(51) International Patent Classification: A61K

(21) International Application Number: PCT/US02/28078

(22) International Filing Date: 29 August 2002 (29.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/317,070 4 September 2001 (04.09.2001) US


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(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published: — without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIOXOLANE AND OXATHIOLANE DERIVATIVES AS INHIBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE

(57) Abstract: The present invention provides 1,3-dioxolane and 1,3-oxathioline derivatives that are inhibitors of RNA-dependent RNA viral polymerase. These compounds are also inhibitors of RNA-dependent RNA viral replication and are useful in the treatment of RNA-dependent RNA viral infection. The invention also describes pharmaceutical compositions containing such 1,3-dioxolane and 1,3-oxathioline derivatives alone or in combination with other agents active against RNA-dependent RNA viral infection. Also disclosed are methods of inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with the compounds of the present invention.
TITe OF THE INVENTION
DIOXOLANE AND OXATHIOLANE DERIVATIVES AS INHIBITORS OF RNA-
DEPENDENT RNA VIRAL POLYMERASE

FIELD OF THE INVENTION
The present invention provides 1,3-dioxolane and 1,3-oxathiolane
derivatives which are inhibitors of RNA-dependent RNA viral polymerase. These
compounds are inhibitors of RNA-dependent RNA viral replication and are useful for
the treatment of RNA-dependent RNA viral infection.

BACKGROUND OF THE INVENTION
Hepatitis C virus (HCV) infection is a major health problem that leads
to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a
substantial number of infected individuals, estimated to be 2-15% of the world’s
population. There are an estimated 2.7 million infected people in the United States
alone. The viral disease is transmitted parenterally by contaminated blood and blood
products, contaminated needles, or sexually and vertically from infected mothers or
carrier mothers to their off-spring. Current treatments for HCV infection, which are
restricted to immunotherapy with recombinant interferon-α alone or in combination
with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is
no established vaccine for HCV. Consequently, there is an urgent need for improved
therapeutic agents in order to effectively combat chronic HCV infection. The state of
the art in the treatment of HCV infection has been reviewed, and reference is made to
the following publications: B. Dymock, et al., “Novel approaches to the treatment of
hepatitis C virus infection,” Antiviral Chemistry & Chemotherapy, 11: 79-96 (2000);
therapies,” Molecular Medicine Today, 5: 393-399 (1999); D. Moradpour, et al.,
“Current and evolving therapies for hepatitis C,” European J. Gastroenterol. Hepatol.,
11: 1189-1202 (1999); and R. Bartenschlager, “Candidate Targets for Hepatitis C
Virus-Specific Antiviral Therapy,” Intervirology, 40: 378-393 (1997), all of which are
incorporated by reference herein in their entirety.

Different approaches to HCV therapy have been taken, which include
the inhibition of viral serine proteinase (NS3 protease), helicase, and RNA-dependent
RNA polymerase (NS5B), and the development of a vaccine.

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The HCV virion is an enveloped positive-strand RNA virus with a single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and B, and NS5A and B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV.


There exists a great need for improved therapeutic options for treating RNA-dependent RNA viral infections, in particular, Flaviviridae viral infections, and, especially, hepatitis C virus infections.

Methods for the treatment or prevention of Flaviviridae viral infection, including hepatitis C virus infection, were disclosed in WO 01/32153 (published 10 May 2001). The purine analogs disclosed therein were all 7-aza-purines.

1,3-Oxathiolanes having antiviral properties, in particular, anti-HIV properties, were disclosed in EP 0 382 526 A2 (published 16 August 1990) and U.S. Patent No. 5,466,806. 1,3-Oxathiolanes substituted with cytosine useful in the treatment of hepatitis C virus infection were disclosed in WO 97/06804 (published 27 February 1997). Specifically disclosed was (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (also known as lamivudine).

It has now been found that 1,3-dioxolanes and 1,3-oxathiolanes substituted with a 1H-pyrrolo[2,3-d]pyrimidine ("7-deaza-purine") nucleobase are potent inhibitors of RNA-dependent RNA viral replication. The triphosphate derivatives of these compounds are inhibitors of RNA-dependent RNA viral polymerase. These compounds are useful to treat RNA-dependent RNA viral infection.

It is therefore an object of the present invention to provide 1,3-dioxolane and 1,3-oxathiolane derivatives containing a 7-deaza-purine nucleobase which are useful as inhibitors of RNA-dependent RNA viral polymerase.

It is another object of the present invention to provide 1,3-dioxolane and 1,3-oxathiolane derivatives which are useful as inhibitors of the replication of an RNA-dependent RNA virus.

It is another object of the present invention to provide 1,3-dioxolane and 1,3-oxathiolane derivatives which are useful in the treatment of RNA-dependent RNA viral infection.

It is another object of the present invention to provide pharmaceutical compositions comprising the novel compounds of the present invention in association with a pharmaceutically acceptable carrier.

It is another object of the present invention to provide pharmaceutical compositions comprising the 1,3-dioxolane and 1,3-oxathiolane derivatives for use as RNA-dependent RNA viral polymerase inhibitors.

It is another object of the present invention to provide pharmaceutical compositions comprising the 1,3-dioxolane and 1,3-oxathiolane derivatives for use as inhibitors of RNA-dependent RNA viral replication.

It is another object of the present invention to provide pharmaceutical compositions comprising the 1,3-dioxolane and 1,3-oxathiolane derivatives for use in the treatment of RNA-dependent RNA viral infection.

It is another object of the present invention to provide pharmaceutical compositions comprising the 1,3-dioxolane and 1,3-oxathiolane derivatives in combination with other agents active against an RNA-dependent RNA virus.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral polymerase.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral replication.
It is another object of the present invention to provide methods for the treatment of RNA-dependent RNA viral infection.

It is another object of the present invention to provide methods for the treatment of RNA-dependent RNA viral infection in combination with other agents active against an RNA-dependent RNA virus.

It is another object of the present invention to provide 1,3-dioxolane and 1,3-oxathioline derivatives and their pharmaceutical compositions for use as a medicament for the inhibition of RNA-dependent RNA viral replication and/or the treatment of RNA-dependent RNA viral infection.

It is another object of the present invention to provide for the use of the 1,3-dioxolane and 1,3-oxathioline derivatives of the present invention and their pharmaceutical compositions for the manufacture of a medicament for the inhibition of RNA-dependent RNA viral replication and/or the treatment of RNA-dependent RNA viral infection.

These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention provides a method for inhibiting RNA-dependent RNA viral polymerase, a method for inhibiting RNA-dependent RNA viral replication, and/or a method for treating RNA-dependent RNA viral infection in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound of structural formula I:

![Structural formula I](image)

or a pharmaceutically acceptable salt thereof; wherein X is O or S(O)$_n$;
n is 0, 1, or 2;
R¹ is hydrogen, methyl, hydroxymethyl, or fluoromethyl;
R² and R³ are each independently hydrogen or C₁₋₄ alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁₋₄ alkoxy, C₁₋₄ alkylthio, or one to three halogen atoms;
R⁴ is H, C₁₋₁₀ alkylcarbonyl, P₃O₉H₄, P₂O₆H₃, or P(O)R¹₀R¹¹;
R⁵ is H, C₁₋₄ alkyl, C₂₋₄ alkynyl, halogen, cyano, carboxy, C₁₋₄ alkylcarboxy, azido, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, or (C₁₋₄ alkyl)₀₋₂ aminomethyl;
R⁶ is hydrogen, cyano, nitro, C₁₋₃ alkyl, NHCONH₂, CONR⁹R⁹, CSN⁹R⁹, COOR⁹, C(NH)NH₂, hydroxy, C₁₋₃ alkoxy, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazol-2-yl), or (imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C₁₋₃ alkoxy;
R⁷ and R⁸ are each independently hydrogen, hydroxy, halogen, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₃₋₆ cycloalkylamino, or di(C₃₋₆ cycloalkyl)amino;
each R⁹ is independently H or C₁₋₄ alkyl; and
R¹⁰ and R¹¹ are each independently hydroxy, OCH₂CH₂SC(=O)C₁₋₄ alkyl,
OCH₂O(C=O)OC₁₋₄ alkyl, NHCHMeCO₂Me, OCH(C₁₋₄ alkyl)O(C=O)C₁₋₄ alkyl,

Also encompassed within the present invention are pharmaceutical compositions containing the compounds alone or in combination with other agents active against RNA-dependent RNA virus.

DETAILED DESCRIPTION OF THE INVENTION
The present invention provides a method for inhibiting RNA-dependent RNA viral polymerase, a method for inhibiting RNA-dependent RNA viral replication, and/or a method for inhibiting RNA-dependent RNA viral infection in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of structural formula I:
or a pharmaceutically acceptable salt thereof; wherein
X is O or S(O)ₙ;
n is 0, 1, or 2;

5 R¹ is hydrogen, methyl, hydroxymethyl, or fluoromethyl;
R² and R³ are each independently hydrogen or C₁-₄ alkyl, wherein alkyl is optionally
substituted with hydroxy, amino, C₁-₄ alkoxy, C₁-₄ alkylthio, or one to three halogen
atoms;
R⁴ is H, C₁-₁₀ alkylcarbonyl, P₃O₉H₄, P₂O₆H₃, or P(O)R¹₀R¹₁;
10 R⁵ is H, C₁-₄ alkyl, C₂-₄ alkynyl, halogen, cyano, carboxy, C₁-₄ alkylxycarbonyl,
azido, amino, C₁-₄ alkylamino, di(C₁-₄ alkyl)amino, hydroxy, C₁-₆ alkoxy, C₁-₆
alkylthio, C₁-₆ alkylsulfonyl, or (C₁-₄ alkyl)₀-₂ aminomethyl;
R⁶ is hydrogen, cyano, nitro, C₁-₃ alkyl, NHCONH₂, CONR⁶⁹R⁹⁹, CSNR⁹R⁹⁹,
COOR⁹, C(=NH)NH₂, hydroxy, C₁-₃ alkoxy, amino, C₁-₄ alkylamino, di(C₁-₄
alkyl)amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazol-2-yl), or (imidazol-2-yl); wherein
alkyl is unsubstituted or substituted with one to three groups independently selected
from halogen, amino, hydroxy, carboxy, and C₁-₃ alkoxy;
R⁷ and R⁸ are each independently hydrogen, hydroxy, halogen, C₁-₄ alkoxy, amino,
C₁-₄ alkylamino, di(C₁-₄ alkyl)amino, C₃-₆ cycloalkylamino, or di(C₃-₆
cycloalkyl)amino;
20 each R⁹ is independently H or C₁-₄ alkyl; and
R¹₀ and R¹¹ are each independently hydroxy, OCH₂CH₂SC(=O)C₁-₄ alkyl,
OCH₂O(C=O)OC₁-₄ alkyl, NHCHMeCO₂Me, OCH(C₁-₄ alkyl)O(C=O)C₁-₄ alkyl,
In one embodiment of the present invention is the method of inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with a compound of structural formula II:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₂O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alkylxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alkylthio;
R⁷ and R⁸ are each independently hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and
each R⁹ is independently hydrogen or C₁-4 alkyl.

In a class of this embodiment of the present invention is the method of inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with a compound of structural formula III:
or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or
trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alklyloxy carbonyl,
CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally
substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alkylthio;
10 R⁸ is hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4
alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino;
each R⁹ is independently hydrogen or C₁-4 alkyl; and
R¹² is hydrogen, C₁-4 alkyl, or C₃-6 cycloalkyl.

In another class of this embodiment of the present invention is the
method of inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-
dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection
with a compound of structural formula IV:

or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alkylxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alkylthio;
R⁸ is hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and
each R⁹ is independently hydrogen or C₁-4 alkyl.

In yet another class of this embodiment of the present invention is the method of inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with a compound of structural formula V:

![Structural Formula V](image)

or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alkylxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alkylthio;
R⁸ is hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and
R⁹ is hydrogen or C₁-4 alkyl.
In a third embodiment of the present invention, the RNA-dependent RNA viral polymerase is a positive-sense single-stranded RNA-dependent RNA viral polymerase. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral polymerase is a *Flaviviridae* viral polymerase or a *Picornaviridae* viral polymerase. In a subclass of this class, the *Picornaviridae* viral polymerase is a rhinovirus polymerase or hepatitis A virus polymerase. In a second subclass of this class, the *Flaviviridae* viral polymerase is selected from the group consisting of hepatitis C virus polymerase, yellow fever virus polymerase, dengue virus polymerase, West Nile virus polymerase, Japanese encephalitis virus polymerase, and bovine viral diarrhea virus (BVDV) polymerase. In a subclass of this subclass, the *Flaviviridae* viral polymerase is hepatitis C virus polymerase.

In a fourth embodiment of the present invention, the RNA-dependent RNA viral replication is a positive-sense single-stranded RNA-dependent RNA viral replication. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral replication is *Flaviviridae* viral replication or *Picornaviridae* viral replication. In a subclass of this class, the *Picornaviridae* viral replication is rhinovirus replication or hepatitis A virus replication. In a second subclass of this class, the *Flaviviridae* viral replication is selected from the group consisting of hepatitis C virus replication, yellow fever virus replication, dengue virus replication, West Nile virus replication, Japanese encephalitis virus replication, and bovine viral diarrhea virus replication. In a subclass of this subclass, the *Flaviviridae* viral replication is hepatitis C virus replication.

In a fifth embodiment of the present invention, the RNA-dependent RNA viral infection is a positive-sense single-stranded RNA-dependent viral infection. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral infection is *Flaviviridae* viral infection or *Picornaviridae* viral infection. In a subclass of this class, the *Picornaviridae* viral infection is a rhinovirus infection or a hepatitis A virus infection. In a second subclass of this class, the *Flaviviridae* viral infection is selected from the group consisting of hepatitis C virus infection, yellow fever virus infection, dengue virus infection, West Nile virus infection, Japanese encephalitis virus infection, and bovine viral diarrhea virus infection. In a subclass of this subclass, the *Flaviviridae* viral infection is a hepatitis C virus infection.

Illustrative of the invention is a method for inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or
treating RNA-dependent RNA viral infection comprising administering a therapeutically effective amount of a compound selected from the group consisting of:

- cis-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
- cis-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
- cis-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
- cis-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
- cis-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
- cis-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
- cis-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-1,3-oxathiolane; 
cis-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl]-
1,3-oxathiolane; 
cis-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl]-
1,3-oxathiolane; 
cis-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-1,3-oxathiolane; 
cis-(2,4)-\textit{trans}-(4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-
5-methyl-1,3-dioxolane; 
cis-(2,4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-5-methyl-
1,3-dioxolane; 
cis-(2,5)-\textit{trans}-(4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-
4-methyl-1,3-oxathiolane; and 
cis-(2,4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-4-methyl-
1,3-oxathiolane; 
and the corresponding 2-triphosphates; 
or a pharmaceutically acceptable salt thereof.

Further illustrative of the invention is a method for inhibiting RNA-
dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, 
and/or treating RNA-dependent RNA viral infection comprising administering a 
therapeutically effective amount of a compound selected from the group consisting of: 
(2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-1,3-dioxolane; 
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-1,3-
dioxolane; 
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-1,3-
dioxolane; 
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-
1,3-dioxolane; 
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-
1,3-dioxolane; 
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-\textit{d}]pyrimidin-7-yl)-
1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and

(2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;
or a pharmaceutically acceptable salt thereof.

The present invention also provides the following novel compounds
which are useful as inhibitors of RNA-dependent RNA viral polymerase. The
compounds are also inhibitors of RNA-dependent RNA viral replication and are
useful for the treatment of RNA-dependent RNA viral infection:
cis-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
cis-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
cis-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-(2,4)-trans-(4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
cis-(2,4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
cis-(2,5)-trans-(4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and

cis-(2,4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;
or a pharmaceutically acceptable salt thereof.

Embodiments of the novel compounds of the present invention useful as inhibitors of RNA-dependent RNA viral polymerase, as inhibitors of RNA-dependent RNA viral replication, and/or for the treatment of RNA-dependent RNA viral infection are:
(2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathioliolate;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathioliolate;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathioliolate;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathioliolate;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathioliolate;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathioliolate;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,4R)-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and
(2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;
or a pharmaceutically acceptable salt thereof.

In a further embodiment the novel compounds of the present invention are useful as inhibitors of positive-sense single-stranded RNA-dependent RNA viral polymerase, inhibitors of positive-sense single-stranded RNA-dependent RNA viral replication, and/or for the treatment of positive-sense single-stranded RNA-dependent RNA viral infection. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA virus is a Flaviviridae virus or a Picornaviridae virus. In a subclass of this class, the Picornaviridae virus is a rhinovirus or a hepatitis A virus. In a second subclass of this class, the Flaviviridae virus is selected from the group consisting of hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Japanese encephalitis virus, and bovine viral diarrhea virus (BVDV). In a subclass of this subclass, the Flaviviridae virus is hepatitis C virus.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration.
Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, iso-hexyl, and the like.

The term “alkenyl” shall mean straight or branched chain alkenes of two to six total carbon atoms, or any number within this range (e.g., ethenyl, propenyl, butenyl, pentenyl, etc.).

The term “alkynyl” shall mean straight or branched chain alkynes of two to six total carbon atoms, or any number within this range (e.g., ethynyl, propynyl, butynyl, pentynyl, etc.).

The term “cycloalkyl” shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl).

The term “alkoxy” refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C1-4 alkoxy), or any number within this range [i.e., methoxy (MeO-), ethoxy, isopropoxy, etc.].

The term “alkythio” refers to straight or branched chain alkylsulfides of the number of carbon atoms specified (e.g., C1-4 alkythio), or any number within this range [i.e., methylthio (MeS-), ethylthio, isopropylthio, etc.].

The term “alkylsulfonyl” refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e.g., C1-6 alkylsulfonyl), or any number within this range [i.e., methylsulfonyl (MeSO2-), ethylsulfonyl, isopropylsulfonyl, etc.].

The term “alkyloxycarbonyl” refers to straight or branched chain esters of a carboxylic acid derivative of the present invention of the number of carbon atoms specified (e.g., C1-4 alkyloxycarbonyl), or any number within this range [i.e., methyloxycarbonyl (MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl].

The term “aryl” includes both phenyl and naphthyl. The aryl group is optionally substituted with one to three groups independently selected from C1-4 alkyl, halogen, cyano, nitro, trifluoromethyl, C1-4 alkoxy, and C1-4 alkythio.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term “substituted” shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or pluraly.
The term “triphosphate” refers to a triphosphoric acid ester derivative of the 2-hydroxymethyl group of a compound of the present invention having the following general structural formula VI:

![Structural formula VI](image)

(VI)

wherein $X$, $R^1$-$R^3$, and $R^5$-$R^8$ are as defined above. The compounds of the present invention are also intended to include pharmaceutically acceptable salts of the triphosphate ester as well as pharmaceutically acceptable salts of the monophosphate and diphosphate ester derivatives of the structural formulae VII and VIII, respectively.

![Structural formula VII](image)

(VII)

![Structural formula VIII](image)

(VIII)
The term "composition", as in "pharmaceutical composition," is intended to encompass a product comprising the active ingredient(s) and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The terms “administration of” and “administering a” compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need.

Another aspect of the present invention is concerned with a method of inhibiting HCV NS5B polymerase, inhibiting HCV replication, or treating HCV infection with a compound of the present invention in combination with one or more agents useful for treating HCV infection. Such agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, interferon-β, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and levovirin, and a combination of peginterferon-α and levovirin. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon-α2a (Pegasys™), interferon-α2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon-α2b (PegIntron™), a recombinant consensus interferon (such as interferon alfacon-1), and a purified interferon-α product. Amgen’s recombinant consensus interferon has the brand name Infergen®. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379 (assigned to ICN Pharmaceuticals). In accordance with this method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment, and the term “administering” is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention
with other agents useful for treating HCV infection includes in principle any combination with any pharmaceutical composition for treating HCV infection. When a compound of the present invention or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent active against HCV, the dose of each compound may be either the same as or different from the dose when the compound is used alone.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Both substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, GB-2337262, WO 02/48116, WO 02/48172, and U.S. Patent No. 6,323,180. HCV NS3 protease as a target for the development of inhibitors of HCV replication and for the treatment of HCV infection is discussed in B.W. Dymock, “Emerging therapies for hepatitis C virus infection,” Emerging Drugs, 6: 13-42 (2001).

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in de novo guanine nucleotide biosynthesis. Ribavirin is readily phosphorylated intracellularly and the monophosphate derivative is an inhibitor of IMPDH. Thus, inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the present invention may also be administered in combination with an inhibitor of IMPDH, such as VX-497, which is disclosed in WO 97/41211 and WO 01/00622 (assigned to Vertex); another IMPDH inhibitor, such as that disclosed in WO 00/25780 (assigned to Bristol-Myers Squibb); or mycophenolate mofetil [see A.C. Allison and E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent amantadine (1-aminoadamantane) [for a comprehensive description of this agent, see J. Kirschbaum, Anal. Profiles Drug Subs, 12: 1-36 (1983)]. The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-C-branched ribonucleosides disclosed in
R. E. Harry-O'kuru, et al., J. Org. Chem., 62: 1754-1759 (1997); M. S. Wolfe, et al., Tetrahedron Lett., 36: 7611-7614 (1995); U.S. Patent No. 3,480,613 (Nov. 25, 1969); International Publication Number WO 01/90121 (29 November 2001); International Publication Number WO 01/92282 (6 December 2001); and International Publication Number WO 02/32920 (25 April 2002); and International Publication Number WO 02/57287 (25 July 2002); the contents of each of which are incorporated by reference in their entirety. Such 2'-C-branched ribonucleosides include, but are not limited to, 2'-C-methyl-cytidine, 2'-C-methyl-uridine, 2'-C-methyl-adenosine, 2'-C-methyl-guanosine, and 9-(2-C-methyl-β-D-ribofuranosyl)-2,6-diaminopurine.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in WO 02/51425 (4 July 2002), assigned to Mitsubishi Pharma Corp.; WO 01/79246, WO 02/32920, and WO 02/48165 (20 June 2002), assigned to Pharmasset, Ltd.; WO 01/68663 (20 September 2001), assigned to ICN Pharmaceuticals; WO 99/43691 (2 Sept. 1999); WO 02/18404 (7 March 2002), assigned to Hoffmann-LaRoche; WO 02/57425 (25 July 2002), assigned to Merck & Co. and Isis Pharmaceuticals; and U.S. 2002/0019363 (14 Feb. 2002).


By “pharmaceutically acceptable” is meant that the carrier, diluent, or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Also included within the present invention are pharmaceutical compositions comprising the compounds of the present invention in association with a pharmaceutically acceptable carrier. Another example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.
Also included within the present invention are pharmaceutical compositions useful for inhibiting RNA-dependent RNA viral polymerase in particular HCV NS5B polymerase comprising an effective amount of a compound of the present invention and a pharmaceutically acceptable carrier. Pharmaceutical compositions useful for treating RNA-dependent RNA viral infection in particular HCV infection are also encompassed by the present invention as well as a method of inhibiting RNA-dependent RNA viral polymerase in particular HCV NS5B polymerase and a method of inhibiting RNA-dependent viral replication and in particular HCV replication. Additionally, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of another agent active against RNA-dependent RNA virus and in particular against HCV. Agents active against HCV include, but are not limited to, ribavirin, leovirin, viramidine, thymosin alpha-1, an inhibitor of HCV NS3 serine protease, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and leovirin, and a combination of peginterferon-α and leovirin. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), interferon-α2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), a consensus interferon, and a purified interferon-α product. For a discussion of ribavirin and its activity against HCV, see J.O. Saunders and S.A. Raybuck, “Inosine Monophosphate Dehydrogenase: Consideration of Structure, Kinetics, and Therapeutic Potential,” *Ann. Rep. Med. Chem.*, 35: 201-210 (2000).

Another aspect of the present invention provides for the use of the 1,3-dioxolane and 1,3-oxathiolane derivatives and their pharmaceutical compositions for the manufacture of a medicament for the inhibition of RNA-dependent RNA viral replication and/or the treatment of RNA-dependent RNA viral infection. Yet a further aspect of the present invention provides for 1,3-dioxolane and 1,3-oxathiolane derivatives and their pharmaceutical compositions for use as a medicament for the inhibition of RNA-dependent RNA viral replication and/or for the treatment of RNA-dependent RNA viral infection.

The pharmaceutical compositions of the present invention comprise a compound of structural formula I as an active ingredient or a pharmaceutically
acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of structural formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a
lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of structural formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of structural formula I are administered orally.

For oral administration to humans, the dosage range is 0.1 to 1000 mg/kg body weight in divided doses. One preferred dosage range is 0.1 to 200 mg/kg body weight in divided doses. Another preferred dosage range is 0.5 to 100 mg/kg body weight in divided doses. For oral administration, the compositions are preferably provided in the form of tablets or capsules containing 1.0 to 1000 milligrams of the active ingredient, particularly, 1, 5, 10, 15, 20, 25, 50, 75, 100, 150,
200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The compounds of the present invention contain one or more asymmetric centers which are marked by an asterisk (*) on the general formula I and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of structural formula I. Thus, the present invention is meant to include 1,3-dioxolane and 1,3-oxathiolane derivatives having either the β-D or β-L stereochemical configuration for the five-membered residue as depicted below. The β-D and β-L forms constitute optical antipodes (mirror images of one another or enantiomers).

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I.

Compounds of structural formula I may be separated into their individual diastereoisomers by, for example, fractional crystallization from a suitable
solvent, for example methanol or ethyl acetate or a mixture thereof, or via chiral
cchromatography using an optically active stationary phase.

Alternatively, any stereoisomer of a compound of the structural
formula I may be obtained by stereospecific synthesis using optically pure starting
materials or reagents of known configuration.

The compounds of the present invention may be administered in the
form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable
salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or
acids including inorganic or organic bases and inorganic or organic acids. . Salts of
basic compounds encompassed within the term "pharmaceutically acceptable salt"
refer to non-toxic salts of the compounds of this invention which are generally
prepared by reacting the free base with a suitable organic or inorganic acid.
Representative salts of basic compounds of the present invention include, but are not
limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate,
bitartrate, borate, bromide, camysylate, carbonate, chloride, clavulanate, citrate,
dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluteptate, gluconate,
glutamate, glycollylasanilate, hexylresorcinate, hydrabamine, hydroybromide,
hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate,
malate, maleate, mandelate, mesylate, methylbromide, methylchloride, methyl sulfate,
mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate,
pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate,
polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate,
teoclrate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the
invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof
include, but are not limited to, salts derived from inorganic bases including aluminum,
ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic,
mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the
ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from
pharmaceutically acceptable organic non-toxic bases include salts of primary,
secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as
arginine, betaine, caffeine, choline, N,N-dibenzylethlenediamine, diethylamine, 2-
diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-
ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine,
isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine,
polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present invention, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as acetate or maleate, can be employed. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

Preparation of the Dioxolane and Oxathiolane Derivatives of the Invention


Useful intermediates in the preparation of compounds of the present invention of structural formula I wherein X represents O and R² and R³ are hydrogen are (2R)-2-benzoyloxymethyl-4-(R,S)-acetoxy-1,3-dioxolane (IX) and (2S)-2-benzoyloxymethyl-4-(R,S)-acetoxy-1,3-dioxolane (X).
Useful intermediates in the preparation of compounds of the present invention of structural formula I wherein X represents S and R² and R³ are hydrogen are (2S)-2-benzoyloxymethyl-5-(R,S)-acetoxy-1,3-oxathiolane (XXVI) and (2R)-2-benzoyloxymethyl-5-(R,S)-acetoxy-1,3-oxathiolane (XXVII), whose syntheses are described in U.S. Patent No. 5,466,806, which is incorporated by reference herein in its entirety.

Generally the compounds of the present invention are prepared as outlined in Schemes 1 and 2 below by converting intermediates IX, X, XXVI, and XXVII into their corresponding 4-bromo (X=O) or 5-bromo (X=S) derivatives XI and XII, respectively, for example by treatment with bromotrimethylsilane in dichloromethane or HBr/acetic acid in dichloromethane. The bromo compounds can subsequently be reacted with the appropriately substituted 1H-pyrrolo[2,3-d]pyrimidine of structural formula XIII in the presence of potassium hydroxide and tris[2-(2-methoxyethoxy)ethyl]amine in acetonitrile or, alternatively, with the anion of the appropriately substituted 1H-pyrrolo[2,3-d]pyrimidine of structural formula XIII in a suitable organic solvent, such as tetrahydrofuran, acetonitrile, or N,N-dimethylformamide. The anion can be generated with a base such as sodium hydride in a suitable organic solvent, such as tetrahydrofuran, N,N-dimethylformamide, and acetonitrile. A number of precursor 5-substituted pyrrolo[2,3-d]-pyrimidines are disclosed in WO 02/57287 (25 July 2002), the contents of which are incorporated by reference herein in their entirety. The final step in the process consists of removal of
the benzyl or benzoyle protecting group on the C-2 hydroxymethyl group of the 1,3-dioxolane or 1,3-oxathioline ring, such as by catalytic hydrogenation or by mild basic hydrolysis, respectively. For the preparation of compounds having an optionally substituted amino group at the 4-position of the pyrrolo[2,3-d]pyrimidine ring, an appropriately substituted 4-chloro-1H-pyrrolo[2,3-d]pyrimidine is employed in the condensation reaction with intermediate XI or XII, and the 4-chloro group in the derived condensation product is displaced by reaction with an optionally substituted amine, such as aqueous ammonia, methanolic ammonia, and liquid ammonia, at elevated temperatures. Treatment with such an amine may also proceed in the same step with removal of the benzyol protecting group on the C-2 hydroxymethyl group of the 1,3-oxathioline. Otherwise the benzyol protecting group may be removed in a further step by mild basic hydrolysis. Benzyl protection may be removed by catalytic hydrogenation subsequent to optional substitution of the 4-chloro functionality. Preferred conditions for cleavage of the benzyl protecting group are transfer hydrogenation conditions using Pd/C and ammonium formate in refluxing methanol or hydrogenation in methanol using palladium hydroxide as catalyst.

For the preparation of compounds having an optionally substituted hydroxyl group at the 4-position of the pyrrolo[2,3-d]pyrimidine ring, an appropriately substituted 4-chloro-1H-pyrrolo[2,3-d]pyrimidine is employed in the condensation reaction with intermediate XI or XII, and the 4-chloro group in the derived condensation product is hydrolyzed with aqueous base, such as with aqueous sodium hydroxide in 1,4-dioxane, containing about 4-5 equivalents of mercaptoethanol. These conditions will also cleave the hydroxymethyl benzoyle protecting group on the dioxolane or oxathiolate ring.

For the preparation of compounds of the present invention wherein \( R^6 \) is cyano and \( R^7 \) is hydroxy, the 4-chloro group in the intermediate derived from the condensation reaction above is displaced by reaction with syn-2-pyridinealdoxime and tetramethylguanidine in a mixture of DMF and dioxane.
Scheme 1

(IX) \[ \text{bromination} \rightarrow \text{XI} \]

(XIII) \[ \text{base} \rightarrow \] (X = O or S)

(Y = benzyl for X=O and benzoyl for X=S)

deprotection

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Useful starting materials in the preparation of compounds of the present invention of structural formula I wherein X is O, R² is hydrogen, and R³ is methyl are (4R,5S)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (XIV) and (4S,5R)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (XV), which are available from commercial suppliers.
Structures XIV and XV can be converted into intermediates XIX, XX, XXIV and XXV as outlined in Schemes 3 and 4 below by reaction with benzyl oxy acetaldehyde and para-toluene sulfonic acid (pTSA), followed by mild basic hydrolysis, for example with aqueous LiOH in THF, followed by reaction with lead tetraacetate and pyridine in a suitable organic solvent such as acetonitrile.

**Scheme 3**

(Bn= benzyl)

(XIV) \[\xrightarrow{\text{BnO}}\] (XVI) 

(XVII) \[\xrightarrow{\text{BnO}}\] (XVIII) 

(XIX) \[\xrightarrow{\text{Pb(OAc)}_4}\] (XX)
Intermediates XIX, XX, XXIV, and XXV can be converted into compounds of the present invention by introduction of the appropriately substituted 1H-pyrrolo[2,3-d]pyrimidine ("7-deaza-purine") following procedures outlined in Schemes 1 and 2 above.

Useful starting materials in the preparation of compounds of the present invention of structural formula I wherein X is S, R² is hydrogen, and R³ is methyl are (2S,3R)- and (2S,3S)-3-mercaptop-2-hydroxybutanoic acid (XXVIII and XXIX, respectively).
As outlined in Scheme 5, methyl trans-2,3-epoxybutanoate (prepared by epoxidation of methyl crotonate) can be saponified with alcoholic NaOH [following the procedure for preparation of the corresponding potassium salt described in J. Org. Chem., 61: 7212-7216 (1996)] and the derived sodium salt treated with sodium sulfide in methanol to yield an isomeric mixture of XXVIII and XXIX (similar to the method described in Tetrahedron Lett. 6625-6628, 1991) which can be converted into intermediates XXXIV, XXXV, XXXVI and XXXVII by condensation with benzoyloxyacetaldehyde upon exposure to boron trifluoride etherate and further treatment with lead tetraacetate in DMF [similar to the method described in Tetrahedron Lett., 33: 4625-4628, (1992)].
Intermediates XXXIV, XXXV, XXXVI and XXXVII can be converted into the corresponding (2S,4R,5R)-, (2R,4R,5S)-, (2S,4S,5R)- and (2R,4S,5S)-2-hydroxymethyl-5-(substituted)-4-methyl-1,3-oxathiolanes of the present invention using the procedures outlined in Scheme 1 and 2.

Examples of the preparation of the 1,3-dioxolane and 1,3-oxathiolane derivatives of the present invention are given below. These examples, however, are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed. Those skilled in the art of nucleoside and nucleotide synthesis will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these and other compounds of the present invention. All temperatures are degrees Celsius unless otherwise noted.

EXAMPLE 1

(2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane and (2R,4S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane
Step A: \((2R,4R)-2\text{-benzyloxymethyl}-4-(4\text{-chloro}-1\text{-H-pyrrolo}[2,3-d]\text{pyrimidin}-7\text{-yl})-1,3\text{-dioxolane}\) and \((2R,4S)-2\text{-benzyloxymethyl}-4-(4\text{-chloro}-1\text{-H-pyrrolo}[2,3-d]\text{pyrimidin}-7\text{-yl})-1,3\text{-dioxolane}\)

To a pre-cooled (0°C) solution of \((2R)-2\text{-benzyloxymethyl}-4\text{-acetoxy}-1,3\text{-dioxolane}\) (IX; \(X = O\)) (380 mg, 1.50 mmol) in dichloromethane (6 mL) was added bromotrimethylsilane (0.390 mL, 3.00 mmol) dropwise. The resulting solution was stirred at 0°C for 15 min, then allowed to come to room temperature and stirred for another 30 min. The solution was evaporated in vacuo, coevaporated once from acetonitrile (10 mL) and redissolved in acetonitrile (6 mL). The solution was added to a vigorously stirred solution of 4-chloro-1\text{-H-pyrrolo}[2,3-d]\text{pyrimidine} (230 mg, 1.50 mmol), KOH (252 mg, 4.50 mmol) and tris[2-(2\text{-methoxyethoxy})ethy]amine (0.096 mL, 0.30 mmol) in acetonitrile (8 mL). The mixture was stirred at room temperature for 20 min, and then poured into a stirred mixture of saturated aqueous sodium bicarbonate (100 mL) and diethyl ether (150 mL). The organic phase was separated, dried over magnesium sulfate, and evaporated in vacuo. The crude product was purified on silica gel using ethyl acetate/hexane (1:4) as the eluent to give the desired compounds (23% (cis) and 15% (trans)) as colorless oils.

Step B: \((2R,4R)-2\text{-benzyloxymethyl}-4-(4\text{-amino}-1\text{-H-pyrrolo}[2,3-d]\text{pyrimidin}-7\text{-yl})-1,3\text{-dioxolane}\) and \((2R,4S)-2\text{-benzyloxymethyl}-4-(4\text{-amino}-1\text{-H-pyrrolo}[2,3-d]\text{pyrimidin}-7\text{-yl})-1,3\text{-dioxolane}\)

To the individual compounds from Step A (0.080 g, 0.23 mmol) was added methanolic ammonia (10 mL). This mixture was stirred in a sealed container at 80°C for 12 h, cooled and evaporated under diminished pressure. The crude product was purified on silica gel using a gradient of dichloromethane in methanol as the eluent to give the desired (61% (cis) and 61% (trans)) compounds.
Step C: (2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane and (2R,4S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane

To the individual compounds from Step B (0.035 g, 0.107 mmol) in methanol (8 mL) were added ammonium formate (0.044 g, 0.70 mmol) and 10% Pd/C (0.025 g). The resulting mixture was heated to reflux for 45 min. The mixture was cooled, filtered through celite and evaporated in vacuo. The filtrates were adsorbed onto silica gel and purified over silica gel using a gradient of dichloromethane in methanol as the eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired products (63% (cis) and 63% (trans)).

$^1$H-NMR (200 MHz, methanol-d$_4$) (cis): $\delta$ 3.73 (d, J = 3.2 Hz, 2H), 4.24 (dd, J = 5.6, 9.6 Hz, 1H), 4.36 (dd, J = 2.0, 9.6 Hz, 1H), 5.10 (t, J = 3.2 Hz, 1H), 6.59 (m, 2H), 7.39 (d, J = 3.6 Hz, 1H), 8.07 (s, 1H).

$^1$H-NMR (200 MHz, methanol-d$_4$) (trans): $\delta$ 3.61 (d, J = 3.2 Hz), 4.33 (dd, J = 3.2, 9.2 Hz, 1H), 4.44 (dd, J 5.6, 9.2 Hz, 1H), 5.46 (t, J = 4.3 Hz, 1H), 6.64 (m, 2H), 7.27 (d, J = 3.8 Hz, 1H), 8.09 (s, 1H).

EXAMPLE 2

(2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane triphosphate and (2R,4S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane triphosphate
To a solution of the appropriate compound from Example 1 (0.10 mmol) in trimethylphosphate (0.5 mL) is added 4Å molecular sieves (about 20). The mixture is stirred overnight in a sealed container, cooled to 0°C and phosphorus oxychloride (0.014 mL, 0.15 mmol) is added. The mixture is stirred for 3 h at 0°C, then tributylamine (0.060 mL, 0.25 mmol), tributylammonium pyrophosphate (0.25 mmol, 181 mg) and acetonitrile (0.25 mL) are added. The mixture is stirred for an additional 30 min at 0°C, and the reaction then quenched by addition of triethylammonium bicarbonate (1M) (0.5 mL) and water (5 mL). The crude product is purified by ion-exchange chromatography and desalted by reverse-phase high performance liquid chromatography.

EXAMPLE 3

(2R,4R)-2-hydroxymethyl-4-(4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane and (2R,4S)-2-hydroxymethyl-4-(4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane
Step A: (2R,4R)-2-benzylxymethyl-4-(4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane and (2R,4S)-2-benzylxymethyl-4-(4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane

A suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine in acetonitrile (5.0 mL) was added bis-(trimethylsilyl)acetamide (0.52 mL, 2.12 mmol) and the solution was heated under reflux for 30 min. The solution was cooled to 0°C and to this was added the solution of (2R)-2-benzylxymethyl-4-acetoxy-1,3-dioxolane (IX; X = O) (0.13 g, 0.50 mmol) in acetonitrile (3.0 mL) and trimethylsilyl trifluoromethanesulphonate (0.31 mL, 1.70 mmol) dropwise. After the addition was completed, the reaction mixture was stirred at room temperature for 2 h. The solution was taken in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (2 x 50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified over silica gel using a gradient of hexane and ethyl acetate as eluent to give the products as a diastereomeric mixture (yield 16%).

Step B: (2R,4R)-2-hydroxymethyl-4-(4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane and (2R,4S)-2-hydroxymethyl-4-(4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane

To a solution of the compounds from Step A in methanol (3 mL) was added ammonium formate (0.02 g) and 10% Pd/C (0.015 g). The resulting mixture was heated to reflux for 30 min. The mixture was cooled to room temperature and filtered. The filtrate was adsorbed directly onto silica gel and purified over silica gel using a gradient of dichloromethane in methanol as eluent to give the desired compound as a mixture of diastereoisomers.

1H NMR (200 MHz, methanol-d₄) (cis): δ 3.86 (d, 2H), 4.29 (d, 2H), 5.09 (t, 1H), 6.60 (m, 2H), 7.03 (d, 1H), 8.63 (s, 1H).
\(^1\)H NMR (200 MHz, methanol-d\(_4\)) (trans): \(\delta\) 3.67 (m, 2H), 4.11 (m, 1H), 4.58 (dd, 1H), 5.57 (t, 1H), 6.50 (dd, 1H), 7.05 (d, 1H), 8.18 (s, 1H).

**EXAMPLE 4**

\((2R,4R)-2\text{-hydroxymethyl}-4-(4\text{-hydroxy-1H-pyrrolo}[2,3-\text{d}]pyrimidin-7-yl)-1,3\text{-dioxolane triphosphate and (2R,4S)-2\text{-hydroxymethyl}-4-(4\text{-hydroxy-1H-pyrrolo}[2,3-\text{d}]pyrimidin-7-yl)-1,3\text{-dioxolane triphosphate}\)

To a solution of the appropriate compound from Example 3 (0.10 mmol) in trimethylphosphite (0.5 mL) is added 4Å molecular sieves (about 20). The mixture is stirred overnight in a sealed container, cooled to 0°C and phosphorus oxychloride (0.014 mL, 0.15 mmol) is added. The mixture is stirred for 3 h at 0°C, then tributylamine (0.060 mL, 0.25 mmol), tributylammonium pyrophosphate (0.25 mmol, 181 mg) and acetonitrile (0.25 mL) are added. The mixture is stirred for an additional 30 min at 0°C, and the reaction then quenched by addition of triethylammonium bicarbonate (1M) (0.5 mL) and water (5 mL). The crude product is purified by ion-exchange chromatography and desalted by reverse-phase high performance liquid chromatography.
EXAMPLE 5

(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane

Step A:  (2R,4S,5R)-2-(benzoyloxymethyl)-5-methyl-1,3-dioxolane-4-carboxylic acid methyl ester

To a solution of (4S,5R)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylic acid methyl ester (5.25 g, 30.1 mmol) and benzoyloxyacetalddehyde (4.53 g, 30.1 mmol) in toluene (40 mL) at 80°C was added para-toluensulfonic acid (0.255 g, 1.33 mmol). The solution was distilled under vacuum at 80°C for 40 min. The reaction mixture was cooled to room temperature and evaporated to dryness. The crude product was purified on silica gel using 1:3 ethyl acetate/hexane as the eluent affording the title compound as a mixture of diastereoisomers (4.01 g) which was used in the next step.

Step B:  (2R,4S,5R)-2-(benzoyloxymethyl)-5-methyl-1,3-dioxolane-4-carboxylic acid

To a solution of the compounds from Step A (4.01 g, 16.8 mmol) in tetrahydrofuran (THF) (7 mL) was added 1N LiOH (7 mL) at 4°C. The mixture was stirred at room temperature for 60 min, the THF was removed in vacuo and the solution acidified to pH 2 using 30% aq. HCl. The aqueous phase was extracted with ethyl acetate (200 mL), and the organic phase dried over magnesium sulfate and evaporated in vacuo. The crude product was purified on silica gel using 2% acetic acid/dichloromethane as the eluent to give the title compound (2.5 g).

Step C:  (2R,4RS,5R)-2-benzoyloxymethyl-4-acetoxy-5-methyl-1,3-dioxolane
To a pre-cooled solution of the compound from Step B (2.5 g, 9.92 mmol) and pyridine (1.13 g, 14.3 mmol) in acetonitrile was added lead tetraacetate (5.50 g, 12.4 mmol) over 10 min. The mixture was stirred overnight at room temperature, filtered and poured into a solution of saturated aqueous sodium bicarbonate. The organic phase was separated, and the aqueous phase extracted with ethyl acetate. The combined organic phase was concentrated and purified by column chromatography on silica gel using ethyl acetate/hexane (1:3) as the eluent to give the product as a diastereoisomeric mixture (1.01 g).

**Step D:** (2R,4R,5R)-2-benzylxoxymethyl-4-(4-chloro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5R)-2-benzylxoxymethyl-4-(4-chloro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane

To a pre-cooled (0°C) solution of the compound from Step C, (2R,4RS,5R)-2-benzylxoxymethyl-4-acetoxy-5-methyl-1,3-dioxolane (XXIV; X = O) (200 mg, 0.75 mmol) in dichloromethane (3 mL) was added bromotrimethylsilane (0.459 mg, 3.00 mmol) dropwise. The resulting solution was stirred at 0°C for 30 min, then allowed to come to room temperature and stirred for another 30 min. The solution was evaporated in vacuo, coevaporated once from acetonitrile (10 mL) and redissolved in acetonitrile (5 mL). The solution was added to a vigorously stirred solution of 4-chloro-1H-pyrrolo[2,3-d]pyrimidine (153 mg, 1.00 mmol), KOH (168 mg, 3.00 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (65 mg, 0.20 mmol) in acetonitrile (5 mL). The mixture was stirred at room temperature for 20 min, and then poured into a stirred mixture of saturated aqueous sodium bicarbonate (75 mL) and diethyl ether (100 mL). The organic phase was separated, dried over magnesium sulfate, and evaporated in vacuo. The crude product was purified on silica gel using ethyl acetate/hexane (1:4) as the eluent to give the desired compounds (94.8 and 61.1 mg of the cis and trans isomers, respectively) as colorless oils.

**Step E:** (2R,4R,5R)-2-benzylxoxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5R)-2-benzylxoxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane

To the individual compounds from Step D (60 mg, 0.17 mmol) was added methanolic ammonia (10 mL). This mixture was stirred in a sealed container at
80°C for 12 h, cooled and evaporated in vacuo. The crude product was purified on silica gel using dichloromethane/methanol (19:1) as the eluent to give the desired compounds (49.2 and 46.9 mg of the cis and trans isomers, respectively) as colorless oils.

**Step F:**

(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane

To the individual compounds from Step E (40 mg, 1.07 mmol) in methanol (3 mL) was added Pd(OH)_2 on carbon (5 mg). The resulting mixture was stirred under hydrogen for 48 h, filtered through celite and evaporated in vacuo to give the desired products (18 and 17 mg of the cis and trans isomers, respectively) as hygroscopic solids.

**1H-NMR (200 MHz, methanol-d_4) (cis):** δ 0.92 (d, J=6.2 Hz, 3H), 3.73 (d, J = 2.6 Hz, 2H), 4.36 (m, 1H), 5.10 (t, J = 2.6 Hz, 1H), 6.64 (d, J=4.8 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 7.92 (d, J= 3.7 Hz, 1H), 8.26 (s, 1H).

**1H-NMR (200 MHz, methanol-d_4) (trans):** δ 1.44 (d, J=6.4 Hz, 3H), 3.67 (d, J = 3.2 Hz, 2H), 4.58 (m, 1H), 5.54 (t, J = 3.2 Hz, 1H), 6.12 (d, J=5.4 Hz, 1H), 6.95 (d, J = 3.8 Hz, 1H), 7.65 (d, J= 3.8 Hz, 1H), 8.27 (s, 1H).

**EXAMPLE 6**

(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane triphosphate and (2R,4S,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane triphosphate
To a solution of the appropriate compound from Example 5 (0.10 mmol) in trimethylphosphate (0.5 mL) is added 4Å molecular sieves (about 20). The mixture is stirred overnight in a sealed container, cooled to 0°C and phosphorus oxychloride (0.014 mL, 0.15 mmol) is added. The mixture is stirred for 3 h at 0°C, then tributylamine (0.060 mL, 0.25 mmol), tributylammonium pyrophosphate (0.25 mmol, 181 mg) and acetonitrile (0.25 mL) are added. The mixture is stirred for an additional 30 min at 0°C, and the reaction then quenched by addition of triethylammonium bicarbonate (1M) (0.5 mL) and water (5 mL). The crude product is purified by ion-exchange chromatography and desalted by reverse-phase high performance liquid chromatography.

EXAMPLE 7

(2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimdin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimdin-7-yl)-5-methyl-1,3-dioxolane
Step A: (2R,4R,5S)-2-(Benzyloxymethyl)-5-methyl-1,3-dioxolane-4-carboxylic acid methyl ester

To a solution of (4R,5S)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylic acid methyl ester (5.25 g, 30.1 mmol) and benzylxyacetaldehyde (4.53 g, 30.1 mmol) in toluene at 80°C is added para-toluenesulfonic acid (0.255 g, 1.33 mmol). This solution is distilled under vacuum. The reaction mixture is cooled to room temperature and evaporated to dryness. The crude product is purified on silica gel using ethyl acetate/hexane as the eluent affording the title compound as a mixture of diastereoisomers which is used in the next step.

Step B: (2R,4R,5S)-2-(Benzyloxymethyl)-5-methyl-1,3-dioxolane-4-carboxylic acid

To a solution of the compounds from Step A (4.01, 16.8 mmol) in THF (7 mL) is added 1.0 N LiOH (7 mL) at 4°C. The mixture is stirred at room temperature for 60 min, the THF is removed in vacuo and the solution acidified to pH 2 using 30% aqueous HCl. The aqueous phase is extracted with ethyl acetate (200 mL), and the organic phase dried over magnesium sulfate and evaporated in vacuo. The crude product is purified on silica gel using 2% acetic acid/dichloromethane as the eluent to give the title compound.

Step C: (2R,4RS,5R)-2-benzyloxymethyl-4-acetoxy-5-methyl-1,3-dioxolane

To a pre-cooled solution of the compound from Step B (2.5 g, 9.92 mmol) and pyridine (1.13 g, 14.3 mmol) in acetonitrile is added lead tetraacetate (5.50 g, 12.4 mmol) over 10 min. The mixture is stirred overnight at room temperature, filtered and poured into a solution of saturated aqueous sodium bicarbonate. The organic phase is separated, and the aqueous phase extracted with ethyl acetate. The combined organic phase is concentrated and purified by column chromatography on
silica gel using ethyl acetate/hexane (1:3) as the eluent to give the product as a diastereoisomeric mixture.

Step D: (2R,4R,5S)-2-benzyloxymethyl-4-(4-chloro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5S)-2-benzyloxymethyl-4-(4-chloro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane

To a pre-cooled (0°C) solution of the compound from Step C, (2R,4RS,5R)-2-benzyloxymethyl-4-acetoxy-5-methyl-1,3-dioxolane (XXIV; X = O) (266 mg, 1.00 mmol) in dichloromethane (5 mL) is added bromotrimethylsilane (0.459 mg, 3.00 mmol) dropwise. The resulting solution is stirred at 0°C for 30 min, then allowed to come to room temperature and stirred for another 30 min. The solution is evaporated in vacuo, co-evaporated once from acetonitrile (10 mL) and re-dissolved in acetonitrile (5 mL). The solution is added to a vigorously stirred solution of 4-chloro-1H-pyrrolo[2,3-d]pyrimidine (153 mg, 1.00 mmol), KOH (168 mg, 3.00 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (65 mg, 0.20 mmol) in acetonitrile (5 mL). The mixture is stirred at room temperature for 20 min, and then poured into a stirred mixture of saturated aqueous sodium bicarbonate (75 mL) and diethyl ether (100 mL). The organic phase is separated, dried over magnesium sulfate, and evaporated in vacuo. The crude product is purified on silica gel using ethyl acetate/hexane as the eluent to give the desired compounds.

Step E: (2R,4R,5S)-2-benzyloxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5S)-2-benzyloxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane

To the individual compounds from Step D (60 mg, 0.17 mmol) is added methanolic ammonia (10 mL). This mixture is stirred in a sealed container at 80°C for 12 h, cooled and evaporated in vacuo. The crude product is purified on silica gel using dichloromethane/methanol (19:1) as the eluent to give the desired compounds as colorless oils.

Step F: (2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane and (2R,4S,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane
To the individual compounds from Step E (40 mg, 0.11 mmol) in methanol (3 mL) is added Pd(OH)$_2$ on carbon (5 mg). The resulting mixture is stirred under hydrogen for 48 h, filtered through celite and evaporated in vacuo to give the desired products.

**EXAMPLE 8**

(2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-$d$]pyrimidin-7-yl)-5-methyl-1,3-dioxolane 2-triphosphate and (2R,4S,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-$d$]pyrimidin-7-yl)-5-methyl-1,3-dioxolane 2-triphosphate

![Chemical Structure]

To a solution of the appropriate compound from Example 7 (0.10 mmol) in trimethylphosphate (0.5 mL) is added 4Å molecular sieves (about 20). The mixture is stirred overnight in a sealed container, cooled to 0°C and phosphorus oxychloride (0.014 mL, 0.15 mmol) is added. The mixture is stirred for 3 h at 0°C, then tributylamine (0.060 mL, 0.25 mmol), tributylammonium pyrophosphate (0.25 mmol, 181 mg) and acetonitrile (0.25 mL) are added. The mixture is stirred for an additional 30 min at 0°C, and the reaction then quenched by addition of triethylammonium bicarbonate (1M) (0.5 mL) and water (5 mL). The crude product is
purified by ion-exchange chromatography and desalted by reverse-phase high performance liquid chromatography.

EXAMPLE 9

\[(2S,5R)-2\text{-hydroxymethyl-5-(4-amino-1}H\text{-pyrrolo[2,3-}d\text{]pyrimidin-7-yl)}-1,3\text{-oxathiolane}\]

Step A: \[(2S,5R)-2\text{-benzoyloxymethyl-5-(4-chloro-1}H\text{-pyrrolo[2,3-}d\text{]pyrimidin-7-yl)}-1,3\text{-oxathiolane}\]

This compound is prepared from \[(2S)-2\text{-benzoyloxymethyl-5-acetoxy-1,3-oxathiolane (XXVI)} (2.82 g, 10 mmol)\] according to the procedure described for Example 1, Step A.

Step B: \[(2S,5R)-2\text{-hydroxymethyl-5-(4-amino-1}H\text{-pyrrolo[2,3-}d\text{]pyrimidin-7-yl)}-1,3\text{-oxathiolane}\]

This compound is made from the compound of Step A \[(0.38 g, 1.0 mmol)\] according to the procedure described for Example 1, Step B.

EXAMPLE 10

\[(2S,5R)-2\text{-hydroxymethyl-5-(4-amino-1}H\text{-pyrrolo[2,3-}d\text{]pyrimidin-7-yl)}-1,3\text{-oxathiolane 2-triphosphate}\]
This compound is made from the compound of Example 9 (25 mg, 0.1 mmol) according to the procedure for Example 2.

EXAMPLE 11

(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane

Step A: Methyl trans-2,3-epoxybutanoate
This compound is prepared according to the procedure of Glabe et al., J. Org. Chem., 61: 7212-7216 (1996).

Step B: Sodium trans-2,3-epoxybutanoate
A cold solution of NaOH (10 g, 0.25 mol) in ethanol (200 mL) is added in portions to a 0°C solution of the compound from Step A (29.0 g, 0.25 mol) in ethanol (100 mL) and the solution is stirred at room temperature overnight. The sodium salt is filtered, washed with cold ethanol and recrystallized from ethanol to give the desired compound.

Step C: (2S,3R)- and (2S,3S)-3-mercaptop-2-hydroxybutanoic acid
A mixture of compound from Step B (12.4 g, 0.1 mol) and sodium sulfide (7.81 g, 0.1 mol) in methanol (500 mL) is stirred at room temperature for 6 h and then evaporated. The residue is suspended in water (300 mL) and the pH adjusted to 5 with 2N HCl, extracted three times with methylene chloride, dried (MgSO₄) and solvent evaporated under diminished pressure to yield a mixture of diastereomers which is used in the condensation Step D below without further purification.

**Step D:**

(2S,4R,5R)-, (2S,4S,5R)-, (2S,4S,5R)-, (2R,4R,5R)-2-benzoyloxy methyl-4-methyl-1,3-oxathiolane-5-carboxylic acid

Boron trifluoride diethyl etherate (2.2 mL, 17.5 mmol) is added dropwise to the mixture of compound from Step C (3.4 g, 25 mmol) and 2-benzoyloxyacetaldehyde (4.1 g, 25 mmol) in acetonitrile (100 mL). The reaction mixture is stirred at room temperature for 1 day, then quenched with water (5 mL) and evaporated in vacuum to give a mixture of diastereomeric acids, which are separated on a silica gel column with hexanes/EtOAc as eluent.

**Step E:**

(2S,4R,5RS)-5-acetoxy-2-benzoyloxy methyl-4-methyl-1,3-oxathiolane

To a solution of the (2S,4R,5R)-isomer from Step D (1.41 g, 5 mmol) in DMF (25 mL) is added slowly lead tetraacetate (2.7 g, 6 mmol) at 0-5 °C. The mixture is stirred at room temperature overnight, evaporated and the residue partitioned between saturated aqueous sodium bicarbonate (100 mL) and CH₂Cl₂ (200 mL). The aqueous layer is again extracted with CH₂Cl₂ (2 × 100 mL) and the combined extracts washed with water, brine, dried (MgSO₄) and evaporated under diminished pressure. The crude product is purified on a silica gel column with hexanes/EtOAc as eluent to give the desired compound as a diastereomeric mixture.

**Step F:**

(2S,4R,5R)-2-benzoyloxy methyl-5-(4-chloro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane

This compound is prepared from the compound of Step E (2.96 g, 10 mmol) according to the procedure described for Example 1, Step A.

**Step G:**

(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane
This compound is made from the compound of Step F (0.39 g, 1.0 mmol) according to the procedure described for Example 1, Step B.

EXAMPLE 12

(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane 2-triphosphate

This triphosphate derivative is prepared from the compound of Example 11 (27 mg, 0.1 mmol) according to the procedure for Example 2.

EXAMPLE 13

(2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane

Step A: (2S,4S,5RS)-5-acetoxy-2-benzoyloxymethyl-4-methyl-1,3-oxathiolane
This compound is prepared from the (2S,4S,5R)-isomer of Step D of Example 11 (1.41 g, 5 mmol), following the procedure described for Example 11, Step E.

Step B: (2S,4S,5R)-2-benzyloxymethyl-5-(4-chloro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane

This compound is prepared from the compound of Step A (2.96 g, 10 mmol) according to the procedure described for Example 1, Step A.

Step C: (2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane

This compound is made from the compound of Step B (0.39 g, 1.0 mmol) according to the procedure described for Example 1, Step B.

EXAMPLE 14

(2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane 2-triphosphate

This triphosphate derivative is prepared from the compound of Example 13 (27 mg, 0.1 mmol) according to the procedure for Example 2.

BIOLOGICAL ASSAYS

The assays employed to measure the inhibition of viral RNA-dependent RNA polymerase and RNA-dependent RNA viral replication are described below.
The effectiveness of the compounds of the present invention as inhibitors of HCV NS5B RNA-dependent RNA polymerase (RdRp) was measured in the following assay.

5 A. Assay for Inhibition of HCV NS5B Polymerase:

This assay was used to measure the ability of the compounds of the present invention to inhibit the enzymatic activity of the RNA-dependent RNA polymerase (NS5B) of the hepatitis C virus (HCV) on a heteromeric RNA template.

10 Procedure:

Assay Buffer Conditions: (50 µl -total/reaction)
20 mM Tris, pH 7.5
50 µM EDTA
5 mM DTT
15 2 mM MgCl₂
80 mM KCl
0.4U/µl RNASin (Promega, stock is 40 units/µL)
0.75 µg t500 (a 500-nt RNA made using T7 runoff transcription with a sequence from the NS2/3 region of the hepatitis C genome)
20 1.6 µg purified hepatitis C NS5B (form with 21 amino acids C-terminally truncated)
1 µM A₃,C,U,GTP (Nucleoside triphosphate mix)
[alpha-³²P]-GTP or [alpha-³²P]-GTP

The compounds were tested at various concentrations up to 100 µM

25 final concentration.

An appropriate volume of reaction buffer was made including enzyme and template t500. Compounds of the present invention were pipetted into the wells of a 96-well plate. A mixture of nucleoside triphosphates (NTP’s), including the radiolabeled GTP, was made and pipetted into the wells of a 96-well plate. The reaction was initiated by addition of the enzyme-template reaction solution and allowed to proceed at room temperature for 1-2 hours.

30 The reaction was quenched by addition of 20 µL 0.5M EDTA, pH 8.0. Blank reactions in which the quench solution was added to the NTPs prior to the addition of the reaction buffer were included.
50 µL of the quenched reaction were spotted onto DE81 filter disks (Whatman) and allowed to dry for 30 min. The filters were washed with 0.3 M ammonium formate, pH 8 (150 mL/wash until the cpm in 1 mL wash is less than 100, usually 6 washes). The filters were counted in 5-mL scintillation fluid in a scintillation counter.

The percentage of inhibition was calculated according to the following equation: %Inhibition = [1-(cpm in test reaction - cpm in blank) / (cpm in control reaction - cpm in blank)] x 100.

B. Assay for Inhibition of HCV RNA Replication:

The compounds of the present invention were also evaluated for their ability to affect the replication of Hepatitis C Virus RNA in cultured hepatoma (HuH-7) cells containing a subgenomic HCV Replicon. The details of the assay are described below. This Replicon assay is a modification of that described in V.


Protocol:

The assay was an in situ Ribonuclease protection, Scintillation Proximity based-plate assay (SPA). 80,000 cells were plated in 200 µl of media containing 0.8mg/mL G418 in 96-well cytostar plates (Amersham). Compounds were added to cells at various concentrations up to 100 µM in 1% DMSO and cultured for 24 hours. Cells were fixed (20min, 10% formalin), permeabilized (20 min, 0.25% Triton) and hybridized (overnight, 50°C) with a single-stranded 32P RNA probe complementary to the (+) strand NS5B (or other genes) contained in the RNA viral genome. Cells were washed, treated with RNase, washed, heated to 65°C and counted in a Top-Count. Inhibition of replication was read as a decrease in counts per minute (cpm).

Human HuH-7 hepatoma cells, which were selected to contain a subgenomic replicon, carry a cytoplasmic RNA consisting of an HCV 5’ non-translated region (NTR), a neomycin selectable marker, an EMCV IRES (internal ribosome entry site), and HCV non-structural proteins NS3 through NS5B, followed by the 3’ NTR.
The compounds of the present invention were also evaluated for cellular toxicity and anti-viral specificity in the counterscreens described below.

C. COUNTERSCREENS:

The ability of the compounds of the present invention to inhibit human DNA polymerases was measured in the following assay.

a. Inhibition of Human DNA Polymerases alpha and beta:

10 Reaction Conditions:
50 μL reaction volume

Reaction buffer components:
20 mM Tris-HCl, pH 7.5

15 200 μg/mL bovine serum albumin
100 mM KCl
2 mM β-mercaptoethanol
10 mM MgCl₂
1.6 μM dA, dG, dC, dTTP
20 α³²P-dATP

Enzyme and template:
0.05 mg/mL gapped fish sperm DNA template
0.01 U/μL DNA polymerase α or β

25 Preparation of gapped fish sperm DNA template:
Add 5 μL 1M MgCl₂ to 500 μL activated fish sperm DNA (USB 70076);
Warm to 37°C and add 30 μL 65 U/μL exonuclease III (GibcoBRL 18013-011);
Incubate 5 min at 37°C;

30 Terminate reaction by heating to 65°C for 10 min;
Load 50-100 μL aliquots onto Bio-spin 6 chromatography columns (Bio-Rad 732-6002) equilibrated with 20 mM Tris-HCl, pH 7.5;
Elute by centrifugation at 1,000Xg for 4 min;
Pool eluate and measure absorbance at 260 nm to determine concentration.
The DNA template was diluted into an appropriate volume of 20 mM Tris-HCl, pH 7.5 and the enzyme was diluted into an appropriate volume of 20 mM Tris-HCl, containing 2 mM β-mercaptoethanol, and 100 mM KCl. Template and enzyme were pipetted into microcentrifuge tubes or a 96 well plate. Blank reactions excluding enzyme and control reactions excluding test compound were also prepared using enzyme dilution buffer and test compound solvent, respectively. The reaction was initiated with reaction buffer with components as listed above. The reaction was incubated for 1 hour at 37°C. The reaction was quenched by the addition of 20 μL 0.5M EDTA. 50 μL of the quenched reaction was spotted onto Whatman DE81 filter disks and air dried. The filter disks were repeatedly washed with 150 mL 0.3M ammonium formate, pH 8 until 1 mL of wash is < 100 cpm. The disks were washed twice with 150 mL absolute ethanol and once with 150 mL anhydrous ether, dried and counted in 5 mL scintillation fluid.

The percentage of inhibition was calculated according to the following equation: % inhibition = [(1-(cpm in test reaction - cpm in blank))/(cpm in control reaction - cpm in blank)] x 100.

The ability of the compounds of the present invention to inhibit HIV infectivity and HIV spread was measured in the following assays.

c. **HIV Infectivity Assay**

Assays were performed with a variant of HeLa Magi cells expressing both CXCR4 and CCR5 selected for low background β-galactosidase (β-gal) expression. Cells were infected for 48 hours, and β-gal production from the integrated HIV-1 LTR promoter was quantified with a chemiluminescent substrate (Galactolight Plus, Tropix, Bedford, MA). Inhibitors were titrated (in duplicate) in twofold serial dilutions starting at 100 μM; percent inhibition at each concentration was calculated in relation to the control infection.

d. **Inhibition of HIV Spread**

The ability of the compounds of the present invention to inhibit the spread of the human immunodeficiency virus (HIV) was measured by the method described in U.S. Patent No. 5,413,999 (May 9, 1995), and J.P. Vacca, et al., *Proc. Natl. Acad. Sci.*, 91: 4096-4100 (1994), which are incorporated by reference herein in their entirety.
The compounds of the present invention were also screened for cytotoxicity against cultured hepatoma (HuH-7) cells containing a subgenomic HCV Replicon in an MTS cell-based assay as described in the assay below. The HuH-7 cell line is described in H. Nakabayashi, et al., Cancer Res., 42: 3858 (1982).

e. Cytotoxicity assay:

Cell cultures were prepared in appropriate media at concentrations of approximately 1.5 x 10^5 cells/mL for suspension cultures in 3 day incubations and 5.0 x 10^4 cells/mL for adherent cultures in 3 day incubations. 99 µL of cell culture was transferred to wells of a 96-well tissue culture treated plate, and 1 µL of 100-times final concentration of the test compound in DMSO was added. The plates were incubated at 37°C and 5% CO₂ for a specified period of time. After the incubation period, 20 µL of CellTiter 96 Aqueous One Solution Cell Proliferation Assay reagent (MTS) (Promega) was added to each well and the plates were incubated at 37°C and 5% CO₂ for an additional period of time up to 3 hours. The plates were agitated to mix well and absorbance at 490 nm was read using a plate reader. A standard curve of suspension culture cells was prepared with known cell numbers just prior to the addition of MTS reagent. Metabolically active cells reduce MTS to formazan. Formazan absorbs at 490 nm. The absorbance at 490 nm in the presence of compound was compared to absorbance in cells without any compound added. Reference: Cory, A. H. et al., “Use of an aqueous soluble tetrazolium/formazan assay for cell growth assays in culture,” Cancer Commun. 3, 207 (1991).

The following assays were employed to measure the activity of the compounds of the present invention against other RNA-dependent RNA viruses:

a. Determination of In Vitro Antiviral Activity of Compounds Against Rhinovirus (Cytopathic Effect Inhibition Assay):

Viruses:
Rhinovirus type 2 (RV-2), strain HGP, was used with KB cells and media (0.1% NaHCO₃, no antibiotics) as stated in the Sidwell and Huffman reference. The virus, obtained from the ATCC, was from a throat swab of an adult male with a mild acute febrile upper respiratory illness.

Rhinovirus type 9 (RV-9), strain 211, and rhinovirus type 14 (RV-14), strain Tow, were also obtained from the American Type Culture Collection (ATCC) in Rockville, MD. RV-9 was from human throat washings and RV-14 was from a throat swab of a young adult with upper respiratory illness. Both of these viruses were used with HeLa Ohio-1 cells (Dr. Fred Hayden, Univ. of VA) which were human cervical epitheloid carcinoma cells. MEM (Eagle's minimum essential medium) with 5% Fetal Bovine serum (FBS) and 0.1% NaHCO₃ was used as the growth medium.

Antiviral test medium for all three virus types was MEM with 5% FBS, 0.1% NaHCO₃, 50 μg gentamicin/mL, and 10 mM MgCl₂.

2000 μg/mL was the highest concentration used to assay the compounds of the present invention. Virus was added to the assay plate approximately 5 min after the test compound. Proper controls were also run. Assay plates were incubated with humidified air and 5% CO₂ at 37°C. Cytotoxicity was monitored in the control cells microscopically for morphologic changes. Regression analysis of the virus CPE data and the toxicity control data gave the ED₅₀ (50% effective dose) and CC₅₀ (50% cytotoxic concentration). The selectivity index (SI) was calculated by the formula: SI = CC₅₀ ÷ ED₅₀.

b. Determination of In Vitro Antiviral Activity of Compounds Against Dengue, Banzi, and Yellow Fever (CPE Inhibition Assay)
Assay details are provided in the Sidwell and Huffman reference above.

Viruses:
Dengue virus type 2, New Guinea strain, was obtained from the Center for Disease Control. Two lines of African green monkey kidney cells were used to culture the virus (Vero) and to perform antiviral testing (MA-104). Both Yellow fever virus, 17D strain, prepared from infected mouse brain, and Banzi virus, H 336 strain, isolated from the serum of a febrile boy in South Africa, were obtained from ATCC. Vero cells were used with both of these viruses and for assay.

Cells and Media:
MA-104 cells (BioWhittaker, Inc., Walkersville, MD) and Vero cells (ATCC) were used in Medium 199 with 5% FBS and 0.1% NaHCO₃ and without antibiotics. Assay medium for dengue, yellow fever, and Banzi viruses was MEM, 2% FBS, 0.18% NaHCO₃ and 50 µg gentamicin/mL.

Antiviral testing of the compounds of the present invention was performed according to the Sidwell and Huffman reference and similar to the above rhinovirus antiviral testing. Adequate cytopathic effect (CPE) readings were achieved after 5-6 days for each of these viruses.

c. Determination of In Vitro Antiviral Activity of Compounds Against West Nile Virus (CPE Inhibition Assay)

Assay details are provided in the Sidwell and Huffman reference cited above. West Nile virus, New York isolate derived from crow brain, was obtained from the Center for Disease Control. Vero cells were grown and used as described above. Test medium was MEM, 1% FBS, 0.1% NaHCO₃ and 50 µg gentamicin/mL.

Antiviral testing of the compounds of the present invention was performed following the methods of Sidwell and Huffman which are similar to those used to assay for rhinovirus activity. Adequate cytopathic effect (CPE) readings were achieved after 5-6 days.

d. Determination of In Vitro Antiviral Activity of Compounds Against rhino, yellow fever, dengue, Banzi, and West Nile Viruses (Neutral Red Uptake Assay)

After performing the CPE inhibition assays above, an additional cytopathic detection method was used which is described in “Microtiter Assay for Interferon: Microspectrophotometric Quantitation of Cytopathic Effect,” *Appl. Environ. Microbiol.* 31: 35-38 (1976). A Model EL309 microplate reader (Bio-Tek Instruments Inc.) was used to read the assay plate. ED50’s and CD50’s were calculated as above.

**EXAMPLE OF A PHARMACEUTICAL FORMULATION**

As a specific embodiment of an oral composition of a compound of the present invention, 50 mg of Example 1 is formulated with sufficient finely divided
lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

While the invention has been described and illustrated in reference to specific embodiments thereof, those skilled in the art will appreciate that various changes, modifications, and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the human being treated for severity of the HCV infection. Likewise, the pharmacologic response observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended therefore that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.
WHAT IS CLAIMED IS:

1. A method of inhibiting RNA-dependent RNA viral polymerase or inhibiting RNA-dependent RNA viral replication comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of structural formula I:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof; wherein

10 X is O or S(O)\(n\);

n is 0, 1, or 2;

R\(^1\) is hydrogen, methyl, hydroxymethyl, or fluoromethyl;

R\(^2\) and R\(^3\) are each independently hydrogen or C\(_{1-4}\) alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C\(_{1-4}\) alkoxy, C\(_{1-4}\) alkylthio, or one to three halogen atoms;

R\(^4\) is H, C\(_{1-10}\) alkylcarbonyl, P\(_3\)O\(_9\)H\(_4\), P\(_2\)O\(_6\)H\(_3\), or P(O)R\(^{10}\)R\(^{11}\);

R\(^5\) is H, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkynyl, halogen, cyano, carboxy, C\(_{1-4}\) alkyl oxy carbonyl, azido, amino, C\(_{1-4}\) alky lamino, di(C\(_{1-4}\) alkyl)amino, hydroxy, C\(_{1-6}\) alkoxy, C\(_{1-6}\) alkylthio, C\(_{1-6}\) alkyl sulfonyl, or (C\(_{1-4}\) alkyl)\(_0\)-2 aminomethyl;

R\(^6\) is hydrogen, cyano, nitro, C\(_{1-3}\) alkyl, NHCONH\(_2\), CONR\(^9\)R\(^9\), CSNR\(^9\)R\(^9\), COOR\(^9\), C(=NH)NH\(_2\), hydroxy, C\(_{1-3}\) alkoxy, amino, C\(_{1-4}\) alky lamino, di(C\(_{1-4}\) alkyl)amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazol-2-yl), or (imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C\(_{1-3}\) alkoxy;
R7 and R8 are each independently hydrogen, hydroxy, halogen, C1-4 alkoxy, amino, C1-4 alkylamino, di(C1-4 alkyl)amino, C3-6 cycloalkylamino, or di(C3-6 cycloalkyl)amino; each R9 is independently H or C1-4 alkyl; and

R10 and R11 are each independently hydroxy, OCH2CH2SC(=O)C1-4 alkyl, OCH2O(C=O)OC1-4 alkyl, NHCHMeCO2Me, OCH(C1-4 alkyl)O(C=O)C1-4 alkyl,


3. The method of Claim 1 wherein the compound has the structural formula II:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof; wherein

X is O or S;

R2 and R3 are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R4 is H or P3O9H4;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alklyoxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alklythio;
R⁷ and R⁸ are each independently hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and each R⁹ is independently hydrogen or C₁-4 alkyl.

4. The method of Claim 2 wherein the compound has the structural formula II:

![Structural formula II](image)

or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alklyoxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alklythio;
R⁷ and R⁸ are each independently hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and each R⁹ is independently hydrogen or C₁-4 alkyl.

5. The method of Claim 3 wherein the compound has the
structural formula III:

\[
\begin{array}{c}
\text{R}^4\text{O} \\
\text{X} \\
\text{R}^2\text{R}^3\text{R}^6 \\
\text{NHR}^{12}
\end{array}
\]

or a pharmaceutically acceptable salt thereof; wherein

5 \( X \) is O or S;

\( \text{R}^2 \) and \( \text{R}^3 \) are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

\( \text{R}^4 \) is H or \( \text{P}_3\text{O}_9\text{H}_4 \);

\( \text{R}^6 \) is hydrogen, cyano, halogen, C\(_{3-6}\) cycloalkyl, carboxy, C\(_{1-4}\) alkylloxy carbonyl, CONR\(^9\)R\(^9\), oxazolyl, thiazolyl, imidazolyl, or C\(_{1-4}\) alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C\(_{1-4}\) alkoxy, or C\(_{1-4}\) alkylthio;

\( \text{R}^8 \) is hydrogen, hydroxy, halogen, C\(_{1-4}\) alkoxy, amino, C\(_{1-4}\) alkylamino, di(C\(_{1-4}\) alkyl)amino, C\(_{3-6}\) cycloalkylamino, or di(C\(_{3-6}\) cycloalkyl)amino;

each \( \text{R}^9 \) is independently hydrogen or C\(_{1-4}\) alkyl; and

15 \( \text{R}^{12} \) is hydrogen, C\(_{1-4}\) alkyl, or C\(_{3-6}\) cycloalkyl.

6. The method of Claim 4 wherein the compound has the structural formula III:
or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alkylxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alkylthio;
R⁸ is hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino;
each R⁹ is independently hydrogen or C₁-4 alkyl; and
R¹² is hydrogen, C₁-4 alkyl, or C₃-6 cycloalkyl.

7. The method of Claim 3 wherein the compound has the structural formula IV:

or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alkylloxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alkylthio;
R⁸ is hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and
each R⁹ is independently hydrogen or C₁-4 alkyl.

8. The method of Claim 4 wherein the compound has the structural formula IV:

```
  R⁶
 / \ /
/   \ /
O    O
 \   /  \\
 X   R²  R³
    \   / \\
     R⁴O
```

(IV)

or a pharmaceutically acceptable salt thereof; wherein
X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alkylloxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-4 alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-4 alkoxy, or C₁-4 alkylthio;
R⁸ is hydrogen, hydroxy, halogen, C₁-4 alkoxy, amino, C₁-4 alkylamino, di(C₁-4 alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and
each R⁹ is independently hydrogen or C₁-4 alkyl.
9. The method of Claim 3 wherein the compound has the structural formula V:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof; wherein

X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-6 cycloalkyl, carboxy, C₁-4 alkylxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-⁴ alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-⁴ alkoxy, or C₁-⁴ alkylthio;
R⁸ is hydrogen, hydroxy, halogen, C₁-⁴ alkoxy, amino, C₁-⁴ alkylamino, di(C₁-⁴ alkyl)amino, C₃-6 cycloalkylamino, or di(C₃-6 cycloalkyl)amino; and
R⁹ is hydrogen or C₁-⁴ alkyl.

10. The method of Claim 4 wherein the compound has the structural formula V:
or a pharmaceutically acceptable salt thereof; wherein:

X is O or S;
R² and R³ are each independently hydrogen, methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
R⁴ is H or P₃O₉H₄;
R⁶ is hydrogen, cyano, halogen, C₃-₆ cycloalkyl, carboxy, C₁-₄ alklyloxycarbonyl, CONR⁹R⁹, oxazolyl, thiazolyl, imidazolyl, or C₁-₄ alkyl, wherein alkyl is optionally substituted with hydroxy, amino, C₁-₄ alkoxy, or C₁-₄ alkylthio;
R⁸ is hydrogen, hydroxy, halogen, C₁-₄ alkoxy, amino, C₁-₄ alkylamino, di(C₁-₄ alkyl)amino, C₃-₆ cycloalkylamino, or di(C₃-₆ cycloalkyl)amino; and
R⁹ is hydrogen or C₁-₄ alkyl.

11. The method of Claim 3 wherein the compound is selected from the group consisting of:
cis-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
cis-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
cis-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-(2,4)-trans-(4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
cis-(2,4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
cis-(2,5)-trans-(4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and
cis-(2,4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;
or a pharmaceutically acceptable salt thereof.

12. The method of Claim 11 wherein said RNA-dependent RNA viral polymerase is Flaviviridae viral polymerase or Picornaviridae viral polymerase and said RNA-dependent RNA viral replication is Flaviviridae viral replication or Picornaviridae viral replication.

13. The method of Claim 12 wherein said Flaviviridae viral polymerase is selected from the group consisting of hepatitis C virus polymerase, yellow fever virus polymerase, dengue virus polymerase, West Nile virus polymerase, Japanese encephalitis virus polymerase, and bovine viral diarrhea virus (BVDV) polymerase and said Flaviviridae viral replication is selected from the group consisting of hepatitis C virus replication, yellow fever virus replication, dengue virus replication, West Nile virus replication, Japanese encephalitis virus replication, and bovine viral diarrhea virus replication.

14. The method of Claim 13 wherein said Flaviviridae viral polymerase is hepatitis C virus polymerase and said Flaviviridae viral replication is hepatitis C virus replication.

15. The method of Claim 4 wherein the compound is selected from the group consisting of:
cis-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
cis-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
cis-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
cis-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-(2,4)-trans-(4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;

cis-(2,4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;

cis-(2,5)-trans-(4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and

cis-(2,4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;

and the corresponding 2-triphosphates;

or a pharmaceutically acceptable salt thereof.

16. The method of Claim 15 wherein said RNA-dependent RNA
viral infection is Flaviviridae viral infection or Picornaviridae viral infection.

17. The method of Claim 16 wherein said Flaviviridae viral
infection is selected from the group consisting of hepatitis C virus infection, yellow
fever virus infection, dengue virus infection, West Nile virus infection, Japanese
encephalitis virus infection, and bovine viral diarrhea virus infection.

18. The method of Claim 17 wherein said Flaviviridae viral
infection is hepatitis C virus infection.

19. The method of Claim 11 wherein the compound is selected
from the group consisting of:

(2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-
dioxolane;

(2R,4R)-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-
dioxolane;

(2R,4R)-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-
dioxolane;

(2R,4R)-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-
1,3-dioxolane;

(2R,4R)-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-
1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and
(2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;

or a pharmaceutically acceptable salt thereof.

20. The method of Claim 15 wherein the compound is selected from the group consisting of:
(2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and
(2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;
or a pharmaceutically acceptable salt thereof.
21. A method of inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent viral replication, and/or treating RNA-dependent RNA viral infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Claim 1 in combination with a therapeutically effective amount of another agent active against RNA-dependent RNA virus.

22. The method of Claim 21 wherein said agent active against RNA-dependent RNA virus is levovirin, ribavirin, thymosin alpha-1, interferon-β, interferon-α, pegylated interferon-α, a mixture of ribavirin and interferon-α, a mixture of ribavirin and pegylated interferon-α, a mixture of levovirin and interferon-α, or a mixture of levovirin and pegylated interferon-α.

23. A compound selected from the group consisting of:

- cis-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
- cis-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
- cis-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
- cis-2-hydroxymethyl-4-[4-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
- cis-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
cis-2-hydroxymethyl-5-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
cis-(2,4)-trans-(4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
cis-(2,4,5)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
cis-(2,5)-trans-(4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and
cis-(2,4,5)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;
or a pharmaceutically acceptable salt thereof.

24. The compound of Claim 23 selected from the group consisting of:
(2R,4R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-dioxolane;
(2R,4R)-2-hydroxymethyl-4-(2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-dioxolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-cyano-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-methyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-isopropyl-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4-amino-5-carboxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-(4,5-diamino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(imidazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[4-amino-5-(1,3-oxazol-2-yl)-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2S,5R)-2-hydroxymethyl-5-[2-amino-4-hydroxy-1H-pyrrolo[2,3-d]pyrimidin-7-yl]-1,3-oxathiolane;
(2R,4R,5R)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2R,4R,5S)-2-hydroxymethyl-4-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-methyl-1,3-dioxolane;
(2S,4R,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane; and
(2S,4S,5R)-2-hydroxymethyl-5-(4-amino-1H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-methyl-1,3-oxathiolane;
and the corresponding 2-triphosphates;
or a pharmaceutically acceptable salt thereof.


26. The pharmaceutical composition of Claim 25 useful for inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection.

27. A method of inhibiting RNA-dependent RNA viral polymerase or inhibiting RNA-dependent RNA viral replication comprising administering to a mammal in need of such inhibition an effective amount of a compound according to Claim 23.

28. A method of treating an RNA-dependent RNA viral infection comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 23.
29. The method of Claim 28 wherein said RNA-dependent RNA viral infection is *Flaviviridae* viral infection.

30. The method of Claim 29 wherein said *Flaviviridae* viral infection is a hepatitis C virus infection.

31. The method of Claim 30 in combination with a therapeutically effective amount of another agent active against hepatitis C virus.

32. The method of Claim 31 wherein said agent active against hepatitis C virus is levovirin, ribavirin, thymosin alpha-1, interferon-β, interferon-α, pegylated interferon-α, a mixture of ribavirin and interferon-α, a mixture of ribavirin and pegylated interferon-α, a mixture of levovirin and interferon-α, or a mixture of levovirin and pegylated interferon-α.