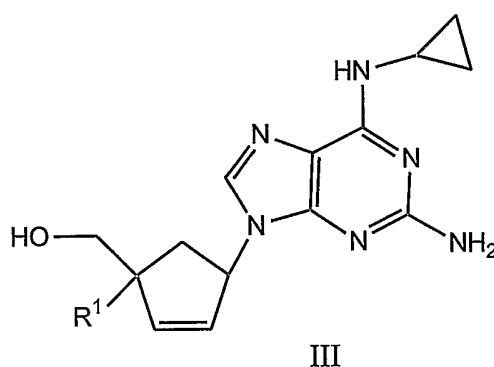
10 5. The compound of claim 1 which is a compound of formula II:



wherein R<sup>1</sup> has any of the values defined in claim 1.

15

6. The compound of claim 1 which is a compound of formula III:



20 wherein R<sup>1</sup> has any of the values defined in claim 1.

7. The compound of any one of claims 1-6 wherein R<sup>1</sup> is alkyl.
8. The compound of any one of claims 1-6 wherein R<sup>1</sup> is methyl.
- 5 9. The compound of any one of claims 1-6 wherein R<sup>1</sup> is fluoromethyl.
10. The compound of any one of claims 1-6 wherein R<sup>1</sup> is alkenyl.
- 10 11. The compound of any one of claims 1-6 wherein R<sup>1</sup> is vinyl.
12. The compound of any one of claims 1-6 wherein R<sup>1</sup> is alkynyl.
13. The compound of any one of claims 1-6 wherein R<sup>1</sup> is ethynyl.
- 15 14. The compound of any one of claims 1-6 wherein R<sup>1</sup> is cyano.
15. The compound of any one of claims 1-6 wherein R<sup>1</sup> is azido.
- 20 16. A pharmaceutical composition, comprising an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
- 25 17. A pharmaceutical composition comprising an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof; a pharmaceutically acceptable excipient; and a therapeutically effective amount of another therapeutic agent.

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18. The pharmaceutical composition of claim 16 which further comprises an AIDS treatment agent selected from an HIV inhibitor agent, an anti-infective agent, and an immunomodulator.
19. The pharmaceutical composition of claim 16 which further comprises an  
5 HIV-protease inhibitor.
20. The pharmaceutical composition of claim 16 which further comprises a reverse transcriptase inhibitor.
21. The pharmaceutical composition of claim 16 which further comprises a non-nucleoside reverse transcriptase inhibitor.
- 10 22. The pharmaceutical composition of claim 16 which further comprises an HIV integrase inhibitor.
23. A method of inhibiting a viral infection in an animal (e.g. a mammal), comprising administering to the animal, an effective amount of a compound of  
15 Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.
24. A method for the treatment or prevention of the symptoms or effects of a viral infection in an animal comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a  
20 pharmaceutically acceptable salt or solvate thereof.
25. A method of inhibiting an HCV infection in an animal comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.
- 25 26. A method for the treatment or prevention of the symptoms or effects of HCV infection in an infected animal comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.

27. A method of inhibiting a viral enzyme comprising contacting a sample suspected of containing viral infected cells or tissues with an effective amount of a compound of Formula I as described in any one of claims 1-15, or a  
5 pharmaceutically acceptable salt or solvate thereof.
28. A method of inhibiting RNA-dependent RNA polymerase in an animal comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.
- 10 29. A compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, for use in medical therapy.
30. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a  
15 medicament useful for inhibiting a viral infection in an animal.
31. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for the treatment or prevention of the symptoms or effects of a viral infection in an animal.
- 20 32. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for inhibiting an HCV infection in an animal.
33. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a  
25 medicament useful for the treatment or prevention of the symptoms or effects of HCV infection in an infected animal.
34. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a

medicament useful for inhibiting an RNA-dependent RNA polymerase in an animal.

35. A process for making a pharmaceutical composition comprising combining a compound of Formula I as described in any one of claims 1-15, or a  
5 pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.



INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/043571

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D473/16 C07D473/18 A61K31/52

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)  
IPC 7 C07D 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, WPI Data, BEILSTEIN Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KATO ET AL: "Enantio- and diastereoselective synthesis of 4?-substituted carbocyclic nucleosides" TETRAHEDRON, vol. 9, no. 6, 1998, pages 911-914, XP002328141 page 911, compounds of formula 5 page 911, paragraph 1 page 912, compounds of formulae 15a-c and 5a-c  ----- -/--	1-35

Further documents are listed in the continuation of box C.  Patent family members are listed in 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

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\* & \* document member of the same patent family

Date of the actual completion of the international search  13 May 2005	Date of mailing of the international search report  30/05/2005
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Name and mailing address of the ISA 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	Authorized officer  Cortés, J
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/043571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US; 1999, --            KATO, KEISUKE ET AL: "Stereoselective            synthesis of 4'-alpha.-alkylcarbovir            derivatives based on an asymmetric            synthesis or chemo-enzymatic procedure"            XP002328143            retrieved from STN            Database accession no. 1999:614511            abstract            &amp; CHEMICAL &amp; PHARMACEUTICAL BULLETIN ,            47(9), 1256-1264 CODEN: CPBTAL; ISSN:            0009-2363, September 1999 (1999-09),</p>	1-35
Y	<p>KO ET AL: "Efficient synthesis of novel            carbocyclic nucleosides via sequential            Claisen rearrangement and ring-closing            metathesis"            TETRAHEDRON LETTERS,            vol. 43, no. 36, 2002, pages 6399-6402,            XP002328182            page 6399; compounds 11,12</p>	1-35
Y	<p>US 6 072 053 A (VINCE ET AL)            6 June 2000 (2000-06-06)            the whole document</p>	1-35
Y	<p>ROBERT S M: "DEVELOPMENT OF THE ROUTE TO            THE NEW ANTI-AIDS DRUG ABACAVIR: A            HIGHLIGHT OF ACADEMIC/INDUSTRY LIAISON"            IDRUGS, CURRENT DRUGS LTD, GB,            vol. 1, no. 8, 1998, pages 896-899,            XP008044472            ISSN: 1369-7056            the whole document</p>	1-35
A	<p>WO 02/100415 A (HOFFMANN-LA ROCHE)            19 December 2002 (2002-12-19)            the whole document</p>	1-35
A	<p>US 5 750 343 A (MAAG)            12 May 1998 (1998-05-12)            the whole document</p>	1-35
P,X	<p>HEGEDUS ET AL: "Synthesis of 4'-Methyl            and 4'-Cyano Carbocyclic 2',3'-Didehydro            Nucleoside Analogues via 1,4-Addition to            Substituted Cyclopentenones"            JOURNAL OF ORGANIC CHEMISTRY,            vol. 69, no. 24,            30 October 2004 (2004-10-30), pages            8492-8495, XP002328142            the whole document</p>	1-35

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/043571

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2005/011709 A (YALE UNIVERSITY) 10 February 2005 (2005-02-10) the whole document -----	1-35

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/043571

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: —  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 23-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/043571

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Information on patent family members

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