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(54) **ANTIVIRAL COMPOUNDS AND METHODS FOR SYNTHESIS AND THERAPY**

(75) Inventors: **Jan M. R. Balzarini**, Heverlee (BE); **Erik D. A. De Clercq**, Lovenjoel (BE); **Antonin Holy**, Horni Pocernice (CZ)

(73) Assignees: **Institute of Organic Chemistry and Biochemistry Academy of Sciences of the Czech Republic** (CZ); **Rega Stichting v.z.w.** (BE)

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(51) **Int. Cl.**[7] **A61K 31/662**; C07F 9/6512

(52) **U.S. Cl.** **514/86**; 514/88; 544/243

(58) **Field of Search** 544/243; 514/86, 514/88

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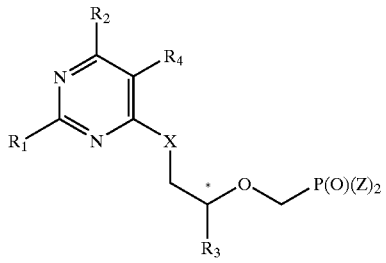
Primary Examiner—Richard L. Raymond
(74) *Attorney, Agent, or Firm*—Max D. Hensley

(57) **ABSTRACT**

Novel compounds are provided having formula (I)

(I)



where

R_1, R_2, R_3, R_4, Z, X and * are defined herein. Also provided are antiviral methods for use and processes for synthesis of the compounds of formula (I).

ANTIVIRAL COMPOUNDS AND METHODS FOR SYNTHESIS AND THERAPY

CROSS REFERENCED TO RELATED APPLICATIONS

This application is based upon U.S. Provisional Application Ser. No. 60/302,212 filed Jun. 29, 2001, and is incorporated herein by reference.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

Acyclic nucleotide analogues containing phosphonate groups are disclosed for example in U.S. Pat. Nos. 4,659,825, 4,808,716, 4,724,233, 5,142,051, 5,302,585, 5,208,221, 5,352,786, 5,356,886, in EP publication numbers 269,947, 481,214, 630,381, 369,409, 454,427, 468,119, 434,450, 618,214 and 398,231 and in WO 95/07920, WO 94/03467 and WO 96/33200. The teachings of these patents include compounds in which a phosphonate group is linked to a defined purine or pyrimidine base, generally at the 1- or 9-position of the pyrimidine or purine bases, respectively, by way of a 2-(methoxy)propyl group, a 2-(methoxy)ethyl group, a 2-methoxy-3-hydroxypropyl group, or a 2-methoxy-3-fluoropropyl group, known respectively as PMP, PME, HPMP and FPMP purine or pyrimidine compounds. These compounds exhibit antiviral and cytostatic activity.

Daluge et al. (34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct. 4–7, 1994) discloses carbovir derivatives in which the 6 position of the purine is substituted with cyclopropylamino, N-cyclopropyl-N-methylamino or N-aziridinyl.

Cihlar et al., "Antimicrobial Agents and Chemotherapy" 39(1):117–124 (1995) disclose N^6-aminohexyl-PMEDAP.

Holy et al., "ACS Symp. Ser." 401:57–71 (1989) and Holy, "Kem. Ind." 38(10):457–462 (1989) describe the antiviral activity of certain N^6-substituted nucleotide analogues.

Additional phosphonate-substituted pyrimidine analogues are disclosed by Holy et al., "Collect. Czech. Chem. Commun." 64:242–256 (1999), Eger et al., "J. Med. Chem." 37:3057–3061 (1994), Wormstadt et al., "J. Heterocyclic Chem." 37:1187–1191 (2000), and Franchetti et al., "Nucleosides & Nucleotides" 14(3–5): 607–610 (1995). The latter three publications have a phosphonate-containing side-chain linked via a 6-N substituent of 2,4-disubstituted pyrimidine.

OBJECTS OF THE INVENTION

It is an object of this invention to provide compounds having antiviral activity, in particular against RNA or DNA viruses such as HIV, HBV or HSV.

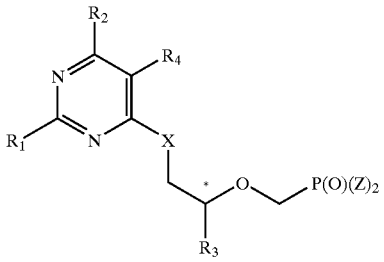
It is an additional object to provide compounds useful in the preparation of ion exchange resins or chiral media.

It is a further object to provide intermediates and methods for making such compounds.

These and other objects will be more fully understood by further reference to the disclosures herein.

SUMMARY OF THE INVENTION

(I)

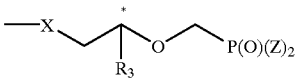


where

R_1 is H, amino or methylsulfanyl;

R_2 is H, methyl, halo, $—N(R_5)_2$, hydroxy, protected hydroxy or a group of the formula (Ia)

(Ia)



R_3 is independently H, methyl, hydroxymethyl, halomethyl or protected hydroxymethyl;

R_4 is H or halo;

X independently is oxygen, sulfur or a bond;

Z independently is hydroxy, an ester or amide;

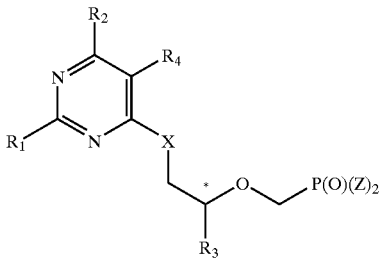
R_5 is independently H, C_1–C_8 alkyl or a protecting group; and

* designates a chiral carbon atom; and

salts and solvates thereof.

The objects also are accomplished by a method for preparation of compounds of the formula (I)

(I)

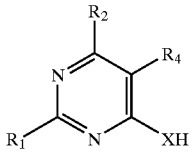


where

R_1, R_2, R_3, R_4, X, Z, R_5 and * are defined above;

comprising reacting a compound of formula (II)

(II)

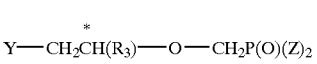


where

R_1 and R_5 are defined above;

R_2 is H, methyl, halo, $—N(R_5)_2$, hydroxy or protected hydroxy; and

with a compound of the formula (III)



(III)

where

Z is an ester or an amide;

* designates a chiral carbon atom;

R_3 is H, methyl, halomethyl or protected hydroxymethyl; and

Y is a leaving group

in dipolar aprotic solvent in the presence of a base to obtain a compound of formula (I) where Z is ester or amide; (b) one or both Z groups optionally are converted to produce the compound of formula (I) where at least one Z is hydroxy.

In another embodiment of this invention, a method is provided for the preparation of compounds of formula (I) where

R_1 is H, amino or methylsulfanyl;

R_2 is $—N(R_5)_2$

R_3 is independently H, methyl, hydroxymethyl, halomethyl or protected hydroxymethyl;

R_4 is H or halo

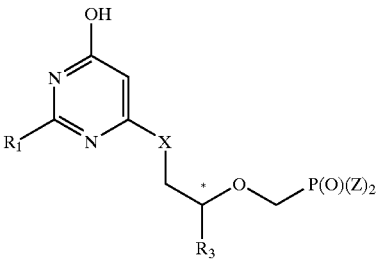
X is oxygen or sulfur;

Z independently is hydroxy, an ester or amide;

R_5 is independently H, C_1–C_8 alkyl or a protecting group; and

* designates a chiral carbon atom

comprising reacting a compound (IV)



(IV)

where

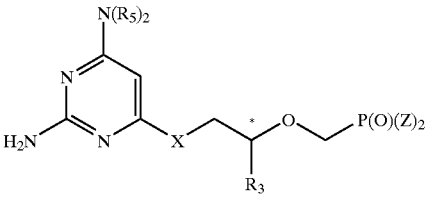
R_3 is H, methyl, halomethyl or protected hydroxymethyl;

X is O or S; and

Z is amide or ester;

with $N(R_5)_2$. One or both Z groups optionally are converted to the compound of formula (I) where at least one Z is hydroxy.

In another embodiment, a method is provided for preparation of compounds of formula (V)



(V)

where

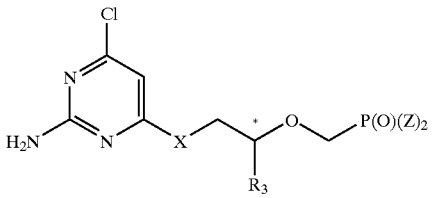
R_5 independently is H, C_1–C_8 alkyl or a protecting group;

X is oxygen or sulfur;

Z independently is hydroxy, an ester or amide; and

* designates a chiral carbon atom;

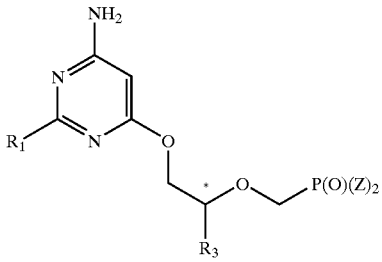
comprising reacting compound (IVa)



(IVa)

with $N(R_5)_2$ in anhydrous solvent, alkali hydroxide or alkali carbonate in aqueous solution and Z is optionally converted to the compound of formula (V) wherein 1 or 2 Z groups are hydroxy.

In another embodiment, a method is provided for the preparation of compounds of formula (VI)



(VI)

where

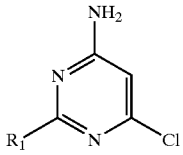
R_1 is H, amino or methylsulfanyl;

R_3 is H, methyl, hydroxymethyl, halomethyl or protected hydroxymethyl;

Z independently is hydroxy, an ester or amide; and

* designates a chiral carbon atom;

comprising reacting a compound of formula (VII)

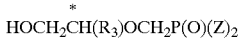


(VII)

where

R_1 is H, amino or methylsulfanyl

with a compound of the formula (VIII)

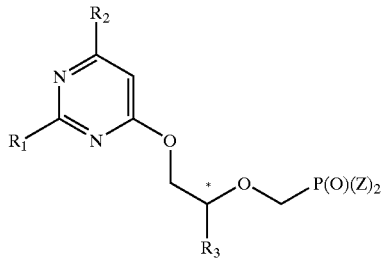


(VIII)

where Z is amide or ester in the presence of a base.

In another embodiment of this invention, a method is provided for the preparation of compounds of formula (XIII)

(XIII)



where

R_1 is H, amino or methylsulfanyl;

* is a chiral carbon atom;

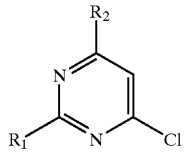
R_2 is H, chloro, hydroxy or amino;

R_3 is H, methyl, halomethyl or hydroxymethyl; and

Z is amide or ester;

comprising (a) reacting a compound of the formula (IX)

(IX)



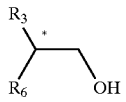
where

R_1 is H, amino or methylsulfanyl;

R_2 is H, chloro or amino;

with a compound of the formula (X)

(X)



where

R_3 is H, methyl, hydroxymethyl, halomethyl or protected hydroxymethyl;

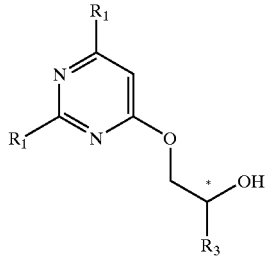
* is a chiral carbon atom;

R_6 is hydroxy or protected hydroxy;

or R_3 and R_6 are joined by a cyclic acetal or ketal protecting group;

in the presence of a base without solvent or in the presence of an aprotic solvent to produce a compound of formula (XI)

(XI)



where

R_1 is H, amino or methylsulfanyl;

R_2 is H, chloro or amino; and

R_3 is H, methyl, halomethyl or protected hydroxymethyl; and

(b) reacting compound (XI) with a compound of the formula (XII)

$$Y—CH_2P(O)(OZ)_2 \quad \text{(XII)}$$

where

Y is a leaving group;

Z is amide or ester in the presence of a base in dimethylformamide or tetrahydrofurane to produce a compound of formula (XIII); and

(c) optionally hydrolyzing Z group in compound (XIII) to produce a compound of formula (VI) where 1 or 2 Z groups are hydroxy and X is oxygen atom.

In another embodiment of this invention, a method is provided for the preparation of compounds of formula (I) where

R_1 is H, amino or methylsulfanyl;

R_3 is H, methyl, hydroxymethyl, halomethyl or protected hydroxymethyl;

R_4 is halo;

X is oxygen;

Z independently is hydroxy, an ester or amide; and

* designates a chiral carbom atom;

comprising (a) reacting a compound of the formula (VI) where

R_1 is H, amino or methylsulfanyl;

R_3 is H, methyl, hydroxymethyl, halomethyl or protected hydroxymethyl;

Z independently is an ester; and

* designates a chiral carbon atom;

with elemental halogen in an inert solvent to produce a compound of formula (I).

Optionally one or both Z groups are converted to hydroxy.

Further objects of this invention are accomplished by a method comprising administering a therapeutically effective amount of a compound of formula (I) to a patient in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, and unless modified by the immediate context, alkyl means branched, normal or cyclic saturated hydrocarbons and includes methyl, ethyl, propyl, cyclopropyl, cyclobutyl, isopropyl, n-, sec-, iso- and tert-butyl, pentyl, isopentyl, 1-methylbutyl, 1-ethylpropyl, neopentyl, and t-pentyl.

Halo typically means chloro, but includes bromo, fluoro, or iodo.

R_1 typically is H or amino, but also can be methylsulfanyl (i.e. methylthio).

R_2 generally is hydroxy or $—N(R_5)_2$ where R_5 independently is H or C_1–C_8 alkyl.

R_3 typically is H or methyl, but may be hydroxymethyl (typically (S) configuration substantially free of the (R) enantiomer) or halomethyl, and, if methyl or halomethyl, preferably is in the (2R) configuration substantially free of the (2S) configuration. Halomethyl generally is fluoromethyl.

As is further described infra, Z is suitably any ester or amide heretofore known for use with nucleotide phosphonates. When Z is an ester, it has the structure OR_7. R_7 ordinarily is H (i.e., Z is hydroxy) in compounds having antiviral activity per se, although other R_7 ester groups described below are suitable for use as protecting groups or as pro-functionalities for prodrug embodiments.

X preferably is O.

Z is an ester or amide when it is desired to protect the compounds of this invention against undesired reactions or when the object is to provide an in vivo prodrug of the compound. Otherwise, Z is OH.

The esters or amides are useful as protected intermediates in the synthesis of compounds of this invention where Z=OH. In this embodiment, the selection of ester or amide may not be important, depending upon the nature of the reaction involved. All that is needed is that the Z substituent not be removed until the step in synthesis at which this is desired, and if this is not apparent on theoretical grounds it can be readily determined by rudimentary experiments. For example, esters in particular are used to protect the phosphonate hydroxy groups against alkylation.

When Z serves as a prodrug functionality, the ester or amide is removed in vivo from the phosphonate. Suitable prodrug esters or amidates optionally are selected based on the substrate specificity of esterases and/or carboxypeptidases expected to be found within cells where precursor hydrolysis is desired. To the extent that the specificity of these enzymes is unknown, one will screen a plurality of nucleotide analogues of this invention until the desired substrate specificity is found. This will be apparent from the appearance of free phosphonate or antiviral activity. One generally selects compounds that are (i) not hydrolyzed or hydrolyzed comparatively slowly in the upper gut, (ii) gut and cell permeable and (iii) are hydrolyzed in the cell cytoplasm and/or systemic circulation. Screens with cells from particular tissues are used to identify precursors that are released in organs susceptible to a target viral or microbial infection, e.g. in the case of liver, precursor drugs capable of hydrolysis in the liver. Other infections, e.g. CMV or HIV, optionally are treated with a precursor that is hydrolyzed at substantially the same rate and to substantially the same degree in all tissues. Assays known in the art are suitable for these purposes, including intestinal lumen stability, cell permeation, liver homogenate stability and plasma stability assays. These assays are used to determine the bioavailability characteristics of the precursors.

Typical examples of ester and amide substituents group Z are found in WO95/07920, WO98/04569 and EP 481214 A1. Any ester or amide genus or species described in these publications (and in the preference order set forth in such publications) can be used as group Z herein.

Usually, both Z are hydroxyl or both are ester and/or amide, i.e, typically 2 or no Z groups are hydroxy. In general, when neither Z is OH then one Z is amide and one is ester. Amides with naturally occurring amino acids and a esters with phenyl are preferred. The free carboxyl(s) of amino acid Z groups generally are esterified with C_1–C_8 alkyl.

In general, Z is hydroxy in compounds to be used directly for antiviral purposes, i.e. such compounds are employed without any requirement for hydrolysis in vivo of the ester or amide.

Protecting groups for hydroxyl include acetals, ketals or C_1–C_8 alkyl. A typical protecting group for amino is trityl. Other conventional protecting groups are known (Greene et

Utilities

The compounds of the invention are useful for the treatment of viruses, or as intermediates in the preparation of such compounds. Exemplary viral infections to be treated or to be tested for susceptibility to compounds of this invention include infections caused by DNA or RNA viruses such as herpesviruses (CMV, HSV 1, HSV 2, EBV, varicella zoster virus [VZV], bovid herpesvirus type 1, equid herpesvirus type 1, HHV-6, papillomaviruses (HPV types 1–55 including carcinogenic HPV), flaviviruses (including yellow fever virus, African swine fever virus and Japanese encephalitis virus), togaviruses (including Venezuelan equine encephalomyelitis virus), influenza viruses (types A–C), retroviruses (HIV-1, HIV-2, HTLV-I, HTLV-II, SIV, FeLV, FIV, MoMSV), adenoviruses (types 1–8), poxviruses (vaccinia virus), enteroviruses (poliovirus types 1–3, Coxsackie, hepatitis A virus, and ECHO virus), gastroenteritis viruses (Norwalk viruses, rotaviruses), hantaviruses (Hantaan virus), polyomavirus, papovaviruses, rhinoviruses, parainfluenza virus types 1–4, rabies virus, respiratory synctial virus (RSV), hepatitis viruses A, B, C and E, and the like.

Preferred compounds of this invention for the treatment of herpes viruses, hepadna viruses and HIV are those in which R_1=NH_2, R_2=NH_2 or OH, X=O and R_3=H or methyl. Other antiviral activities of compounds of this invention are determined by routine assay of antiviral activity using enzyme inhibition assays, tissue culture assays, animal model assays and the like as will be understood by those skilled in the art.

The novel compounds of this invention also are useful per se or as intermediates in the preparation of polymers having a wide variety of diagnostic, therapeutic and industrial utilities.

The compounds of this invention are suitable as intermediates to prepare affinity absorption media bearing substituent groups having properties useful for absorbing compounds from impure mixtures. These are prepared and used in the same fashion as other ion exchange media containing the same substituents, e.g. phosphonate or amino. For example, the phosphonate group of the compounds herein are covalently bound to insoluble matrix and free R_1 amino substituents on the heterocyclic base serve as ion exchange sites. Alternatively, the heterocyclic base amino group is linked to the matrix and the free phosphonate group is then useful in the chromatographic absorption of positively charged molecules. Other immobilized embodiments of the compounds herein are useful in purifying proteins, e.g., enzymes to which the compounds of this invention may bind, e.g. transport proteins (see Cihlar, supra).

Suitable methods of incorporation of the compounds of this invention into insoluble matrices such as polymeric resins will be readily apparent to the skilled artisan. The compounds herein can be immobilized by covalently crosslinking the pyrimidine amino or hydroxy groups to an insoluble matrix. Similarly, compounds of this invention are incorporated into insoluble resins by binding the hydroxy of the phosphonate group or a hydroxymethyl R_3 group to the matrix or resin using covalent linking agents heretofore known. Suitable linking methods are described in Cihlar (supra).

The compounds of this invention also are useful as cross-linkers or spacers in preparing affinity absorption matrices (as opposed to functioning as affinity moieties per se as noted in the preceding paragraphs). The compounds herein contain a multiplicity of functional groups that are suitable as sites for cross-linking desired substances. It is conventional to link affinity reagents such as hormones,

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