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(54) Title: NUCLEOTIDE ANALOGS

(57) Abstract

Novel compounds are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure $-OC(R^2)_2OC(O)X(R)_a$, wherein R^2 independently is H, C_1-C_{12} alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is unsubstituted or is substituted with halo, azido, nitro or OR^3 in which R^3 is C_1-C_{12} alkyl; X is N or O; R is independently H, C_1-C_{12} alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is unsubstituted or is substituted with halo, azido, nitro, -O-, -N=, $-NR^4$-, $-N(R^4)_2$- or OR^3, R^4 independently is -H or C_1-C_8 alkyl, provided that at least one R is not H; and a is 1 or 2, with the proviso that when a is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-containing heterocycle, or (b) one R additionally can be OR^3. The compounds are useful as intermediates for the preparation of antiviral compounds or oligonucleotides, or are useful for administration directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally.

NUCLEOTIDE ANALOGS

BACKGROUND OF THE INVENTION

The present invention relates to intermediates for phosphonomethoxy nucleotide analogs, in particular intermediates suitable for use in the efficient oral delivery of such analogs.

Such analogs per se and various technologies for oral delivery of these and other therapeutic compounds are known. See WO 91/19721, WO 94/03467, WO 94/03466, WO 92/13869, U.S. 5,208,221, 5,124,051, DE 41 38 584 A1, WO 94/10539, WO 94/10467, WO 96/18605, WO 95/07920, WO 95 79/07919, WO 92/09611, WO 92/01698, WO 91/19721, WO 88/05438, EP 0 632 048, EP 0 481 214, EP 0 369 409, EP 0 269 947, U.S. Patent Nos. 3,524,846 and 5,386,030, Engel *Chem. Rev.* 77:349-367 1977, Farquhar et al., *J. Pharm. Sci.* 72:324-325 1983, Starrett et al., *Antiviral Res.* 19:267-273 1992, Safadi et al., *Pharmaceutical Research* 10(9):1350-1355 1993, Sakamoto et al., *Chem. Pharm. Bull.* 32(6):2241-2248 1984, and Davidsen et al., *J. Med. Chem.* 37(26):4423-4429 1994.

SUMMARY OF THE INVENTION

In accordance with this invention, compounds are provided having formula (1a)

$$A\text{-}OCH_2P(Z)_2 \qquad (1a)$$

wherein Z is independently $-OC(R^2)_2OC(O)X(R)_a$, an ester, an amidate or -H, but at least one Z is $-OC(R^2)_2OC(O)X(R)_a$;

A is the residue of an antiviral phosphonomethoxy nucleotide analog;

X is N or O;

R^2 independently is -H, C_1-C_{12} alkyl, C_5-C_{12} aryl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro

or -OR^3 in which R^3 is C$_1$-C$_{12}$ alkyl, C$_2$-C$_{12}$ alkenyl, C$_2$-C$_{12}$ alkynyl or C$_5$-C$_{12}$ aryl;

R independently is -H, C$_1$-C$_{12}$ alkyl, C$_5$-C$_{12}$ aryl, C$_2$-C$_{12}$ alkenyl, C$_2$-C$_{12}$ alkynyl, C$_7$-C$_{12}$ alkyenylaryl, C$_7$-C$_{12}$ alkynylaryl, or C$_6$-C$_{12}$ alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, -N(R^4)$_2$ or -OR^3, where R^4 independently is -H or C$_1$-C$_8$ alkyl, provided that at least one R is not H; and

a is 1 when X is O, or 1 or 2 when X is N;

with the proviso that when a is 2 and X is N, (a) two N-linked R groups can be taken together to form a carbocycle or oxygen-containing heterocycle, (b) one N-linked R additionally can be -OR^3 or (c) both N-linked R groups can be -H;

and the salts, hydrates, tautomers and solvates thereof.

Further embodiments of the compounds of this invention are compounds of formula (1)
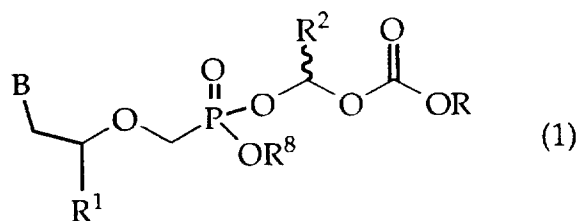
(1)

wherein B is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl;

R is independently -H, C$_1$-C$_{12}$ alkyl, C$_5$-C$_{12}$ aryl, C$_2$-C$_{12}$ alkenyl, C$_2$-C$_{12}$ alkynyl, C$_7$-C$_{12}$ alkenylaryl, C$_7$-C$_{12}$ alkynylaryl, or C$_6$-C$_{12}$ alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or -OR^3 in which R^3 is C$_1$-C$_{12}$ alkyl, C$_2$-C$_{12}$ alkenyl, C$_2$-C$_{12}$ alkynyl or C$_5$-C$_{12}$ aryl;

R^1 is hydrogen, -CH$_3$, -CH$_2$OH, -CH$_2$F, -CH=CH$_2$, or -CH$_2$N$_3$, or R^1 and R^8 are joined to form -CH$_2$-;

R^2 independently is hydrogen or C$_1$-C$_6$ alkyl; and

R^8 is hydrogen or -CHR^2-O-C(O)-OR, or R^8 is joined with R^1 to form -CH$_2$-;

and the salts, hydrates, tautomers and solvates thereof.

Other embodiments comprise orally administering to a patient infected with virus or at risk for viral infection a therapeutically effective amount of a compound of formulas (1a) or (1).

Other embodiments of this invention include a method for preparing a
compound of formula (1a) which comprises reacting the diacid of a
phosphonomethoxy nucleotide analog with $LC(R^2)_2OC(O)X(R)_a$ wherein L is
a leaving group.

5   In particular embodiments of this invention, a method for preparing a
compound of formula (1) is provided which comprises reacting a compound
of formula (4)

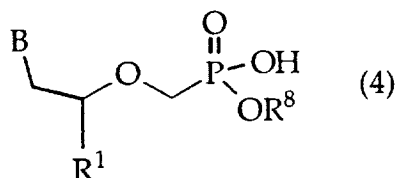$$\underset{R^1}{\overset{B}{\diagdown}}\!\!\!\diagup\!\!\!\overset{O}{\underset{|}{\diagup}}\!\!\!\overset{O}{\underset{\|}{\diagdown}}\!\!\!\underset{OR^8}{\overset{\overset{O}{\|}}{P}}\!\!\!-OH \qquad (4)$$

with $LC(R^2)_2OC(O)X(R)_a$.

10

DETAILED DESCRIPTION OF THE INVENTION

The abbreviations NMP, DMF and DMPU mean, respectively, N-
methylpyrrolidinone, dimethylformamide and N,N'-dimethylpropyleneurea.
15   Heterocycle means aromatic and nonaromatic ringed moieties.
Heterocyclic moieties typically comprise one ring or two fused rings, where
the ring(s) is 5- or 6-membered and typically contains 1 or 2 noncarbon atoms
such as oxygen, nitrogen or sulfur, usually oxygen or nitrogen.

"Alkyl" as used herein, unless stated to the contrary, is C_1-C_{12}
20   hydrocarbon containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms in the
form of normal, secondary, tertiary or cyclic structures. Examples are -CH_3,
-CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$,
-$CH(CH_3)CH_2CH_3$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_2CH_3$,
-$CH(CH_2CH_3)_2$, -$C(CH_3)_2CH_2CH_3$, -$CH(CH_3)CH(CH_3)_2$, -$CH_2CH_2CH(CH_3)_2$,
25   -$CH_2CH(CH_3)CH_2CH_3$, -$CH_2C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_2CH_3$,
-$CH(CH_3)CH_2CH_2CH_2CH_3$, -$CH(CH_2CH_3)(CH_2CH_2CH_3)$,
-$C(CH_3)_2CH_2CH_2CH_3$, -$CH(CH_3)CH(CH_3)CH_2CH_3$, -$CH(CH_3)CH_2CH(CH_3)_2$,
-$C(CH_3)(CH_2CH_3)_2$, -$CH(CH_2CH_3)CH(CH_3)_2$, -$C(CH_3)_2CH(CH_3)_2$,
-$CH(CH_3)C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopropylmethyl, cyclopentyl,
30   cyclobutylmethyl, 1-cyclopropyl-1-ethyl, 2-cyclopropyl-1-ethyl, cyclohexyl,
cyclopentylmethyl, 1-cyclobutyl-1-ethyl, 2-cyclobutyl-1-ethyl, 1-cyclopropyl-1-
propyl, 2-cyclopropyl-1-propyl, 3-cyclopropyl-1-propyl, 2-cyclopropyl-2-propyl,
and 1-cyclopropyl-2-propyl.

"Alkenyl" as used herein, unless stated to the contrary, is C_1-C_{12}
35   hydrocarbon containing normal, secondary, tertiary or cyclic structures.

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Examples are -CH=CH$_2$, -CH=CHCH$_3$, -CH$_2$CH=CH$_2$, -C(=CH$_2$)(CH$_3$),
-CH=CHCH$_2$CH$_3$, -CH$_2$CH=CHCH$_3$, -CH$_2$CH$_2$CH=CH$_2$, -CH=C(CH$_3$)$_2$,
-CH$_2$C(=CH$_2$)(CH$_3$), -C(=CH$_2$)CH$_2$CH$_3$, -C(CH$_3$)=CHCH$_3$, -CH(CH$_3$)CH=CH$_2$,
-C=CHCH$_2$CH$_2$CH$_3$, -CHCH=CHCH$_2$CH$_3$, -CHCH$_2$CH=CHCH$_3$,

5   -CHCH$_2$CH$_2$CH=CH$_2$, -C(=CH$_2$)CH$_2$CH$_2$CH$_3$, -C(CH$_3$)=CH$_2$CH$_2$CH$_3$,
-CH(CH$_3$)CH=CHCH$_3$, -CH(CH$_3$)CH$_2$CH=CH$_2$, -CH$_2$CH=C(CH$_3$)$_2$, 1-cyclopent-
1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, 1-cyclohex-1-enyl, 1-cyclohex-2-
enyl, and 1-cyclohex-3-enyl.

"Alkynyl" as used herein, unless stated to the contrary, is C$_1$-C$_{12}$

10   hydrocarbon containing normal, secondary, tertiary or cyclic structures.
Examples are -CCH, -CCCH$_3$, -CH$_2$CCH, -CCCH$_2$CH$_3$, -CH$_2$CCCH$_3$,
-CH$_2$CH$_2$CCH, CH(CH$_3$)CCH, -CCCH$_2$CH$_2$CH$_3$, -CH$_2$CCCH$_2$CH$_3$,
-CH$_2$CH$_2$CCCH$_3$ and -CH$_2$CH$_2$CH$_2$CCH.

Salt(s) include those derived by combination of appropriate anions

15   such as inorganic or organic acids. Suitable acids include those having
sufficient acidity to form a stable salt, preferably acids of low toxicity. For
example, one may form invention salts from acid addition of certain
organic and inorganic acids, e.g., HF, HCl, HBr, HI, H$_2$SO$_4$, H$_3$PO$_4$, or from
organic sulfonic acids, organic carboxylic acids to basic centers, typically

20   amines. Exemplary organic sulfonic acids include C$_{6-16}$ aryl sulfonic acids,
C$_{6-16}$ heteroaryl sulfonic acids and C$_{1-16}$ alkyl sulfonic acids such as phenyl,
a-naphthyl, b-naphthyl, (S)-camphor, methyl, ethyl, n-propyl, i-propyl, n-
butyl, s-butyl, i-butyl, t-butyl, pentyl and hexyl sulfonic acids. Exemplary
organic carboxylic acids include C$_{1-16}$ alkyl, C$_{6-16}$ aryl carboxylic acids and

25   C$_{4-16}$ heteroaryl carboxylic acids such as acetic, glycolic, lactic, pyruvic,
malonic, glutaric, tartaric, citric, fumaric, succinic, malic, maleic,
hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic
and 2-phenoxybenzoic. Salts also include the invention compound salts
with one or more amino acids. Many amino acids are suitable, especially

30   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 a neutral group
such as glycine, serine, threonine, alanine, isoleucine, or leucine. Salts are
usually biologically compatible or pharmaceutically acceptable or non-

35   toxic, particularly for mammalian cells. Salts that are biologically toxic are
generally used with synthetic intermediates of invention compounds.
The salts of invention compounds may be crystalline or noncrystalline.

A is the residue of a phosphonomethoxy nucleotide analog. The parental compounds have the structure $AOCH_2P(O)(OH)_2$. They are well known and have demonstrated antiviral activity. Per se, they are not part of this invention. In general, A has the structure BQ wherein B is a purine or

5   pyrimidine base or the aza and/or deaza analogs thereof and Q is a cyclic or acyclic aglycon. B is linked to Q through the purine 9 or pyrimidine 1 positions. Examples of these analogs can be found in U.S. Patents 4,659,825, 4,724,233, 5,142,051 and 5,130,427, EP 369,409, EP 398,231, EP 494,370, EP 454,427, EP 270,885, EP 269,947, EP 452,935, WO 93/07157, WO 94/03467, and

10   WO96/23801. Typically, A will have the structure $BCH_2CH(CH_3)$- or BCH_2CH_2-.

The designation "a" is an integer of 1 or 2. If X is N then a is 2 and one R is usually H and the other is not H. If X is O then a is 1.

B generally is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-

15   aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl. Ordinarily, B is adenin-9-yl or 2,6-diaminopurin-9-yl. In formula (1a) compounds, one Z optionally comprises an ester or an amidate. Suitable esters or amidates have been described, e.g., WO 95/07920. Exemplary esters are phenyl, benzyl, o-ethoxyphenyl, p-ethoxyphenyl, 2-pyridyl, 3-pyridyl, 4-

20   pyridyl, N-ethylmorpholino, C_1-C_8 O-alkyl and C_1-C_8 NH-alkyl. However, every compound of the invention will contain at least one $-C(R^2)_2OC(O)X(R)_a$ moiety.

R^2 independently is -H, C_1-C_{12} alkyl, C_5-C_{12} aryl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl,

25   any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or $-OR^3$ in which R^3 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl or C_5-C_{12} aryl. R^2 is usually H or C_1-C_6 alkyl, and typically only one R^2 is other than H. In most embodiments R^2 is H in both instances. The carbon atom to which R^2 is bonded is capable of chiral substitution, in

30   which case R^2 is in the (R), (S) or racemic configuration. In most embodiments, if R^2 is other than H the compounds of this invention are chirally enriched or pure at this site. In general, however, manufacturing is somewhat less expensive if chirality at the R^2 carbon can be avoided. Thus, R^2 is H when it is desired to help minimize the cost of synthesis.

35   X is O or N, typically O. The carbamates (where X=N) tend to be more stable in biological environments than the carbonates. When X is O then a is 1.

5

R independently is -H, C_1-C_{12} alkyl, C_5-C_{12} aryl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkyenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, $-N(R^4)_2$ or $-OR^3$, where R^4 independently is -H or C_1-C_8 alkyl,

5   provided that at least one R is not H. In general, R is C_1-C_6 secondary or normal alkyl which is unsubstituted or substituted with OR^3. When X is N then a is 2. In the latter case one R is usually other than H. Alternatively, two N-linked R groups are joined to form a carbocycle or O-containing heterocycle, typically containing 3 to 5 carbon atoms in the ring.

10   When R is unsaturated, but not aryl, the site of unsaturation is not critical and is in the Z or E configuration. The alkenyl chains of naturally occurring unsaturated fatty acids would be suitable as R groups, for example. R also includes cycloalkenyl or cycloalkynyl containing 1 or 2 unsaturated bonds, typically 1 unsaturated bond. When R is unsaturated,

15   usually it is alkenyl or alkynyl without aryl substitution.

If R is substituted with halo, cyano, azido, nitro or OR^3, typically R will contain 1 of these substituents. If substituted with 2 of these substituents, they are same or different. Generally, substituents found on R are OR^3. An exemplary R group containing an OR^3 substituent is

20    $-CH_2C(CH_2OCH_3)(CH_3)_2$.

When R contains an aryl group, the aryl group generally is bonded directly to X or is linked to X by methylene or ethylene. The aryl group may contain -N= or -O- as a ring atom. In general, the aryl group contains 5 or 6 carbons. If substituted, the aryl moiety is substituted with halo or

25   OR^3 in the ortho, meta or para positions, with R^3 in this instance being typically C_1-C_3. Aryl groups containing 5 carbons are typically 2-, 3- or 4-pyridyl. In general, only one substituent group will be found on the aryl moiety if it is substituted at all. Exemplary aromatic and nonaromatic heterocyclic groups as used herein includes by way of example and not

30   limitation the 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.

35   Chem. Soc.", 82:5566 (1960).

Examples of heterocycles include by way of example and not limitation pyridyl, thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, b-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.
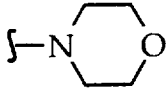
By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, 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 azetidine, 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, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 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 b-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

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R includes the structure $-C_2-C_6R^5C_2-C_6$ where each C_2-C_6 independently is a 2, 3, 4, 5 or 6 carbon linear, branched or cyclic alkyl moiety, e.g., ethylene, ethyl, propylene, propyl, isopropylene, isopropyl, cyclohexyl, etc., and R^5 is -O- or $-NR^6-$ where R^6 is linear, branched or cyclic alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms.

Embodiments include compounds where R^4 is -H or $-CH_3$.

R includes the structure $-C_2-C_{12}R^9$, where each C_2-C_{12} independently is a 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon linear, branched or cyclic alkyl moiety, and R^9 is

N-morpholino ($\xi-N\diagup O$) , N-piperidino, 2-pyridyl, 3-pyridyl or 4-pyridyl.

R also includes $-C(CH_2(X)_{0-1}R^7)_3$, $-CH[C(CH_2(X)_{0-1}R^7)_3]_2$ and $-CH_2(C(X)_{0-1}R^7)_3$, where R^7 is 1, 2, 3, 4, 5 or 6 carbon linear, branched or cyclic alkyl or R^7 is 5 or 6 carbon aryl. In these embodiments, one or two X are typically present, usually 1, X is usually oxygen and R^7 is typically methyl, ethyl, isopropyl, propyl or butyl, usually methyl.

R usually is phenyl, methyl, ethyl, 1-propyl, 2-propyl, *n*-butyl, *i*-butyl, *t*-butyl, pentyl or 3-pentyl.

R^1 is a substituent found in prior art phosphonomethoxy nucleotide analogs. R^1 typically is any of hydrogen, $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CH=CH_2$, $-CH_2N_3$ or R^1 and R^8 are joined to form $-CH_2-$. R^1 is usually H or methyl. If R^1 and R^8 are joined to form methylene, B typically is cytosin-1-yl.

R^3 is C_1-C_{12} alkyl, but typically is C_1-C_6 alkyl.

Compounds of structure (1) typically are those in which B is adenin-9-yl, R^1 is methyl or H, R^8 is $-CHR^2-O-C(O)-OR$ and R, R^2 and R^3 are as set forth above.

The compounds of this invention are optionally enriched or resolved at the carbon atom chiral center linked to R^1 in accordance with prior findings associating optimal antiviral activity with the configuration at this site. Thus, where R^1 is methyl the compounds will be in (R) configuration at this center and will be substantially free of the (S) enantiomer.

Other embodiments include structure (10) and (11) compounds where R and each R^2 are independently chosen and R^2 is C_1-C_6 alkyl

(10)

(11)
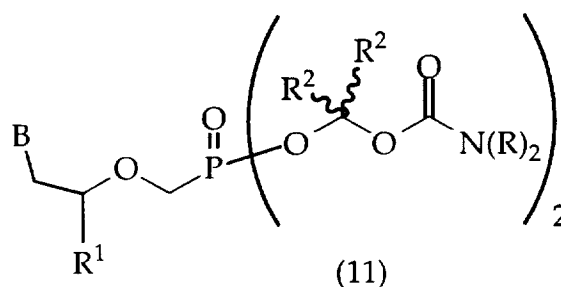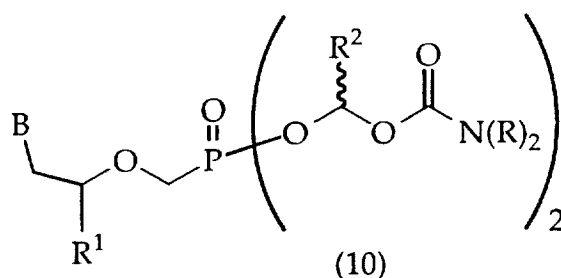
Exemplary embodiments include the compounds named in Table B. Each compound in Table B is depicted as a compound having the formula (8)

(8)
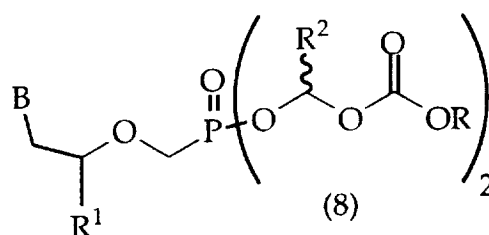
Compounds named in Table B are designated by numbers assigned to B, R, R^1 and R^2 according to the following convention, $B.R.R^1.R^2$, using the numbered structures depicted in Table A. Thus, the compound named 1.2.3.4 specifies adenin-9-yl at B, $-CH_2CH_3$ at both R groups, $-CH_2OH$ at R^1 and $-(CH_2)_2CH_3$ at both R^2 groups.

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TABLE A

B	R^1
1 adenin-9-yl	1 -CH_3
2 guanin-9-yl	2 -H
3 2,6-diaminopurin-9-yl	3 -CH_2OH
4 2-aminopurin-9-yl	4 -CH_2F
5 cytosin-1-yl	5 -$CH=CH_2$
	6 -CH_2N_3

R	R^2
1 -CH_3	1 -H
2 -C_2H_5	2 -CH_3
3 -$(CH_2)_2CH_3$	3 -C_2H_5
4 -$CH(CH_3)_2$	4 -$(CH_2)_2CH_3$
5 -$(CH_2)_3CH_3$	5 -$CH(CH_3)_2$
6 -$CH_2CH(CH_3)_2$	6 -$(CH_2)_3CH_3$
7 -$CH(CH_3)CH_2CH_3$	7 -$CH_2CH(CH_3)_2$
8 -$C(CH_3)_3$	8 -$C(CH_3)_3$
9 -$(CH_2)_4CH_3$	9 -$(CH_2)_4CH_3$
10 -$CH(CH_3)CH_2CH_2CH_3$	10 -$(CH_2)_5CH_3$
11 -$CH(CH_2CH_3)_2$	
12 -$C(CH_3)_2CH_2CH_3$	
13 -$CH(CH_3)CH(CH_3)_2$	
14 -$CH_2CH_2CH(CH_3)_2$	
15 -$CH_2CH(CH_3)CH_2CH_3$	
16 -$CH_2CH_2CH_2CH_2CH_2CH_3$	
17 -$CH(CH_3)CH_2CH_2CH_2CH_3$	
18 -$CH(CH_2CH_3)CH_2CH_2CH_3$	
19 -$C(CH_3)_2CH_2CH_2CH_3$	
20 -$CH(CH_3)CH(CH_3)CH_2CH_3$	
21 -$CH(CH_3)CH_2CH(CH_3)_2$	
22 -$C(CH_3)(CH_2CH_3)_2$	
23 -$CH(CH_2CH_3)CH(CH_3)_2$	
24 -$CH_2C_6H_5$	
25 -C_6H_5	

TABLE B

1.1.1.1 1.1.1.2 1.1.1.3 1.1.1.4 1.1.1.5 1.1.1.6 1.1.1.7 1.1.1.8 1.1.1.9 1.1.1.10 1.1.2.1 1.1.2.2 1.1.2.3
1.1.2.4 1.1.2.5 1.1.2.6 1.1.2.7 1.1.2.8 1.1.2.9 1.1.2.10 1.1.3.1 1.1.3.2 1.1.3.3 1.1.3.4 1.1.3.5 1.1.3.6
1.1.3.7 1.1.3.8 1.1.3.9 1.1.3.10 1.1.4.1 1.1.4.2 1.1.4.3 1.1.4.4 1.1.4.5 1.1.4.6 1.1.4.7 1.1.4.8 1.1.4.9
1.1.4.10 1.1.5.1 1.1.5.2 1.1.5.3 1.1.5.4 1.1.5.5 1.1.5.6 1.1.5.7 1.1.5.8 1.1.5.9 1.1.5.10 1.1.6.1 1.1.6.2
1.1.6.3 1.1.6.4 1.1.6.5 1.1.6.6 1.1.6.7 1.1.6.8 1.1.6.9 1.1.6.10 1.2.1.1 1.2.1.2 1.2.1.3 1.2.1.4 1.2.1.5
1.2.1.6 1.2.1.7 1.2.1.8 1.2.1.9 1.2.1.10 1.2.2.1 1.2.2.2 1.2.2.3 1.2.2.4 1.2.2.5 1.2.2.6 1.2.2.7 1.2.2.8
1.2.2.9 1.2.2.10 1.2.3.1 1.2.3.2 1.2.3.3 1.2.3.4 1.2.3.5 1.2.3.6 1.2.3.7 1.2.3.8 1.2.3.9 1.2.3.10 1.2.4.1
1.2.4.2 1.2.4.3 1.2.4.4 1.2.4.5 1.2.4.6 1.2.4.7 1.2.4.8 1.2.4.9 1.2.4.10 1.2.5.1 1.2.5.2 1.2.5.3 1.2.5.4
1.2.5.5 1.2.5.6 1.2.5.7 1.2.5.8 1.2.5.9 1.2.5.10 1.2.6.1 1.2.6.2 1.2.6.3 1.2.6.4 1.2.6.5 1.2.6.6 1.2.6.7
1.2.6.8 1.2.6.9 1.2.6.10 1.3.1.1 1.3.1.2 1.3.1.3 1.3.1.4 1.3.1.5 1.3.1.6 1.3.1.7 1.3.1.8 1.3.1.9 1.3.1.10
1.3.2.1 1.3.2.2 1.3.2.3 1.3.2.4 1.3.2.5 1.3.2.6 1.3.2.7 1.3.2.8 1.3.2.9 1.3.2.10 1.3.3.1 1.3.3.2 1.3.3.3

1.3.3.4 1.3.3.5 1.3.3.6 1.3.3.7 1.3.3.8 1.3.3.9 1.3.3.10 1.3.4.1 1.3.4.2 1.3.4.3 1.3.4.4 1.3.4.5 1.3.4.6
1.3.4.7 1.3.4.8 1.3.4.9 1.3.4.10 1.3.5.1 1.3.5.2 1.3.5.3 1.3.5.4 1.3.5.5 1.3.5.6 1.3.5.7 1.3.5.8 1.3.5.9
1.3.5.10 1.3.6.1 1.3.6.2 1.3.6.3 1.3.6.4 1.3.6.5 1.3.6.6 1.3.6.7 1.3.6.8 1.3.6.9 1.3.6.10 1.4.1.1 1.4.1.2
1.4.1.3 1.4.1.4 1.4.1.5 1.4.1.6 1.4.1.7 1.4.1.8 1.4.1.9 1.4.1.10 1.4.2.1 1.4.2.2 1.4.2.3 1.4.2.4 1.4.2.5

5   1.4.2.6 1.4.2.7 1.4.2.8 1.4.2.9 1.4.2.10 1.4.3.1 1.4.3.2 1.4.3.3 1.4.3.4 1.4.3.5 1.4.3.6 1.4.3.7 1.4.3.8
1.4.3.9 1.4.3.10 1.4.4.1 1.4.4.2 1.4.4.3 1.4.4.4 1.4.4.5 1.4.4.6 1.4.4.7 1.4.4.8 1.4.4.9 1.4.4.10 1.4.5.1
1.4.5.2 1.4.5.3 1.4.5.4 1.4.5.5 1.4.5.6 1.4.5.7 1.4.5.8 1.4.5.9 1.4.5.10 1.4.6.1 1.4.6.2 1.4.6.3 1.4.6.4
1.4.6.5 1.4.6.6 1.4.6.7 1.4.6.8 1.4.6.9 1.4.6.10 1.5.1.1 1.5.1.2 1.5.1.3 1.5.1.4 1.5.1.5 1.5.1.6 1.5.1.7
1.5.1.8 1.5.1.9 1.5.1.10 1.5.2.1 1.5.2.2 1.5.2.3 1.5.2.4 1.5.2.5 1.5.2.6 1.5.2.7 1.5.2.8 1.5.2.9 1.5.2.10

10   1.5.3.1 1.5.3.2 1.5.3.3 1.5.3.4 1.5.3.5 1.5.3.6 1.5.3.7 1.5.3.8 1.5.3.9 1.5.3.10 1.5.4.1 1.5.4.2 1.5.4.3
1.5.4.4 1.5.4.5 1.5.4.6 1.5.4.7 1.5.4.8 1.5.4.9 1.5.4.10 1.5.5.1 1.5.5.2 1.5.5.3 1.5.5.4 1.5.5.5 1.5.5.6
1.5.5.7 1.5.5.8 1.5.5.9 1.5.5.10 1.5.6.1 1.5.6.2 1.5.6.3 1.5.6.4 1.5.6.5 1.5.6.6 1.5.6.7 1.5.6.8 1.5.6.9
1.5.6.10 1.6.1.1 1.6.1.2 1.6.1.3 1.6.1.4 1.6.1.5 1.6.1.6 1.6.1.7 1.6.1.8 1.6.1.9 1.6.1.10 1.6.2.1 1.6.2.2
1.6.2.3 1.6.2.4 1.6.2.5 1.6.2.6 1.6.2.7 1.6.2.8 1.6.2.9 1.6.2.10 1.6.3.1 1.6.3.2 1.6.3.3 1.6.3.4 1.6.3.5

15   1.6.3.6 1.6.3.7 1.6.3.8 1.6.3.9 1.6.3.10 1.6.4.1 1.6.4.2 1.6.4.3 1.6.4.4 1.6.4.5 1.6.4.6 1.6.4.7 1.6.4.8
1.6.4.9 1.6.4.10 1.6.5.1 1.6.5.2 1.6.5.3 1.6.5.4 1.6.5.5 1.6.5.6 1.6.5.7 1.6.5.8 1.6.5.9 1.6.5.10 1.6.6.1
1.6.6.2 1.6.6.3 1.6.6.4 1.6.6.5 1.6.6.6 1.6.6.7 1.6.6.8 1.6.6.9 1.6.6.10 1.7.1.1 1.7.1.2 1.7.1.3 1.7.1.4
1.7.1.5 1.7.1.6 1.7.1.7 1.7.1.8 1.7.1.9 1.7.1.10 1.7.2.1 1.7.2.2 1.7.2.3 1.7.2.4 1.7.2.5 1.7.2.6 1.7.2.7
1.7.2.8 1.7.2.9 1.7.2.10 1.7.3.1 1.7.3.2 1.7.3.3 1.7.3.4 1.7.3.5 1.7.3.6 1.7.3.7 1.7.3.8 1.7.3.9 1.7.3.10

20   1.7.4.1 1.7.4.2 1.7.4.3 1.7.4.4 1.7.4.5 1.7.4.6 1.7.4.7 1.7.4.8 1.7.4.9 1.7.4.10 1.7.5.1 1.7.5.2 1.7.5.3
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1.7.6.7 1.7.6.8 1.7.6.9 1.7.6.10 1.8.1.1 1.8.1.2 1.8.1.3 1.8.1.4 1.8.1.5 1.8.1.6 1.8.1.7 1.8.1.8 1.8.1.9
1.8.1.10 1.8.2.1 1.8.2.2 1.8.2.3 1.8.2.4 1.8.2.5 1.8.2.6 1.8.2.7 1.8.2.8 1.8.2.9 1.8.2.10 1.8.3.1 1.8.3.2
1.8.3.3 1.8.3.4 1.8.3.5 1.8.3.6 1.8.3.7 1.8.3.8 1.8.3.9 1.8.3.10 1.8.4.1 1.8.4.2 1.8.4.3 1.8.4.4 1.8.4.5

25   1.8.4.6 1.8.4.7 1.8.4.8 1.8.4.9 1.8.4.10 1.8.5.1 1.8.5.2 1.8.5.3 1.8.5.4 1.8.5.5 1.8.5.6 1.8.5.7 1.8.5.8
1.8.5.9 1.8.5.10 1.8.6.1 1.8.6.2 1.8.6.3 1.8.6.4 1.8.6.5 1.8.6.6 1.8.6.7 1.8.6.8 1.8.6.9 1.8.6.10 1.9.1.1
1.9.1.2 1.9.1.3 1.9.1.4 1.9.1.5 1.9.1.6 1.9.1.7 1.9.1.8 1.9.1.9 1.9.1.10 1.9.2.1 1.9.2.2 1.9.2.3 1.9.2.4
1.9.2.5 1.9.2.6 1.9.2.7 1.9.2.8 1.9.2.9 1.9.2.10 1.9.3.1 1.9.3.2 1.9.3.3 1.9.3.4 1.9.3.5 1.9.3.6 1.9.3.7
1.9.3.8 1.9.3.9 1.9.3.10 1.9.4.1 1.9.4.2 1.9.4.3 1.9.4.4 1.9.4.5 1.9.4.6 1.9.4.7 1.9.4.8 1.9.4.9 1.9.4.10

30   1.9.5.1 1.9.5.2 1.9.5.3 1.9.5.4 1.9.5.5 1.9.5.6 1.9.5.7 1.9.5.8 1.9.5.9 1.9.5.10 1.9.6.1 1.9.6.2 1.9.6.3
1.9.6.4 1.9.6.5 1.9.6.6 1.9.6.7 1.9.6.8 1.9.6.9 1.9.6.10 1.10.1.1 1.10.1.2 1.10.1.3 1.10.1.4 1.10.1.5
1.10.1.6 1.10.1.7 1.10.1.8 1.10.1.9 1.10.1.10 1.10.2.1 1.10.2.2 1.10.2.3 1.10.2.4 1.10.2.5 1.10.2.6
1.10.2.7 1.10.2.8 1.10.2.9 1.10.2.10 1.10.3.1 1.10.3.2 1.10.3.3 1.10.3.4 1.10.3.5 1.10.3.6 1.10.3.7
1.10.3.8 1.10.3.9 1.10.3.10 1.10.4.1 1.10.4.2 1.10.4.3 1.10.4.4 1.10.4.5 1.10.4.6 1.10.4.7 1.10.4.8

35   1.10.4.9 1.10.4.10 1.10.5.1 1.10.5.2 1.10.5.3 1.10.5.4 1.10.5.5 1.10.5.6 1.10.5.7 1.10.5.8 1.10.5.9
1.10.5.10 1.10.6.1 1.10.6.2 1.10.6.3 1.10.6.4 1.10.6.5 1.10.6.6 1.10.6.7 1.10.6.8 1.10.6.9 1.10.6.10
1.11.1.1 1.11.1.2 1.11.1.3 1.11.1.4 1.11.1.5 1.11.1.6 1.11.1.7 1.11.1.8 1.11.1.9 1.11.1.10 1.11.2.1
1.11.2.2 1.11.2.3 1.11.2.4 1.11.2.5 1.11.2.6 1.11.2.7 1.11.2.8 1.11.2.9 1.11.2.10 1.11.3.1 1.11.3.2
1.11.3.3 1.11.3.4 1.11.3.5 1.11.3.6 1.11.3.7 1.11.3.8 1.11.3.9 1.11.3.10 1.11.4.1 1.11.4.2 1.11.4.3

40   1.11.4.4 1.11.4.5 1.11.4.6 1.11.4.7 1.11.4.8 1.11.4.9 1.11.4.10 1.11.5.1 1.11.5.2 1.11.5.3 1.11.5.4
1.11.5.5 1.11.5.6 1.11.5.7 1.11.5.8 1.11.5.9 1.11.5.10 1.11.6.1 1.11.6.2 1.11.6.3 1.11.6.4 1.11.6.5
1.11.6.6 1.11.6.7 1.11.6.8 1.11.6.9 1.11.6.10 1.12.1.1 1.12.1.2 1.12.1.3 1.12.1.4 1.12.1.5 1.12.1.6
1.12.1.7 1.12.1.8 1.12.1.9 1.12.1.10 1.12.2.1 1.12.2.2 1.12.2.3 1.12.2.4 1.12.2.5 1.12.2.6 1.12.2.7
1.12.2.8 1.12.2.9 1.12.2.10 1.12.3.1 1.12.3.2 1.12.3.3 1.12.3.4 1.12.3.5 1.12.3.6 1.12.3.7 1.12.3.8

45   1.12.3.9 1.12.3.10 1.12.4.1 1.12.4.2 1.12.4.3 1.12.4.4 1.12.4.5 1.12.4.6 1.12.4.7 1.12.4.8 1.12.4.9
1.12.4.10 1.12.5.1 1.12.5.2 1.12.5.3 1.12.5.4 1.12.5.5 1.12.5.6 1.12.5.7 1.12.5.8 1.12.5.9 1.12.5.10
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1.13.1.2 1.13.1.3 1.13.1.4 1.13.1.5 1.13.1.6 1.13.1.7 1.13.1.8 1.13.1.9 1.13.1.10 1.13.2.1 1.13.2.2
1.13.2.3 1.13.2.4 1.13.2.5 1.13.2.6 1.13.2.7 1.13.2.8 1.13.2.9 1.13.2.10 1.13.3.1 1.13.3.2 1.13.3.3

50   1.13.3.4 1.13.3.5 1.13.3.6 1.13.3.7 1.13.3.8 1.13.3.9 1.13.3.10 1.13.4.1 1.13.4.2 1.13.4.3 1.13.4.4
1.13.4.5 1.13.4.6 1.13.4.7 1.13.4.8 1.13.4.9 1.13.4.10 1.13.5.1 1.13.5.2 1.13.5.3 1.13.5.4 1.13.5.5
1.13.5.6 1.13.5.7 1.13.5.8 1.13.5.9 1.13.5.10 1.13.6.1 1.13.6.2 1.13.6.3 1.13.6.4 1.13.6.5 1.13.6.6
1.13.6.7 1.13.6.8 1.13.6.9 1.13.6.10 1.14.1.1 1.14.1.2 1.14.1.3 1.14.1.4 1.14.1.5 1.14.1.6 1.14.1.7
1.14.1.8 1.14.1.9 1.14.1.10 1.14.2.1 1.14.2.2 1.14.2.3 1.14.2.4 1.14.2.5 1.14.2.6 1.14.2.7 1.14.2.8

55   1.14.2.9 1.14.2.10 1.14.3.1 1.14.3.2 1.14.3.3 1.14.3.4 1.14.3.5 1.14.3.6 1.14.3.7 1.14.3.8 1.14.3.9
1.14.3.10 1.14.4.1 1.14.4.2 1.14.4.3 1.14.4.4 1.14.4.5 1.14.4.6 1.14.4.7 1.14.4.8 1.14.4.9 1.14.4.10
1.14.5.1 1.14.5.2 1.14.5.3 1.14.5.4 1.14.5.5 1.14.5.6 1.14.5.7 1.14.5.8 1.14.5.9 1.14.5.10 1.14.6.1

1.14.6.2 1.14.6.3 1.14.6.4 1.14.6.5 1.14.6.6 1.14.6.7 1.14.6.8 1.14.6.9 1.14.6.10 1.15.1.1 1.15.1.2
1.15.1.3 1.15.1.4 1.15.1.5 1.15.1.6 1.15.1.7 1.15.1.8 1.15.1.9 1.15.1.10 1.15.2.1 1.15.2.2 1.15.2.3
1.15.2.4 1.15.2.5 1.15.2.6 1.15.2.7 1.15.2.8 1.15.2.9 1.15.2.10 1.15.3.1 1.15.3.2 1.15.3.3 1.15.3.4
1.15.3.5 1.15.3.6 1.15.3.7 1.15.3.8 1.15.3.9 1.15.3.10 1.15.4.1 1.15.4.2 1.15.4.3 1.15.4.4 1.15.4.5

5 1.15.4.6 1.15.4.7 1.15.4.8 1.15.4.9 1.15.4.10 1.15.5.1 1.15.5.2 1.15.5.3 1.15.5.4 1.15.5.5 1.15.5.6
1.15.5.7 1.15.5.8 1.15.5.9 1.15.5.10 1.15.6.1 1.15.6.2 1.15.6.3 1.15.6.4 1.15.6.5 1.15.6.6 1.15.6.7
1.15.6.8 1.15.6.9 1.15.6.10 1.16.1.1 1.16.1.2 1.16.1.3 1.16.1.4 1.16.1.5 1.16.1.6 1.16.1.7 1.16.1.8
1.16.1.9 1.16.1.10 1.16.2.1 1.16.2.2 1.16.2.3 1.16.2.4 1.16.2.5 1.16.2.6 1.16.2.7 1.16.2.8 1.16.2.9
1.16.2.10 1.16.3.1 1.16.3.2 1.16.3.3 1.16.3.4 1.16.3.5 1.16.3.6 1.16.3.7 1.16.3.8 1.16.3.9 1.16.3.10

10 1.16.4.1 1.16.4.2 1.16.4.3 1.16.4.4 1.16.4.5 1.16.4.6 1.16.4.7 1.16.4.8 1.16.4.9 1.16.4.10 1.16.5.1
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1.16.6.3 1.16.6.4 1.16.6.5 1.16.6.6 1.16.6.7 1.16.6.8 1.16.6.9 1.16.6.10 1.17.1.1 1.17.1.2 1.17.1.3
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2.11.2.4 2.11.2.5 2.11.2.6 2.11.2.7 2.11.2.8 2.11.2.9 2.11.2.10 2.11.3.1 2.11.3.2 2.11.3.3 2.11.3.4
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55   2.11.4.6 2.11.4.7 2.11.4.8 2.11.4.9 2.11.4.10 2.11.5.1 2.11.5.2 2.11.5.3 2.11.5.4 2.11.5.5 2.11.5.6
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5   2.12.6.3 2.12.6.4 2.12.6.5 2.12.6.6 2.12.6.7 2.12.6.8 2.12.6.9 2.12.6.10 2.13.1.1 2.13.1.2 2.13.1.3
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2.13.2.5 2.13.2.6 2.13.2.7 2.13.2.8 2.13.2.9 2.13.2.10 2.13.3.1 2.13.3.2 2.13.3.3 2.13.3.4 2.13.3.5
2.13.3.6 2.13.3.7 2.13.3.8 2.13.3.9 2.13.3.10 2.13.4.1 2.13.4.2 2.13.4.3 2.13.4.4 2.13.4.5 2.13.4.6
2.13.4.7 2.13.4.8 2.13.4.9 2.13.4.10 2.13.5.1 2.13.5.2 2.13.5.3 2.13.5.4 2.13.5.5 2.13.5.6 2.13.5.7

10   2.13.5.8 2.13.5.9 2.13.5.10 2.13.6.1 2.13.6.2 2.13.6.3 2.13.6.4 2.13.6.5 2.13.6.6 2.13.6.7 2.13.6.8
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15   2.14.5.3 2.14.5.4 2.14.5.5 2.14.5.6 2.14.5.7 2.14.5.8 2.14.5.9 2.14.5.10 2.14.6.1 2.14.6.2 2.14.6.3
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2.15.3.7 2.15.3.8 2.15.3.9 2.15.3.10 2.15.4.1 2.15.4.2 2.15.4.3 2.15.4.4 2.15.4.5 2.15.4.6 2.15.4.7

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2.18.6.6 2.18.6.7 2.18.6.8 2.18.6.9 2.18.6.10 2.19.1.1 2.19.1.2 2.19.1.3 2.19.1.4 2.19.1.5 2.19.1.6
2.19.1.7 2.19.1.8 2.19.1.9 2.19.1.10 2.19.2.1 2.19.2.2 2.19.2.3 2.19.2.4 2.19.2.5 2.19.2.6 2.19.2.7

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2.19.3.9 2.19.3.10 2.19.4.1 2.19.4.2 2.19.4.3 2.19.4.4 2.19.4.5 2.19.4.6 2.19.4.7 2.19.4.8 2.19.4.9
2.19.4.10 2.19.5.1 2.19.5.2 2.19.5.3 2.19.5.4 2.19.5.5 2.19.5.6 2.19.5.7 2.19.5.8 2.19.5.9 2.19.5.10
2.19.6.1 2.19.6.2 2.19.6.3 2.19.6.4 2.19.6.5 2.19.6.6 2.19.6.7 2.19.6.8 2.19.6.9 2.19.6.10 2.20.1.1
2.20.1.2 2.20.1.3 2.20.1.4 2.20.1.5 2.20.1.6 2.20.1.7 2.20.1.8 2.20.1.9 2.20.1.10 2.20.2.1 2.20.2.2

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2.20.6.7 2.20.6.8 2.20.6.9 2.20.6.10 2.21.1.1 2.21.1.2 2.21.1.3 2.21.1.4 2.21.1.5 2.21.1.6 2.21.1.7

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2.22.6.8 2.22.6.9 2.22.6.10 2.23.1.1 2.23.1.2 2.23.1.3 2.23.1.4 2.23.1.5 2.23.1.6 2.23.1.7 2.23.1.8
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5   2.23.2.10 2.23.3.1 2.23.3.2 2.23.3.3 2.23.3.4 2.23.3.5 2.23.3.6 2.23.3.7 2.23.3.8 2.23.3.9 2.23.3.10
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2.23.6.3 2.23.6.4 2.23.6.5 2.23.6.6 2.23.6.7 2.23.6.8 2.23.6.9 2.23.6.10 2.24.1.1 2.24.1.2 2.24.1.3
2.24.1.4 2.24.1.5 2.24.1.6 2.24.1.7 2.24.1.8 2.24.1.9 2.24.1.10 2.24.2.1 2.24.2.2 2.24.2.3 2.24.2.4
10   2.24.2.5 2.24.2.6 2.24.2.7 2.24.2.8 2.24.2.9 2.24.2.10 2.24.3.1 2.24.3.2 2.24.3.3 2.24.3.4 2.24.3.5
2.24.3.6 2.24.3.7 2.24.3.8 2.24.3.9 2.24.3.10 2.24.4.1 2.24.4.2 2.24.4.3 2.24.4.4 2.24.4.5 2.24.4.6
2.24.4.7 2.24.4.8 2.24.4.9 2.24.4.10 2.24.5.1 2.24.5.2 2.24.5.3 2.24.5.4 2.24.5.5 2.24.5.6 2.24.5.7
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3.3.1.3 3.3.1.4 3.3.1.5 3.3.1.6 3.3.1.7 3.3.1.8 3.3.1.9 3.3.1.10 3.3.2.1 3.3.2.2 3.3.2.3 3.3.2.4 3.3.2.5
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3.3.6.5 3.3.6.6 3.3.6.7 3.3.6.8 3.3.6.9 3.3.6.10 3.4.1.1 3.4.1.2 3.4.1.3 3.4.1.4 3.4.1.5 3.4.1.6 3.4.1.7
3.4.1.8 3.4.1.9 3.4.1.10 3.4.2.1 3.4.2.2 3.4.2.3 3.4.2.4 3.4.2.5 3.4.2.6 3.4.2.7 3.4.2.8 3.4.2.9 3.4.2.10
35   3.4.3.1 3.4.3.2 3.4.3.3 3.4.3.4 3.4.3.5 3.4.3.6 3.4.3.7 3.4.3.8 3.4.3.9 3.4.3.10 3.4.4.1 3.4.4.2 3.4.4.3
3.4.4.4 3.4.4.5 3.4.4.6 3.4.4.7 3.4.4.8 3.4.4.9 3.4.4.10 3.4.5.1 3.4.5.2 3.4.5.3 3.4.5.4 3.4.5.5 3.4.5.6
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3.6.1.5 3.6.1.6 3.6.1.7 3.6.1.8 3.6.1.9 3.6.1.10 3.6.2.1 3.6.2.2 3.6.2.3 3.6.2.4 3.6.2.5 3.6.2.6 3.6.2.7
3.6.2.8 3.6.2.9 3.6.2.10 3.6.3.1 3.6.3.2 3.6.3.3 3.6.3.4 3.6.3.5 3.6.3.6 3.6.3.7 3.6.3.8 3.6.3.9 3.6.3.10
45   3.6.4.1 3.6.4.2 3.6.4.3 3.6.4.4 3.6.4.5 3.6.4.6 3.6.4.7 3.6.4.8 3.6.4.9 3.6.4.10 3.6.5.1 3.6.5.2 3.6.5.3
3.6.5.4 3.6.5.5 3.6.5.6 3.6.5.7 3.6.5.8 3.6.5.9 3.6.5.10 3.6.6.1 3.6.6.2 3.6.6.3 3.6.6.4 3.6.6.5 3.6.6.6
3.6.6.7 3.6.6.8 3.6.6.9 3.6.6.10 3.7.1.1 3.7.1.2 3.7.1.3 3.7.1.4 3.7.1.5 3.7.1.6 3.7.1.7 3.7.1.8 3.7.1.9
3.7.1.10 3.7.2.1 3.7.2.2 3.7.2.3 3.7.2.4 3.7.2.5 3.7.2.6 3.7.2.7 3.7.2.8 3.7.2.9 3.7.2.10 3.7.3.1 3.7.3.2
3.7.3.3 3.7.3.4 3.7.3.5 3.7.3.6 3.7.3.7 3.7.3.8 3.7.3.9 3.7.3.10 3.7.4.1 3.7.4.2 3.7.4.3 3.7.4.4 3.7.4.5
50   3.7.4.6 3.7.4.7 3.7.4.8 3.7.4.9 3.7.4.10 3.7.5.1 3.7.5.2 3.7.5.3 3.7.5.4 3.7.5.5 3.7.5.6 3.7.5.7 3.7.5.8
3.7.5.9 3.7.5.10 3.7.6.1 3.7.6.2 3.7.6.3 3.7.6.4 3.7.6.5 3.7.6.6 3.7.6.7 3.7.6.8 3.7.6.9 3.7.6.10 3.8.1.1
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3.8.3.8 3.8.3.9 3.8.3.10 3.8.4.1 3.8.4.2 3.8.4.3 3.8.4.4 3.8.4.5 3.8.4.6 3.8.4.7 3.8.4.8 3.8.4.9 3.8.4.10
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5   3.10.1.10 3.10.2.1 3.10.2.2 3.10.2.3 3.10.2.4 3.10.2.5 3.10.2.6 3.10.2.7 3.10.2.8 3.10.2.9 3.10.2.10
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3.10.6.4 3.10.6.5 3.10.6.6 3.10.6.7 3.10.6.8 3.10.6.9 3.10.6.10 3.11.1.1 3.11.1.2 3.11.1.3 3.11.1.4

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15   3.11.6.10 3.12.1.1 3.12.1.2 3.12.1.3 3.12.1.4 3.12.1.5 3.12.1.6 3.12.1.7 3.12.1.8 3.12.1.9 3.12.1.10
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3.12.5.4 3.12.5.5 3.12.5.6 3.12.5.7 3.12.5.8 3.12.5.9 3.12.5.10 3.12.6.1 3.12.6.2 3.12.6.3 3.12.6.4

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25   3.13.5.10 3.13.6.1 3.13.6.2 3.13.6.3 3.13.6.4 3.13.6.5 3.13.6.6 3.13.6.7 3.13.6.8 3.13.6.9 3.13.6.10
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3.16.3.4 3.16.3.5 3.16.3.6 3.16.3.7 3.16.3.8 3.16.3.9 3.16.3.10 3.16.4.1 3.16.4.2 3.16.4.3 3.16.4.4

40   3.16.4.5 3.16.4.6 3.16.4.7 3.16.4.8 3.16.4.9 3.16.4.10 3.16.5.1 3.16.5.2 3.16.5.3 3.16.5.4 3.16.5.5
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45   3.17.3.10 3.17.4.1 3.17.4.2 3.17.4.3 3.17.4.4 3.17.4.5 3.17.4.6 3.17.4.7 3.17.4.8 3.17.4.9 3.17.4.10
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3.18.2.4 3.18.2.5 3.18.2.6 3.18.2.7 3.18.2.8 3.18.2.9 3.18.2.10 3.18.3.1 3.18.3.2 3.18.3.3 3.18.3.4

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3.18.5.7 3.18.5.8 3.18.5.9 3.18.5.10 3.18.6.1 3.18.6.2 3.18.6.3 3.18.6.4 3.18.6.5 3.18.6.6 3.18.6.7
3.18.6.8 3.18.6.9 3.18.6.10 3.19.1.1 3.19.1.2 3.19.1.3 3.19.1.4 3.19.1.5 3.19.1.6 3.19.1.7 3.19.1.8
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5.10.5.6 5.10.5.7 5.10.5.8 5.10.5.9 5.10.5.10 5.10.6.1 5.10.6.2 5.10.6.3 5.10.6.4 5.10.6.5 5.10.6.6
5.10.6.7 5.10.6.8 5.10.6.9 5.10.6.10 5.11.1.1 5.11.1.2 5.11.1.3 5.11.1.4 5.11.1.5 5.11.1.6 5.11.1.7
40　5.11.1.8 5.11.1.9 5.11.1.10 5.11.2.1 5.11.2.2 5.11.2.3 5.11.2.4 5.11.2.5 5.11.2.6 5.11.2.7 5.11.2.8
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5.11.3.10 5.11.4.1 5.11.4.2 5.11.4.3 5.11.4.4 5.11.4.5 5.11.4.6 5.11.4.7 5.11.4.8 5.11.4.9 5.11.4.10
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5.12.2.4 5.12.2.5 5.12.2.6 5.12.2.7 5.12.2.8 5.12.2.9 5.12.2.10 5.12.3.1 5.12.3.2 5.12.3.3 5.12.3.4
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50　5.12.6.8 5.12.6.9 5.12.6.10 5.13.1.1 5.13.1.2 5.13.1.3 5.13.1.4 5.13.1.5 5.13.1.6 5.13.1.7 5.13.1.8
5.13.1.9 5.13.1.10 5.13.2.1 5.13.2.2 5.13.2.3 5.13.2.4 5.13.2.5 5.13.2.6 5.13.2.7 5.13.2.8 5.13.2.9
5.13.2.10 5.13.3.1 5.13.3.2 5.13.3.3 5.13.3.4 5.13.3.5 5.13.3.6 5.13.3.7 5.13.3.8 5.13.3.9 5.13.3.10
5.13.4.1 5.13.4.2 5.13.4.3 5.13.4.4 5.13.4.5 5.13.4.6 5.13.4.7 5.13.4.8 5.13.4.9 5.13.4.10 5.13.5.1
5.13.5.2 5.13.5.3 5.13.5.4 5.13.5.5 5.13.5.6 5.13.5.7 5.13.5.8 5.13.5.9 5.13.5.10 5.13.6.1 5.13.6.2
55　5.13.6.3 5.13.6.4 5.13.6.5 5.13.6.6 5.13.6.7 5.13.6.8 5.13.6.9 5.13.6.10 5.14.1.1 5.14.1.2 5.14.1.3
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5.14.3.6 5.14.3.7 5.14.3.8 5.14.3.9 5.14.3.10 5.14.4.1 5.14.4.2 5.14.4.3 5.14.4.4 5.14.4.5 5.14.4.6
5.14.4.7 5.14.4.8 5.14.4.9 5.14.4.10 5.14.5.1 5.14.5.2 5.14.5.3 5.14.5.4 5.14.5.5 5.14.5.6 5.14.5.7
5.14.5.8 5.14.5.9 5.14.5.10 5.14.6.1 5.14.6.2 5.14.6.3 5.14.6.4 5.14.6.5 5.14.6.6 5.14.6.7 5.14.6.8
5.14.6.9 5.14.6.10 5.15.1.1 5.15.1.2 5.15.1.3 5.15.1.4 5.15.1.5 5.15.1.6 5.15.1.7 5.15.1.8 5.15.1.9
5.15.1.10 5.15.2.1 5.15.2.2 5.15.2.3 5.15.2.4 5.15.2.5 5.15.2.6 5.15.2.7 5.15.2.8 5.15.2.9 5.15.2.10
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5.18.5.10 5.18.6.1 5.18.6.2 5.18.6.3 5.18.6.4 5.18.6.5 5.18.6.6 5.18.6.7 5.18.6.8 5.18.6.9 5.18.6.10
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5.21.4.5 5.21.4.6 5.21.4.7 5.21.4.8 5.21.4.9 5.21.4.10 5.21.5.1 5.21.5.2 5.21.5.3 5.21.5.4 5.21.5.5
5.21.5.6 5.21.5.7 5.21.5.8 5.21.5.9 5.21.5.10 5.21.6.1 5.21.6.2 5.21.6.3 5.21.6.4 5.21.6.5 5.21.6.6
5.21.6.7 5.21.6.8 5.21.6.9 5.21.6.10 5.22.1.1 5.22.1.2 5.22.1.3 5.22.1.4 5.22.1.5 5.22.1.6 5.22.1.7
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5.23.2.4 5.23.2.5 5.23.2.6 5.23.2.7 5.23.2.8 5.23.2.9 5.23.2.10 5.23.3.1 5.23.3.2 5.23.3.3 5.23.3.4
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5.23.4.6 5.23.4.7 5.23.4.8 5.23.4.9 5.23.4.10 5.23.5.1 5.23.5.2 5.23.5.3 5.23.5.4 5.23.5.5 5.23.5.6
5.23.5.7 5.23.5.8 5.23.5.9 5.23.5.10 5.23.6.1 5.23.6.2 5.23.6.3 5.23.6.4 5.23.6.5 5.23.6.6 5.23.6.7
5.23.6.8 5.23.6.9 5.23.6.10 5.24.1.1 5.24.1.2 5.24.1.3 5.24.1.4 5.24.1.5 5.24.1.6 5.24.1.7 5.24.1.8
5.24.1.9 5.24.1.10 5.24.2.1 5.24.2.2 5.24.2.3 5.24.2.4 5.24.2.5 5.24.2.6 5.24.2.7 5.24.2.8 5.24.2.9
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5.24.4.1 5.24.4.2 5.24.4.3 5.24.4.4 5.24.4.5 5.24.4.6 5.24.4.7 5.24.4.8 5.24.4.9 5.24.4.10 5.24.5.1
5.24.5.2 5.24.5.3 5.24.5.4 5.24.5.5 5.24.5.6 5.24.5.7 5.24.5.8 5.24.5.9 5.24.5.10 5.24.6.1 5.24.6.2

5.24.6.3 5.24.6.4 5.24.6.5 5.24.6.6 5.24.6.7 5.24.6.8 5.24.6.9 5.24.6.10 5.25.1.1 5.25.1.2 5.25.1.3
5.25.1.4 5.25.1.5 5.25.1.6 5.25.1.7 5.25.1.8 5.25.1.9 5.25.1.10 5.25.2.1 5.25.2.2 5.25.2.3 5.25.2.4
5.25.2.5 5.25.2.6 5.25.2.7 5.25.2.8 5.25.2.9 5.25.2.10 5.25.3.1 5.25.3.2 5.25.3.3 5.25.3.4 5.25.3.5
5.25.3.6 5.25.3.7 5.25.3.8 5.25.3.9 5.25.3.10 5.25.4.1 5.25.4.2 5.25.4.3 5.25.4.4 5.25.4.5 5.25.4.6
5 5.25.4.7 5.25.4.8 5.25.4.9 5.25.4.10 5.25.5.1 5.25.5.2 5.25.5.3 5.25.5.4 5.25.5.5 5.25.5.6 5.25.5.7
5.25.5.8 5.25.5.9 5.25.5.10 5.25.6.1 5.25.6.2 5.25.6.3 5.25.6.4 5.25.6.5 5.25.6.6 5.25.6.7 5.25.6.8
5.25.6.9 5.25.6.10

Exemplary embodiments include the following numbered groups of
compounds.

10   **1** Each compound named in Table B having only one carbonate moiety
and a hydroxyl group linked to the phosphorus atom in place of the second
carbonate moiety, i.e., $B-CH_2-CHR^1-O-CH_2-P(O)(OH)-O-CHR^2-O-C(O)-OR$.
Thus, the group 1 compound named 1.4.1.1 in Table B has the structure:
$adenin-9-yl-CH_2-CH(CH_3)-O-CH_2-P(O)(OH)-O-CH_2-O-C(O)-OCH(CH_3)_2$.

15   **2** Compounds named in Table B having only one carbonate moiety
and having only the R^1 moiety, #3 (-CH_2OH), which is modified such that R^8
of formula (1) compounds is joined with R^1 to form -CH_2-. Thus, the group 2
compound named 1.4.3.1 in Table B has the structure:
$adenin-9-yl-CH_2-CH(CH_2-\lozenge)-O-CH_2-P(O)(O-\lozenge)-O-CH_2-O-C(O)-OCH(CH_3)_2$,

20   where the symbols $\lozenge$ indicate a covalent bond that links the oxygen and
carbon atoms together.

3 Compounds named in Table B and compounds named by compound
groups 1 and 2 where each purine base listed in Table A is the 3-deaza analog,
e.g., 3-deazaadenin-9-yl. Thus, the group 3 compound defined in Table A and
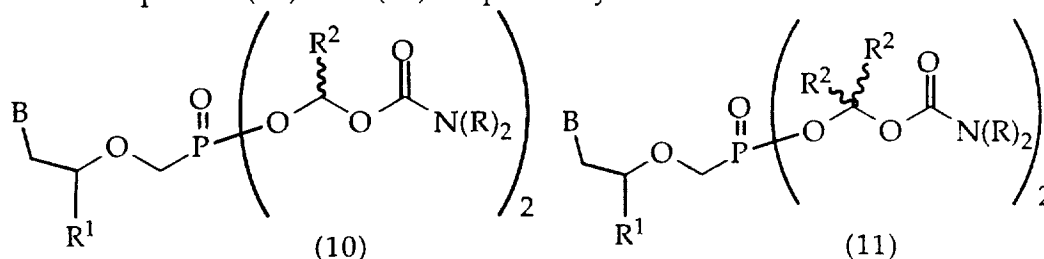
25   named 1.4.1.1 in Table B has the structure:
$3-deazaadenin-9-yl-CH_2-CH(CH_3)-O-CH_2-P(O)(-O-CH_2-O-C(O)-OCH(CH_3)_2)_2$.
The group 3 compound defined in Table A and named 1.4.1.1 in compound
group 1 has the structure:
$3-deazaadenin-9-yl-CH_2-CH(CH_3)-O-CH_2-P(O)(OH)-O-CH_2-O-C(O)-OCH(CH_3)_2$.

30   **4** Compounds named in Table B and compounds named by compound
groups 1 and 2 where each purine base listed in Table A is the 1-deaza analog,
e.g., 1-deazaadenin-9-yl. Thus, the group 4 compound defined in Table A and
named 1.4.1.1 in Table B has the structure:
$1-deazaadenin-9-yl-CH_2-CH(CH_3)-O-CH_2-P(O)(-O-CH_2-O-C(O)-OCH(CH_3)_2)_2$.

35   The group 3 compound defined in Table A and named 1.4.1.1 in compound
group 1 has the structure:
$1-deazaadenin-9-yl-CH_2-CH(CH_3)-O-CH_2-P(O)(OH)-O-CH_2-O-C(O)-OCH(CH_3)_2$.

5 Compounds named in Table B and compounds named by compound
groups 1 and 2 where each purine base listed in Table A is the 8-aza analog,

40   e.g., 8-azaadenin-9-yl.

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6 Compounds named in Table B and compounds named by compound groups 1-5 where R moieties 1-25 listed in Table A are replaced with the following groups:

1 -cyclopropyl (cyclopropyl replaces -CH₃, which is R moiety 1 in Table A)

2 -CH_2-cyclopropyl

3 -$(CH_2)_2$-cyclopropyl

4 -$(CH_2)_3$-cyclopropyl

5 -$(CH_2)_4$-cyclopropyl

6 -cyclobutyl

7 -CH_2-cyclobutyl

8 -$(CH_2)_2$-cyclobutyl

9 -$(CH_2)_3$-cyclobutyl

10 -$(CH_2)_4$-cyclobutyl

11 -cyclopentyl

12 -CH_2-cyclopentyl

13 -$(CH_2)_2$-cyclopentyl

14 -$(CH_2)_3$-cyclopentyl

15 -$(CH_2)_4$-cyclopentyl

16 -cyclohexyl

17 -CH_2-cyclohexyl

18 -$(CH_2)_2$-cyclohexyl

19 -$(CH_2)_3$-cyclohexyl

20 -$(CH_2)_4$-cyclohexyl

21 -$CH(CH_3)CH_2$-cyclopropyl

22 -$CH(CH_3)CH_2$-cyclobutyl

23 -$CH(CH_3)CH_2$-cyclopentyl

24 -$CH(CH_3)CH_2$-cyclohexyl

25 -$(CH_2)_{0-4}$-cyclooctyl.

Thus, the group 6 compound defined in Table A and named 1.16.1.1 in Table B has the structure:

adenin-9-yl-CH_2-$CH(CH_3)$-O-CH_2-P(O)(-O-CH_2-O-C(O)-O-cyclohexyl)₂. The group 6 compound defined in Table A and named 1.16.1.1 in compound group 1 has the structure:

adenin-9-yl-CH_2-$CH(CH_3)$-O-CH_2-P(O)(OH)-O-CH_2-O-C(O)-O-cyclohexyl. The group 6 compound defined in Table A and named 1.16.1.1 in compound group 3 has the structure:

3-deazaadenin-9-yl-CH_2-$CH(CH_3)$-O-CH_2-P(O)(-O-CH_2-O-C(O)-O-cyclohexyl)₂.

7 Compounds named in Table B and compounds named by compound groups 1-5 where R moieties 1-25 listed in Table A are replaced with the following groups:

1 7 carbon alkyl*	4 10 carbon alkyl	7 -$(CH_2)_2C_6H_5$
2 8 carbon alkyl	5 11 carbon alkyl	8 -$(CH_2)_3C_6H_5$
3 9 carbon alkyl	6 12 carbon alkyl	9 -$(CH_2)_4C_6H_5$
10 -$C(CH_3)_2CH(CH_3)_2$		
11 -$CH(CH_3)C(CH_3)_3$		

23

$12 \ -(CH_2)_2CH(C_2H_5)CH_2CH_3$
$13 \ -(CH_2)_2CH(C_2H_5)(CH_2)_2CH_3$
$14 \ -(CH_2)_2CH(C_2H_5)(CH_2)_3CH_3$
$15 \ -(CH_2)_3CH(C_2H_5)CH_3$
$16 \ -(CH_2)_3CH(C_2H_5)CH_2CH_3$
$17 \ -(CH_2)_3CH(C_2H_5)(CH_2)_2CH_3$
$18 \ -CH_2CH(C_2H_5)CH_2CH_3$
$19 \ -CH_2CH(C_2H_5)(CH_2)_2CH_3$
$20 \ -CH_2CH(C_2H_5)(CH_2)_3CH_3$
$21 \ -(CH_2)_2CH(C_3H_7)CH_2CH_3$
$22 \ -(CH_2)_2CH(C_3H_7)(CH_2)_2CH_3$
$23 \ -(CH_2)_2CH(C_3H_7)(CH_2)_3CH_3$
$24 \ -CH_2CH=CH_2$
$25 \ -CH=CHCH_3.$

* Alkyl groups are linear, branched, cyclic or monounsaturated (-C=C-).

8   Compounds named in Table B and compounds named by compound groups 1-5 where R moieties 1-25 listed in Table A are replaced with the following groups:

$1 \ -(CH_2)_2OCH_3$
$2 \ -(CH_2)_3OCH_3$
$3 \ -(CH_2)_4OCH_3$
$4 \ -(CH_2)_5OCH_3$
$5 \ -(CH_2)_6OCH_3$
$6 \ -(CH_2)_2OCH_2CH_3$
$7 \ -(CH_2)_3OCH_2CH_3$
$8 \ -(CH_2)_4O(CH_2)_2CH_3$
$9 \ -(CH_2)_5O(CH_2)_2CH_3$
$10 \ -(CH_2)_6O(CH_2)_2CH_3$
$11 \ -(CH_2)_2O(CH_2)_2CH_3$
$12 \ -(CH_2)_3O(CH_2)_2CH_3$
$13 \ -(CH_2)_4O(CH_2)_2CH_3$

$14 \ -(CH_2)_5O(CH_2)_2CH_3$
$15 \ -(CH_2)_6O(CH_2)_2CH_3$
$16 \ -(CH_2)_2OCH(CH_3)_2$
$17 \ -(CH_2)_3OCH(CH_3)_2$
$18 \ -(CH_2)_4OCH(CH_3)_2$
$19 \ -(CH_2)_5OCH(CH_3)_2$
$20 \ -(CH_2)_6OCH(CH_3)_2$
$21 \ -(CH_2)_2O(CH_2)_3CH_3$
$22 \ -(CH_2)_2OCH_2CH(CH_3)_2$
$23 \ -(CH_2)_2OC(CH_3)_3$
$24 \ -(CH_2)_2OC_5H_{11}$
$25 \ -(CH_2)_2OC_6H_{13}.$

9   Compounds named in Table B and compounds named by compound groups 1-5 where R moieties 1-25 listed in Table A are replaced with the following groups:

$1 \ -CH(CH_3)CH_2OCH_3$
$2 \ -CH(CH_3)(CH_2)_2OCH_3$
$3 \ -CH(CH_3)(CH_2)_3OCH_3$
$4 \ -CH(CH_3)(CH_2)_4OCH_3$
$5 \ -CH(CH_3)CH_2OCH_2CH_3$
$6 \ -CH(CH_3)(CH_2)_2OCH_2CH_3$
$7 \ -CH(CH_3)(CH_2)_3OCH_2CH_3$
$8 \ -CH(CH_3)(CH_2)_4OCH_2CH_3$
$9 \ -CH(CH_3)CH_2O(CH_2)_2CH_3$
$10 \ -CH(CH_3)(CH_2)_2O(CH_2)_2CH_3$
$11 \ -CH(CH_3)(CH_2)_3O(CH_2)_2CH_3$
$12 \ -CH(CH_3)(CH_2)_4O(CH_2)_2CH_3$
$13 \ -CH(CH_3)CH_2OCH(CH_3)_2$

24

14 -CH(CH$_3$)(CH$_2$)$_2$OCH(CH$_3$)$_2$
15 -CH(CH$_3$)(CH$_2$)$_3$OCH(CH$_3$)$_2$
16 -CH(CH$_3$)(CH$_2$)$_4$OCH(CH$_3$)$_2$
17 -CH(CH$_3$)CH$_2$OC$_4$H$_9$
18 -CH(CH$_3$)(CH$_2$)$_2$OC$_4$H$_9$
19 -CH(CH$_3$)(CH$_2$)$_3$OC$_4$H$_9$
20 -CH(CH$_3$)(CH$_2$)$_4$OC$_4$H$_9$
21 -CH(CH$_3$)CH$_2$OC$_5$H$_{11}$
22 -CH(CH$_3$)(CH$_2$)$_2$OC$_5$H$_{11}$
23 -CH(CH$_3$)(CH$_2$)$_3$OC$_5$H$_{11}$
24 -CH(CH$_3$)(CH$_2$)$_4$OC$_5$H$_{11}$
25 -CH(CH$_3$)CH$_2$OC$_6$H$_{13}$.

10 Compounds named in Table B and compounds named by compound groups 1-5 where R moieties 1-25 listed in Table A are replaced with the following groups:

1 -CH(CH$_3$)(CH$_2$)$_2$OC$_6$H$_{13}$
2 -CH(CH$_3$)(CH$_2$)$_3$OC$_6$H$_{13}$
3 -CH(CH$_3$)(CH$_2$)$_4$OC$_6$H$_{13}$
4 -CH$_2$CH(CH$_3$)OCH$_3$
5 -(CH$_2$)$_2$CH(CH$_3$)OCH$_3$
6 -(CH$_2$)$_3$CH(CH$_3$)OCH$_3$
7 -(CH$_2$)$_4$CH(CH$_3$)OCH$_3$
8 -CH$_2$CH(CH$_3$)OCH$_2$CH$_3$
9 -(CH$_2$)$_2$CH(CH$_3$)OCH$_2$CH$_3$
10 -(CH$_2$)$_3$CH(CH$_3$)OCH$_2$CH$_3$
11 -(CH$_2$)$_4$CH(CH$_3$)OCH$_2$CH$_3$
12 -CH$_2$CH(CH$_3$)OCH$_2$CH$_3$
13 -(CH$_2$)$_2$CH(CH$_3$)O(CH$_2$)$_2$CH$_3$
14 -(CH$_2$)$_3$CH(CH$_3$)O(CH$_2$)$_3$CH$_3$
15 -(CH$_2$)$_4$CH(CH$_3$)O(CH$_2$)$_4$CH$_3$
16 -CH$_2$CH(CH$_3$)OCH(CH$_3$)$_2$
17 -(CH$_2$)$_2$CH(CH$_3$)OCH(CH$_3$)$_2$
18 -(CH$_2$)$_3$CH(CH$_3$)OCH(CH$_3$)$_2$
19 -(CH$_2$)$_4$CH(CH$_3$)OCH(CH$_3$)$_2$
20 -CH$_2$CH(CH$_3$)OC$_4$H$_9$
21 -(CH$_2$)$_2$CH(CH$_3$)OC$_4$H$_9$
22 -(CH$_2$)$_3$CH(CH$_3$)OC$_4$H$_9$
23 -(CH$_2$)$_4$CH(CH$_3$)OC$_4$H$_9$
24 -CH$_2$CH(CH$_3$)OC$_5$H$_{11}$
25 -(CH$_2$)$_2$CH(CH$_3$)OC$_5$H$_{11}$

11 Compounds named in Table B and compounds named by compound groups 1-5 where R moieties 1-25 listed in Table A are replaced with the following groups:

1 -(CH$_2$)$_3$CH(CH$_3$)OC$_5$H$_{11}$
2 -(CH$_2$)$_4$CH(CH$_3$)OC$_5$H$_{11}$
3 -CH$_2$CH(CH$_3$)OC$_6$H$_{13}$
4 -(CH$_2$)$_2$CH(CH$_3$)OC$_6$H$_{13}$

5   5 -(CH$_2$)$_3$CH(CH$_3$)OC$_6$H$_{13}$
       6 -(CH$_2$)$_4$CH(CH$_3$)OC$_6$H$_{13}$
       7 -(CH$_2$)$_2$OCH(CH$_3$)C$_2$H$_5$
       8 -(CH$_2$)$_2$OCH(CH$_3$)(CH$_2$)$_2$CH$_3$
       9 -(CH$_2$)$_2$OCH(CH$_3$)CH(CH$_3$)$_2$
      10 -(CH$_2$)$_2$OCH(CH$_3$)(CH$_2$)$_3$CH$_3$
      11 -(CH$_2$)$_2$OCH(CH$_3$)C(CH$_3$)$_3$
      12 -(CH$_2$)$_2$OCH(CH$_3$)CH(CH$_3$)CH$_2$CH$_3$
      13 -(CH$_2$)$_2$OCH(CH$_3$)CH$_2$CH(CH$_3$)$_2$
10   14 -(CH$_2$)$_3$OCH(CH$_3$)C$_2$H$_5$
      15 -(CH$_2$)$_3$OCH(CH$_3$)(CH$_2$)$_2$CH$_3$
      16 -(CH$_2$)$_3$OCH(CH$_3$)CH(CH$_3$)$_2$
      17 -(CH$_2$)$_3$OCH(CH$_3$)(CH$_2$)$_3$CH$_3$
      18 -(CH$_2$)$_3$OCH(CH$_3$)C(CH$_3$)$_3$
15   19 -(CH$_2$)$_3$OCH(CH$_3$)CH(CH$_3$)CH$_2$CH$_3$
      20 -(CH$_2$)$_3$OCH(CH$_3$)CH$_2$CH(CH$_3$)$_2$
      21 -(CH$_2$)$_4$OCH(CH$_3$)C$_2$H$_5$
      22 -(CH$_2$)$_4$OCH(CH$_3$)(CH$_2$)$_2$CH$_3$
      23 -(CH$_2$)$_4$OCH(CH$_3$)CH(CH$_3$)$_2$
20   24 -(CH$_2$)$_4$OCH(CH$_3$)(CH$_2$)$_3$CH$_3$
      25 -(CH$_2$)$_4$OCH(CH$_3$)C(CH$_3$)$_3$

12 Compounds named in Table B and compounds named by
compound groups **1-5** where R moieties 1-25 listed in Table A are replaced
with the following groups:
25   1 -(CH$_2$)$_2$O(CH$_2$)$_3$CH$_3$
       2 -(CH$_2$)$_2$O(CH$_2$)$_4$CH$_3$
       3 -(CH$_2$)$_2$O(CH$_2$)$_5$CH$_3$
       4 -(CH$_2$)$_3$O(CH$_2$)$_3$CH$_3$
       5 -(CH$_2$)$_3$O(CH$_2$)$_4$CH$_3$
30   6 -(CH$_2$)$_3$O(CH$_2$)$_5$CH$_3$
       7 -(CH$_2$)$_2$OC$_6$H$_5$
       8 -(CH$_2$)$_2$OC$_6$H$_5$
       9 -(CH$_2$)$_2$OC$_6$H$_5$
      10 -CH(C$_2$H$_5$)CH$_2$OCH$_3$
35   11 -CH(C$_2$H$_5$)CH$_2$OC$_2$H$_5$
      12 -CH(C$_2$H$_5$)CH$_2$O(CH$_2$)$_2$CH$_3$
      13 -CH(C$_2$H$_5$)CH$_2$OCH$_2$(CH$_3$)$_2$
      14 -CH(C$_2$H$_5$)CH$_2$O(CH$_2$)$_3$CH$_3$
      15 -CH(C$_2$H$_5$)CH$_2$OCH(CH$_3$)C$_2$H$_5$
40   16 -CH(C$_2$H$_5$)CH$_2$OCH$_2$CH(CH$_3$)$_2$
      17 -CH(C$_2$H$_5$)CH$_2$OC(CH$_3$)$_3$
      18 -CH(C$_2$H$_5$)CH$_2$O(CH$_2$)$_4$CH$_3$
      19 -CH(C$_2$H$_5$)CH$_2$O(CH$_2$)$_2$CH(CH$_3$)$_2$
      20 -CH(C$_2$H$_5$)CH$_2$O(CH$_2$)$_5$CH$_3$
45   21 -CH(C$_2$H$_5$)CH$_2$O(CH$_2$)$_3$CH(CH$_3$)$_2$
      22 -CH$_2$CH(C$_2$H$_5$)OCH$_3$
      23 -CH$_2$CH(C$_2$H$_5$)OC$_2$H$_5$
      24 -CH$_2$CH(C$_2$H$_5$)OC$_3$H$_7$

26

25 -CH₂CH(C₂H₅)OC₄H₉.

    13 Compounds named in Table B and compounds named by compound groups **1-5** where R moieties 1-25 listed in Table A are replaced with the following groups:

5   1 -(CH₂)₂O-cyclopropyl
        2 -(CH₂)₂O-cyclobutyl
        3 -(CH₂)₂O-cyclopentyl
        4 -(CH₂)₂O-cyclohexyl
        5 -(CH₂)₂OCH₂-cyclopropyl

10   6 -(CH₂)₂OCH₂-cyclobutyl
        7 -(CH₂)₂OCH₂-cyclopentyl
        8 -(CH₂)₂OCH₂-cyclohexyl
        9 -(CH₂)₂O-(CH₂)₂cyclopropyl
       10 -(CH₂)₂O-(CH₂)₂cyclobutyl

15   11 -(CH₂)₂O-(CH₂)₂cyclopentyl
       12 -(CH₂)₂O-(CH₂)₂cyclohexyl
       13 -(CH₂)₃O-cyclopropyl
       14 -(CH₂)₃O-cyclobutyl
       15 -(CH₂)₃O-cyclopentyl

20   16 -(CH₂)₃O-cyclohexyl
       17 -(CH₂)₃OCH₂-cyclopropyl
       18 -(CH₂)₃OCH₂-cyclobutyl
       19 -(CH₂)₃OCH₂-cyclopentyl
       20 -(CH₂)₃OCH₂-cyclohexyl

25   21 -CH(CH₃)CH₂O-cyclopropyl
       22 -CH(CH₃)CH₂O-cyclobutyl
       23 -CH(CH₃)CH₂O-cyclopentyl
       24 -CH(CH₃)CH₂O-cyclohexyl
       25 -CH(CH₃)CH₂OCH₂-cyclohexyl.

30   **14** Compounds named in Table B and compounds named by compound groups **1-5** where R moieties 1-25 listed in Table A are replaced with the following groups:
       1 -C(CH₂OCH₃)₃
       2 -C(C₂H₅)₂(CH₂OCH₃)

35   3 -CH(C₂H₅)(CH₂OCH₃)
       4 -CH₂(CH₂OCH₃)
       5 -C(CH₃)₂(CH₂OCH₃)
       6 -CH(CH₃)(CH₂OCH₃)
       7 -C(CH₂OC₂H₅)₃

40   8 -C(C₂H₅)₂(CH₂OC₂H₅)
       9 -CH(C₂H₅)(CH₂OC₂H₅)
       10 -CH(C₄H₉)(CH₂OCH₃)
       11 -CH₂C(CH₂OCH₃)₃
       12 -CH₂C(C₂H₅)₂(CH₂OCH₃)

45   13 -CH₂CH(C₂H₅)(CH₂OCH₃)
       14 -CH(CH₂OCH₃)₂
       15 -CH₂C(CH₂OCH₃)₃

16 -CH$_2$CH(CH$_2$OCH$_3$)$_2$
17 -C(CH$_2$OC$_2$H$_5$)$_3$
18 -CH(CH$_2$OC$_2$H$_5$)$_2$
19 -CH$_2$C(CH$_2$OC$_2$H$_5$)$_3$
5   20 -CH$_2$CH(CH$_2$OC$_2$H$_5$)$_2$
21 -C(C$_2$H$_5$)$_2$(CH$_2$OC$_3$H$_7$)
22 -CH(C$_3$H$_7$)(CH$_2$OCH$_3$)
23 -C(C$_3$H$_7$)$_2$(CH$_2$OCH$_3$)
24 -CH(C$_3$H$_7$)(CH$_2$OC$_2$H$_5$)
10 25 -C(C$_3$H$_7$)$_2$(CH$_2$OC$_2$H$_5$)

15   The following groups of compounds **A-J**.

A   Compounds named in groups **8-14** where the oxygen atom (-O-) in the R moiety is replaced with -NH-.

15   B   Compounds named in groups **8-14** where the oxygen atom in the R moiety is replaced with -N(CH$_3$)-.

C   Compounds named in groups **8-14** where the oxygen atom in the R moiety is replaced with -N(C$_2$H$_5$)-.

D   Compounds named in groups **8-14** where the oxygen atom in the R
20 moiety is replaced with -N(CH$_2$CH$_2$CH$_3$)-.

E   Compounds named in groups **8-14** where the oxygen atom in the R moiety is replaced with -N(CH(CH$_3$)$_2$-.

F   Compounds named in groups **8-14** where the oxygen atom in the R moiety is replaced with *n*-butyl substituted nitrogen (-N(CH$_2$)$_3$CH$_3$)-).

25   G   Compounds named in groups **8-14** where the oxygen atom in the R moiety is replaced with *i*-butyl substituted nitrogen.

H   Compounds named in groups **8-14** where the oxygen atom in the R moiety is replaced with *t*-butyl substituted nitrogen.

I   Compounds named in groups **8-14** where the oxygen atom in the R
30 moiety is replaced with linear, branched or cyclic 5 carbon alkyl substituted nitrogen.

J   Compounds named in groups **8-14** where the oxygen atom in the R moiety is replaced with linear, branched or cyclic 6 carbon alkyl substituted nitrogen.

35 Thus, the group **15B** compound defined in Table A and named 1.1.1.1 in compound group **8** has the structure:
adenin-9-yl-CH$_2$-CH(CH$_3$)-O-CH$_2$-P(O)(-O-CH$_2$-O-C(O)-O-(CH$_2$)$_2$N(CH$_3$)$_2$)$_2$.
The group **15B** compound defined in Table A and named 1.1.1.1 in compound group **1**, as named under group **8**, has the structure:
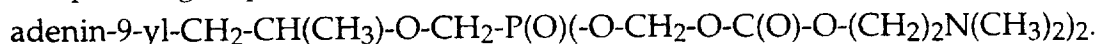
adenin-9-yl-CH$_2$-CH(CH$_3$)-O-CH$_2$-P(O)(OH)-O-CH$_2$-O-C(O)-O-(CH$_2$)$_2$N(CH$_3$)$_2$.
The group **15B** compound defined in Table A and named 1.16.1.1 in
compound group 3, as named under group 8, has the structure:
3-deazaadenin-9-yl-CH$_2$-CH(CH$_3$)-O-CH$_2$-P(O)(-O-CH$_2$-O-C(O)-O-

5   (CH$_2$)$_2$N(CH$_3$)$_2$)$_2$.

16 Compounds named in Table B and compounds named by
compound groups **1-5** where R moieties 1-25 listed in Table A are replaced
with the following groups:

    1 -(CH$_2$)$_2$R^9
10 2 -(CH$_2$)$_3$R^9
    3 -(CH$_2$)$_4$R^9
    4 -(CH$_2$)$_5$R^9
    5 -(CH$_2$)$_6$R^9
    6 -(CH$_2$)$_7$R^9
15 7 -(CH$_2$)$_8$R^9
    8 -CH(CH$_3$)CH$_2$R^9
    9 -CH(CH$_3$)(CH$_2$)$_2$R^9
    10 -CH(CH$_3$)(CH$_2$)$_3$R^9
    11 -(CH$_2$)$_2$R^9
20 12 -(CH$_2$)$_3$R^9
    13 -(CH$_2$)$_4$R^9
    14 -(CH$_2$)$_5$R^9
    15 -(CH$_2$)$_6$R^9
    16 -(CH$_2$)$_7$R^9
25 17 -(CH$_2$)$_8$R^9
    18 -CH(CH$_3$)CH$_2$R^9
    19 -CH(CH$_3$)(CH$_2$)$_2$R^9
    20 -CH(CH$_3$)(CH$_2$)$_3$R^9
    21 -(CH$_2$)$_2$R^9
30 22 -(CH$_2$)$_3$R^9
    23 -(CH$_2$)$_4$R^9
    24 -(CH$_2$)$_5$R^9
    25 -(CH$_2$)$_6$R^9

In moieties 1-10, R^9 is N-morpholino, in moieties 11-20, R^9 is 2-pyridyl and in
35 moieties 21-25, R^9 is 3-pyridyl.

17 Compounds named in Table B and compounds named by
compound groups **1-5** where R moieties 1-25 listed in Table A are replaced
with the following groups:

    1 -(CH$_2$)$_2$R^9
40 2 -(CH$_2$)$_3$R^9
    3 -(CH$_2$)$_4$R^9
    4 -(CH$_2$)$_5$R^9
    5 -(CH$_2$)$_6$R^9

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6 -$(CH_2)_2CH(CH_3)R^9$
7 -$(CH_2)_3CH(CH_3)R^9$
8 -$(CH_2)_4CH(CH_3)R^9$
9 -$(CH_2)_2R^9$
5   9 -$(CH_2)_3R^9$
11 -$(CH_2)_4R^9$
12 -$(CH_2)_5R^9$
13 -$(CH_2)_6R^9$
14 -$(CH_2)_6CH_3$
10   15 -$(CH_2)_7CH_3$
16 -$(CH_2)_8CH_3$
17 -$(CH_2)_9CH_3$
18 -$(CH_2)_{10}CH_3$
19 -$(CH_2)_{11}CH_3$
15   20 -$(CH_2)_4CH(CH_3)_2$
21 -$(CH_2)_5CH(CH_3)_2$
22 -$(CH_2)_6CH(CH_3)_2$
23 -$(CH_2)_7CH(CH_3)_2$
24 -$(CH_2)_8CH(CH_3)_2$
20   25 -$(CH_2)_9CH(CH_3)_2$.

In moieties 1-5, R^9 is 4-pyridyl, in moieties 6-9 R^9 is N-morpholino and in moieties 9-13, R^9 is N-piperidyl.

18 The following groups of compounds A-J.

A Compounds named in Table B and compounds named by groups 1-
25   17 where compound (8) is replaced with compound (9)

(9)
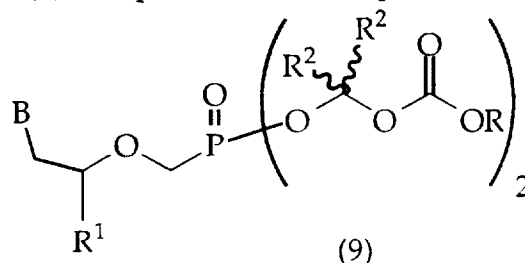
where one R^2 is as specified in Table A and the other R^2 is -CH_3.

B Compounds named in Table B and compounds named by compound groups 1-17 where compound (8) is replaced with compound (9)
30   where one R^2 is as specified in Table A and the other R^2 is -CH_2CH_3.

C Compounds named in Table B and compounds named by compound groups 1-17 where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -$(CH_2)_2CH_3$.

D Compounds named in Table B and compounds named by
35   compound groups 1-17 where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -$CH(CH_3)_2$.

E Compounds named in Table B and compounds named by compound groups **1-17** where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -$(CH_2)_3CH_3$.

F Compounds named in Table B and compounds named by compound groups **1-17** where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -$(CH_2)_4CH_3$.

G Compounds named in Table B and compounds named by compound groups **1-17** where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -$CH_2CH(CH_3)_2$.

H Compounds named in Table B and compounds named by compound groups **1-17** where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -$C(CH_3)_3$.

I Compounds named in Table B and compounds named by compound groups **1-17** where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -C_5H_{11}.

J Compounds named in Table B and compounds named by compound groups **1-17** where compound (8) is replaced with compound (9) where one R^2 is as specified in Table A and the other R^2 is -C_6H_{13}.

Thus, the group **18A** compound defined in Table A and named 1.4.2.3 in Table B has the structure:
adenin-9-yl-CH_2-CH_2-O-$CH(CH_3)$-P(O)(-O-C(C_2H_5)(CH_3)-O-C(O)-O-$CH(CH_3)_2$)$_2$.
The group **18A** compound defined in Table A and named 1.4.1.1 in compound group 1 has the structure:
adenin-9-yl-CH_2-$CH(CH_3)$-O-CH_2-P(O)(OH)-O-$CH(CH_3)$-O-C(O)-O-$CH(CH_3)_2$.
The group **18A** compound defined in Table A and named 1.1.1.1 in compound group 3, as named under compound group 8, has the structure:
3-deazaadenin-9-yl-CH_2-$CH(CH_3)$-O-CH_2-P(O)(-O-$CH(CH_3)$-O-C(O)-O-($CH_2)_2OCH_3$)$_2$.

19 Compounds named in Table B and compounds named by compound groups **1-18** where compound (8) and compound (9) are replaced with compound (10) and (11) respectively

(10)   (11)

where both R moieties are the same. Thus, the group **19** compound defined in Table A and named 1.4.1.1 in Table B has the structure:

31

adenin-9-yl-CH$_2$-CH(CH$_3$)-O-CH(CH$_3$)-P(O)(-O-CH$_2$-O-C(O)-N-CH(CH$_3$)$_2$)$_2$.
The group **19** compound defined in Table A and named 1.4.1.1 in compound
group **1** has the structure:
adenin-9-yl-CH$_2$-CH(CH$_3$)-O-CH$_2$-P(O)(OH)-O-CH$_2$-O-C(O)-N-CH(CH$_3$)$_2$. The

5   group **19** compound defined in Table A and named 1.1.1.1 in compound
group **3**, as named under compound group **8**, has the structure:
3-deazaadenin-9-yl-CH$_2$-CH(CH$_3$)-O-CH$_2$-P(O)(-O-CH$_2$-O-C(O)-N-
(CH$_2$)$_2$OCH$_3$)$_2$.

The compounds of this invention are, to varying degrees, chemically

10   stable. It is preferable that the compounds be chemically stable in order to
ensure an adequate shelf-life and proper biodistribution upon oral
administration. In general, embodiments are selected that have a t 1/2 at pH
7.4 of greater than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 hours and preferably in
addition possess a t 1/2 at pH 2.0 of greater than 1, 10 or 100 hours. For

15   example, the t-butyl carbonate found in Table 1 has a t 1/2 that is less stable
than these parameters and therefor is not preferred. In addition, the optimal
compounds of this invention should have bioavailability in beagle dogs (as
set forth in more detail below) that exceeds about 20%, preferably, about 30%.

20   Synthetic Methods
The carbamates and carbonates of this invention are prepared from the
diacids of the phosphonomethoxy nucleotide analogs and the synthon
LCH(R^2)OC(O)X(R)$_a$. L is a leaving group such as Cl, although it will be
appreciated that any of the conventional leaving groups used in organic

25   chemistry in nucleophilic substitution reactions can be successfully employed
in place of chloro. In particular, leaving groups include halides, such as Cl, Br
and I, and sulfonic acid esters such as methane, benzene or toluene sulfonic
acid esters. The synthon is prepared by reacting LCH(R^2)OC(O)L with HOR for
preparation of the carbonate synthon or HNR$_2$ for the preparation of the

30   carbamate synthon. The synthon is then reacted with the nucleotide analog
of choice, typically PMPA, to form the desired carbamate or carbonate adducts.
The carbamates are prepared by reacting the synthon with the nucleotide
analog under typical conditions of nucleophilic attack, for example in
Et$_3$N/DMF at room temperature. The carbonates are formed by reacting the

35   appropriate synthon with the nucleotide analog in the presence of an organic
base, typically an amine base. In addition, masked leaving groups such as
thioethers, which may be activated by, for example, oxidation, and coupled
directly to the phosphonic acid moiety may be used. Intermediates may be

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made with other leaving groups in this way, for example diphenylphosphinic
acids, and others known in the chemistry of formacetals and glycosylation.
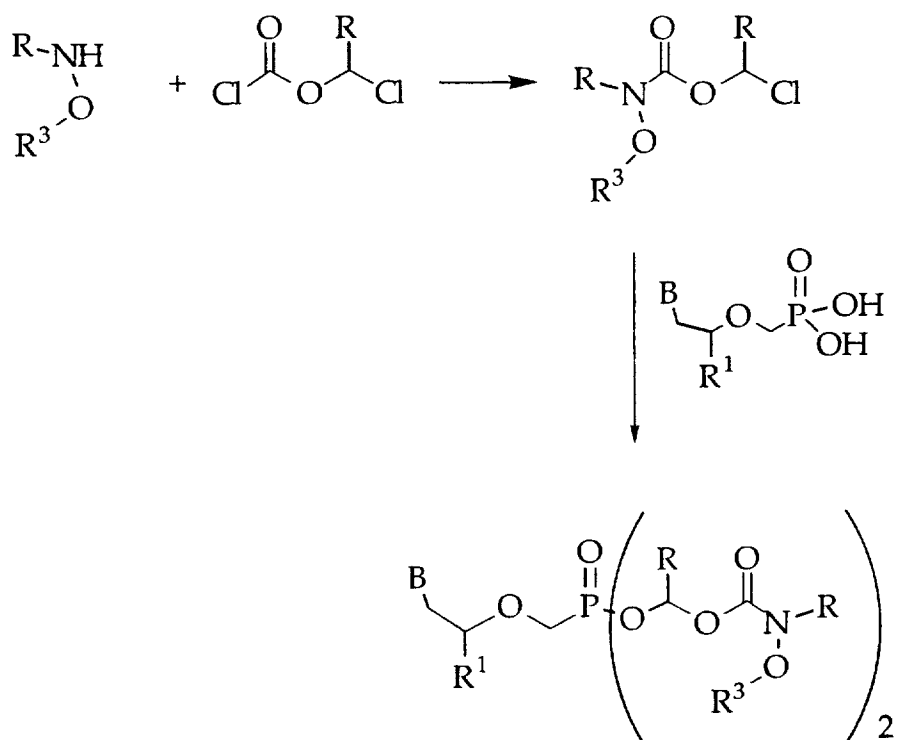
5

Compounds where X=N and R=OR³ may be prepared by alkylation
with the appropriate haloalkyl, O-alkyl carbamate. N, O-
dialkylhydroxylamines are known in the literature, and may be prepared by
alkylation of hydroxylamine, or by reductive amination of aldehydes or

10   ketones with alkyl hydroxylamines. The dialkylhydroxylamines may be
acylated with the appropriately substituted haloalkyl chloroformate under
conditions analagous to those used to prepare the unsubstituted chloromethyl
carbamates. Phosphonates may then be alkylated with the haloalkyl, O-alkyl
carbamates to give the prodrugs under conditions used for the carbonates and

15   carbamates. Leaving groups other than chloride may of course be used
throughout.

In a typical method, the carbonate compounds of this invention are
prepared by reacting L-CHR²-O-C(O)-OR with (4) to yield a compound of
formula (1).

20

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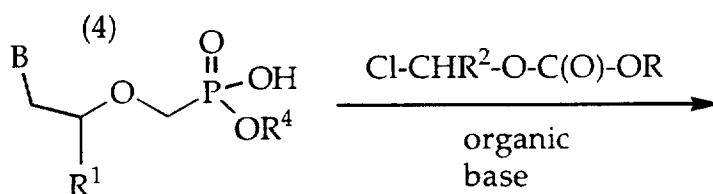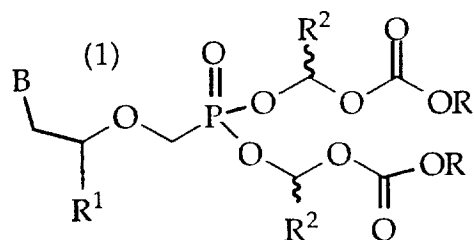
The reaction typically proceeds in two concurrent steps in which the monoester forms first, and then the diester as the reaction proceeds longer. In this situation monoester is not typically isolated as an intermediate.

5   In order to make a diester that contains different carbonate or carbamate functionalities the monoester intermediate is recovered from the early reaction and the reaction is then completed with for example a second L-CHR^2-O-C(O)-OR reagent, thereby resulting in substitution with a second ester different from the first.

10   One optionally conducts the carbonate synthesis reactions using at least about 1.0 and typically 2 equivalents of L-CHR^2-O-C(O)-OR. The reaction is conducted in the presence of an organic base in an organic solvent at a reaction temperature of about 4-100° for about 4-72 hours. Exemplary suitable organic bases include triethylamine or Hunig's base. Exemplary suitable

15   organic solvents include DMF, DMPU, or NMP.

The monoester or diester products are purified by standard methods including flash column chromatography or salting out. Suitable salts for purification and/or formulation will final product include the sulfuric acid, phosphoric acid, lactic acid, fumaric or citric acid salts or complexes of the

20   diester or monoester compounds of structures (1) or (1a).

Utilities

The compounds of this invention are useful in the treatment or prophylaxis of one or more viral infections in man or animals, including infections caused by DNA viruses, RNA viruses, herpesviruses (CMV, HSV 1,
5   HSV 2, VZV, and the like), retroviruses, hepadnaviruses, (e.g. HBV), papillomavirus, hantavirus, adenoviruses and HIV. Other infections to be treated with the compounds herein include MSV, RSV, SIV, FIV, MuLV, and other retroviral infections of rodents and other animals. The prior art describes the antiviral specificity of the nucleotide analogs, and the parental
10   drug specificity is shared by the compounds of this invention. Dosages, viral targets, and suitable administration routes to best attack the site of infection are well known in the art for the parental drugs. Determination of proper doses is a straightforward matter for the clinician, taking into account the molecular weight of the compounds of this invention and, when
15   adminstering them orally, their bioavailability in animals or as deduced in clinical trials with humans. Oral dosages of the compounds of this invention in humans for antiviral therapy will range about from 0.5 to 60 mg/Kg/day, usually about from 1 to 30 mg/Kg/day and typically about from 1.5 to 10 mg/Kg/day.
20   The compounds of this invention also are useful as intermediates in the preparation of detectable labels for oligonucleotide probes. The compounds are hydrolyzed to yield the diacid, diphosphorylated and incorporated into an oligonucleotide by conventional enzymatic or chemical means. The incorporated base from the compound of the invention will be
25   capable of participating in base pairing and thus will not interfere substantially with the binding of the oligonucleotide to its complementary sequence (E. De Clercq *Rev. Med. Virol.* 3:85-96 1993). However, if it does interfere with binding of the oligonucleotide containing the analog to the complementary sequence, the compound of the invention optionally is
30   incorporated into the oligonucleotide as the 3' terminal base, an innocuous position and a conventional site for oligonucleotide labeling. The aglycon donated by the nucleotide analog that is incorporated into the oligonucleotide is detected by any means, such as NMR or by binding to antibodies specific for the nucleotide analog.
35

Pharmaceutical Formulations

Compounds of the invention and their pharmaceutically, i.e. physiologically, acceptable salts (hereafter collectively referred to as the active

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ingredients), are administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural).

5   Generally, the compounds of this invention are administered orally, but if an embodiment is not sufficiently orally bioavailable it can be administered by any of the other routes noted above.

        While it is possible for the active ingredients to be administered as pure compounds it is preferable to present them as pharmaceutical formulations.

10   The formulations of the present invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient.

15   The formulations include those suitable for topical or systemic administration, including oral, rectal, nasal, buccal, sublingual, vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations are in unit dosage form and are prepared by any of the methods well known in

20   the art of pharmacy. 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 liquid carriers or finely divided solid carriers or both, and then, if necessary,

25   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 granules; as solution or a suspension in an aqueous liquid or a non-aqueous

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

        A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing

35   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 moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may

optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

For infections of the eye or other external tissues, e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream

5   containing the active ingredient(s) in an amount of, for example, 0.01 to 10% w/w (including active ingredient(s) in a range between 0.1% and 5% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 3% w/w and most preferably 0.5 to 2% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a

10 water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

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,

15 sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which 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.

20   The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise 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

25 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 emulsifying wax, and the wax together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

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

The choice of suitable oils or fats for the formulation is based on

35 achieving the desired cosmetic properties. Thus 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 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

5   properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The

10   active ingredient is suitably present in such formulations in a concentration of 0.01 to 20%, in some embodiments 0.1 to 10%, and in others about 1.0% 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

20   salicylate.

Formulations suitable for nasal or inhalational administration wherein the carrier is a solid include a powder having a particle size for example in the range 1 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35

25   microns, etc). Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents. Inhalational therapy is readily

30   administered by metered dose inhalers.

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.

35   Formulations suitable for parenteral administration are sterile and include aqueous and non-aqueous 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 may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring

5   only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as recited above, or an

10   appropriate fraction thereof, of an active ingredient.

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.

15   The present 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 to cats, dogs, horses, rabbits and other animals

20   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 be used to provide controlled release

25   pharmaceutical formulations containing a matrix or absorbent material and as active ingredient one or more compounds of the invention in which the release of the active ingredient can be controlled and regulated to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the compound. Controlled release formulations adapted for oral administration

30   in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

All citations found herein are incorporated by reference.

The following examples further illustrate the invention but are not to be construed as limiting the invention.

35

EXAMPLES

<u>Example 1</u>
PMPA Synthesis

PMPA • H$_2$O
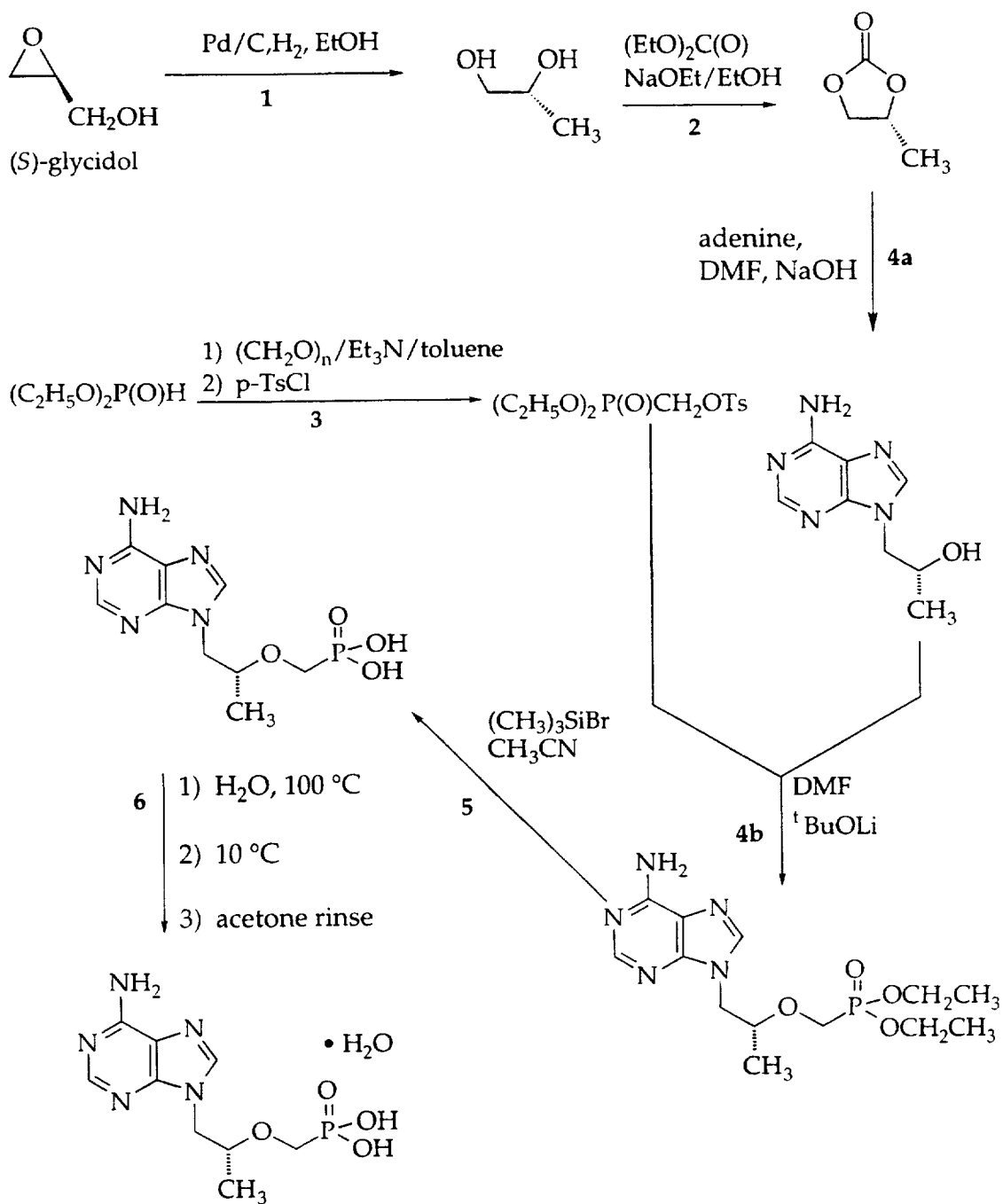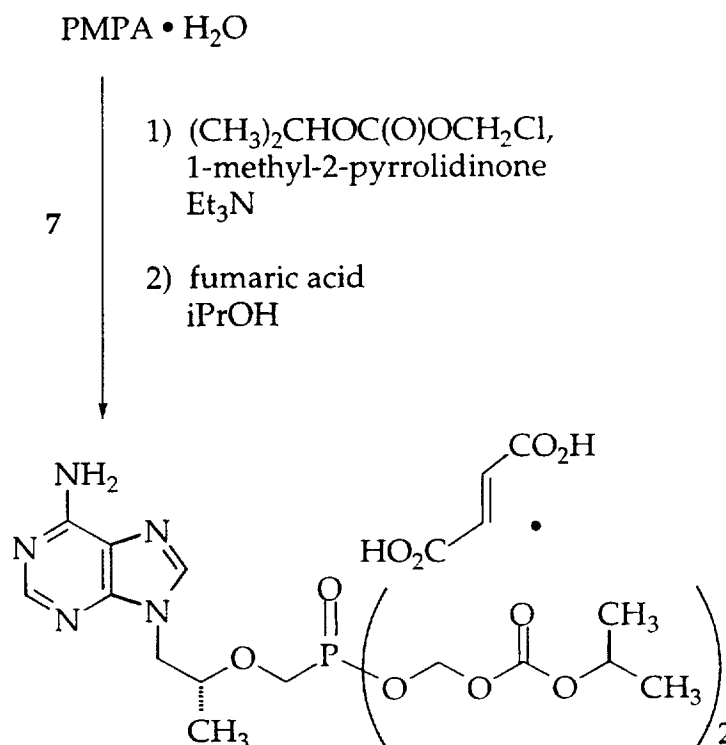
Process Summary

PMPA is prepared as follows: (S)-Glycidol is reduced to (R)-1,2-
5   propanediol by catalytic hydrogenation, which is then reacted with diethyl
carbonate to afford (R)-1,2-propylene carbonate. The carbonate is reacted with
adenine and catalytic amounts of a base such as sodium hydroxide to give (R)-
9-[2-(diethylphosphonomethoxy)propyl]adenine which, without isolation, is
reacted with lithium alkoxide (alkyl containing 1, 2, 3, 4, 5 or 6 carbon atoms,
10   e.g., n-hexoxide, n-pentoxide, n-butoxide, i-butoxide, t-butoxide, n-propoxide,
i-propoxide, ethoxide, methoxide) and diethyl p-toluenesulfonyl-
oxymethylphosphonate (prepared by reacting diethyl phosphite and
paraformaldehyde, and tosylating the product in situ). The resulting (R)-9-[2-
diethylphosphonomethoxypropyl]adenine is deesterified with
15   bromotrimethylsilane to give crude PMPA, which is then purified by
precipitation from water with pH adjustment. The product is further purified
by recrystallization with water to afford PMPA monohydrate.

The process uses a small amount of a base such as NaOH at step 1,
which increases the reaction rate about 10-fold compared to the same reaction
20   lacking the base. Step 1 also uses hydrogen gas instead of using a reagent such
as HCO$_2$NH$_4$ to generate hydrogen in situ. The process uses lithium alkoxide
at step 4b, which is mildly exothermic on addition to the reaction mixture.
The use of a highly reactive base such as NaH, results in an exothermic

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reaction that generates hydrogen gas in a reaction is difficult to control. The use of NaH thus requires more labor and care to use than lithium alkoxide. Lithium alkoxide bases also give a product that has an improved by-product profile compared to that obtained using NaH, e.g., lower amounts of starting
5   material or overalkylated products usually result from the use of lithium alkoxide.

The scale of the following method is proportionately reduced or increased if desired. The scheme and process steps depict synthesis of (R)-PMPA. One can practice the method using chirally impure starting materials
10   such as (R,S)-glycidol to obtain a chiral mixture of intermediates or of the final product.

One can increase or decrease the scale of the process steps described below if desired. The scheme and process steps depict synthesis of (R)-PMPA and (R)-bis(POC)PMPA. One can practice the method using chirally impure
15   starting materials such as (R,S)-glycidol to obtain a chiral mixture of intermediates, e.g., a chiral mixture of 1,2-propylene carbonate, PMPA or bis(POC)PMPA.

Step 1. (R)-1,2-Propanediol: (S)-Glycidol (1.0 kg, 13.5 moles) is added to
20   a reactor containing (i) an inert, e.g., nitrogen, atmosphere and (ii) a stirred suspension of 5% palladium on activated carbon (50% wet) catalyst (100 g) in denatured ethyl alcohol containing 2 mole% sodium hydroxide (7.85 kg EtOH and 54 g of 16.7% NaOH solution). The contents of the inerted reactor containing catalyst and the ethanol solution is usually cooled to about 0°C
25   (usually about -5 to 5°C) before the (S)-glycidol is added. Hydrogen gas at no more than 20 psi is then introduced to the inerted reaction vessel containing reactants at a temperature of no more than 25°C. The mixture is agitated for approximately 4–5 hours, until hydrogen consumption stops. Reaction completion is monitored by TLC (trace or no (S)-glycidol remaining). The
30   mixture is then filtered e.g., diatomaceous earth (about 150 g), to remove solids and the filtrate is concentrated *in vacuo* at no more than 50°C, until volatile collection stops or is very slow, to obtain an oil containing the crude product. The crude product is used directly in the next step. Title compound yield is about 100%.
35

Step 2. (R)-1,2-Propylene carbonate: Diethyl carbonate (1.78 kg, 15.1 moles) and sodium ethoxide in denatured ethyl alcohol (210 g of 21% w/w sodium ethoxide in ethanol) are added to (R)-1,2-propanediol (1.0 kg

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theoretical based on the quantity of (S)-glycidol used in step 1 above), and the solution is heated to 80 to 150°C to distill off the ethanol. If necessary to achieve reaction completion, additional diethyl carbonate (0.16 kg) is added to the reaction mixture, followed by distillation to remove ethanol. Reaction

5   completion is monitored by TLC showing a trace or no detectable (R)-1,2-propanediol. The residue is fractionally distilled at 120°C and 10–17 mm Hg, to yield the title compound as a colorless liquid. The product purity is typically 96% or greater purity by GC analysis.

10   **Step 3. Diethyl p-toluenesulfonyloxymethylphosphonate:** In a reactor containing an inert atmosphere, e.g., nitrogen, a mixture of diethyl phosphite (0.80 kg), paraformaldehyde (0.22 kg), and triethylamine (0.06 kg) in toluene (0.11 kg) is heated at 87°C for about 2 hours, then refluxed for about 1 hour, until the reaction is complete as monitored by TLC showing a trace or no

15   detectable diethyl phosphite. During the reaction, the inert atmosphere is maintained. Toluene is necessary to moderate the reaction, which may otherwise explode. Reaction completion is optionally confirmed by ^{1}H NMR (diethyl phosphite peak at δ 8.4–8.6 ppm no longer detected). The solution is cooled to about 1°C (typically about -2 to 4°C) and p-toluenesulfonyl chloride

20   (1.0 kg) is added and then triethylamine (0.82 kg) at about 5°C is slowly added (exothermic addition) while maintaining the temperature at no more than about 10°C (typically 0 to 10°C). The resulting mixture is warmed to 22°C and stirred for at least about 5 hours (typically about 4.5 to 6.0 hours), until the reaction is complete as shown by TLC (trace or no p-toluenesulfonyl chloride

25   detectable) and optionally confirmed by ^{1}H NMR (p-toluenesulfonyl chloride doublet at δ 7.9 ppm no longer detected). The solids are removed by filtration and washed with toluene (0.34 kg). The combined washings and filtrate are washed either twice with water (1.15 kg per wash), or optionally with a sequence of water (1.15 kg), 5% aqueous sodium carbonate (3.38 kg), and then

30   twice with water (1.15 kg). After each wash, the reactor contents are briefly agitated, allowed to settle and the lower aqueous layer is then discarded. If the reaction results in an emulsion, brine (0.23 kg of water containing 0.08 kg NaCl) may be added to the first organic/water mixture, followed by agitating the reactor contents, allowing the solids to settle, discarding the lower

35   aqueous layer, adding 1.15 kg water, agitating, allowing solids to settle and again discarding the lower aqueous layer. The organic phase is distilled *in vacuo* at no more than 50°C (to LOD at 110°C of no more than 10% and water

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content, by KF titration, no more than 0.3%), affording a yield of about 60-70% of the title compound as an oil of about 85–95% purity, exclusive of toluene.

Step 4. (R)-9-[2-(Diethylphosphonomethoxy)propyl]adenine: In a reactor
5   containing an inert atmosphere, e.g., nitrogen, a mixture of adenine (1.0 kg), sodium hydroxide (11.8 g), (R)-1,2-propylene carbonate (0.83 kg), and N,N-dimethylformamide (6.5 kg) is heated to about 130°C (typically about 125-138°C) for about 18-30 hours until the reaction is complete as optionally monitored by area normalized HPLC showing no more than about 0.5%
10 adenine remaining. The resulting mixture is cooled to about 25°C, typically about 20-30°C, and contains the stage I intermediate, (R)-9-(2-hydroxypropyl)adenine, which may precipitate out at this point. After cooling, lithium t-butoxide (3.62 kg), 2.0 M in tetrahydrofuran is added to the stage I intermediate, to produce the lithium salt of (R)-9-(2-
15 hydroxypropyl)adenine in a mildly exothermic addition. The slurry is treated with diethyl p-toluenesulfonyloxymethylphosphonate (1.19 kg) and the mixture is heated to a temperature of about 32°C, typically about 30-45°C, and is stirred for at least about 2 hours (typically about 2-3 hours) during which time the mixture becomes homogeneous. More diethyl p-
20 toluenesulfonyloxymethylphosphonate (1.43 kg) is added and the mixture is stirred at a temperature of about 32°C (typically about 30-45°C) for at least about 2 hours (typically about 2-3 hours). Additional lithium t-butoxide (0.66 kg), 2.0 M in tetrahydrofuran and diethyl p-toluenesulfonyloxymethylphosphonate (0.48 kg) are added twice more, each
25 time followed by stirring the mixture, which is at a temperature of about 32°C for at least about 2 hours. Reaction completion is optionally monitored by area normalized HPLC showing no more than about 10% of stage I intermediate remaining. If the reaction is incomplete, additional lithium t-butoxide (0.33 kg), 2.0 M in tetrahydrofuran and diethyl p-
30 toluenesulfonyloxymethylphosphonate (0.24 kg) are added and the reaction mixture is maintained at a temperature of about 32°C for at least about 2 hours to achieve reaction completion. The mixture is then cooled to about 25°C (typically about 20-40°C) and glacial acetic acid (0.5 kg) is then added. The resulting mixture is concentrated *in vacuo* at a final maximum mixture
35 temperature of about 80°C under about 29 in Hg vacuum. The residue is cooled to about 50°C (typically about 40-60°C) and water (1.8 kg) is added and the reaction is rinsed forward with additional water (1.8 kg). The solution is continuously extracted with dichloromethane (about 35 kg) for 12–48 hours

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with periodic additions of glacial acetic acid (0.2 kg) to the aqueous phase after
about 5 hours and after about 10 hours of continuous extraction time.
Extraction completion is optionally confirmed by area normalized HPLC as
shown by no more than about 7% of (R)-9-[2-

5   (diethylphosphonomethoxy)propyl]adenine remaining in the aqueous phase.
The combined dichloromethane extracts are concentrated initially at
atmospheric pressure then *in vacuo* at an extract temperature of no more
than about 80°C to give the title compound as a viscous orange oil. The title
compound yield is about 40-45% by weight normalized HPLC and its purity is

10   typically 60-65% by area normalized HPLC. The actual weight of the title
compound after concentration is approximately 1.6 times the theoretical
weight (or 3.8 times the expected yield). The additional observed weight is
attributed to impurities and/or solvents remaining after the continuous
extraction and concentration.

15

Step 5. (R)-9-[2-(Phosphonomethoxy)propyl]adenine, crude:
Bromotrimethylsilane (1.56 kg) is added to a reactor containing a mixture of
crude (R)-9-[2-(diethylphosphonomethoxy)propyl]adenine (1.0 kg calculated
based on adenine input from step 4 above) and acetonitrile (0.9 kg) with

20   cooling to maintain a temperature no higher than about 50°C. The lines are
rinsed forward with acetonitrile (0.3 kg) and the mixture is refluxed at about
60-75°C for about 2–4 hours with moderate agitation to avoid splashing the
reactor contents. Reaction completion is monitored by area normalized HPLC
showing no more than about 3% total of monoethyl PMPA and diethyl PMPA

25   remaining. If the reaction is incomplete, additional bromotrimethylsilane
(0.04 kg) is charged into the reactor and the reaction is refluxed for at least
about 1 hour with moderate agitation. The volatiles are removed by
distillation at no higher than about 70°C initially at atmospheric pressure and
then *in vacuo* (about 24-27 in Hg) at no higher than about 70°C. The reactor is

30   then cooled to about 20°C (typically about 15-25°C) and water (1.9 kg) is added
(exothermic addition) to the residue with the temperature maintained at no
higher than about 50°C. The mixture is cooled to 20°C and washed with
dichloromethane (1.7 kg) by agitating for about 30 minutes. The isolated
aqueous phase is then filtered through a 1 μm cartridge filter, diluted with

35   water (3.2 kg), heated to about 40°C (typically about 35-50°C) and adjusted to
pH about 1.1 (typically about 0.9-1.3) with aqueous sodium hydroxide (about
0.15 kg NaOH as a 50% solution) while the temperature is maintained at
about 45°C. PMPA seed crystals are added to the mixture and the pH is

adjusted to about 2.8 (typically about 2.6-3.0) with a 50% aqueous sodium
hydroxide solution (about 0.15 kg NaOH required) while the temperature is
maintained at about 45°C (typically about 35-50° C). The solution is cooled to
about 22°C (typically about 15-25°C) over about 3–20 hours with slow to
5   moderate agitation that avoids splashing the contents, during which time the
product should precipitate, beginning at about 35°C. The pH of the slurry is
adjusted to about 3.2 (typically about 3.1-3.3), usually using 50% aqueous
sodium hydroxide or concentrated hydrochloric acid, if necessary. The slurry
is cooled to approximately 5°C, typically about 0-10°C, and slowly agitated for
10   at least about 3 hours in that temperature range. The solids are collected by
filtration, washed sequentially with cold water (0.35 kg) and acetone (0.3 kg)
giving crude PMPA as a damp solid typically of about 97% purity. The
product is heated to about 50°C and dried *in vacuo* to a water content of less
than 10%. The quantity of diethyl PMPA is calculated from the quantity of
15   adenine used in the preceding step of the synthesis (assuming 100% yield) and
not from the net weight of the crude diethyl PMPA, which may contain other
compounds.

Step 6. (R)-9-[2-(Phosphonomethoxy)propyl]adenine, pure: A
20   suspension of the crude PMPA (1.00 kg corrected for water content) (Step 5
product) in water is heated to about 100°C (typically about 95-110°C) with
moderate to high agitation until all solids dissolve, and the resulting solution
is clarified by filtration while hot, rinsing forward using additional hot water
(1 kg, about 95-110°C). The filtrate is heated to 100°C prior to cooling, first to
25   about 30°C (typically about 20-25°C) over about 3–5 hours with slow agitation,
then cooling is continued to about 10°C (typically about 5-15°C). After
holding at about 10°C for at least about 3 hours, the solids are collected by
filtration and washed sequentially with cold water (1.5 kg, about 0-10°C) and
then acetone (1 kg). The wet cake is dried *in vacuo* at about 50 °C (typically
30   about 40-60°C) to a water content of about 5.9% (typically about 3.9-7.9%),
affording pure PMPA monohydrate. The product purity is typically 98% or
greater by both area normalized and weight normalized HPLC. If the
chemical purity is unsatisfactory, the product may be repurified by a repeat of
this step.
35

Optional recrystallization: 0.75 g of PMPA (preparation A) was
recrystallized from H$_2$O (11.3 mL, 15:1 wt. ratio) by heating the suspension to
95-100°C. Upon cooling to room temperature, the crystallized PMPA was

chilled in a freezer. After 3 h the crystals were filtered on a coarse frit fit with
Tyvek™, the filter cake rinsed with ice-cold H_2O and acetone, and air dried to
constant weight to give a fluffy white solid (Preparation B). Recovery was
0.64 g (85.3%). HPLC showed 98.5-98.9% pure PMPA. No 14.7 min impurity

5   was observed. Recrystallized liquors (1039-91-23) showed 71.4% pure PMPA
with a major impurity at 4.8 min (26.9%), possibly solvent. 14.7 min impurity
= 0.05%.

Preparation B PMPA was recrystallized again from 9.6 mL (15:1 wt.
ratio) H_2O heated to 95-100°C. Upon cooling to room temperature, the

10   crystallized PMPA was chilled in a freezer overnight. The PMPA was filtered
through a coarse frit fit with Tyvek™ and the filter cake was rinsed with ice-
cold H_2O and acetone, then sucked dry to constant weight to afford a fluffy,
white solid (Preparation C). Recovery was 0.52 g (81.3%). HPLC (JH52807,
JH52810) showed 99.3-99.5% pure PMPA. The largest impurity at 19 min =

15   0.22%. Recrystallized liquors showed 64.9% pure PMPA with 0.01% 14.7 min
impurity and 0.09% 19 min impurity.

Preparation C PMPA (0.50 g) was recrystallized from approximately 7.5
mL boiling H_2O (15:1 wt. ratio). Upon cooling to room temperature, the
PMPA was filtered on a coarse frit fit with Tyvek™. The filter cake was rinsed

20   with ice-cold H_2O and acetone then sucked to dryness to afford a fluffy white
solid (Preparation D). The filtrate was also concentrated to afford a white solid
(Preparation E).
Recovery: Filter cake: 0.41 g (82%), Filtrate: 0.08 g = 0.49 g combined (98%).
HPLC analysis showed the filtrate (Preparation E) was 99.9% pure. PMPA

25   prepared in this fashion is used to manufacture the compounds of this
invention.

Step 7. Bis(POC)PMPA fumarate: In a reactor with an inert
atmosphere, e.g., nitrogen, a mixture of 1-methyl-2-pyrrolidinone (4.12 kg),

30   PMPA monohydrate (1.00 kg), triethylamine (0.996 kg), are agitated for about
15-45 min., typically about 30 min, and then chloromethyl-2-propyl carbonate
(2.50 kg) is added and the mixture is heated to about 55-65°C, typically about
60°C and agitated without splashing the contents for about 3–6 hours, typically
about 4 hours, until the reaction is complete, as optionally indicated by HPLC

35   (no more than 15% mono(POC)PMPA present). The mixture is diluted with
isopropyl acetate (10.72 kg), cooled to about 15-30°C, typically about 25°C, as
rapidly as possible, and while holding the reactor contents at a of about 15-
30°C, typically at about 25°C, the mixture is agitated for about 20-60 minutes,

47

typically about 30 minutes. The solids are removed by filtration and washed
with isopropyl acetate (4.44 kg). The combined organic phases at about 15-
30°C, typically about 25°C, are extracted twice with water (3.28 kg) using
moderate agitation for about 1-10 min. to avoid forming an emulsion
5   followed by allowing the phases to separate. The combined aqueous phases
are back-extracted twice with isopropyl acetate (3.56 kg) (about 15-30°C,
typically about 25°C). All organic phases are combined and washed with water
(2.20 kg) (about 15-30°C, typically about 25°C) using moderate agitation for
about 1-10 min. to avoid forming an emulsion, then the combined organic
10   phases, which are at about 25-43°C, but at no more than 45°C, are concentrated
in vacuo (about 26.5-28" Hg) to approximately 30% of the original volume
(about 10-12 L/kg PMPA monohydrate). After a polishing filtration using an
in-line 1 μm filter, the concentration of the organic phase is resumed at about
20-38°C, but no higher than 40°C under a vacuum (about 28" Hg) until a pale
15   yellow oil remains. The oil is dissolved in a warmed solution (about 45-55°
C, typically about 50°C) of fumaric acid (0.38 kg) in 2-propanol (6.24 kg) with
vigorous agitation until solids dissolve, about 0.5-2.0 hours. The warm
solution is then optionally filtered using an in-line 1 μm filter while
minimizing cooling of the solution. The filtrate at about 34-50°C, typically at
20   about 40°C, is agitated using the minimum agitation needed to obtain a
homogenous solution. The resulting solution is cooled to about 30-33°C,
typically about 32°C, over about 30 minutes using minimal agitation,
optionally seeded with a small quantity of bis(POC)PMPA fumarate (about 100
mg), and cooled to about 12-18°C, typically about 15°C, over about 1-2 hours,
25   typically over about 1 hour. Seed crystals may not be needed if crystal
formation begins before seed crystals are added. Crystals may form over a
range of about 12-33°C as the solution is cooled. Crystallization will occur at
lower temperatures if the solution is further chilled, e.g., to about -10° to
about 11°C. Agitation is discontinued when crystal formation begins. The
30   mixture is allowed to stand at about 15°C for at least about 12 hours, typically
about 12-30 hours. The resulting slurry is filtered (Tyvek) and the filter cake is
washed with a premixed solution of isopropyl acetate (0.70 kg) in butyl ether
(2.44 kg) (1: 4 v/v). The filter cake, which is at no more than 40°C, is dried *in*
vacuo for about 1 to 3 days and the dried product is optionally milled (Fitzmill
35   M5A fitted with a 0.050" screen), affording bis(POC)PMPA fumarate as white,
fine, powder-like crystals of about 97.0 to 99.5% purity.

Example 2
Preparation of Alkyl Chloromethylcarbonates

5
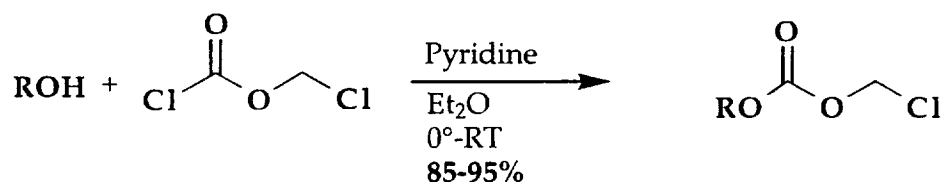
A solution of the alcohol (73 mmol) and chloromethyl chloroformate (Fluka, 6.23 mL, 70 mmol) in diethyl ether was cooled to 0°C under argon. Pyridine (5.7 mL, 70 mmol) was added dropwise with stirring over 10 minutes. The solution was stirred at 0°C for one hour, then allowed to warm

10   to room temperature and stirred for three additional hours. The ether solution was filtered, washed with 1 M HCl, dried over MgSO4, filtered, and concentrated on a rotary evaporator. Brief application of 0.1 torr vacuum gave the alkyl chloromethyl carbonates in 85-95% yields. Ethyl chloromethyl carbonate is somewhat volatile, and cannot be left on the rotovap too long, or

15   the yield suffers (87-35%).

Example 3
Preparation of the Bis-ethyl Oxymethyl Carbonate of PMPA
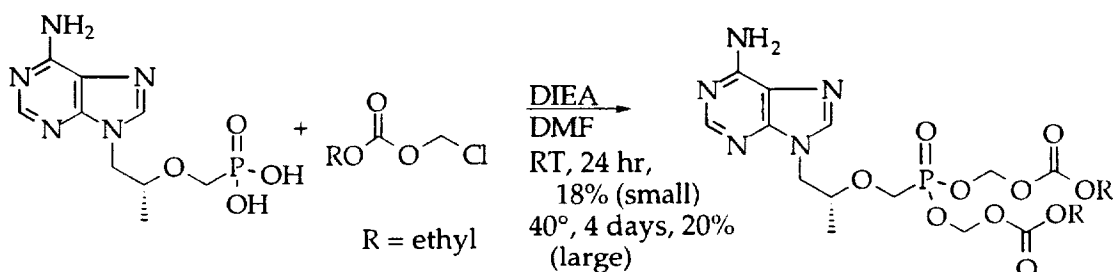
20

R= Et. Anhydrous PMPA (5 g, 16 mmol) and DIEA (Hunig's base) (11.5 mL, 66 mmol) were placed in anhydrous DMF (50 mL). The chloromethyl carbonate (49 mmol) was then added and the suspension heated to 50°C under

25   argon with rapid mechanical stirring. After 1 hr the reaction was clear and the temperature was lowered to 35°C and the reaction stirred for 48 hr. The DMF was removed on a rotary evaporator, and the reaction partitioned between CH2Cl2 and water. The CH2Cl2 layer was dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was

30   taken up in methylene chloride and applied to a silica gel column (150 g SiO2). It was eluted with 500 mL each 0,3,6,9,12,15,18% (v/v) isopropanol in

methylene chloride, and then with 2000 mL 21%. Appropriate fractions were pooled and evaporated to give the desired product.

<u>Example 4</u>

Preparation of the Bis-n-butyl Oxymethyl Carbonate of PMPA
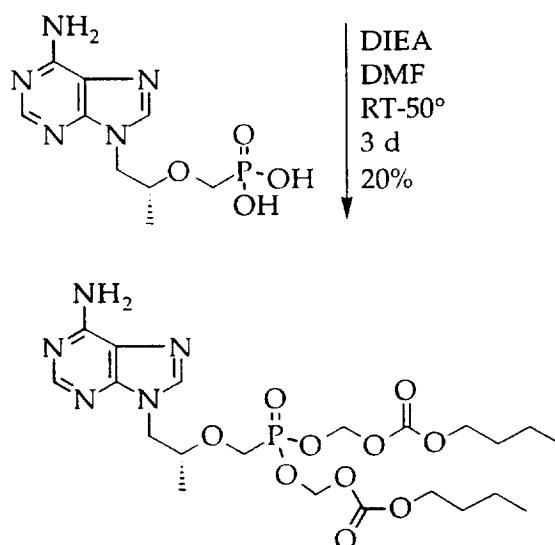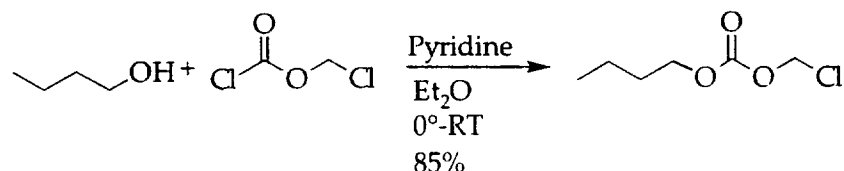
<u>Butyl chloromethyl carbonate.</u> A solution of butyl alcohol (50 mmol) and chloromethyl chloroformate (4.5 mL, 50 mmol) in diethyl ether (200 mL) was cooled to 0°C under argon. Pyridine (5.7 mL, 50 mmol) was added dropwise with stirring over 5 min. The solution was stirred at 0°C for 15 min, then allowed to warm to room temperature and stirred for three additional hours. The ether solution was filtered, washed with 1 M HCl, and then twice with water, dried over MgSO4, filtered, and concentrated on a rotary evaporator to give butyl chloromethyl carbonate (7 g, 85%).

<u>Dibutyl PMPA carbonate.</u> Anhydrous PMPA (4 g, 13 mmol) and DIEA (10.5 mL, 60 mmol) were placed in anhydrous DMF (40 mL). Butyl chloromethyl carbonate (40 mmol) was then added and the suspension stirred at room temperature for 48 hr. The reaction was then heated to 50°C for 18hr. The DMF was removed on a rotary evaporator, and the reaction partitioned between CH2Cl2 (250 mL) and water (250 mL). The CH2Cl2 layer was washed

50

once with saturated aqueous NaHCO3, dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was taken up in methylene chloride and applied to a silica gel column (150 g SiO2). It was eluted with 1000 mL CH2Cl2, 500 mL each 0,3,6,9,12,15,18% (v/v) isopropanol

5   in methylene chloride, and then with 2000 mL 21% isopropanol in methylene chloride. Appropriate fractions were pooled and evaporated to give the desired product.

Example 5

10   Synthesis of Bis-n-propyl Oxyethyl Carbonate of PMPA
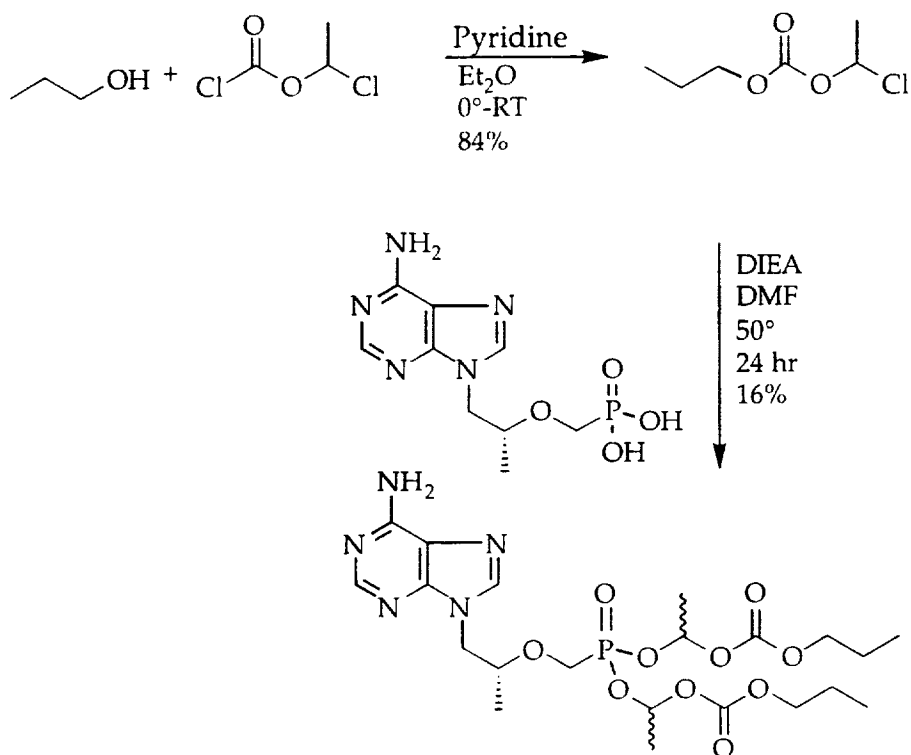
Preparation of propyl-1-chloroethyl carbonate. A solution of propyl alcohol

15   (70 mmol) and 1-chloroethyl chloroformate (7.6ml, 70 mmol) in diethyl ether (200 mL) was cooled to 0°C under argon. Pyridine (70 mmol) was added dropwise with stirring over 5 min. The solution was stirred at 0°C for 15 min, then allowed to warm to room temperature and stirred for 4.5 additional hours. The ether solution was filtered, washed with 1 M HCl, and then twice

20   with water, dried over MgSO4, filtered, and concentrated on a rotary evaporator to give propyl-1-chloroethyl carbonate (9.8 g, 84%). Anhydrous PMPA (0.3 g, 1 mmol) and DIEA (0.7 mL, 4 mmol) were placed in anhydrous DMF (2 mL) under argon. Propyl-1-chloroethyl carbonate (3 mmol) was then

added and the suspension stirred at 50°C for 20 hr. The DMF was removed on a rotary evaporator, and the reaction partitioned between CH2Cl2 and water. The CH2Cl2 layer was dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was taken up in methylene

5 chloride and applied to a silica gel column (25 g SiO2). It was eluted with 100 mL CH2Cl2, 50 mL each 3,6,9,12,15,18% (v/v) isopropanol in methylene chloride, and then with 200 mL 21% isopropanol in methylene chloride. Appropriate fractions were pooled and evaporated to give the desired product.

10   Example 6
                Synthesis of Chloromethyl Isopropyl Carbonate

        To a cold solution (approximately 10°C) of chloromethylchloroformate
    (65 mL) in diethyl ether (1.4L) was added isopropanol (56 mL) followed by a
15 dropwise addition of pyridine (60 mL). After the addition the cold bath was removed and the reaction mixture was stirred for 18 h. The reaction mixture was poured into a separation funnel containing cold water (100 mL). The ether layer was separated and washed with water (100 mL x 2) and then dried over Na2SO4. Evaporation of the solvent furnished the chloromethyl
20 isopropyl carbonate (107 g, 95%). Chloromethyl isobutyl carbonate, chloromethyl neopentyl carbonate, chloromethyl tert butyl carbonate and chloromethyl 3-pentyl carbonate are synthesized in a similar manner.

                                Example 7
25   Synthesis of Bis Isopropyl Oxymethyl Carbonate of PMPA

        To a stirred suspension of PMPA (7.26 g, 0.026 mmol) in DMF (100 mL)
    at 50°C was added Et3N (10.8 mL, 0.0778 mmol). The reaction mixture became
    homogeneous and chloromethyl isopropyl carbonate (12.1 g, 0.0778 mol) was
30 added to the reaction mixture and stirring continued at 50°C (oil bath temperature) for 20 h. The solvents were removed under reduced pressure and the crude was chromatographed on a silica gel column. Elution with 10% isopropanol in CH2Cl2 removed all the non polar impurities. Further elution with the same solvent mixture furnished the prodrug, 1.3 g (approximately
35 10%).

                                Example 8
               Synthesis of Bis Isopropyl Oxymethyl Carbonate of PMPA

                                  52

To a stirred suspension of PMPA (1 g, 3.57 mmol) in DMF (5 mL) were added Et3N (1.5 mL, 10.71 mmol) and chloromethyl isopropyl carbonate (1.67 g, 10.71 mmol). The reaction mixture was then diluted with ethyl acetate (100 mL) and filtered. The filtrate was washed with water (2 x 50 mL) and finally

5   with brine (10 mL). The crude obtained after removal of the solvent was dried under vacuum. The resulting oil was dissolved in isopropanol (7 mL) and citric acid (260 mg) was added. The mixture was stirred for 16 h at room temperature and then cooled to 0°C. The product was crystallized and crystals were filtered and dried. Mp 76-81°C.

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Example 9
Preparation of chloromethylcarbamates
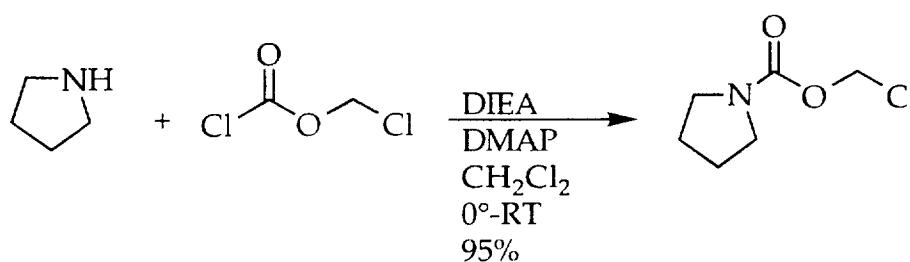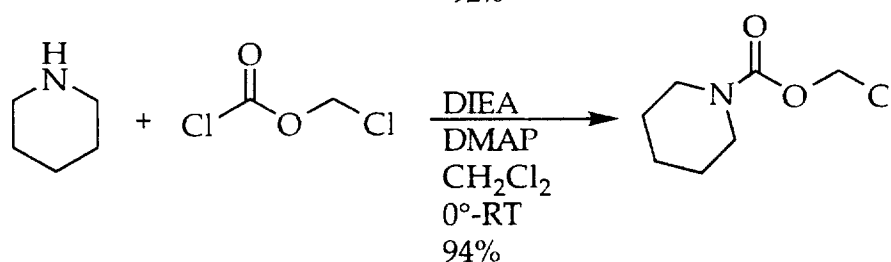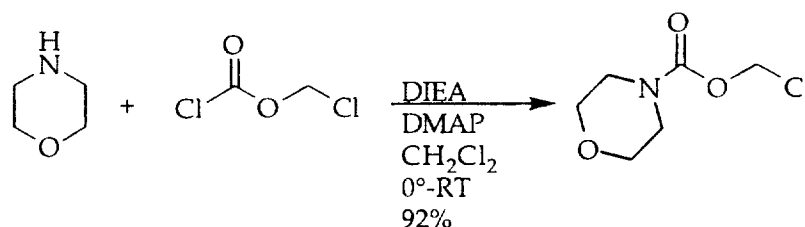
15

A solution of the amine (24 mmol), DIEA (30 mmol), and DMAP (.5 mmol) in methylene chloride (5 mL) was added dropwise to a cold (0°C) solution of chloromethyl chloroformate (25 mmol) in methylene chloride (45 mL) over 5 min. The solution was allowed to warm to room temperature

20   over 1.5 hr. The solution was diluted into ethyl acetate (100 mL), and washed with saturated sodium bicarbonate, 1 M HCl, and saturated sodium chloride. It was then dried over magnesium sulfate, filtered, and evaporated to give the desired chloromethyl carbamate.

Example 10

Synthesis of Bis Morpholino Oxymethyl Carbamate of PMPA
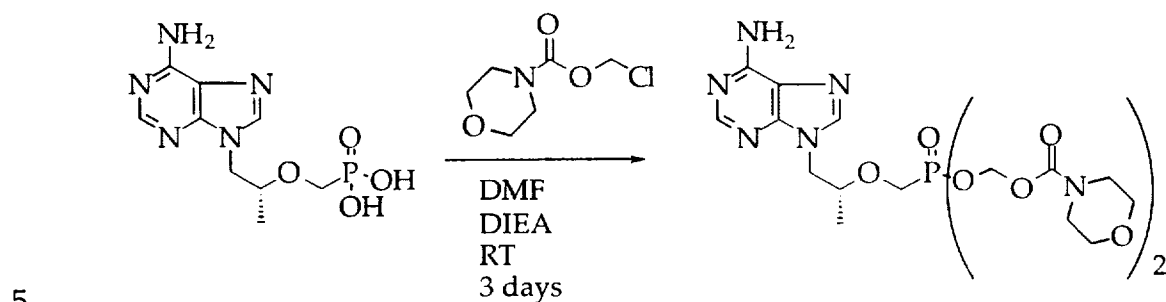
Anhydrous PMPA (0.3 g, 1 mmol) and DIEA (1 mL, 6 mmol) were placed in anhydrous DMF (2 mL). Chloromethyl morpholino carbamate (3 mmol) was then added and the suspension stirred at room temperature for 3 days. The reaction was partitioned between CH_2Cl_2/isopropanol and 0.1 M citrate buffer (pH 6). The CH_2Cl_2 layer was washed with water, dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was taken up in methylene chloride and applied to a silica gel column (5 g SiO$_2$). It was eluted with 25 mL each 0,3,6,9,12,15,18% (v/v) isopropanol in methylene chloride, and then with 100 mL 21% isopropanol in methylene chloride. Appropriate fractions were pooled and evaporated to give the desired product.

Example 11

Synthesis of Bis Piperidino Oxymethyl Carbamate of PMPA
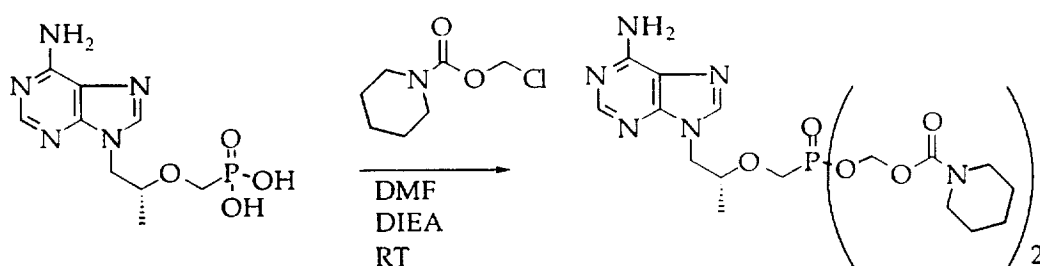
Anhydrous PMPA (0.3 g, 1 mmol) and DIEA (0.7 mL, 4 mmol) were placed in anhydrous DMF (2 mL). Chloromethyl piperidino carbamate (3 mmol) was then added and the suspension stirred at room temperature for 3 days. More DIEA (4 mmol) and chloromethyl piperidino carbamate (100 µl) were added, and the reaction stirred for 27 hr. The reaction was partitioned between CH_2Cl_2/isopropanol and 0.1 M citrate buffer (pH 6). The CH_2Cl_2

layer was dried over magnesium sulfate, filtered, and concentrated on a rotary
evaporator. The residue was taken up in methylene chloride and applied to a
silica gel column (5 g SiO₂). It was eluted with 25 mL each 0,3,6,9,12,15,18%
(v/v) isopropanol in methylene chloride, and then with 100 mL 21%

5   isopropanol in methylene chloride. Appropriate fractions were pooled and
evaporated to give the desired product.

Example 12
Other Carbamate Intermediates

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To a solution of chloromethylchloroformate (4.16 mL) in CH₂Cl₂ (30
mL) were added tert butyl amine (4.9 mL) and proton sponge (10 g). The
reaction mixture was stirred for 18 h and then it was poured into a separation
funnel containing cold 0.5N HCl (100 mL). The CH₂Cl₂ layer was separated

15 and washed with water (100 mL x 2) and then dried over Na₂SO₄.
Evaporation of the solvent furnished the chloromethyl tert butyl carbamate (8
g). Chloromethyl n-butyl carbamate (R =n-butyl) and chloromethyl dimethyl
carbamate (R = Me) were prepared in the same fashion.

Example 13
Other Oxymethyl Alkyl Carbamate Prodrugs of PMPA

To a stirred suspension of PMPA (4.51 g, 0.016 mmol) in DMF (50 mL)
was added Et₃N (6.7 mL, 0.048 mmol). The reaction mixture became

25 homogeneous and chloromethyl tert butyl carbamate (8 g, 0.048 mol) was
added to the reaction mixture and stirring continued at room temperature for
3 days. The solvents were removed under reduced pressure and the crude
was chromatographed on a silica gel column. Elution with 10% isopropanol
in CH₂Cl₂ removed all the less polar impurities. Further elution with the

30 same solvent mixture furnished the prodrug (1.25g). The n-butyl and methyl
carbamates were prepared in the same fashion from the intermediates of the
preceding example.

Example 14
Chemical Stability of PMPA Carbonates

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The solution stability of PMPA carbonates was studied at pH 7.4 at 37°C
in 10 mM buffer (NaH₂PO₄ and Na₂HPO₄) with the total ionic strength

adjusted to 0.15 M with KCl. The assays were performed by adding 200 µL of a
PMPA carbonate stock solution (about 1 mg/mL in DMSO) to 10 mL of pre-
equilibrated buffer at 37°C. Samples were removed at specific times points
and analyzed by HPLC. The chemical t 1/2 is expressed in terms of the

5   number of hours required to hydrolyze 50% of the carbonate at the specified
pH.

Example 15

Oral Bioavailability of PMPA and PMPA Carbonates in Beagle Dogs

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PMPA (9-[(R)-2-(phosphonomethoxy)propyl]adenine) and PMPA
carbonates were examined to determine the effect of dose on the
pharmacokinetics of PMPA in beagle dogs, in particular the bioavailability of
PMPA following oral administration to beagle dogs.

15   PMPA monohydrate was synthesized by Gilead Sciences.
Tetrabutylammonium hydrogen phosphate (TBAHP) was obtained from
Fluka (Ronkonkoma, NY). Acetonitrile was obtained from Baxter
(Muskegon, MI). Dibasic potassium phosphate, monobasic potassium
phosphate, and sodium acetate trihydrate were obtained from Mallinckrodt

20   (Paris, KY). Chloroacetaldehyde and trifluoroacetic acid (TFA) were from
Aldrich (Milwaukee, WI).

The intravenous formulations used as standards were isotonic aqueous
solutions containing 50 mg/mL PMPA. Compound was added to 10 mL of
WFI (water for injection from Abbott Laboratory) and 1N NaOH was added to

25   adjust the pH to 7.4. The solutions were diluted to 15 mL with WFI and
sterile filtered with a 0.2 µm filter. The PMPA dose was 10 mg/kg (0.2 mL/kg).

The intravenous formulation for a 1 mg/kg dose was prepared as
described above except only 75 mg of PMPA was added to WFI and the final
concentration was 5 mg/mL. The dose was 1 mg/kg (0.2 mL/kg). Oral

30   formulation of carbonates were prepared in 20-40% PEG 400/50 mM citric acid
and were adjusted to pH 2.2. Doses ranged from 6.2-10 mg eq of PMPA/kg and
are shown in Table 1.

Two groups of five adult male beagle dogs were used. The mean body
weight at the time of the first dose was 9.6 ± 0.4 Kg (range 9.2-10.2). The dogs

35   were fasted 12-18 hours prior to dosing and until 6 hours post-dose. For
pentagastrin pretreatment, dogs were given a single intramuscular injection
of pentagastrin (Peptavlon 0.25 mg/mL, Ayerst Laboratories, Inc.,

56

Philadelphia, PA) at a dose of 6 µg/kg, 20 minutes prior to dosing. Water was
provided *ad lib.*

Each formulation was administered as a single dose to five male beagle
dogs. Individual vials of each formulation were provided for each animal.

5   The intravenous formulation was administrated via a cephalic vein. The
oral suspension was administered by gavage, followed by two 10 mL water
washes. At least one week washout period was allowed between
administrations.

Blood samples (4.0 mL) were collected by direct jugular access from each

10   animal into heparinized tubes. Animals remained conscious throughout the
sample collection period. Blood was processed immediately for plasma by
centrifugation at 2000 rpm for 10 minutes. Plasma samples were frozen and
maintained at $\leq$ -20°C until analyzed.

Urine samples were collected over 0-24 and 24-48 hours time periods.

15   Urine samples from 0-24 and 24-48 hours were divided into aliquots and
mixed based on the volume collected and analyzed to determine amount of
PMPA recovered from urine during 0-48 hours.

PMPA in Plasma and Urine was determined as follows. PMEA (9-(2-
phosphono-methoxyethyl)adenine; adefovir) was used as the internal

20   standard for both analyses. The total concentration of PMPA in dog plasma or
urine samples was determined by derivatizing PMPA and PMEA with
chloroacetaldehyde to yield a highly fluorescent N^1, N^6-ethenoadenine
derivative as described (Russell, J. et al. (1991) Determination of 9-[(2-
Phosphonylmethoxy)-ethyl]Adenine in Rat Urine by High-Performance

25   Liquid Chromatography with Fluorescence Detection. *J. Chromatogr.
(Netherlands)*, **572**, 321-326.).

Sample Extraction for PMPA in plasma and urine was performed as
follows. Plasma (200 µL) and internal standard (20 µL of 10 µg/mL PMEA
providing a final PMEA concentration of 1 µg/mL) were mixed with 400 µL of

30   acetonitrile containing 0.1 % TFA to precipitate protein. Samples were then
evaporated to dryness under reduced pressure at room temperature (Savant
SpeedVac). Urine samples (20 µL) and internal standard (30 µL of 10 µg/mL
PMEA providing a final PMEA concentration of 1.5 µg/mL) were used directly
for derivatization without drying.

35   The samples were derivatized for analysis as follows. Dried plasma
samples or urine samples were reconstituted or mixed in 200 µL
derivatization cocktail (0.34% chloroacetaldehyde in 100 mM sodium acetate,
pH 4.5), vortexed, and centrifuged for 10 minutes at 14,000 rpm in an

Eppendorf Centrifuge 5402. Supernatant was then transferred to a clean screw capped tube and incubated at 95°C for 40 minutes. Derivatized samples were quenched on ice and evaporated to dryness under reduced pressure at room temperature. Dried samples were reconstituted in 200 μL Mobile Phase A (see

5 below), vortexed and centrifuged for 10 minutes at 14,000 rpm in an Eppendorf Centrifuge 5402. The supernatant was then transferred to autoinjector vials for HPLC analysis.

The plasma and urine samples were analyzed by HPLC with Fluorescence Detection as follows. The HPLC system comprised a Model

10 P4000 solvent delivery system with a Model AS3000 autoinjector and a Model F2000 Fluorescence detector (Thermo Separation, San Jose, CA). The column was a Zorbax RX-C18 (5 μm, 150 x 4.6 mm) (MAC-MOD, Chadds Ford, NY) equipped with a Brownlee RP-18 Newguard guard column (7 μm, 15 x 3.2 mm) (Alltech, Deerfield, IL). The mobile phases used were: A, 2% acetonitrile

15 in 25 mM potassium phosphate buffer with 5 mM TBAHP, pH 6.0; B, 65% acetonitrile in 25 mM potassium phosphate buffer with 5 mM TBAHP, pH 6.0. The flow rate was 1.5 mL/min and the column temperature was maintained at 35°C by a column oven. The gradient profile was 100% A until 2.0 min, then a linear gradient to 100% B by 13.0 minutes, returning immediately to

20 100% A. Detection was by fluorescence with excitation at 236 nm and emission at 420 nm, and the injection volume was 50 μL. Total cycle time between injections was 25 min. Data was acquired and stored by a Peak Pro data acquisition system (Beckman, Palo Alto, CA).

The pharmacokinetic parameters for intravenous and oral

25 formulations of PMPA and PMPA carbonates were assessed using non-compartmental methods. Intravenous data were analyzed using PCNONLIN Model 201 (5); oral data were analyzed using Model 200. Additional pharmacokinetic parameters were calculated as follows:

30 $CL = Dose/AUC$ $(0-\infty)$; where CL is the total plasma clearance.

$Vss = CL \times MRT$; where Vss is the apparent volume of distribution at steady state. MRT is the mean residence time.

The initial plasma concentration (Co) was determined by extrapolation of log

35 transformed data to zero time. Bioavailability was expressed as

$$\text{Bioavailability (\%)} = \frac{\text{AUC}(0-\infty) \text{ oral or prodrug}}{\text{AUC}(0-\infty) \text{ intravenous}} \times 100$$

Urinary recovery was expressed as

$$\text{Urinary Recovery (\%)} = \frac{\text{amount (mg) of PMPA in urine (0-48 hr)}}{\text{amount (mg) of PMPA dosed}} \times 100$$

5   Oral bioavailability of t-Bu, 3-pentyl, isopropyl, Et carbonate parameters
were compared by unpaired t-tests (StatView® Version 4.0, Software for the
Statistical Analysis. Abacus Concepts, Inc., Berkeley, CA). A P value of ≤ 0.05
was considered significant.

Biological t1/2: Dog liver was obtained fresh from Pharmakon USA
10   (Waverly, PA). Liver homogenate was prepared following a standard
protocol. Dog liver was rinsed three times with ice-cold 50 mM
sodium/potassium phosphate buffer and homogenized with a Tekmar
Tissumizer homogenizer (VWR 33995-060). The homogenate was
centrifuged at 9000 g (11,000 rpm for Eppendorf Centrifuge 5402; Brinkmann
15   Instruments, Westbury, NY) at 4°C for 20 minutes. The supernatant was
designated as the S9 fraction. The concentration of protein in the S9 fraction
was determined using a Bio-Rad Protein Assay Kit II, with bovine serum
albumin as standard. Esterase activity was determined using o-nitrophenyl
butyrate as substrate and activity was calculated based on the increase in
20   absorbance at 420 nm after a 1 min incubation. The homogenates were stored
as 1.0 mL aliquots at -70°C.

Intestinal Homogenate: Dog intestinal segments (jejunum/ileum) were
obtained fresh from Pharmakon USA (Waverly, PA) and intestinal
25   homogenate was prepared as described for liver. The intestinal homogenates
were stored as 1.0 mL aliquots at -70°C.
       Human intestinal homogenate (S9) was obtained from Keystone Skin
Bank (Exton, PA) at concentration of 20 mg protein/mL.

30   Study Design: Enzymatic stability studies involving plasma and intestinal
homogenate were performed with 90% biological fluids.

Stability Measurement: One blank (drug free) incubation was performed for
each biological fluid. All biological fluid tubes (open) were preincubated
35   without PMPA prodrugs in a shaker bath at 37°C and 100 oscillation/min for 5
minutes. PMPA prodrugs was added to the test incubations (final
concentration: 20 µg/mL), mixed and maintained at 37°C and 100
oscillations/min. Samples (50 µL) were withdrawn at 0, 30, and 60 minutes

and the reaction was quenched with 100 µL of 0.1% trifluoroacetic acid (TFA) in acetonitrile. Quenched samples were centrifuged for 5 minutes at 14,000 rpm in an Eppendorf Centrifuge 5402, and the supernatant was used for HPLC analysis.

5

Calculations: For each incubation, the observed rate constant for degradation was calculated by plotting the log of the peak area of PMPA prodrugs versus time of incubation (min). The slope was the observed rate constant (k_{obs}). The half life was calculated according to the following equation:

10
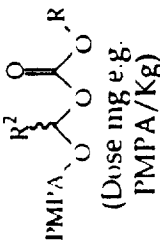
$$t1/2 \text{ (min)} = \frac{0.693}{k_{obs}}$$
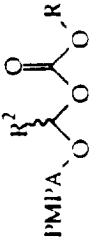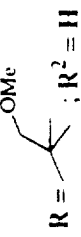
If the observed rate constant for degradation was less than 0.01 min^{-1}, then t1/2 was expressed as stable.
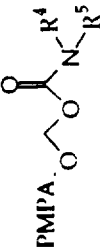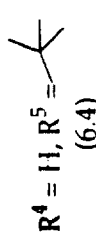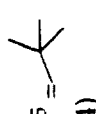
15   The results of the beagle study are shown below in Table 1.

TABLE 1
PMPA Prodrug Summary

PRODRUGS CARBONATES (Dose mg e.g. PMPA/Kg)	Chemical t1/2 (hr) pH 7.4	Chemical t1/2 (hr) pH 2.0	Log PC pH 7.4	Biological t1/2 (min) (Dog) (Human) Intestine	Plasma	Liver	% of PMPA IV (1 mg/kg) AUC PMPA	Monoester	Prodrug	other	Urinary Recovery (% as PMPA)
Bis-t-Bu COM PMPA; R²=H (6.45)	0.4	0.4	1.93	26.6 (<5)	21.2	14.9	36.2 ± 6.76	--	--	--	34.9 ± 14.0
Bis-IBu COM PMPA; R²=H (7.2)	9	>150	2.0	15 (<5)	<5	<5	24.5 ± 8.82	--	--	--	TBD
Bis-neoPentylCOM PMPA; R²=H (7.7)	6	>150	3.2	<5 (<5)	<5	<5	18.9 ± 6.57	--	--	--	TBD
Bis-nBuCOM PMPA; R²=H (8.0)	6	>150	2.7	<5 (<5)	<5	<5	17.3 ± 2.57	--	--	--	TBD
Bis-3-PentylCOM PMPA; R²=H (6.2)	8	>150	3.2	30 (<5)	15	<5	33.9 ± 9.02	--	--	--	TBD

PRODRUGS CARBONATES PMPA-O-O-C(=O)-O-R (R², R)	Chemical t1/2 (hr) pH 7.4	Chemical t1/2 (hr) pH 2.0	Log PC pH 7.4	Biological t1/2 (min) (Dog)(Human) Intestine	Plasma	Liver	% of PMPA IV (1 mg/kg) AUC PMPA	Monoester	Prodrug	other	Urinary Recovery (% as PMPA)
Bis-EtCOM PMPA R = ...; R² = H (10)	7		0.6	23.3 (<5)	16.6	<5	29.3 ± 3.4	~2	0	0	TBD
Bis-EtCOE PMPA R = ...; R² = Me	4			62.4	42.6	<5	N A	N A	N A	N A	N A
Bis-Methoxy diMeCOM PMPA OMe R = ...; R² = H	9		1.0	Stable (30)	77.6	100.8	N A	N A	N A	N A	N A
Bis-isopropylCOM PMPA R = ...; R² = H (9)	9		1.25	52.6 (<5)	20.5	<5	35.8 ± 14.7	3.1 ± 0.67	0	0	TBD

PRODRUGS CARBAMATES $PMPA\underset{O}{\overset{O}{|}}O\underset{N}{|}\overset{R^4}{\underset{R^5}{|}}$	Chemical t1/2 (hr)		Log PC	Biological t1/2 (min) (Dog) (Human)			% of PMPA IV (1 mg/kg) AUC				Urinary Recovery (% as PMPA)
	pH 7.4	pH 2.0	pH 7.4	Intestine	Plasma	Liver	PMPA	Monoester	Prodrug	other	
Bis-tBuNCOM PMPA $R^4 = H, R^5 = $ (6.4)	0.4			107.5	99.5	166.5	8.86 ± 2.38	---	9.97 ± 2.52	---	
Bis-di-n-proNCOM PMPA $R^4 = R^5 =$	13			Stable	Stable	76	NA	NA	NA	NA	NA

Example 16
Antiviral Activity of PMPA and PMPA Carbonates in Tissue Culture

PMPA (9-[(R)-2-(phosphonomethoxy)propyl]adenine) and PMPA
5   carbonates were examined to determine their activity against HIV-1. The
antiviral activity of the carbonates 5a, 5c-g against HIV-1(IIIB) was determined
in MT-2 cells and the IC_{50} (50% inhibitory concentration) and CC_{50}
(concentration to kill 50% of the cells) values were measured. The carbonate
prodrugs exhibited increased potency (about 2.5-500 fold) compared to PMPA
10   (Table 2). Although cytotoxicity of the prodrugs also increased, the selectivity
indices were improved compared to PMPA. The increased activity can be
attributed to increased cellular uptake of the prodrugs followed by effective
intracellular conversion to PMPA, which undergoes subsequent
phosphorylation to the antivirally active diphosphate metabolite. The t-butyl
15   carbonate 5d exhibited only 2.5 fold increased activity over PMPA with
reduced selectivity possibly due to chemical instability. The antiviral activity
data indicate good permeability of alkyl methyl carbonate prodrugs into cells,
possibly due to their increased lipophilicity. The partition coefficient values
support this hypothesis, with all prodrugs being more lipophilic ($logP = 0.6$-
20   3.2) compared to PMPA ($logP = -2.5$).
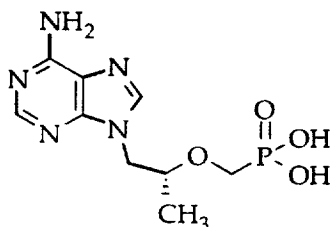
2
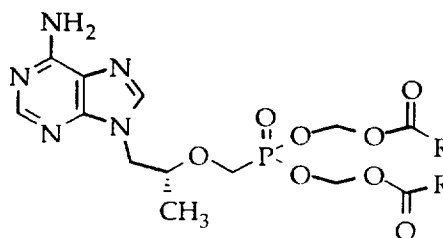
5

a. R = -OEt
c. R = $-OBu^{iso}$
d. R = $-OBu^{t}$
e. R = $-OPen^{neo}$
f. R = $-OPro^{iso}$
g. R = 3-OPen

Table 2. Antiretroviral activity of PMPA and PMPA prodrugs against HIV-
1.

5

compound	IC$_{50}$[a] (μM)	CC$_{50}$[b] (μM)	SI[c]
2	0.5	250	500
5a	0.002	40	20000
5c	< 0.001	30	30000
5d	0.2	10	50
5e	< 0.001	3	3000
5f	0.003	50	16600
5g	< 0.001	40	40000

[a]IC$_{50}$ - 50% inhibitory concentration; [b]CC$_{50}$ - Concentration to kill 50% of the cells; [c]SI - Selectivity Index(CC$_{50}$/IC$_{50}$); n.d - not determined; DMSO used as control.

10

CLAIMS

We claim:

1.   A compound having formula (1a)

$$\overset{\displaystyle O}{\underset{\displaystyle }{\underset{\displaystyle \text{A-OCH}_2\text{P(Z)}_2}{\parallel}}} \quad \text{(1a)}$$

wherein Z is independently $-OC(R^2)_2OC(O)X(R)_a$, an ester, an amidate or -H, but at least one Z is $-OC(R^2)_2OC(O)X(R)_a$;

A is the residue of an antiviral phosphonomethoxy nucleotide analog;

X is N or O;

R^2 independently is -H, $C_1\text{-}C_{12}$ alkyl, $C_5\text{-}C_{12}$ aryl, $C_2\text{-}C_{12}$ alkenyl, $C_2\text{-}C_{12}$ alkynyl, $C_7\text{-}C_{12}$ alkenylaryl, $C_7\text{-}C_{12}$ alkynylaryl, or $C_6\text{-}C_{12}$ alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or $-OR^3$ in which R^3 is $C_1\text{-}C_{12}$ alkyl, $C_2\text{-}C_{12}$ alkenyl, $C_2\text{-}C_{12}$ alkynyl or $C_5\text{-}C_{12}$ aryl;

R is independently -H, $C_1\text{-}C_{12}$ alkyl, $C_5\text{-}C_{12}$ aryl, $C_2\text{-}C_{12}$ alkenyl, $C_2\text{-}C_{12}$ alkynyl, $C_7\text{-}C_{12}$ alkyenylaryl, $C_7\text{-}C_{12}$ alkynylaryl, or $C_6\text{-}C_{12}$ alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, $-N(R^4)_2$ or $-OR^3$, where R^4 independently is -H or $C_1\text{-}C_8$ alkyl, provided that at least one R is not H; and

a is 1 when X is O, or 1 or 2 when X is N;

with the proviso that when a is 2 and X is N, (a) two N-linked R groups can be taken together to form a carbocycle or oxygen-containing heterocycle, (b) one N-linked R additionally can be $-OR^3$ or (c) both N-linked R groups can be -H;

and the salts, hydrates, tautomers and solvates thereof.

2.   The compound of claim 1 having formula (1)

wherein B is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl;

66

R is independently -H, C_1-C_{12} alkyl, C_5-C_{12} aryl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or -OR^3 in which R^3 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl or C_5-C_{12}
5   aryl;

R^1 is hydrogen, -CH_3, -CH_2OH, -CH_2F, -$CH=CH_2$, or -CH_2N_3, or R^1 and R^8 are joined to form -CH_2-;

R^2 independently is hydrogen or C_1-C_6 alkyl; and

R^8 is hydrogen or -CHR^2-O-C(O)-OR, or R^8 is joined with R^1 to form
10   -CH_2-;

and the salts, hydrates, tautomers and solvates thereof.

3.   The compound of claim 2 wherein R^2 is -H.

15   4.   The compound of claim 3 wherein R^1 is -CH_3.

5.   The compound of claim 1 wherein R^2 is -H.

6.   The compound of claim 1 wherein one R^2 is -CH_3 and the other
20   R^2 is H.

7.   The compound of claim 1 wherein R^3 is C_1-C_6 alkyl or phenyl.

8.   The compound of claim 1 wherein R^3 is -CH_3 or -C_2H_5.
25
9.   The compound of claim 1 wherein X is O.

10.   The compound of claim 1 wherein X is N and one R^3 is H.

30   11.   The compound of claim 4 wherein the compound is enriched or resolved at the carbon atom chiral center linked to R^1.

12.   The compound of claim 4 wherein at least about 90% of the compound is in the (R) configuration at the R^1 site.
35
13.   The compound of claim 12 wherein B is adenin-9-yl.

14.   The compound of claim 13 wherein each R is ethyl.

40   15.   The compound of claim 13 wherein each R is isopropyl.

67

16.   The compound of claim 13 wherein each R is 3-pentyl or neopentyl.

17.   The compound of claim 13 wherein each R is *t*-butyl or isobutyl.

18.   The compound of claim 4 wherein B is 2,6-diaminopurin-9-yl.

19.   The compound of claim 3 wherein R^1 is H.

20.   The compound of claim 19 wherein B is adenin-9-yl.

21.   The compound of claim 4 wherein R is C_1-C_{12} alkyl.

22.   The compound of claim 3 wherein R^1 is -CH_2OH.

23.   The compound of claim 22 wherein B is cytosin-1-yl.

24.   The compound of claim 1 named in Table B and compound groups **1-19**.

25.   The compound of claim 22 wherein at least about 90% of the compound is in the (S) configuration at the R^1 site.

26.   A method comprising orally administering to a patient infected with virus or at risk to viral infection a therapeutically effective amount of a compound of claim 1.

27.   A method for preparing a compound of formula (1a) comprising reacting the diacid of a phosphonomethoxy nucleotide analog with L-$CH(R^2)OC(O)X(R)_n$ wherein L is a leaving group.

28.   A method for preparing a compound of formula (1) comprising reacting a compound of formula (6)

$$B \diagdown \diagup O \diagdown \diagup \overset{\overset{O}{\parallel}}{P} \diagdown OH \quad (6)$$
$$\underset{R^1}{|} \qquad\qquad OR^8$$
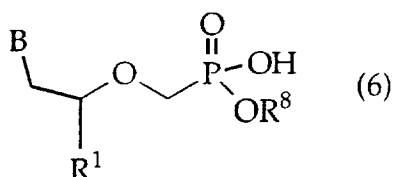
with L-CHR^2-O-C(O)-OR and recovering a compound of formula (1),

wherein B is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-

5   9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl;

R^1 is hydrogen, -CH$_3$, -CH$_2$OH, -CH$_2$F, -CH=CH$_2$, -CH$_2$N$_3$ or R^1 and R^8

are joined to form -CH$_2$-; and

R^8 is hydrogen, -CHR^2-O-C(O)-OR or R^8 is joined with R^1 to form -CH$_2$-

; and

10   R^2 is H, C$_1$-C$_{12}$ alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl,

alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is unsubstituted or is

substituted with halo, azido, nitro or OR^3 in which R^3 is C$_1$-C$_{12}$ alkyl;

R is independently H, C$_1$-C$_{12}$ alkyl, aryl, alkenyl, alkynyl, alkyenylaryl,

alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is

15   unsubstituted or is substituted with halo, azido, nitro or OR^3, provided that at

least one R is not H; and

L is a leaving group.

29.   The method of claim 30 comprising conducting the reaction

20   using at least about 1.0 equivalent of L-CHR^2-O-C(O)-OR.

30.   The method of claim 31 comprising conducting the reaction in

the presence of an organic base in an organic solvent at a reaction temperature

of about 4-100°C for about 4-72 hours.

25

31.   The method of claim 28 wherein the compound of formula (1) is

recovered by forming a salt, precipitating the salt and recovering the

precipitated salt.

30   32.   The method of claim 31 wherein the salt is formed from sulfuric

acid, phosphoric acid, lactic acid, or citric acid.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6   C07F9/6561   A61K31/675   C07F9/6512

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 6   C07F   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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LINDAHL A ET AL: "Synthesis of an acryloxymethyl prodrug of the inositol phosphate.alpha.-trinositol" J. CARBOHYDR. CHEM. (JCACDM,07328303);96; VOL.15 (5); PP.549-554, PERSTORP PHARMA;PERSTORP; S-284 80; SWED. (SE), XP002043027 see the whole document ---	1-32
Y	WO 95 07920 A (GILEAD SCIENCES INC ;BISCHOFBERGER NORBERT W (US); JONES ROBERT J) 23 March 1995 cited in the application see the whole document ---	1-32
	-/--	

[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 October 1997	2 0 -10- 1997

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

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page 1 of 2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92 09611 A (BEECHAM GROUP PLC) 11 June 1992 cited in the application see the whole document ---	1-32
Y	EP 0 481 214 A (SQUIBB BRISTOL MYERS CO) 22 April 1992 cited in the application see the whole document -----	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9507920 A	23-03-95	US 5656745 A AU 7875294 A AU 7956594 A BR 9407510 A EP 0719273 A EP 0719274 A WO 9507919 A US 5591851 A	12-08-97 03-04-95 03-04-95 07-01-97 03-07-96 03-07-96 23-03-95 07-01-97
WO 9209611 A	11-06-92	AU 9044091 A	25-06-92
EP 0481214 A	22-04-92	CA 2051239 A JP 4230694 A US 5663159 A	15-03-92 19-08-92 02-09-97