FORM 7A
THE PATENTS ACT,
153895
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]
We, INDIA CARES, India Cares, 2nd Floor, A1 Sarvodaya Enclave, Opposite Mothers International School, New Delhi 110017, India hereby give representation by way of opposition to the grant of patent in respect of application No: 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 made by Gilead Pharmassct LLC, 303A College Road East, Princeton, New Jersey, 08540,United States of America (U.S.A.) and published on 09 May 2008 on the following grounds:
i. Section 25(1)(b): Lack of novelty
ii. Section 25(1)(e): Lack of inventive step
iii. Section 25(1)(f): Subject of claims 1 to 10 is not an invention within the meaning of this Act or is not patentable under this Act
iv. Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
v. Section 25(1)(h): The Applicant has failed to disclose to the Controller the information required under Section 8.

Our address for service in India is:

## RAJESHWARI \& ASSOCIATES

AMSOFT BUSINESS CENTRE
UNITECH TRADE CENTRE
Sector 43, Gurgaon- 122002.
Haryana, India.
Tel: +91-11-41038911;
Fax: +91-11-43851067
Mobile No. 9910048684
Dated, this $23^{\text {rd }}$ day of June, 2015.


To
The Controller of Patents,
The Patent Office, Delhi

## BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND
IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND
IN THE MATTER OF:

INDIA CARES
... PETITIONER/OPPONENT

VS.

Pharmasset, Inc.
... RESPONDENTS/APPLICANTS

## PRE-GRANT OPPOSITION BY INDIA CARES

Volume-I of IV
MASTER INDEX

| S. No. | Particulars | Page No. |
| :--- | :--- | :--- |
|  | $\frac{\text { Volume-I }}{\text { (Page Nos. 1 to 376) }}$ |  |
| 1. | Representation u/s 25(1) by the Petitioner/Opponent | $1-37$ |


| 2. | List of Annexures | 38-39 |
| :---: | :---: | :---: |
| 3. | Annexure-1 <br> D. Lavanchy (2011)," Evolving epidemiology of hepatitis C virus", Clin Microbiol Infect; 17: 107-115. | 40-48 |
| 4. | Annnexure-2 <br> R De Francesco et al (2003), New therapies on the horizon for hepatitis C: Are we close? Clin Liver Dis, Feb;7(1):211-42, xi. | 49-80 |
| 5. | $\begin{array}{\|l} \text { Annexure-3 } \\ \text { Copy of WO 2001/90121 } \end{array}$ | 81-376 |
|  | $\text { (Page } \frac{\text { Volume-II }}{\text { Nos. } 377 \text { to } 678)}$ |  |
| 6. | $\begin{array}{\|l} \text { Annexure-4 } \\ \text { Copy of WO 2001/92282 } \end{array}$ | 377-678 |
|  | $\text { (Page } \frac{\text { Volume-III }}{\text { Nos. } 679 \text { to } 957)}$ |  |
| 7. | Annexure-5 <br> US Patent No. 6348587 | 679-722 |
| 8. | $\begin{array}{\|l} \text { Annexure-6 } \\ \text { Copy of WO 2002/057425 } \end{array}$ | $723-957$ |
|  | $\text { (Page } \begin{aligned} & \frac{\text { Volume-IV }}{\text { Nos. } 958 \text { to 1286) }} \end{aligned}$ |  |
| 9. | $\begin{aligned} & \text { Annexure-7 } \\ & \text { Copy of WO } 2002 / 057287 \end{aligned}$ | 958-1.042 |
| 10. | $\begin{array}{\|l} \hline \text { Annexure-8 } \\ \text { WO 1999/43691 } \end{array}$ | 1043-1151 |
| 11. | Annexure-9 <br> Park BK and Kitteringham NR (1994), "Effects of fluorine substitution on drug metabolism: pharmacological and toxicological implications", Drug Metab. Rev., 26, 605. | 1152-1190 |
| 12. | Annexure-10 <br> Gumina, G et al, (2001), "Synthesis and potent anti-HIV activity of L-3'-fluoro-2', $3^{\prime}$-unsaturated cytidine", ORGANIC | 1191-1194 |



Dated this $23^{\text {rd }}$ day of June, 2015.

# BEFORE THE CONTRÓLLER OF PATENTS, THE PATENT OFFICE, DELHI 

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND

IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND

IN THE MATTER OF:

INDIA CARES
India Cares, 2nd Floór, Al Sarvodaya Enclave, Opposite Mothers International School, New Delhi 110017

VS.

Pharmasset, Inc.
A Corporation organized and existing under and by virtue of the laws of the state of Delaware. 303A, College Road East, Princeton New Jersey 08540, United States of America.

## STATEMENT OF FACTS AND EVIDENCE

## I. INTRODUCTION

India Cares is $\dot{a}$ is a registered public charitable trust having its office at India Cares, 2nd Floor, A1 Sarvodaya Enclave, Opposite Mothers International School, New Delhi i10017. Its main objective is to help penple living with HIV/AIDS and people at risk for this disease by providing treatment, counselling, prevention, and testing services. and undertaking other charitable activities aimed to alleviate the effects of the disease and promote the public health. Over the years, India Cares has advocated vigorously to lower drug prices for essential medicines in order to improve access to lifeşaving HIV/ȦÍDS treatments worldwide.

## II. THE PUBLIC HEALTH RISK POSED BY HEPATITIS C AND NEED FOR AFFORDABLE TREATMẸNT

a. Hepatitis $C$ is a liver disease caused by the hepatitis $C$ virus (HCV). The virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Left untreated, Hepatitis $C$ can lead to liver cirrhosis, liver cancer or liver failure and ultimately death.
b. According to the World Health Organization (WHO), there are somewhere between 130-150 million people in the world suffering with chronic hepatitis $C$ infection. A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. 350,000 to 500,000 people die each year from hepatitis C-related liver diseases. There is currently no vaccine for hepatitis $C$.
c. India is estimated to have approximately 18.2 million people living with the Hepatitis C virus, with 96,000 dying each year - making it a hidden epidemic. [See D. Lavanchy (2011)," Evolving epidemiology of hepatitis C virus", Clin Microbiol Infect; 17: 107-115, a copy of which is annexed as Annexure-1.]
d. Hepatitis $C$ is especially of concern for those co-infected with HIV, as several studies have shown that HIV-HCV 'co-infection leads to increased rates of disease progression.
e. In 2014, U.S. drug manufacturer Gilead Sciences (which acquired applicant Pharmasset, Inc. in 2012) made headlines over its release of a new, breakthrough treatment for HCV - Sovaldi (sofosbuvir) - as well as for the drug's high price. Seeking to capitalize on its success, Gilead launched Sovaldi in the U.S. at a breath-taking cost of $\$ 84,000$. In Germany and the UK, it launched the drug at the equivalent of $\$ 66,000$ and $\$ 57,000$ respectively. Yet studies show that the drug is very cheap to produce, at around $\$ 68$ to $\$ 13 \dot{6}$ per 12 week treatment course.
f. Not surprisingly, prices set by Gilead-Pharmasset have raised concerns by many groups that the drugs' high price will impair patients' access to these life saving drugs..
g. Numerous governmental and nongovernmental organizations, health advocates have expressed concern over Gilead/Pharmasset's pricing. For example, WHO states "Although the production cost of DAAs [directly acting antiviral agents] is low, the initial prices set by companies are very high and likely to make access to these drugs difficult even in high-income countries." Thus, "Much needs to be done to ensure that these advances lead to greater access to treatment globally."
h. Gilead announced that in India it planned to sell the brand version of Sovaldi for $\$ 900$, and that it had signed voluntary licensing agreements with several Indian generic drug manufacturers to produce the drug for sale in India and 91 other developing and middle-income countries at less. But even at the anticipated price discounts, there is global concern among health experts that the drug is still not affordable for people in India, where the gross national income per capita is only $\$ 3,590$ (2011) and the vast majority of Indians do not have insurance.
i. Although, Gilead has provided voluntary licenses to certain generic companies, the price of the drug is still expensive. Some developing countries have been excluded from regions covered by the voluntary license deal. For example, China is not on the list of countries to which Indian manufacturers can sell Sovaldi, yet China.has the greatest number of people infected, at 29.8 million. The voluntary licensing agreements are not bringing coverage to middle-income countries such as Ukraine, Thailand, Mexico and Brazil. Moreover, even in countries covered by the licensing agreements, Gilead has imposed an "anti-diversion" program which demands the licensee comply with $a^{\circ} \dot{w e b}$ of onerous and potentially harmfúl procedures. that aim to preserve ${ }^{\circ}$ Gilead's ability to charge exorbitant prices jn developed countries. (up to US $\$ 1,000$ per pill, or $\$ 84,000$ per treatment course).
j. It is critical that people living with HCV have access to life-saving therapies and are not barred by prices artificially inflated by monopolies that cost human lives at the expense of exorbitant profits of the drug company. Competition is one of the most effective ways to lower product costs. Patents thwart competitive pressures to lower prices by allowing the patent holder to set monopolistic prices for their patented product. In the
context of.medicines, patents often impede access to treatment due to their high prices. India Cares is deeply concerned that Hepatitis $C$ patents could put lifesaving drugs out of the reach of hospitals and providers and the thousands of patients they treat.
III. INDIAN PATENT I,AW: THE IMPORTANCE OF STRICI INTERPRETATION
(i) The history of India's patent law reflects a* deep and abiding belief that medicine and food, which are vital to the health of the community, should be made available to everyone at reasonable prices and that no monopoly should be granted to them. This theme has run like a thread through the many amendments of the law and courts in India have also reflected upon it.
(ii) In 1995, however, all members of the World Trade Organization, including India, signed on to the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), a comprehensive multi-lateral agreement that set detailed minimum standards for the protection and enforcement of intellectual property rights. TRIPS required India to make patents available to all kinds of inventions, in all technologies including medicines.
(iii) TRIPS mandated India to provide product patent protection to inventions in all fields including pharmaceuticals by 1 January 2005. India and other developing countries soon realised that their obligation to protect right to health of their citizens would be restricted by granting patent protection for pharmaceutical products which had the likelihood of having adverse impact on public health. Hence in 2001, WTO members adopted the Doha Declaration on TRIPS and Public Health, which reaffirmed the flexibility of TRIPS member states to circumvent patent rights for the sake of better
access to essential medicines. The Declaration states that Member Countries to the W.TO have agreed that TRIPS should not prevent the members from taking measures to protect public health. Thus, Doha Declaration provided the flexibility to the Member countries to decide the standards of patentability as per their national requirement.
(iv) In recent years, India has striven to harmonize its patent law with TRIPS while maintaining its commitment to protect and promote public health, not just for Indians, but for people in other parts of the world, especially developing countries. Being a sovereign nation, India was mindful of the public health concerns in introducing pharmaceutical patents into its Patent Act. After considerable debate and deliberations, the Patents Act 1970 achieved its current form in 2005. The Indian patent Act amended in 2002 and 2005 to conform to the TRIPS agreement offers suggestions concerning the use of flexibilities offered under Article 27 of TRIPS. Section 3(d) consciously limits patentability to prevent evergreening of patents: India thus set sstricter patentability criteria to ensure that patents are granted to genuine inventions and to prevent "evergreening"-extending, patent monopolies by patenting routine and minor modification to already existing substances. The Indian Parliament has also set a stricter standard for inventive step. This has been recognised by the Hon'ble Supreme Court of India too in Novartis $A G v$. Union of India and others, (2013) 6 SCC 1. The Supreme Court has held that therapeutic efficacy must be established by submitting appropriate research and clinical data.
(v) Thus, Section 3(d), as amended in 2005 in the Patents Act, 1970 illustrates India's unique public-health oriented approach to patents. Section 3(d) was interpreted by the Supreme Court in In Novartis AG v. Union of India and others, (2013) 6 SCC 1 . The Supreme Court explained that the efficacy requirement of Section 3(d) means proving that a substance has enhanced
therapeutic efficacy. [re. in. para. 180-192]. The Supreme Court has also held in paragraph 188 that "Bioavailability falls outside the area of efficacy in case of a medicine....". Further, in paragraph 189, the Court held that ".... the position that emerges is that just increased bioavailability alone may not necessarily lead to an enhancement of therapeutic efficacy....". The Supreme Court has also held that "... whether or not an increased in bioavailability leads to enhancement of therapeutic efficacy in any given case must be specifically claimed and established by research data....".
(vi) In Novartis, the Supreme Court applied Section 3(d) strictly, in accordance with its legislative purpose.. Thus, the patent act ought to be read and interpreted is in light of the above developments surrounding the Amending Act. It is submitted that the Hon'ble Controller while deciding this pregrant opposition and while applying and interpreting section 3(d), section $2(1)(\mathrm{j})$ and section $2(1)(\mathrm{ja})$ ought to bear: in mind the intention of the Parliament while enacting this amending Act and ought to give these standards strictest possible interpretation in order to ensure that the patent protection does not impede access to medicines and good healthcare.

## IV. BACKGROUND OF ALLEGED INVENTION

(i) The present application has been filed on 21 April 2004, claiming a priority from US 60/474368 filed 30 May, 2003.
(ii) This application is a national phase entry of International Application No. PCT/US2004/012472 (international Publication No. WO 2005/003147) in India, which was subsequently allotted Indian Patent Application No. 6087/DELNP/2005, i.e. the present Application.
(iii) Thus the priority date of the impugned àpplication is 30 May 2003. A document which is published before this date, would be a prior art.
(iv) Present application relates to nucleoside analogues with modifications on 2' positions at the sugar. More specifically, the impugned application claims that the 2 'fluoro substitution on the ribnse ring.
(v) Nucleoside analogues are nucleosides which contain a nucleic acid analogue and a sugar. Nucleoside analogues are used for the treatment of cancer and viral infections.
(vi) Nucleoside analogues are used as inhibitors•of HIV, hepatitis B and herpes viruses. Their antitumor and antiviral uses were known long before the date of priority of the impugned application.. It is also known that nucleoside analogues are converted to monophosphate prodrugs which would facilitate in drug delivery. It was also known that nucleoside analogues are also administered as compositions, in combination with other pharmaceutical active agents. Various types of nucleosides were known and active compounds were sẏnthesized and were marketed before 2003. For instance, anti-HIV drugs such.as Zidovudine, Emtriciatabine are such examples of nucleoside analogues.
(v) Nucleoside analogues. to treat HCV were also known before 2003. For instance R De Francesco et al (2003), New therapies on the horizon for hepatitis C: Are we close? Clin Liver Dis, Feb;7(1):211-42, xi, a copy of which is annexed as Annexure-2 discloses various strategies for treating $\mathrm{HCV}^{\circ}$ that were being pursued for treating HCV. These strategies include the use of nucleoside analogues to inhibit NS5B enzymatic activity. Francesco et al, confirms that NS5B had been identified as a target for the development of anti-HCV therapies by early 2003 and suggests that inhibition of this pivotal enzyme would lead to the suppression of HCV replication in infected cells (see page' 225 paragraph 3 ). It further identifies
that novel series of nuclensides that are candidates for the treatment of HCV. It also identifies $\beta$-D-2'-methyl-ribofuranosyl-guanosine which was found to be phosphorylated in cultured cells and was also found to be orally bioavailable in primates. (See page 228, paragraph 3-5).
(viii) From the 1980s or before, it was well known that nucleoside analogue synthesis might bee performed hy making a modification $t u$ an existing nucleoside that is sugar with the desired base already attached (often known as the "nucleoside route"), or by first preparing a sugar with the desired modifications before attaching the base by glycosylation (often known as the "sugar route"). The sugar route itself might involve either modifying a sugar.which was already readily available, or starting with small molecules which could be used to build up the sugar with the desired modifications in place. During this period, there was a preference for fluorine based nucleosides as fluorine was known to increase biological activity of the compounds. Some of nucleoside analogues with fluorine modifications included gemcitabine, mericitabine etc.
(ix) The alleged invention is only one such modification of an already_known and disclosed nucleoside analogue. The starting compounds as well as the 2'fluoro modification on the ribose ring is disclosed and anticipated by the prior art. Further the 2' modification on the ribose ring is a very well known technique in the art and has been practiced by the scientist and chemists for many years.
(x) The claims as filed on 24.07.2014 and on record are as below:

1. The compound claimed is: (2!R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) or its pharmaceutically acceptable salt of the structure:

wherein the Base is a pyrimidine base represented by the following formula


X is $\mathrm{O} ; \mathrm{Rl}$ and R7 are independently H , a monophosphate, a diphosphate, or a triphosphate; and R 3 is H and R 4 is NH 2 or OH
2. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R7 is H and R1 is a monophosphate, a diphosphate, or a triphosphate.
3. Thic nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R7 is H and R 1 is a diphosphate or a triphosphate.
4. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R 7 is H and R 1 is a triphosphate.
5. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R1 and R7 are H .
6. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:

## a.


7. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:
b.

8. A method of synthesizing the nucleoside as claimed in claim 1 , which comprises glycosylating the pyrimidine with a compound having the following structure:

wherein R is $\mathrm{Cl}-\mathrm{C} 4$ lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among $\mathrm{C}(\mathrm{O})-\mathrm{Cl}-\mathrm{Cl0}$ alkyl, $\mathrm{C}(\mathrm{O})$ phenyl, $\mathrm{C}(\mathrm{O})$ biphenyl, $\mathrm{C}(\mathrm{O})$ naphthyl, $\mathrm{CH} 2-\mathrm{Cl}-\mathrm{Cl} 0$ alkyl, $\mathrm{CH} 2-\mathrm{Cl}-\mathrm{C} 10$ alkenyl, CH2-phenyl, CH2-biphenyl, CH2-naphthyl, CH2O-C1-C10 'alkyl, $\mathrm{CH} 2 \mathrm{O}-$ phenyl, CH 2 O -biphenyl, CH 2 O -naphthyl, $\mathrm{SO} 2-\mathrm{Cl}-$ C10 alkyl, SO2-phenyl, SO2-biphenyl, SO2- naphtyl, tertbutyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).
9. A method of synthesizing the nucleoside as claimed in claim 1 , which comprises selectively deprotecting a $3^{\prime}-\mathrm{OPg}$ or a $5^{\prime}-\mathrm{OPg}$ of a compound having the following structure:

c.

wherein, each Pg is independently a protecting group selected from among $\mathrm{C}(\mathrm{O})-\mathrm{Cl}-\mathrm{Cl} 0$ alkyl, $\mathrm{C}(\mathrm{O})$ phenyl, $\mathrm{C}(\mathrm{O})$ biphenyl, $\mathrm{C}(\mathrm{O})$ naphthyl, $\mathrm{CH} 3, \mathrm{CH} 2-\mathrm{Cl}-\mathrm{Cl} 0$ alkyl, $\mathrm{CH} 2-\mathrm{Cl}-\mathrm{Cl} 0$ alkenyl, CH 2 -phenyl: CH 2 -biphenyl, CH 2 -naphthyl, $\mathrm{CH} 2 \mathrm{O}-\mathrm{Cl}-\mathrm{Cl} 0$ alkyl, 'CH2O-phenyl, 'CH2O-biphenyl, CḢ2O-naphthyl, SO2-C1-Cl0 alkyl, SỌ2*phenyl, SO2-biphenyl, SO2- naphtyl, tertbutyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-( 1,1,3,3-tetraisopropyldisiloxanylidene).
10. A. nucleoside as claimed in any of the Claims. 1 to 7 as and when used for the preparation of a pharmaceutical composition or - medicament.

## V. ADMISSIONS OF APPLICANT

(i) Before discussing the grounds, it is pertinent to lay down the admissions of the applicant in the specification:

1. $\quad$ Use of nucleosiđe analogues for the treatment of hepatitis $C$ virus was known [see page 12 of the Complete Specification of the Impugned Application]
2. WO 2001/90121 a copy of which is annexed as Annexure-3 and WO 2001/92282 a copy of which is annexed as Annexure-4 disclosed nucleosides for the treatment of hepatitis C virus. These applications disclosed administering an effective amount of a biologically active $1^{\prime}, 2^{\prime}, 3^{\prime}$, or $4^{\prime}$-branched $\beta$-D or $\beta$-L nucleosides or a pharmaceutically acceptable salt or derivative therenf. [see page 12 of the Complete Specification of the Impugned Application]
3. 'Modification with fluorine at the 2 ' position of the sugar was known. [see page 13 of the Complete Specification of the Impugned Application] US Patent No. 6348587, a copy of which is annexed as Annexure-5 to Schinazi et al., discloses a family of 2 '-fluoro nucleoside compounds that are useful in the treatment of hepatitis $C$ virus infection. [seepage 17 of the Complete Specification of the Impugned Appličation]
4. Modification at the 2' position with methyl (up) and hydroxyl (down) is known. [see page 13 of the Complete'Specification of the Impugned Application]
5. Fluorinated derivatives of nucleoside analogues have been preferred. [see page $47^{\circ}$ of the Complete Specification of the Impugned Application]

## V. GROUNDS

## V.A. Clainn 1-10 are not new, lack novelth, are anticipated bv prior publication and, thergfore, should be rejected under Section 25(1)(b)(ii) of the Patents Act.

1. The invention as claimed in Claims 1-10 lacks novelty and is not patentable under Section 25(1)(b)(c) of the Patents Act, 1970 (as amended in 2005;
hereinafter referred to as "the Act"). It is submitted that none of the claims of 6087/DELNP/2005 are novel and they are all liable to be rejected on this ground alone.
2. Section $2(1)(\mathrm{j})$ defines an "invention" as " a new product or process involving an inventive step and capable of industrial application." (emphasis added). Therefore, all inventions, in order to be patentable must satisfy the criteria of novelty.

## Anticipation by WO $\mathbf{2 0 0 2 / 0 5 7 4 2 5}$

3. It is submitted that all claims 1 to 10 of the impugned patent application are anticipated by disclosure in WO 2002/057425 (hereinafter WO ' 425 Application) titled "Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase" published on $25^{\circ}$ July 2002, a copy of which is submitted as Annexure-6.
4. The WO '425 Application discloses nucleoside derivatives used as inhibitors of RNA-dependent RNA viral polymerase, particularly used for inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication and for the treatment of hepatitis $C$ infection. It also discloses compounds and derivatives including triphosphates; monophosphates, their stereochemical configuration, a pharmaceutically acceptable salt thereof and pharmaceutical compositions.
5. Further, '425 Application discloses a compound of general formula:

(I)

Or its pharmaceutically acceptable salts thereof;
6. The basic scaffold in WO ' 425 Application discloses a sugar attached to a nitrogenous base. Further it also sets out and encompasses various substitutions for the nitrogenous base which may be selected from a purines or pyrimidines base and several substituents for $R^{1}, R^{2}, R^{3}$ and $Y$. This also suggests that $R^{1}$ could be $C_{1}-C_{4}$ alkyl which includes methyl and $R^{2}$ includes fluorine [See pages 7, 8 and 9 of the Complete Specification of WO '425 Application]. Further, specific examples of uridine derivatives and 5 'methyluridine are provided in Examples 46-51 (pages 88-95) and Examples 102 and 103 (pages 134-138). Furthermore, WO ' 425 Application also describes within the pharmaceutically compositions of the claimed compounds (pages 48-51) and their pharmaceutically acceptable salt forms (pages 53-54): Furthermore, WO ' $425^{\circ}$ describes the claimed compounds would occur as racemates, racemic mixtures, single enantiomers, diasteromeric mixtures and individual diasteriomers (pages 51-52).
7. Thus the basic scaffold disclosed in WO ' 425 Application embraces the compounds claimed in the impugned application and hence anticipates the alleged invention. As claimed in impugned application, the '425 Application also discloses that the base attached to the sugar could be purines or pyrimidines. The same is illustrated by the table herein below:

| Impugned Patent <br> Application | WO2002/057425 |
| :--- | :--- |
| (6087/DELNP/2005) |  |$\quad . \quad$| Disclosed as Formula III, Page- 17, |
| :--- |
| and Claim-5 and claim-6 |.


|  <br> wherein the Base is a pyrimidine base represented by the following formula <br> X is $\mathrm{O} ; \mathrm{R1}$ and $\mathrm{R7}$ are independently H, a monophosphate, a diphosphate, or a triphosphate; and R 3 is H and R4 is NH 2 or $\dot{\mathrm{OH}}$ |  <br> (III) <br> Rl is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the nther of R ${ }^{2}$ and $\mathrm{P}^{7}$ io solected from the gruap conslsting of hydrogen, hydroxy, <br> flunm, <br> or <br> Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{9}{ }^{\mathrm{R}}{ }^{10}$; |
| :---: | :---: |

8. Thus, it is submitted that WO ' 425 Application encompasses the compounds disclosed and claimed in the impugned application.
9. Therefore, the general scaffold and all compounds encompassed within the general scaffold are anticipated by disclosure in WO '425 Application. In addition the limitations of claims 2,3,4,5 are also met and disclosed by 425 . The general formula disclosed in WO' ' 425 Application is below:
(b)

Wherein $\qquad$

Y is $\mathrm{H}, \mathrm{C} 1-10$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{Og} \mathrm{H} 4, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H} 3$, or $\mathrm{P}(0) \mathrm{R}^{9} \mathrm{R} 10$;

Thus the monophosphāte, diphosphate and triphosphate are disclosed in WO ' 425 Application
10. Further the nucleoside of claims 6,7 are embraced by the disclosure of WO '425 Application.
11. The method of synthesising a nucleotide as claimed in claim 8 is also embraced by the general disclosure of WO ' 425 Application.
12. It is submitted that all claims 1 to 10 are anticipated by disclosure in prior art by an individual reading of either $\mathrm{WO}^{\circ} \cdot 425$ Application.
13. Thus, all claims 1 to 10 ought to be rejected on this ground only.

## Anticipation by WO 2002/057287

14. In the alternate and without prejudice to the above, it is submitted that all claims 1 to. 10 of the impugned patent application are anticipated by disclosures WO. 2002/057287 (hereinafter referred to as WO '287 Application) a copy of the same is annexed and marked as Annexure-7.
15. The WO' '287 Application embraces the nucleoside compounds claimed in claim 1 to 7 of the impugned application.
16. The WO ' 287 Application discloses nucleoside compounds and derivatives thereof, their synthesis, and their use as inhibitors of RNA-dependent RNA viral polymerase. These compounds of the present invention are. inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection, such HCV. These compounds are particularly used to inhibit NS5B polymerase or inhibitors of HCV replication. The WO ' 287 Application discloses following structure:

(I)
17. The WO' 287 Application discloses that the nitrogenous base attached to the sugar could be purine or pyrimidines. It also suggests modifications at the 2' positions. It discloses that $R^{1}$ includes methyl and $R^{2}$ could be fluorine: [See pages 7, 8, 9, and 78-80] The '287 Application specifically states that substitutions at the 2 ' position is independent of each other.
18. The WO ' 287 Application also describes the synthesis of such compounds. [see Scheme 1, pages 25-26 of the Complete Specification of the WO '287 Application]
19. The WO '287 Application enwompasses the compounds claimed in claims 2, 3, 4 and 5 of the impugned application. The general formula disclosed is below:

(I)

Wherein .....
$\mathrm{R}^{5}$ is hydrogen, $\mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(0) \mathrm{R}{ }^{13} \mathrm{R} 14$;

Thus the monophosphate, diphosphate and triphosphate are disclosed in WO '287 Application.
20. The WO '287 Application discloses the pharmaceutical compositions and pharmaceutically acceptable salt of the compounds disclosed therein. The compounds disclosed in the ' 287 Application could occur in one or more asymmetric centers and can occur as racemates and racemic mixtures, single enantiomers, diasteromeric mixtures and individual diasteriomers.
21. Thus in the light of the disclosures in WO " 425 Application and/or WO '287 Application, claims 1 to 10 ought to be rejected on this ground only.

## V.B. Claims 1 to 10 are obvious, do not involve a technical advance and lack inventive step as defined under Section 2(1)(ia) and are, therefore, should be rejected under Section 25(1)(e) of the Patents Act.

a. Claims 1-10 does not involve a technical advance as compared to the existing knowledge and are obvious to a person skilled in the art light of disclosures in the prior art. Claims $1-1 \dot{0}$ ought to be rejected under S. 2.5 (1)(e).
b. Section $2(1)(\mathrm{ja})$ of the Act defines an inventive step as "a feature of an invention that involves technical advance as compared to the existing knowledge $\ldots$ and that makes the invention not obvious to a person skilled in the art'?
c. The requirement of inventive step, as defined in section $2(1)(\mathrm{ja})$, encompasses•a twofold requirement-firstly the feature involved in the alleged invention ought to involve a technical advance as compared to the existing knowledge and secondly, the feature should not be obvious to the person skilled in art.
d. The alleged invention is directed to nucleoside analogs used for the treatment of the hepatitis C virus. It is well known that nucleosides analogues are synthetic compounds which are analogues of naturally occurring nucleosides.:
e. The impugned application claims to provide nucleoside analogs with modification with fluorine at $2^{\prime}$ position of the sugar as the alleged invention.

Nucleoside analogs to treat HCV are known

Before the date of priority it was well known, those nucleoside analogues were used for the treatment of hepatitis C virus. See Annexure-2, which discloses that nucleoside analogues were being developed as inhibitors of NS5B polymerase inhibitor. This is also admitted by the Applicant.

## 2'fluoro modifications at 2'position of the sugar was known

It was known that $2^{\prime}$ modified nucleoside analogues were widely being investigated and their anti- HCV activity in vitro as well as in vivo was also known to a person skilled in the art. For instance, the publication No. WO 1999/43691 to Emory University, entitled "2'Fluoronucleosides", a copy of which is annexed as Annexure-8 discloses the use of certain 2' fluoronucleosides to treat ${ }^{1} \mathrm{HCV}$. Further US Patent $6,348,587$ to Emory University published in February 2002 discloses a class of 2 '-fluoronulceoside compounds which could be used for the treatment of hepatitis $B$ infection, hepatitis C infection, HIV and abnormal cellular proliferation, including lumors and cancer. The 2' substituent is disclosed to be in either the "up" or "down" position. Thus way before the priority date, it was known that modification using fluorine at the 2 ' positions either up or down was very well known. This is also admitted by the Applicant. [See page 13 of the Complete Specification of the Impugned Application]

## Use of fluorine to enhance metabolism of the drug

Fluorination is a process of inserting fluorine into a molecule. Fluorine substitution has been extensively investigated in drug research and biochemistry and has been regarded as a useful strategy to increase metabolic stability. Fluorine when attached to a reaction centre, can act as good leaving group and when placed near the reaction centre it can dramaticatly change chemical reactivity at that centre with it strong
inductive effect. Park BK and Kitteringham NR (1994); "Effects of fluorine substitution on drug metabolism: pharmacological and toxicological implications"; Drug Metab. Rev., 26, 605 a copy of which is annexed as Annexure-9, discloses that introduction of fluorinc substitution cuan alter the chemical properties, disposition and biological activity of drugs. It also discloses that inclusion of a fluorine atom in a drug molecule can influence both the disposition of the drug and the inleraction of the drug with its pharmacolugical target. It discloses that fluorine substitution can have two types of impacts on the drugs, firstly, the effects of fluorine substitution on the inter and intramolecular furces that affect binding of ligands, and thus introduce receptor subtype selectivity, at cholinergic and adrenergic receptors are now well understood. Fluorine substitution can also have a profound effect on drug disposition, in terms of distribution, drug clearance, routes, and extent of drug metabolism. It concludes that the introduction of fluorine into a molecule can alter both the rate and route of drug metabolism. It also states that fluorination can affect the pharmacokinetics of the drug. Further substitution of fluorine can reduce toxicity by blocking the formation of toxic metabolite. Further, fluorine substitution also has a favourable effect of increasing the metabolic stability has been discussed in Gumina, G et al, (2001), "Synthesis and potent antiHIV 'activity of L-3'-fluoro-2',3'-unsaturated cytidine", ORGANIC LETTERS, 3 (26), 4177-4180) a copy of which is annexed as Annexure10.

Pankiewicz (2000), "Fluorinated Nucleosides", Carbohydrate Research, 327, 87-105 a copy of which is annexed as Annexure-11, discusses the development in the field of fluorinated. nucleosides with special focus on nucleosides which contain fluorinated glycone moiety. Pankiewicz discloses that some of the early studies were on $2^{\prime}$-deoxy- $\mathbf{2}^{\prime}$ fluoro
nucleosides showed promising therapeutic potential for developing anticancer and anti-viral agents. It also states that more than $77 \%$ of fluorinated nucleosides synthesized to date contain fluorine atom at $\mathrm{C}-2^{\prime}$ of the sugar. It states that a fluorine atom at a sugar carbon in nucleosides causes only a minor change of the shape of the modified structure. Fluorine is a good mimic of a proton or a hydroxyl group and is able to form hydrogen bonding (as an acceptor). It suggests that tluorination at the $\mathrm{C}-2$ position showed therapeutic activity in anti-cancer and anti-viral agents.

The applicant has also admitted that fluorinated derivatives were preferred during this period.

Methods of fluorinating nucleoside analogues was also known to a person skilled in the art

A number of reagents have been used to conduct fluorination reactions. For instance, W.J. Middleton; (1975) " "New Fluorinating Reagents. Dialylaminosulfur Fluorides", J. Org. Chem., 40, 574-578 a copy of which is annexed as Annexure-12, discloses the use of fluorinating agents such as DAST and dialkylaminosulfur trifluorides to replace hydroxyl group of alcohols with a fluorine group. Middleton ett al also discloses the reaction conditions to perform such fluorination reactions. Several examples have been disclosed wherein the hydroxyl group of alcohol is converted to the fluoro group.

## Using DAST could also result in the inversion of the configuration was known

Before the date of priority and as discussed above, the mechanisms for converting arabinonucleoside to a $2^{\prime}$-F-ribonucleoside was well developed, was predictable and the chemical reagents for such conversions were also known. For instance ${ }^{-}$P. Herdewijn et al (1989), "The Application of
diethylaminosulfur trifluoride to the synthesis of fluorinated nucleosides, Nucleosides and Nucleotides", 8(1), 65-96, a copy of which is annexed as Annexure-13, disclosed that three different methods are used to synthesise nucleosides fluorinated in the sugar moiety using DAST and illustrates that all reactions resulted in the inversion of the configuration. Several other authors have also documented that fluorination with DAST could result in the inversion of the configuration. For instance, Van Aerschot, taught that the reaction of arabinouridine with DAST to prepare $2^{\prime}$ F-ribouridine in a single step transformation could result in simultaneous inversion of the stereochemistry at the 2 '-carbon of arabinouridine.

Further, J. .Wachtmeister et al. (1999), "Synthesis of 4 -substituted carbocyclic 2,3-dideoxy-3-C-hydroxymethyl mucleoside analogues as potential ant-viral agents", Tetrahedron, 55, 10761-10770, a copy of which is annexed as Annexure-14 discloses that fluorination of a tertiary alcohol in a cyclopentanol compound with DAST- $25 \%$ yield \& with Deoxo-Fluor$43 \%$ yield. It discloses that fluorination of a tertiary alcohol in a cyclopentanol compound with inversion of stereochemistry can be carried out with DAST with a yield of $25 \%$ as well as with deoxo- fluor with a yield of $43 \%$. He disclosed the chemistry. for transforming a tertiary OH of a pentose analog to a tertiary F with a fluorinating reagent'such as DAST, or Deoxofluor in a single step resulted in the replacement if the tertiary OH with $F$ and the simultaneous inversion of the stereochemistry at the tertiary carbon. During this period it was well known and recognised in the nucleoside field that DAST reacts readily with tertiary alcohols. Thus the skilled person in art would have chosen DAST as fluorinating agent for converting an arabinonucleoside to a 2'-F-ribonucleoside because DAST reaction would predictably result in inversion of stereochemistry.

## Fluorine and hydroxy group are isostere

It is well known that bioisoteres are frequently used in drug design as the resultant compounds are easily accepted by the body. It is common chemical strategy to use bioisosteric substitution to a lead compound, to synthesize compounds that have less undesirable characteristics (for example low bioavailability, inadequate half-life and potential to form reactive metabolites).
f. It is well known that one of the most common classical bioisosteric substitutions is the incorporation of fluorine into a compound in replacement of a hydroxyl group. See Annexure-9.
g. The rationale for such replacement is based on the fact that the size of the fluorine atom is intermediate between that of hydrogen and oxygen, and that the substitution of the hydroxy group with fluorine is particularly lavoured when the presence of an electronegative atom is necessary for the interaction of the ligand with the target protein. Fluorine has the strongest clectronegativity in the periodic table, both fluorine and hydroxyl group can form hydrogen bonds. See K. Harada, J et al (1987), "Synthesis and Anticytomegalovirus and Antiherpes Simplex Virus Activity of 5'Modified Analogues of 2'-Fluoroarabinosylpyrimidine Nucleosides", J. Med. Chem., 30, 226-229; a copy of which is annexed as Annexure-15.

## Similar nucleoside analogues with methyl (up) and hydroxy (down) at 2' position were known

The Opponents submit that nucleoside analogues with methyl (up) and hydroxy (down) at 2 ' position were known way before the priority date of the impugned application. Akira Matsuda et al (1987), "Radical deoxygenation of tert-alcohols in 2 '-branched-chain sugar pyrimidine
nucleosides: synthesis and antileukemic activity of $2^{\prime}$-deoxy- $2^{\prime}$ ( S )methylcytidine" Chemical \& Pharmaceutical Bulletin, 35(9):3967-70, a copy of which is annexed as Annexure-16 discloses the synthesis of 2'-deoxy-2'(S)-methylcytidine and their use in anti-leukemic activity.' The nitrogenous base compounds claimed in claim 6 and 15 of the impugned patent application is chemically similar to the compound disclosed in Matsuda comprising of a sugar molecule substituted with a nitrogenous base at position 1'-position, methyl group at 2 '-position in up configuration and a hydroxyl group at 3'-position.

## Nucleoside Analogues which suggest methyl (up) and fluorine (down) at 2' position were known

(i) The WO' 425 Application discloses the nucleoside analogues, which discloses the following:

1. Nucleoside analogues for the treatment of HCV . These nucleotide analogues are inhibitors of RNA polymerase and particularly inhibitors of NS5B polymerase.
2. It gives a similar Markush as that of the impugned application. [see page 7 of the Complete Specification of ' 425 Application]
3. Further it also gives various. substitutions for the nitrogenous base 'which may be' selected from a purines or pyrimidines base, and several substituents for $R^{1}, R^{2}, R^{3}$ and $Y$. These substitutions include uridine and cytidine bases as disclosed in the impugned application.
4. . Further it also suggests a modification at $2^{\prime}$ position. It provides substitutions which are independent of each at 2 , positions. It also points out that $\mathrm{R}^{1}$ could be $\mathrm{C}_{1}-\mathrm{C}_{4}$ alkyl which includes methyl and $R^{2}$ includes fluorine [See pages 7,8 and 9 of the Complete Specification of ' 425 Application]
5. It suggests that at $2^{\prime}$ position, it could be methyl (up) and hydroxyl or fluorine (down).
(ii) In the alternative and without prejudice to the above argument, the WO '287 Application discloses the following:
6. It diṣcloses the nucleoside compounds and derivatives thereof, their synthesis, and their use as inhibitors of RNAdepeụ́dènt RNA viral polymerase.
7. It discloses the inhibitors of NS5B polymerase used to treat HCV.
8. It discloses that the nitrogenous base attached to the sugar could be purine or pyrimidine.
9. It discloses modifications at the 2 ' positions. It discloses that $R^{1}$ includes methyl and $R^{2}$ could be fluorine. [See pages 7, 8 , 9, and 78-80]
10. It provides methods of synthesis of these compounds.

11. It discloses that a substitution at the $2^{\prime}$ position is independent I of each other.
h. Thus, á skilled person trying to develop on new nucleoside analogues for the treatment of hepatitis C virus would be aware that:
(i) Nuclcoside analogues are used to treat hepatitis $C$ virus were known and admitted.
(ii) Nucleosides with modifications with fluorine at 2'position of the - sugar was known and admitted.
(iii) Methods of fluorinating nucleoside analogues was also known to a person skilled in the art.
(iv) Using DAST could also result in the inversion of the configuration was known.
(v) Use of fluorine to enhance metabolism of the drug were known.
(vi) Fluorine and hydroxy groups are isostere and are easily interchangeable was known.
(vii) Similar nucleoside analogues with methyl (up) and hydroxy (down) at 2' position were known.
(viii) Nucleosides which suggest methyl (up) and fluorine (down) at $2^{\prime}$ position were known.
i. In the light of the above submissions, the claims $1-10$ are obvious to a person skilled in art and hence the claims 1-10 ought to be rejected in toto.

## V.C. Claims 1-10 fail under Section 3(d), are not an invention within the meaning of

 this Act and should be rejected under Section 25(1)(f) of the Patents Act.1. As discussed above, Section 3(d) is a unique provision of Indian patent law designed to prevent "evergreening." It is vital that the provision be-strictly construed, as instructed by the Supreme Court in Novartis, to protect the public health interest the amendment is designed to safeguard.
2. Under Section 3(d), salts, esters, ethers, polymorphs, metabolites, pure form; particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.
3. In other words Section 3(d) prevents a patent from being granted for simply minor chunges to prior art, even if the change makes the compound novel or inventive because of new and unexpected characteristics resulting from the change. In addition, an applicant must show significantly enhanced therapeutic efficacy as compared to the nearest prior art molecule which is structurally and functionally close.
4. It is an established position of law that Section 3(d) has to be satisfied independently of Sections $2(1)(\mathrm{j})$ and $2(1)(\mathrm{ja})$ [see Novartis AGv Union of India and others, (2013) 6 SCC 1].
5. In view of the above, the subject matter claimed in the present invention amounts to a new use of a known substance and therefore not an invention in accordance with Section 3(d) of the Patents Act.
6. Claims are not patentable under Section 3(d): It is submitted that claims 1-7 of the current set of claims are drawn to nucleoside analogs. It is pertinent to note that previously, in the claims as filed, the Applicant had claimed large number of compounds and has now confined themselves to claims 1-7 without assigning any reason. It is also submitted that no therapeutic efficacy is demonstrated with regard to all the compounds now claimed under claims 1-7 in comparison with the closest prior art compounds including the compounds originally claimed but now surrendered. Since therapeutic efficacy as mandated in law is not demonstrated, the claims are liable to be rejected on this ground alone. Further, claims 8 and 9 are drawn to method of synthesizing the nucleoside of claim 1 . This method is a mere glycosylation of pyrimidine with compounds of Formula 1-4. This is a process already known in the art and therefore, mere use of a known process is not patentable under Section 3(d) of the Act.
7. Composition is not patentable within the meaning of Section $3(\mathrm{e})$ : It is submitted that the composition as claimed in claim 10 is not patentable within the meaning of Section 3(e) as the composition does not demonstrate any synergy. Apart from the fact that no specific composition is defined or specifically claimed, in the event, the claim is interpreted as a composition, such composition is a mere adniixture of known substances, which result only in aggregation of the properties of the individual components and do not provide any enhanced synergy. A composition demonstrating mere aggregation of properties is not patentable under Section 3(e).
8. Therefore, based on the aforesaid facts and submissions the impugned application is liable to be revoked on this ground alone.
V.D. The complete specification does not sufficiently and clearly describe the invention as claimed in Claims 2 \& 9 and should be rejected under 25(1)(g) of the Patents Act.
a. Section 25(1) (g) of the Patents Act provides a ground for opposition if the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
b. Section $10(4)$ of the Patents Act requires the complete specification to fully and particularly describe the inventions and its operation or use.
c. Without prejudice to other grounds raised herein, the complete specification does not sufficiently and clearly describe all the claims of the present application.

## Claims broad and indeterminate:

a. It is submitted that the best method of performing the invention is not disclosed by the specification of the impugned patent application. For example, claim 1 and its dependant claims 2 to 5 are drawn to nucleoside or pharmaceutical acceptable salt of the said nucleoside. Claim 1 embraces a large number of compounds and the specification does not provide sufficient guidance as to the actual preparation of such compounds. In particular, the specification does not provide the reaction conditions whereby all of the compounds of Claim 1 may be prepared. Similarly, the specification does not provide enough guidance whereby all the compounds embraced within the scope of claims 2-5 may be prepared.
b. Claim 1-5 and claims $16-7$ include the nucleoside as well as its pharmaceutically acceptable salt. However, the specific salt are not identified either in the claims or in the specification, leaving a person skilled in the art to conduct undue number of experiments to arrive, at the specific salt that may be pharmaceutically acceptable and demonstrate
or its own gives no guidance to a person skilled in the art to prepare any of the compounds claimed in the impugned application.

## Claims unsupported:

a. The specification is drawn to certain nucleoside compounds claimed in claims 1-7 and method of synthesizing such compounds as claimed in claims 8-9 and use of the compounds in a pharmaceutical composition. However, the specification provides no support for subsistence of any of these claims. The reasons therefore are elaborated in the foregoing paragraphs and the sane are not being repeated herein for the sake of brevity. For all these reasons, it is also submitted that the best mode of performing the invention is also not disclosed in the specification. If the Applicant has now confined their invention to the claims $1 \frac{10}{} 10$, it is submitted that the best method of performing the invention in terms of claims 1-10 is not disclosed and the same are liable to be rejected, the reasons being set out hereinabove. In the absence of any such support, the claims are liable to be rejected.
b. Further, as per the Patents Act, the claims of a patent must be sufficiently supported by the description. The impugned patent fails on account because:

## Claims covetous:

a. Claims 1-10 even though drawn to nucleoside compounds and methods for their preparation, the specification does not demonstrate any instance of the importance of the said specific compounds claimed in claims 1-7. There is no clarity about the workable range of the said compounds. It is not clear whether the entire range of compounds as claimed in claims 1-7 are equally
effective, workable and provide the desired antiviral effect as claimed qua some compounds.
b. In view of the above the claims are broad and are not fairly based on the matter disclosed in the specification as filed.

## V.E. The Patent Applicant has not complied with the requirements of Section 8. Therefore, the present applicution should be rejected under Section 25(1)(h) of <br> the Patents Act.

a. In view of the fact that the Patent Applicant has evidently not complied with the requirements of Section 8 of the Patents Act, the Patent Application should be rejected under Section 25(1)(h) of the Patents Act.
b. The Applicant is required to provide all the information regarding the prosecution of the corresponding applications until the grant of the Indian Application to the Controller in writing from time to time and also within the prescribed time, which applicant failed to comply with.
c. Under section 8(1) of the Act the applicant was under obligation to furnish to the Patent Office details of corresponding foreign applications and also to furnish an undertaking under section 8(1) (b) and subsequently furnished further details with respect to corresponding foreign applications including their status from time to time. The opponent thereby states that the applicant is required to provide all the information regarding the prosecution of his equivalent applications till the grant of his Indian Application to the Controller in writing from time to time and also within the prescribed time, which the applicant has failed to do. The applicant has failed to finfish statement and undertaking under section 8 , therefore the
d. Accordingly the applicant is under the obligation to submit the application in respect of the same or substantially the same invention or to file along with his application a statement setting out his knowledge for such an application being prosecuted by some person through whom he claims or by snme person dcriving title from him. However, the applicant has failed to furnish statement and undertaking under section 8 , and the opponent therefore demands rejection on this ground also.
e. $\therefore$ It is submitted that the Applicant/Respondent has failed to disclose the details of corresponding foreign applications filed, and on this ground alone the patent application should be rejected.

VI: : In sum, India Cares urges the Honorable Controller to be mindful of upholding the rights to health granted by the Constitution and Patent Act and of how applying. the law more broadly than intended will put life-saving drugs beyond the reach of millions of sick individuals in India and in many developing and under-developed countries.
VII. The Opponent craves leave to amend the opposition and add further grounds and documents as when required.
VIII. Further the Opponent craves leave to adduce evidence in support of the Opposition.

$$
\stackrel{!}{i}
$$

IX. The Applicant has not followed the set procedure prescribed by the Act to amendment the claims: Hence the amended claims ought to be rejected in limine.

## HEARING REQUESTED

X. The Opponent hereby requests a hearing under section 25(1) of the Patents Act, 1970 (hereinafter referred to as "the Patents Act") and Rule 55 of the Patents Rules (hereinatter referred to as "the Rules").

## PRAYERS

Given all of the foregoing, the Opponents humbly pray:
(i) For an order rejecting patent application 6087/DELNP/2005 for feasons as stated above;
(ii) For an order rejecting any request by the Applicant for leave to amend its Application;
(iii) For a copy of any reply statement and evidence and $/$ or amended specifications that may be filed by the Applicant and a further opportunity to file a rejoinder and rebut the same;
(iv) For leave to amend the opposition or add additional grounds, as and when required;
(v) For leave to submit further documents as and when required;
(vi) For a hearing under section 25(1) of the Patents Act read with rule 55(1) of the Patents Rules;
(vii) For cósts;
(viii) the Opponent may be allowed to make further submissions and file rejoinder or other appropriate evidence in case the applicant makes any amendments in the claims;
(ix) any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this $23^{\text {rd }}$ day of June 2015

Cheha arue
FOR RAJESHWARI \& ASSOCIATES
AGENT FOR THE OPPONENT

## LIST OF ANNEXURES

| S. No. | Particulars | Page No. |
| :---: | :---: | :---: |
| 1 | Annexure-1 <br> D. Lavanchy," Evolving epidemiology of hepatitis C virus", (2011) Clin Microbiol Infect; 17: 107-115. | 40-48 |
| 2 | Annexure-2 <br> Nucleoside analogues to treat HCV were also known before 2003. For instance R De Francesco et al, New therapies on the horizon for hepatitis C: Are we close? Clin Liver Dis. 2003 Feb; 7(1):211-42, xi. | 49-80 |
| 3 | $\begin{aligned} & \text { Annexure-3 } \\ & \text { Copy of WO 2001/90121 } \end{aligned}$ | 81-376 |
| 4 | $\begin{aligned} & \text { Annexure-4 } \\ & \text { Copy of WO } 2001 / 92282 \end{aligned}$ | 377-678 |
|  | Annexure-5 <br> US Patent No. 6348587. | 679-722 |
| 6 | $\frac{\text { Annexure-6 }}{\text { Copy of WO }} 2002 / 057425$ | 723-957 |
| 7 | $\begin{aligned} & \text { Annexure- } 7 \\ & \text { Copy of WO 2002/057287 } \end{aligned}$ | 958-1042 |
| 8 | $\begin{aligned} & \hline \text { Annexure-8 } \\ & \hline \text { WO 1999/43691 } \end{aligned}$ | 1043-1151 |
| 9 | Annexure-9 <br> Park BK and Kitteringham NR (1994), "Effects of fluorine substitution on drug metabolism: pharmacological and toxicological implications", Drug Metab. Rev., 26, 605 | 1152-1190 |
| 10 | Annexure-10 <br> Gumina, G et al, (2001), "Synthesis and potent anti-HIV activity of L-3'-fluoro- $2^{\prime}, 3^{\prime}$-unsaturated cytidine", ORGANIC LETTERS, 3 (26), 4177-4180. | 1191-1194 |
| $11$ | Annexure-11 <br> Pankiewicz (2000), "Fluorinated Nucleosides", Carbohydrate Research, 327, 87-105. | 1195-1213 |
| PO DE ${ }^{12}$ | $\text { Annexure-12 }_{\mathrm{W}_{2} J_{2}, ~ M i d d l e t p p_{2}}(1975)_{5} \text { "New Fluorinating Reagents. }$ | 1214-1218 |


|  | Dialylaminosulfur Fluorides", J. Org. Chem., 40, 574-578. |  |
| :---: | :---: | :---: |
| 13 | Annexure-13 <br> P Herdewijn et al (1989), "The Application of diethylaminosulfur trifluoride to the synthesis of fluorinated nucleosides, Nucleosides and Nucleotides", 8(1), 65-96. | 1219-1250 |
| 14 | Annexure-14 <br> J. Wachtmeister et al (1999), "Synthesis of 4 -substituted carbocyclic 2,3-dideoxy-3-C-hydroxymethyl mucleoside analogues as potential ant-viral agents", Tetrahedron, 55, 10761-107.70 | 1251-1260 |
| 15 | Annexure-15 <br> K. Harada,J et al (1987), "Synthesis and Anticytomegalovirus and Antiherpes Simplex Virus Activity of 5'-Modified Analogues of 2'-Fluoroarabinosylpyrimidine Nucleosides', J. Med. Chem., 30, 226-229. | 1261-1264 |
| 16 | Anncxure-16 <br> Akira Matsuda et al (1987), "Radical deoxygenation of tertalcohols in 2 '-branched-chain sugar pyrimidine nucleosides: synthesis and antileukemic activity of $2^{\prime}$-deoxy- $2^{\prime}$ (S)methylcytidine". Chemical \& Pharmaceutical Bulletin, 35(9):3967-70. | 1265-1274 |

# Evolving epidemiology of hepatitis C virus 

D. Lavanchy<br>Interlifescience, Massogno Ticino, Switzerland


#### Abstract

More than 20 years after the discovery of the hepatitis $C$ virus (HCV), it is now well established that HCV is of global importance affecting all countries, leading to a major global health problem that requires widespread active interventions for its prevention and control. Chronic hepatitis $C$ was linked to the development of cirrhosis and hepatocellular carcinoma in many areas of the world. Current epidemiological assessments have identified complex patterns with highly variable local prevalence rates between countries and within countries. HCV infection patterns have not significantly changed in most parts of the world since 1997, when first analyzed, partly due to the lack of new and more accurate data. The assessment of the national HCV prevalence and transmission modes should be complated to enable national authorities to prioritize preventive measures and to make the most appropriate use of available resources. The 'patchy' epidemiological situation in some areas will continue to complicate the task of the establishment of global, regional and national base line data. The present assessment finds a global prevalence of $2.35 \%$. affecting 160 million chronically infected individuals. There is an urgent need for more accurate Information on the costs and burden of HCV to society. Twenty-one year after the discoserr of HCV, the assessment is far from being complete and little progress has been made in the past 10 years in many countries. In some countries significant increases have been reported and this may also apply to countries were insufficient data exist. A safe and effclient vaccine against HCV is urgently needed.


Keywords: Epidemiology, HCV, hepatitis C, prevalence, review
Article published online: 22 November 2010
Clii Microbial Infect 201I: 17: 107-115

Corresponding author: D. Lavanchy, ruelle es Chataigniers I,
CH -1026 Dénges VD. Switzerland
E-mail: lavanchyd@gmail.com
of cases of acute hepatitis $C$ progress to chronic infection; 10-20\% of these will develop complications of chronic liver disease, such as liver cirrhosis, within two to three decades of onset, and $1-5 \%$ will develop liver cancer. [3-7], making HCV a health problem of global importance [8]. Heavy alcohot consumption, particularly in females, age and HCV/human immunodeficiency virus (HIV) co-infection may be associated with more rapid progression of HCV liver disease, especially fibrosis [9]. Additional prospective longitudinal studies. are needed to determine whether other factors, such as schisto: somiasis and clonorchiasis, and exposure to toxic solvents, a common occurrence in developing countries, are associated with disease progression. There is an urgent need for more accurate information on the long-term outcome, with its consequences for, and costs and burden, to, society.

## Transmission

There are still large gaps in our knowledge of the global epidemiology of HCV. The relative contributions of the various
sources of infection have rarely been investigated in popula-tion-based epidemiological studies in most geographical areas. The assessment of national HCV prevalence and transmission modes should be completed to enable national authorities to prioritize preventive measures and to make the most appropriate use of available resources. In addition, many unanswered questions exist concerning the roles of risk factors and lifestyle conditions that may be associated with HCV spread in different regions of the world. Epidemioological studies on the roles of potential risk factors, such as medical procedures, injections for medications and immunizations, injections applied outside of medical settings, tattoo- : ing, and scarification techniques, have shown wide geographical variations with major implications for local populations and potential prevention and control programmes.

As HCV can be sexually transmitted (albeit rarely between healthy individuals), the role of co-infection with other sexually transmitted diseases, such as HIVIAIDS, need to be further 'studied, especially for those that can result in open genital sores, such as chlamydial infection, chancroid and syphilis.

## Hepatitis C Global Prevalence

HCV has been shown to have a worldwide distribution, occurring among persons of all ages, genders, races and. regions of the world. The socio-economic burden of HCV has not yet been defined in most countries. Where the epidemiology of hepatitis $C$ has been studied, the consequences of chronic hepatitis $C$, HCC and end-stage liver cirrhosis have been shown to increasingly impact on national health systems [10]. New infections still occur, because of the continued use of unscreened or inappropriately screened blood transfusions and blood products, the failure to sterilize medi-
cal equipment adequately, and the increase in intravenous drug use in previously unaffected areas. Global, regional and national monitoring will be necessary to evaluate results and address shortcomings. The quality and coverage of popula-tion-based HCV prevalence should be improved, by using: (i) a representative population sample; and (ii) accurate diagnosetic tests. To better evaluate the incidence trends and burden of chronic. disease, the prevalence of HICV infection should be stratified according to age, ethnicity and gender. Since the first publication in 1997 [ 8 ], published evidence for the prevalence of HCV still remains disappointedly limited, as information is still inadequate in many countries, most published prevalence studies being of limited scope, representing only a segment of the population [11-13].(e.g. pregnant women, blood donors or hospital admissions), with only a few studies using sampling techniques that represent the entire population.

## Prevalence of hepatitis $C$ worldwide

As most acute HCV infections ( $60-70 \%$ ) are asymptomatic [14-16], data ${ }^{\circ}$ on the incidence of new cases of HCV infection are difficult to obtain and therefore scarce. Some risk groups, such as haemophiliacs, haemodialysis patients, patients transfused with unscreened blood and unscreened blood products, inmates of long-term correctional facilities, and persons with occupational exposure, clearly have a high incidence and prevalence of HCV infection [17-24].

As measurement of incidence fails to produce reliable numbers, because of the mostly asymptomatic form of acute infection, most approximations are based on reviews of pub. lished prevalence data, which estimated that 130-170 million persons, or 2-3\% of the world's population, are infected. with HCV [25-27]. The current estimates are given in Fig. 1 and Tables I and 2. Prevalence estimates are 400000 chron-


FIG. I. Hepatitis C global prevalence 2010 (\%).
© 2011 The Author
Clinical Microbiology and Infection © 2011 European Society of Clinical Microbiology and Infectious Diseases. CMI, 17, 107-1 15 .


TABLE I. (Continued)


TABLE 2. Hepatitis C regional prevalence 2010

| Region | Andi-HCV (\%) | No. HCV. Infected |
| :--- | :---: | :---: |
| Africa | 3.2 | 28100000 |
| Americas | 1.5 | 14000000 |
| Asia | 2.1 | 83000000 |
| Australia and Oceania | 1.2 | 400000 |
| Europe | 2.3 |  |
| Middle East | 4.7 | 17500000 |
| Total | 2.35 | 16000000 |

italy infected subjects in Australia and Oceania, 14 million in the Americas, 16 million in the Middle East, 17.5 million in Europe, 28 million in Africa, and $\mathbf{6 J}$ million in Asia [12].

The published data suggest that most populations in the Americas, western Europe and Southeast Asia have prevalance rates of antibody to HCV (anti-HCV) under $2.5 \%$. Anti-HCV prevalence rates for eastern Europe average from $1.5 \%$ to $5 \%$, those for the Western Pacific region from $2.5 \%$ to $4.9 \%$, and those for the Middle East and Central Asia from $1 \%$ to more than $12 \%$ [27]. In terms of absolute numbers, the majority of infected people live in Central/Southeast Asia and the Western Pacific regions (Table 2), a finding similar to that for chronic hepatitis $B$ infection.

Only a few studies on cost estimates are available. In the USA, the current estimate of the annual costs of acute and chronic hepatitis $C$ exceeds US $\$ 600$ million [29]; and over
the period 2010-2019, the total costs are expected to be US \$184 billion [30], giving an indication of how important the burden of chronic HCV infection can be for national health systems, even in a low-endemicity country ( $1.8 \%$ ). The European Monitoring Centre for Drugs and Drug Addiction estimated the HCV-related costs in ten European Union countries to be $€ 50$ million, excluding HCV drug therapy and monitoring, thereby demonstrating that, oven with no public health action, HCV causes significant costs to society. The estimates for Spain were approximately $€ 3$ billion for the period 2010-2030.[31], and in Canada the costs are estimated at CD $\$ 150$ million annually until 2040 [32]

## Epidemiological trends

As representative prevalence data are still not available from many countries, and progress since 1997 has been scarce, the local, national and regional baseline estimates of the rate of infection, the number of individuals chronically infected and the burden of disease are not established, making it impossible to assess correctly the impact of control and prevention measures. In addition, highly significant differences in subnational population groups have been documented.

For instance, in China, Bao et al. [33] found that the prevalence in non-injection drug users varied from $0 \%$ (Anhui) to 40.00\% (Fujian). Intravenous drug use is increasing in China, posing a new challenge to public health authorities for the implementation of harm reduction programmes [34]. Only a few studies have addressed the prevalence of HCV in China. In a cross-sectional study conducted in six different regions of the country, the overall prevalence of HCV was $0.58 \%$, which was much lower than the $2.7 \%$ estimated by the WHO [35]. On the other hand, the prevalence in, the genaral population was found to be $2.1 \%$ in Fujian province [36], $9.6 \%$ in Henan province [37] and $25 \%$ in a rural community of elderly people [38]. Therefore, in China, the geographical distribution of HCV infection is heterogeneous, and patterns differ between rural and urban settings, but, with the significant increase in intravenous drug use, it is expected that the prevalence will generally increase in China.

Hepatitis $C$ is an emerging infection in India as well, and is already responsible for a significant proportion of liver disease in various states. However, the prevalence appears to be highly variable ('patchy'), according to the geographical site or the. population group analysed (0.09-7.89\%) [39]. Most of the studies of prevalence have been conducted in blood banks, and have shown prevalence rates of $<2 \%$, but in professional donors prevalence rates between $55.3 \%$ and $87.3 \%$ have been found. The consequences of chronic HCV infection will probably be significant increases in morbidity and mortality in India in the years to come.
© 2011 The Author
Clinical Microbiology and Infection ©201। European Society of Clinical Microbiology and Infectious Diseases. CM1, 17, 107-115.

Changing trends in HCV over the past 50 years have also been observed in Japan, where $70 \%$ of cases of HCC are attributable to HCV, and HCC is the fourth leading cause of death in males and the fifth in females. HCV started to-spread in the 1930s among intravenous drug users (amphetamines) before, during and aiter World War II, or through medical procedures such as blood traņfusion and the use of contaminated syringes. The prevalence of HCV infection is much lower in the younger generation than in the older generation aged $>55$ years ( $0.1-0.2 \%$ vs. $>2 \%$ ) [40]. Therefore, the tocal number of patients with HCV infection is considered to have decreased. The incidence of HCC has steadily increased over the last 50 years, but it is now decreasing in Japan, mainly because of the decreased prevalence of HCV-related HCC. A similar trend has been observed in Italy [ 41,42 ].

Pakistan is a developing cou'ntry of i70 million people, and recent investigations have shown that about 10 million (5.9\%) people are presumed to be infected with HCV [43]. Public health authorities are raising awareness about viral hepatitis among healthcare workers and the general population, but tremendous efforts are still required to combat various risk factors involved in HCV: transmisșion, particularly because of the non-implementation of international standards regarding blood transfusion and male injection practices.

Egypt has a very high prevalence of HCV, reaching as much as. $32 \%$ in the population of young males requesting visas for foreign travel [44-47], and the country suffers high morbidity and mortality from chrọnic liver disease, cirrhosis and HCC. Approximately $20 \%$ of Egyptian blood donors are anti-HCV-positive [44]. Geographically, the desert areas of Egypt have the lowest rates of anti-HCV positivity; rural areas tend to have higher rates than cities; and rates in the Nile Delta (Lower Egypt) are higher than in the Nile Valley (Middle Egypt and Upper Egypt) [44,46,47]. The strong homogeneity of HCV subtypes found in Egypt (mostiy 4a) [48-50] suggests an epidemic spread of HCV [49]. The risk factor(s) originally responsible for the establishment of HCV in the general population may not necessarily be the same as those responsible for transmitting the virus today. Therefore, both traditional risk factors and risk factors that may be unique to Egypt need to be considered in explaining the transmission of HCV in this country. The prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis with tartar emetic (potassium antimony tartrate), and the data suggest that Egypt's mass campaigns do indeed represent the world's largest example of iatrogenic transmission of a blood-borne pathogen [51]; the large reservoir of chronic HCV infection established in the course of these campaigns remains the most likely reason for today's high prevalence of HCV, which
may be largely responsible for the continuing endemic transmission of HCV today [52]. Egypt has a unique HCV prevalencé pattern that is not comparable with those of its eastern Mediterranean neighbours. However, in the recent past, intravenous drug use has been'shown to have increased in the Middle East, as documented for Iran [53]. It is therefore expected that the prevalence of HCV will increase in the next 10 years.

For Africa; HCV prevalence data are incomplete, but'show considerable variation from one, population studied to another, with prevalence rates from $0 \%$ to $51 \%$ [54-57]. More than 28 million people are chronically infected with HCV on this continent. It is currently difficult to determine trends concerning current and future infection rates.

In Europe, too, the HCV prevalence data are often incomplete, outdated, or inconclusive. The current estimates are that 7.3-8.8 million people (1.1-1.3\%) are chronically infected in the European Union, a figure that is almost double the first estimates performed in 1997 [27], indicating that HCV is also a major health problem in Europe [58], and an increase is forecasted for the next decade [59-61]. For the whole of the European continent, it is estimated that 17.5 million individuals are infected. Recently, a 3 -month pilor study carried out by the Hepatitis C Trust in pharmacies in England found that the prevalence of HCV infection was almost four times as high as previously estimated. The pilot study found a prevalence of $15 \%$, which is significantly more than the $4 \%$ determined by tests carried out in general practitioner surgeries in 2008 [62], emphasizing that the study design has major consequences for outcomes in population-based studies, and calling for caucion when evaluating published HCV prevalence figures, even in well-studied countries.

In addition to anti-HCV-based prevalence studies, longitudinal genotype observation adds a further tool for monitoring epidemiological trends. Measurement of the spatial introduction of new genotypes in a population, and the rate of sequence evolution or natural recombinations in viruses introduced at a given time in a cohort, provides the possibility of evaluating the history of the past geographical spread of HCV through different populations, shedding light on the demographic, social and biological factors that are at the basis of ancient and current unrecognized routes of transmission. Genotypes 1-3 have a worldwide distribution [48,6365]. Genotypes 4 and 5 are found principally in Africa, and genotype 6 is distributed in Asia [66]. Endemic areas for specific genotypes are found in West Africa (types 1 and 2), West Central Africa (type 4), the Indian subcontinent (type 3), Central Africa (type 4) and Southeast Asia (type 6). An endemic area for genotype 5 has not been found [49,6773], except for a local county in central France, where

Clinical Microbiology and Infection ©2011 European Sociery of Clinical Microbiology and Infectious Diseases. CM1. 17. 107-115

HCV Sa contamination of the local population was associated with living in a rural area called Vic-le-Comte. Abergel et al. suggest that HCV 5a spread by an iatrogenic route before 1972, and then via transfusion to the whole county [74]. When a limited diversity of HCV subtypes is found in a ertain geographical area, it may be attributed to the recent introduction of HCV into the population, as was documented for Canada [75] or Australia [76]. The molecular epidemiology of HCV genotype 2 points to West and Central Africa, mostly along the African Atlantic coast, as its endemic place of origin. Markov et al. have found an eastwards spread from the West African coast to Cameroon that took place over several centuries [77]. Molecular clock analysis dates the common ancestor of HCV to GuineaBissau, around 1470 (1414-1582). Isolates from Madagascar and Martinique suggest that the historical slave trade and the possible parenteral HCV exposure during public health campaigns undertaken during the colonial. era may have played a role in the dissemination of HCV genotypes 2 a and 2 c. In summary, the geographical distribution of HCV genotypes and the rate of genetic variation are consistent with the global distribution of HCV, and are compatible with a long history of infection in most populations of the world, presceding, in many geographical locations, the era of modern medicine by many centuries.

HCV-related cirrhosis and deaths from $\dot{H C C}$ are likely ta increase dramatically within the next decade, egg. in Australia [78,79], Canada [80]. France [81], the UK [59-61] and the USA [82]. Owing to the increase in intravenous drug use in China, India and the Middle East, increases are likely to occur within this decade in these regions too, and because China and India are the countries with the largest populaions, a $1 \%$ increase in both would result in an additional $\mathbf{2 5}$ million HCV-infected subjects. If patients are left undiag. nosed and untreated, the future burden of the disease for healthcare resources and society will be substantial. A declining burden in the years to come is expected only in Italy [42,83], Japan [84], South Korea [84] (accompanied by a decrease in the incidence of HCC in these two countries) [85] and the USA [86].

## Strategies for Prevention in Light. of the Undetermined Epidemiology <br> $\qquad$ $\therefore$

HCV-prevention programmes are needed, at. the -local, national, regional and global levels if the spread of HCV and the burden of hepatitis $C$ are to be reduced. To achieve these objectives, the implementation of measures that reduce the risk of contracting HCV infection is required, a task that
was unfulfilled in. many areas in 2010. Such programmes need to ensure that blood supplies and related products are free of infection, and that safe injection methods are practised within and outside medical settings. The use of disposable syringes for immunization and injections is particularly crucial in developing countries. Risk-education counselling for professionals and the public is of paramount importance. Where this is affordable, persons with chronic hepatitis $C$ should be identified and targeted for special counselling and medical management. in order to reduce due risk of them developing HCV-related disease complications. Healthcare professionals and the public, who are crucial for the effective prevention of HCV transmission, should be educated about the risk of transmission of blood-borne pathogens (HCV, hepatitis B virus and HIV) by contaminated injection and other medical equipment, as well as by traditional and folk medical prosedures or practices [87-89], and should receive appropriate education and training concerning the importance of controlling such infections in all medical, surgical and dental facilities, including the us eq of standard precautions, safe injection pac. tics, proper sterilization techinques, and high-level disinfeczion where appropriate, avoiding the re-use and sharing of contaminated equipment and supplies, and avoiding contamination of multi-use supplies, such as medication vials. The use of devices or products that prevent re-use or contamination of medical and dental equipment should be encouraged (e.g. autodestruct syringes), noting that cost-effective-devices are available [90-92].

## Conclusions

From the above, it can be seen that the assessment of the national, regional and global prevalence of chronic HCV represents an enormous task that may never be fully achieved. The 'patchy' epidemiological situation in some areas will contine to complicate the task of the establishment of global, regional and national baseline data, and this will also apply to the use of modelling that is currently undertaken by the CDC and by others. Therefore, new. and inventive methodologies may have to be applied in order to estimate the actual baseline of the HCV epidemic and to evaluate future prevention and control activities. There is a need for better public awareness,.coordinated national and regional action plans, and better data that take into account representative population samples. Improved assessment of -risk factors in high-risk groups, the different' genders and 'forgotten' ethnic groups is needed. Education should be culturally appropriate and address the concerns of all populations with HCV. Twenty-one years after the discovery of HCV, the assess-

S2011 The Author
Clinical Microbiology and Infection G201I European Society of Clinical Microbiology and Infectious Diseases, CMI. 17, 107-1 15
ment is far from being complete, and little progress has been made in the past 10 years in many countries. The global figures have not changed significantly, with a global estimate of 160 million infecred people and a global prevalence of $2.35 \%$ (Tables 1 and 2). However, in some countrics; significant increases have been reported, and this may also apply to countries where insufficient data exist.

Physicians, healthcare workers and public health officials should be aware-and many are not-that many subjects are unaware of their infections, provide timely testing and antiviral treatment when needed, and avoid further iatrogenic transmission. It is a public health responsibility to ensure that prevention and control measures, in particular drug treatment, should be accompanied by the appropriate assessment and monitoring, using inventive and locally adapted methodologies for the evaluation of the baseline and the follow-up activities. Targeted populations should have equitable access to care and guaranteed, sustained supplies of medications, as well as clinical monitoring. Needless to say, in today's context a safe and efficient vaccine against HCV is urgently needed, and even a vaccine with suboptimal efficiency will probably help to better control HCV.

## Transparency Declaration

The author declares no conflict of interest.

## References

1. Smith DB, Mellor J, Jaryis-LM et al. Variation of the hepactitis $C$ virus 5 non-coding region: implications for secondary structure, virus detection and typing. The International HCV Collaborative Study Group. J Gen Virol 1995; 76 (Ph 7): 1749-1761.
2. World Health Organization. World Heefith Reporn, Geneva, Swizzerland 1996.
3. Di Bisceglie AM. Order SE, Klein Jlet ol. The role of chronic viral hepatitis in hepatocellular carcinoma in the United States. Am J Gastroenterol 1991: 86: 335-338.
4. Fattovich G. Giustina G, Degos Fet al. Morbidity and mortality in - compensated cirrhosis type $C$ : a retrospective follow-up study of 384 pasients. Gastroenterology 1997; 112: 463-472.
5. Kiyosawa K, Sodeyama T. Tanaka E et al. Interrelationship of blood itransfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of anuibody to hepatitis $C$ virus. Hepotology 1990; 12 (4 Pt 1): 671-675.
6: Seeff LB, Buskell-Bales Z, Wright EC et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. N Engl / Med 1992; 327: 1906-1911.
6. The Global burden of Hepatizis C working Group. Global burden of disease (GBD) for hepatitis C. J Clin Phormocol 2004; 44: 20-29.
7. Heparitis C: global prevalence (update). Wkly Epidemiol Rec 1997; 72: 341-344.
8. Poynard T, Mathurin P, Lai CL et al. A comparison of fibrosis progression in chronic liver diseases. J Hepatol 2003; 38: 257-265.
9. Adier M, Goubau P, Nevens F, Van Vlierberghe H. Hepatitis C virus: the burden of the disease. Acto Gastroenterol Belg 2002; 65: 83-86.
10. Jeannel D, fretz C, Traore Y et al. Evidence for high genetic diversity and long-tein endemleity of hepatitis $C$ virus genotypes 1 and 2 in West Africa. J Med Virol 1998; 55: 92-97.
12.' Martinson FE, Weigle KA, Mushahwar IK, Weber DJ, Royce R, Lemon SM. Seroepidemiological-survey of hepatitis B and C virus infecrions in Ghariaian children. J Med Virol 1996; 48: 278-283.
11. Richard-Lenoble D. Traore $O$, Kombila M, Roingeard P, Dubois F. Goudeau A. Hepatitis B, C, D, and E markers in rural equatorial Afrid can villages (Gaboil). Am J Frop Med Hyg 1995; 53: 338-341.
12. Korecz RL, Abbey H. Coleman E, Gitrick G. Non-A, non-B posttransfusion hepatitis. Looking back in the second decade. Ann Intern Med 1993: 119: 110-115.
13. Aach RD, Stevens CE, Hollinger FB et ol. Hepatitis $C$ virus infection in post-transfusipn hepatitis. An analysis with first- and second-generation assays. N Engl J Med 1991; 325: 1325-1329.
14. Alter $H$, Jetı B, Polito $A$ et al. Analysis of the role of hepatitis $C$ virus in transfusion-associated hepatitis. In: Viral Hepatitis and Liver Disease. Hollinger fB, Lemon SM, Margolis HS, eds. Baltimore, MD: Williams \&.Wilkins, 1991; 396-402.
15. Hagan H, McGough JP, Thiede H, Weiss NS, Hopkins S, Alexander ER. Syringe exchange and risk of infection with hepatitis $B$ and $C$ viruses. Am J Epidemiol 1999; '149: 203-213.
16. Tanaka E. Kiyosawa K, Sodeyama $T$ et ol. Prevalence of antibody to hepatitis $C$ virus in Japanese schoolchildren: comparison with adult blood donors. Am J Trop Med Hyg 1992; 46: 460-464.
17. Broers B, Junet C, Bourquin M, Deglon JJ. Perrin L, Hirschel B. Prevalence and incidence rate of HIV, hepatitis $B$ and $C$ among drug users on methadone maintenance treatment in Geneva between 1988 and 1995. AIDS 1998: 12: 2059-2066.
18. Dutra U, Raina V, Garg PK et al. A prospective study on the incidence of hepatitis $B \& C$ infections amongst patients with lymphoproliferative disorders. Indion J Med Res 1998; 107: 78-82.
19. van Beek I, Dwyer R, Dore GJ, Luo K, Kaldor JM. Infection with HIV and hepatitis $C$ virus among injecting drug users in a prevention setcing: retrospective cohort study. BMJ 1998; 317: 433-437.
20. Crofts N, Jolley D. Kaldor J, van Beek I, Wodak A. Epidemiology of hepaticis $C$ virus infection among injecting drug users in Australia. J Epidemial Community Healch 1997; 51: 692-697.
21. el-Ahmady O , Halim AB, Mansour O , Salman T. Incidence of hepaticis C virus in Egyptians. J Hepatol 1994; 21: 687.
22. Fabrizi F, Martin P. Dixit $\vee$ et al. Acquisition of hepatitis $C$ virus in hemodialysis patients: a prospective study by branched DNA signal amplification assay. Am / Kidney Dis 1998; 31: 647-654.
23. Hepatitis C-global prevalence (update) Wkly Epidemiol Rec 2000; 75: 18-19.
24. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis $C$ virus infection. Loncet infect Dis 2005; 5: 558-567.
25. Hepatitis C: global prevalence. Wkly Epidemiol Rec 1997; 72: 65-69.
26. Alavian SM, Ahmadzad-AsI M, Lankarani KB, Shahbabaie MA, Bahrami Ahmadi $A, K a b i r ~ A$. Hepatitis $C$ infection in the general population of Iran: a systemacic review. Hepot Mon 2009; 9: 211-223.
27. Moyer LA, Mast EE, Alter MJ. Hepatitis C: part I. Routine serologic testing and diagnosis. Am fom Physicion 1999; 59: 79-88.
28. Shah BB, Wong JB. The economics of hepatitis C. Clin Liver Dis 2006; 10: 717-734.
29. Buti M, Sán Miguel R, Brosa M, et at. Estimating the impact of hepatitis $C$ virus therapy on future liver-related morbidity, mortality and costs related to chronic hepatitis $C$. J Hepatal 2005; 42: 639645.
30. El Saadany S, Coyle D, Giulivi A, Alzal M. Economic burden of hepatithis $C$ in Canada and the potential impact of prevention. Results from a disease model. Eur / Health Econ 2005: 6: 159-165.
31. Bay YP, Liu ZM. Systematic review of HIV and HCV infection among drug users in China. Int J STO AIDS 2009: 20: 399-405.
32. Kia X, Lu J. Bai J, Mu R. Epidemiology of hepatitis C virus infection among injection divvy users in China: systematic review and metaanalysis. Public Health 2008; 122: 990-1003.
33. Lu J, Chou Y, Lin $X$ et al. General epidemiological parameters of viral hepatitis $A, B, C$, and $E$ in six regions of China: a cross-sectional surly in 2007. PLo ONE 2009; 4: e8467.
36: $\mathrm{Li} \mathrm{L}, \mathrm{He} \mathrm{J}$, Zhao L. Epidemiologic features of viral hepatitis in Fujian. Zhonghua $\mathrm{L}_{\mathrm{L}}$ King Bung Xe Oo Zhi 1998: 19: 89-92.
j). Chang M, Sun XD, Mark S̄D et al. Hepatitis $C$ virus infection, Linxian. China. Emerg Infect Dis 2005; 11: 17-21.
34. Chang $M$, Fan J, Li H et all. Alternative risk factors of HCV infection in a rural community in China. Epidemiol Infect 2010; 138: 1032-1035.
35. Mukhopadhyaya A. Hepatitis C in India. J Biosci 2008: 33: 465-473.
36. Chung $H$, Jed $T$, Kudo M. Changing trends in hepatitis $C$ infection over the past 50 years in Japan. Intervirology 2010; 53: 39-43.
37. D'Amelio R. Male A. Mariano A et al. Stable low levels of hepatitis C virus infection among Italian young males over the past decade. Dig Liver Dis 2006: 38: 64-65.
38. Mariano A. Scalia Tomba G. Tosti ME, Spada E, Male A. Estimating the incidence, prevalence and clinical burden of hepatitis ${ }^{\circ} \mathrm{C}$ over time in lully. Stand Jinfea Dis 2009; 41: 609-699.
39. Waked Y. Shafi T, Safi SZ, Qadri I. Hepatitis $\dot{C}$ virus in Pakistan: a systematic review of prevalence, genotypes and risk factors. World / Gastroenterol 2009: 15: 5647-5653.
40. Arthur RR, Masan NF, Abdallah MY et al. Hepatitis C antibody prev-- alence in blood donors in different governorates in Egypt. Trans R Soc TroD Med Hyg 1997: 91: 271-274.
41. el Gohary A, Hassan A, Nooman Z et al. High prevalence of hepatiti $C$ virus among urban and rural population groups in Egypt Acta Trap 1995: 59: 155-161.
42. Mohamed MK, Rakhaa M, Shoeir S, Saber M. Viral hepatitis C inferton among Egyptians, the magnitude of the problem: epidemiological and laboratory approach. J Egypt Public Health. Assoc 1996; 71: 79-112.
43. al-Sayed NM, Gomatos PJ, Rodier GR et al. Seroprevalence survey of Egyptian tourism workers: for hepatids B virus, hepatitis C virus, human immunodeficiency virus, and Treponema pallidum infections: association of hepatitis $C$ virus' infections with specific regions of Egypt. Am J Trap Med Hyg 1996; 55: 179-184.
44. McOmish F, Yap PL, Dow BC et al. Geographical distribution- of heptitis $C$ virus genotypes in blood donors: an international collaboraLive survey. J Clii Microbial 1994; 32: 884-892.
45. Mellor J, Holmes EC, Jarvis LM, Yap PL. Simmons P. Investigation of the pattern of hepatitis $C$ virus sequence diversity in different geographical regions: implications for virus classification. The International! HCV Collaborative Study Group. / Gen Viol 1995: 76 ( Pt 10): 2493-2507.
46. Quint I, el-Salman D, Monier MK et al. HCV infection in Egyptian patients with acute hepatitis. Dig Dis Sci 1997; 42: 2017-2023.
47. Frank C, Mohamed MK, Strickland GT et al. The role of parenteral antischistosomal therapy in the spread of hepatitis $C$ virus in Egypt Lancet 2000; 355: 887-891.
48. Miller FD, Abu-Raddad LJ. Evidence of intense ongoing endemic transmission of hepatitis $C$ virus in Egypt Proc Natl Aced Sci USA 2010; 107: 14757-14762.
49. Razzaghi E. Rahimi Movaghar A. Hosseini. M, Madani S. Chatterjee A. Rapid situation assessment of drug abuse in Iran. Iranian Welfare Oranization and UNDCP, Tehran, Iran, 1999.
50. Triki H, Said N, Ben Selah $A$ et of. Seroepidemiology of hepatitis B, C and delta viruses in Tunisia. Trans $R$ Soc Prop Med Hrs 1997: 91: 11-14.
51. Darwish MA, Faris R, Clemens JD, Rio MR, Edelman R. High seroprevalence of hepatitis $A, B, C$, and $E$ viruses in residents in an Egypthan village in The Nile Delta: a pilot study. Am / Trow Med Hyg 1996: 54: 554-558.
52. Stevens $\mathcal{W}$. Kamali A, Karita E et al. Baseline morbidity in 2.990 adult African volunteers recruited to characterize laboratory reference intervals for future HIV vaccine clinical trials. PLO5 ONE 2008; 3: e2043.
53. Madzime S, William MA, Mohamed $K$ et al. Seroprevalence of hepatithis $C$ virus infection among indigent urban pregnant women in Simbabe. Cent Afr J Med 2000; 46: 1-4.
54. Muhlberger N, Schwarzer R, Letumeier B, Sroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic
 Public Health 2009: 9: 34.
55. Sweeting MJ, De Angelis D, Brant LJ, Harris HE, Mann AG, Ramsay ME. The burden of hepatitis $C$ in England. J Viral Hepatol 2007; 14: 570-576.
56. Hutchinson SJ, McIntyre PG. Molyneaux P et al. Prevalence of hepatiti $\dot{C}$ among injectors in Scotland 1989-2000: declining trends among young injectors halt in the late 1990s. Epidemiol Infect 2002; 128: 473-477.
57. Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis $C$ among injection drug users in Scotland. Hepatology 2005; 42: 711-723.
58. Diagnosing viral hepatitis in the community. The hepatitis $C$ Trust, January 2010: hce:://www.hepctrust.org.uk/Resources/HepC/HCV\%20 Reports/Trus/Diagnosing\%20viral\%20hepatitis\%20in\%20the\%20com munity\%20A\%20month\%20pharmacy\%20testing\%20pilotpdf.
59. Bush J, Purcell RH, Miller RH. At least 12 genotypes of hepatitis $C$ virus predicted by sequence analysis of the putative El gene of isolates collected worldwide. Proc Not Acid Sci USA 1993; 90: 8234-8238.
60. Davidson F, Simmonds P, Ferguson J et al. Survey of major genotypes -and subtypes of hepatitis C virus using RFLP of sequences amplified from the 5' non-coding region. J Gen Virol 1995; 76 (Pt 5): 1197-1 204.
61. Stuyver L, Wyseur A, van Arnhem W, Hernandez F, Martens G Second-generation line probe assay for hepatitis $C$ virus genotyping. J Chin Microbial 1996; 34: 2259-2266.
62. Li CS, Chan PK, Tang JW. Molecular epidemiology of hepatitis C genotype ba from patients with chronic hepatitis $C$ from Hong Kong. J Med Viral 2009; 81: 628-633.
63. Simmonds P, Alberti A, Alter HJ et al, A proposed system for the nomenclature of hepatitis $C$ viral genotypes. Hepatology 1994; 19: 1321-1324.
64. Stuyver L: van Arnhem W, Wyseur A, Hernandez F, Delaporte E, Martens $G$. Classification of hepatitis $C$ viruses based on phylogemetic analysis of the envelope I and nonstructural SB regions and identification of five additional subtypes. Proc Not Aced ${ }^{-S c^{-} U S A^{-1} 1994 ; ~}$ 91: 10134-10138.
65. Tokita $H$, Okamoto $H$, Luengrojanakul $P$ et al. Hepatitis $C$ virus varyants from Thailand classifiable into five novel genotypes in the sixth (6b). seventh (7c, 7d) and ninth (qb, qc) major genetic groups. I Gen Viral 1995; 76 (Pr 9): 2329-2335.
66. Tokita $H$. Okamoto H, Tsuda F et al. Hepatitis $C$ virus variants from Vietnam are classifiable into the seventh, eighth, and ninth major genetic groups. Proc Nad Aced Sci.USA 1994; 91: 11022-11026.
67. Tokita $H$, Shrestha SM, Okamoto $H$ et al. Hepatitis $C$ virus variants from Nepal with novel genotypes and their classification into the third major group. J Gen Virol 1994; 75 (Pt 4): 931-936.
68. Mellon J. Walsh EA, Prescott LE et al. Survey of type 6 group variants of hepatitis $C$ virus in Southeast $A_{s i a}$ by using a core -based genotyping assay, J Clime Microbiol 1996; 34: 417-423.
69. Ruggieri $A$, Argentina $C$, Kouruma $F$ et al. Heterogeneity oof hepaticis $C$ virus genotype 2 variants in West Central Africa (Guinea Cionakry). J Gen Viral 1996; 77 (PC 9): 2073-2076.

## ©2011 The Author

Clinical Microbiology and Infection ©2011 European Society of Clinical Microbiology and Infectious Diseases, CMI, 17; 107-115
74. Abergel $A$, Ughetto $S$, Dubost $S$ et al. The epidemiology and virology of hepatitis $C$ virus genotype $S$ in central France. Aliment Phormacol Ther 2007: 26: 1437-1446.
75. Bernier L. Willems B. Delage G. Murphy DG. Identification of numerous hepatiuis $C$ virus genotypes in. Montreal, Canada. J Clin Microbiol 1996: 34: 2815-2818.
76. McCaw R, Maaven L, Locarnini SA, Bowden DS. Hepatitis $C$ virus genotypes in Australia. J Virol Heporod 1997: 4: 351-357.
7i. Markov PV, Pepin J, Frost E, Deslandes S, Labbe AC. Pybus OG. Phy-- logeography and molecular epidemiology of hepautis $C$ virus geno. type 2 in Árica. J Gen Virol 2006; 90 (Pt 9): 2086-2096.
78: Dore GJ, Law M. MacDonald M. Kaldor JM. Epidemiology of hepatitis $C$ virus infection in Australia. / Clin Virol 2003; 26:- 17.1$18 \overline{4}$.
79. Hepatitis C Virus Projections Working Group. Estimates and projections of the hepatitis $C$ virus .epidemic in Australia 2002. Darlinghurst, NSW 2010: Australian National Council on AIDS, Hepatitis C and Related Diseases. Hepatitis C Sub-Committee, Hepatitis C Virus Projections Working Group. Estimates and Projections of the Hepatitis C Virus Epidemic in Australia 2002. National Centre in HIV Epidemiology and Clinical Research. The University of New South Wales: 2002.
80. Zou S, Tepper M. El Saadany S. Prediction of hepatitis C burden in Canada. Con J Gastroenterol 2000; 14: 575-580.
81. Deuffic-Burban S. Mathurin P, Valleron AJ. Modelling the past current and future HCV burden in France: detailed analysis and perspectives. Stot Methöds Med Res 2009: 18: 233-252.
82. Deuffic-Burban S, Poynard T, Sulkowski MS, Wong JB. Estimating the future health burden of chronic hepatitis $\bar{C}$ and human immunodeficiency virus infections in the United States. J Viral Hepatol 2007; 14; 107-1 15.
83. Sagnelli E, Stroffolini T, Mele A et al. The importance of HCV on the burden of chronic liver disease in |taly: a multicenter prevalence study of 9,997 cases. J Med Virol 2005; 75: 522-527.
84. Kim SR, Kudo M, Hino O. Han KH, Chung YH, Lee HS. Epidemiology of hepatocellular carcinoma in. Japan and Korea. A review. Oncot' ogy 2008; 75 (suppl 1): 1316.
85. Tanaka $H$, Imai $Y$, Hiramatsu $N$ et ol. Declining incidence of hepatocellular carcinoma in Osaka, Japan, from 1990 to 2003. Ann Intern Med 2008; 148: 820-826.
86. Rosen HR, Ghou S, Sasaki AW, Greecll DR. Molecular epidemiology of hepatitis $C$ infection in US veteran fiver transplant recipients: evidence for decreasing relative prevalence of genotype IB. Am / Gostroantorel 1 Pp9 9 94 : $3015=3019$.
87. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Preveñtion Board, Antwerp. Belgium. / Virol Hepatol 1999; 6: 3547.
88. Alter, MJ. Epidemiology of Hepatitis C. Hepatology 1997, 26(S3): 62S65S.
89. EASL International Consensus Conference on Hepatitis C. Consensus Statement. Journal of Hepatology, 1999, 31: 3-8.
90. Pruss-Ustun A, Rapiti E, Hutin Y. Estimation of the global burden of disease atuributable to contaminated sharps injuries among health. care workers. Am J ind Med 2005; 48: 482-490.
91. FitrSimons D. Francois G, De Carli G et al. Hepatitis $B^{-}$virus, hepatitis $C$ virus and other blood-borne infections in healthcare workers: guidelines for prevention and management in industrialised countries. Occup Environ Med 2008; 65: 446-451.
92. Perz JF, Thompson ND, Schaefer MK, Patel PR. US' outbreak, investigations highlight the need for safe injection practices and basic infection control. Clin Liver Dis 2010; 14: 137-151.

Clinics in
Liver Disease

# New therapies on the horizon for hepatitis $C$ : are we close? 

Raffaele De Francesco, $\mathrm{PhD}^{\mathrm{a}, *}$, Charles M. Rice, $\mathrm{PhD}^{\mathrm{b}}$<br>${ }^{4}$ Istituto di Ricerche di Biologia Molecolare P. Angeletti, Via Pontina KM 30,600, 00040 Pomezia, Rome, Italy<br>${ }^{\mathrm{b}}$ Laboratory of Virology and Infectious Disease. Center for the Study of Hepatitis C, The Rockefeller University: 1230 York Ave., New York, NY 10021, USA

The late 1980s and 1990s were marked by a series:of spectacular breakthroughs in the treatment, diagnosis, and prevention of post-transfusion non-A, non-B hepatitis, now known to be caused primarily by hepatitis C virus (HCV) [1]. Modern treatment began with the demonstration that interferon-alpha (IFN- $\alpha$ ) was effective for treating patients with chronic HCV-associated hepatitis [2]. IFN treatment was initially given as a thrice-weekly injection for 6 months, and later extended to 12 months to decrease the risk of relapse. Unfortunately, some HCV genotypes, in particular genotype I, were not readily eliminated by IFN monotherapy. The combination of IFN and the nucleoside analog D-ribavirin increased sustained virologic response almost threefold, even for resistant genotypes [3,4]. The most recent advance, a combination of D-ribavirin and pegylated IFN- $\alpha$, yields a sustained virologic response of nearly $40 \%$ to $50 \%$ in genotype 1 -infected patients, and about $80 \%$ to $90 \%$ in those infected with genotypes 2 and 3 [5,6]. In spite of these remarkable advances, the current treatment is ineffective in many patients, has significant side effects, and is often poorly tolerated (see the ärticle by Dis. Fried and McHutchison elsewhere in this issue).

Despite the use of interferon and D-ribavirin for treatment of viral infections for decades, very little is known about how they actually work. Type I interferons, like IFN- $\alpha$, induce a number of genes with antiviral activities; they also act as immunomodulators affecting diverse cells in the immune system including antigen-presenting cells. Recent studies in cell culture indicate that both type I and type II (gamma) IFNs can dramatically: inhibit HCV replication

[^0][7-10]. This direct inhibitory effect at the level of the infected cell presumably plays some role in the rapid decline in HCV RNA levels after administration of IFN in vivo [11]. The mode of action of D-ribavirin, an inhibitor of a key enzyme in purine nucleotide biosynthesis inosine monophosphate dehydrogenase (IMPDH), is even less well understood. Immunomodulatory, inhibitory, and mutagenic mechanisms for D-ribavirin have been proposed [12]. In the future, improvements in IFNs and D-ribavirin-like molecules may yield more cffcctive treatment options with lower toxicity. It is unlikely, however, that simply improving current treatment will be able to control or eliminate all HCV infection. Toward this goal, more specific anti-HCV approaches are needed. In this article, we summarize progress in this exciting area as the first wave of new compounds moves into human clinical trials.

## The HCV lifecycle: dim light in a black box

The molecular cloning of the virus responsible for the majority of posttransfusion hepatitis, HCV , catalyzed an explosion of basic and clinical research [1]. The HCV genome structure immediately led to grouping with the Flaviviridae, a family of positive-strand RNA viruses that can cause severe disease in humans and animals. Although a great deal is known about other members of this family, unraveling the details of HCV replication and setting up meaningful antiviral screening assays have been frustratingly difficult and slow. A major roadblock has been the inability to grow the virus efficiently in cell culture. As described in the next section, major advances have been made in the last several years that have expedited drug discovery efforts.

Based largely on our knowledge of other members of the family, the lifecycle of HCV is outlined in Fig. 1 [13,14]. HCV is an enveloped virus whose density is quite variable when isolated from infected patients and animals. The envelope contains two species of viral glycoproteins, E1 and E2, anchored in the lipid envelope via hydrophobic stretches at their C termini [15]. The envelope surrounds a nucleocapsid composed of the capsid or core (C) protein and a $9.6-\mathrm{kb}$ genome RNA. Candidate receptors for HCV binding to host cells include the E2-binding tetraspannin "CD81 and the low-density lipoprotein receptor (LDLR) [16]. Binding of virus to host cells could be blocked by antibodies capable of neutralizing the virus or by antagonists that inhibit interaction of the virus particle with functional host receptors.

Though these approaches remain possibilities, the absence of robust neutralization and infectivity assays has inhibited progress in this area. The lack of infectivity assays has also hindered attempts to identify inhibitors targeting the steps of entry, fusion of the virion envelope with host membranes, and uncoating of the nucleocapsid to liberate.the genome RNA for translation initiation. The first tractable step in the replication cycle that can be targeted with today's systems is translation of the incoming genome RNA. As described in more detail below translationgigitianon is wided byatighly conserved RNA element that


Fig. I. IKCV lifecycle. Sequential stages in the HCV replication cycle are summarized, beginning with virus binding to the host cell (hepatocyte) surface. Though each of these steps provides an opportunity for therapeutic intervention, validated assays for inhibitor screening and evaluation have been developed for only a subset (translation, polyprotein processing, and RNA replication).
functions as an internal ribosome entry site (IRES) capable of directly binding to initiation factor eIF3 and the 40S ribosomal subunit. This element allows efficient translation of the uncapped HC.V genome RNA and provides an attractive virusspecific process to target. Translation of the genome RNA yields a greater than 3000 amino-acid-long polyprotein that is processed into 10 mature proteins by the action of at least four proteases, two cellular, and two viral. The order and nomenclature of the HCV proieins is: $\mathrm{NH}_{2}$-C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH (Fig. 2). The cellular signal peptidase and signal peptide peptidase are responsible for cleavages separating the structural proteins located in the N-terminal third of the polyprotein (C-p7), whereas the virally encoded NS2-3 protease mediates a single autocatalytic cleavage at the NS2/NS3 site and the NS3-4A serine protease cleaves at four downstream sites. Processing of the polyprotein is essential for forming an active HCV RNA replicase, and both of the viral proteases are being actively pursued as antiviral targets.

The HCV replicase is cytoplasmic and membrane associated, consisting of at least NS3-NS5B, together with additional as yet undefined host components. The major enzymatic components of the RNA replication machinery are the NTPase/ helicase activity located in the C-terminal two-thirds of NS3 and the NS5B RN-Adependent RNA polymerase (RdRP). Both of these enzymes have been extensively studied biochemically and have yielded high-resolution structures that are aiding drug discovery efforts. The first step in the RNA replication process involves the synthesis of a complementary negative-strand copy of the incoming genome RNA. Although confusion 等xists is the literature, it is generally believed



Fig. 2. Genetic organization and processing of HCV polyprotein Arrows indicate cleavage by hostand HCV-encoded proteinases as indicated. The black bar indicates portion of the El signal sequence removed from C' by SPP cleavage. Diamonds in the E1 and E2 region indicate glycosylation of the envelope proteins El and E2.
Abbreviations: C, capsid; E, envelope; F, frameshift protein; NS, nonstructural; SPP, signal peptide peptidase.
that this occurs' by a primer-independent de nov initiation mechanism similar to_ phage phis [17]. The negative strand template is then used for synthesis of additional genome-length RNA that can in turn be used for translation, replication or packaging into progeny virus.

Efficient assembly and release of HCV particles has not been recapitulated in the laboratory. Thus, whereas these are attractive steps for intervention, it has not been possible to establish systems to study them or for antiviral screening. Based on results with other members of the Flaviviridae, it seems likely that HCV buds into intracellular vesicles and is transported out of the cell by the host secretory pathway and released into the extracellular space. It is interesting that iminosugars, that act as glucosidase inhibitors to interfere with proper carbohydrate maturation of glycoproteins, have been shown to inhibit infectious virus production of a another member of this family, the pestivirus bovine viral diarrhea virus (BVDV) as well as HBV (see [18] for a recent review of the antiviral potential of iminosugars).

## Approaches for identifying and evaluating antivirals

After the elucidation of the HCV genome structure and characterization of the polyprotein processing scheme, several groups purified HCV-encoded enzymes IPO DEL

The primary targets of these early efforts were the NS3-4A serine protease, the NS3 helicase, and the NS5B RdRP. Crystallographic structures (see below) were determined for each of these enzymes and the first of these, the serine protease, revealed a rather featureless substrate-binding cleft that was predicted to challenge medicinal chemists searching for selective inhibitors. This has certainly turned out to be the case. Inhibitory compounds identified in biochemical screens are ideally tested for efficacy in cell-based systems, such as a virus-infected cell. This turned out to be a majur roadblock for $\mathrm{HC}^{-} \mathrm{V}$ and was solved only recently for the RNA replication process. In the meantime, several groups created surrogate cell-based assays for HCV functions (proteases and IRES) [19-21] or turned their attention to close relatives studies. A major breakthrough came in 1999 when Lohmann et al [22] described engineered subgenomic HCV RNAs or "replicons". that were capable of limited replication in a human hepatoma Huh- 7 cell line (see article by Drs. Pietchmann and Bartenschlager in this issue). The inclusion of a dominant selectable marker, allowed the selection of adaptive variants that replicated to high levels in these cells [ $7,10,23,24$ ]. Although thus far restricted to this cell line and genotype $1 b$ isolates, this system provides an important cell-based model for evaluating inhibitory compounds identified in biochemical screens. It also can be used for direct screening of other compounds to identify inhibitors of as yet unknown viral or cellular targets required for efficient HCV replication.

In terms of preclinical animal studies, the path has been no less challenging. Humans and our closest relative, the chimpanzee, are the only hosts susceptible to HCV infection. Many groups have tried to establish small animal models for HCV infection and antiviral studies. Despite intensive efforts, it was only last year that a robust murine model was reported. Mercer et al [25] were able to engraft human hepatocytes into an immunodeficient mouse strain that was homozygous for a hepatotoxic transgene. These animals were susceptible to HCV infection and supported high levels of persistent HCV replication in the engrafted human tissue. Although the model is challenging given the need for primary human tissue, it could prove very useful for evaluating in vivo efficacy of a limited number of compounds.

## Conserved HCV RNA elements: antisense and ribozyme approaches

Replication of HCV requires not only translation of the incoming genome RNA but also selective recognition of this RNA by the RNA replication machinery. These processes are mediated by conserved RNA elements that typically function in cis (as part of the genome RNA or its complement). As mentioned above, translation is mediated by an IRES element in the $5^{\prime}$ NTR of the HCV genome. Key features of this 341 -nt RNA element, highly conserved in primary sequence and secondary structure, are summarized in Fig. 3 [26]. Beside its role in translation initiation, the $5^{\prime}$ NTR (or its complement at the $3^{\prime}$ end of negative strand RNA) 2 centains $\frac{1}{5}$ signals that are important for RNA


Fig. 3. Conserved RNA elements in HCV genome RNA. Schematic of the 9.6 kb HCV genome with the conserved RNA elements in the $5^{\prime}$ NTR, the NS5B coding region, and the $3^{\prime}$ NTR highlighted. The $5^{\prime}$ NTR, in particular the IRES, has received the most attention as a potential antiviral target.
replication. These include $5^{\prime}$ terminal stem-loop structure (SLI) that is not required for translation as well as sequences that overlap with the IRES [27,28]. Another highly conserved sequence in the HCV genome immediately follows the $5^{\prime}$ NTR and includes the $5^{\prime}$ part of the C protein coding region. Recent work suggests that this sequence is conserved because it encodes an additional protein in an overlapping reading frame that is now called the ARFP (alternative reading frame protein) [29] or $F$ (frameshift protein) [30]. Other conserved RNA features in the HCV genome are found in the NS5B coding region $[29,31,32]$ and in the $3^{\prime}$ NTR. The $3^{\prime}$ NTR of HCV is quite atypical compared with cellular mRNAs. It consists of a short region that is variable among genotypes and dispensable for replication [33,34], a poly (U/UC) tract of heterogeneous length and composition, and a highly conserved sequence of 98 bases that terminates with a highly stable 46 -base stem-loop structure. Sequences at or near the $3^{\prime}$ ends of the viral positive- and negative-strand RNA are likely to be involved in regulating the initiation of negative- and positive-strand RNA synthesis, respectively. As for other RNA viruses, we expect that RNA elements elsewhere in the genome may also participate in these processes. Biochemical and genetic evidence now support the importance of these conserved RNA elements at the $5^{\prime}$ and $3^{\prime}$ ends of the 'genome in both translation $[26,35,36]$ and RNA


Fig. 4. X-ray crystallographic structures of specific HCV enzymes. (A) NS3-4A proteinase domain (left, bottom): the residues forming the catalyțic triad are shown in yellow. A serine-trap inhibitor (compound 2) is covalently linked to the catalytic serine and occupies the enzyme active site. The NS4A cofactor (red) and the bound zinc ion (gray) are shown. (B) NS3 helicase domain: singlestranded nucleic acid bound to the helicase-active site (yellow). Subdomains I, II, and III are recognizable by different colors. (C) NS3-4A proteinase-helicase (middle): the C-terminal product of the NS3/NS4A cleavage reaction occupies the proteinase-active site (gray). (D) NS5B RNA-dependent-RNA polymerase (right): the thumb, palm, and finger subdomains are indicated (blue, green, and red, respectivelyl. The two magnesium ions (gray) and the active site aspartates (yellow) are shown in the active site. A GTP motecule is bound at the allosteric site on the surface of the thumb domain.'

Conserved RNA elements in the HCV genome, the cognate-binding proteins, and the interactions required for their function are all possible targets for antiviral development. Thus far, conserved HCV RNA elements have received less attention than other targets. Several nucleic acid-based'approaches [37], including antisense oligonucleotides, ribozymes, RNA aptamers, RNA decoys, and RNA interference ( RNA i ) are being explored and two of these have progressed into clinical trials. In both these cases, specificity is achieved by base-pairing with the conserved HCV target sequences. Antisense oligonucleotides hybridize to target RNAs, leading to RNase H-mediated cleavage and degradation or interference with mRNA function such as translation. For RNA viruses with a cytoplasmic replication cycle such as $H C V$, the latter mechanism of action is more likely. A number of studies have shown that antisense oligonucleotides directed at the HCV IRES or conserved downstream sequences can selectively inhibit translation in vitro, in cells or in the liver of mice $\left[388_{4} 42\right]$. One potential antisense drug, ISIS
IPO DELHI 2

14803 (HepaSense ${ }^{\text {TN }}$ ISIS, Carlsbad, CA), has entered phase I/II clinical trials. Early dosing studies in patients that had failed IFN or IFN plus ribavirin have shown mild reduction in viral titer in some patients [43]: Larger clinical trials are currently under way.

In the case of ribozymes, short HCV-specific sequences flanking the catalytic ribozyme core kybridize to the HCV target and lead to ribozyme-mediated cleavage and inactivation. This approach has the potential advantage that ribozymes are calalytic and can theoretically degrade multiple HCV RNAs. As for antisense oligonucleotides, not all sites in an RNA are accessible to ribozymes and the optimal target sequence must be empirically determined. The feasibility of HCV-directed ribozymes was first shown using infected hepatocytes [44-47]. The concept was developed further in a series of preclinical studies. A number of ribozymes were screened, and one cleaving at HCV 5 ${ }^{\prime}$ NTR position 195 in loop IIIb of the IRES possessed the greatest efficacy. Effficacy was measured using in vitro assays, as well as cell-based assay-measuring IRÉS-driven reporter genes or poliovirus replićation using at engineered HCV -poliovirus chimeric virus for which replication was dependent on HCV IRES-mediated translation [48]. Ribozymes could be stabilized by inclusion of $\cdot 2^{\prime}$-O-methyl-nucleotides, $2^{\prime}$-deoxy- $2^{\prime}$-C-allyl uridine, a $3^{\prime}$ inverted abasic cap, and phosphorothioate linkages and were readily taken up by the liver in vivo [49]. More recent work revealed a synergistic inhibition of the HCV-poliovirus'chimera by combining the ribozyme with interferon alpha•[50]. If this combination leads to higher efficacy at lower doses, it could be advantageous for manufacturing (ribozymes are expensive to produce) and lowering undesirable side effects (IFN).

RNA interference is the newest entry into RNA sequence-specific antiviral approaches [51]. The RNAi pathway is initiated by cleavage of double-stranded RNA into 21-23 nt duplexes, termed small interfering RNAs (siRNAs). Strands of siRNA are incorporated into an RNA-induced silencing complex and target, complementary RNAs for degradation. Much of this pathway has been worked out in plants, Drosophila melanogaster and Caenorhabditis elegans, but it is now clear that RNAi operates in mammalian cells as well [52-54]. siRNAs can also be made synthetically and transfected into cells or expressed intracellularly from pol III-transcribed cassettes. Recent studies have shown that siRNA can be used to inhibit replication of HIV [53-\$6] and poliovirus [57], and to downregulate translation of HCV IRES-driven reporter RNAs [58] and replication of HCV replicons [59].

Antisense oligonucleotides and ribozymes (and peptide nucleic acids, RNA decoys, RNA aptamers, and siRNAs), because of their size and charge, are not orally bioavailable because they do not readily cross cellular membranes. They are also susceptible to degradation by host nucleases. As mentioned earlier, modifications have been made that greatly enhance stability, cell permeability, and target specificity. These molecules are also readily taken up by the liver, making them especially attractive for therapy of hepatotropic viruses like HCV. Rather than systemic administration, however, another option is to deliver and express RNA-based HCV -specific ighibitoss via vectors designed for permanent
gene therapy, such as modified lentiviruses or adeno-associated virus. Uninfected hepatocytes or, hepatocyte "preçursors, if successfully transduced, would be resistant to HCV infection. In theory, these cells would eventually repopulate the liver as HCV-infected'. nonresistant cells were .eliminated by the immune system or by toxic effects of virus infection. This concept, suggested years ago by David Baltimore, is termed "intracellular immunization" [60].

Other strategies using functional genomic screens:to identify cellular factors that regulate the function of the HCV [RES have identified possible therapeutic targets. In one study, Krüger et al [61] found that downregulation of ccllular translation initiation factors eIF2Bgamma and eIF2gamma inhibited translation mediated by the HCV IRES under conditions that did not inhibit translation of capped cellular mRNAs or cell growth. In a second study, a subunit of the human 20S proteosome (PSMA7) was implicated in IRES-mediated translation [62]. Interestingly, the proteosome inlibitor, MG132, exhibited a dose-dependent inhibitory effect on HCV IRES-mediated translation. Whether similar effects will be observed in the replicon system or in vivo remains to be determined, but these studies mark the beginning of functional studies into HCV-host interactions that will undoubtedly lead to a wealth of new opportunities for new drug development.

## HCV-encoded enzymes and their inhibitors

All of the known enzymatic activities associated with HCV' gene products, namely the NS2-3 and NS3-4A proteinases, the NS3 helicase, and the NS5B RdRP, represent potential drug discovery targets. The demonstration that knocking out each individual HCV-encoded enzymatic activity by site-directed mutagenesis in a full-length infectious HCV cDNA clone abrogated its infectious potential in chimpanzees validates these targets [63].

## Viral proteinases

At least four different proteolytic enzymes are involved in the proteolytic maturation of the HCV polyprotein [64-66]. Processing at the internal signal sequences found within the $\mathrm{NH}_{2}-\mathrm{C}-\mathrm{NS} 2$ region is mediated by the host signal peptidase and occurs in the endoplasmic (ER) lumen. After undergoing cleavage by the signal peptidase and release of $E 1$ in the $E R$, the signal sequence between the core and El proteins is further processed by the intramembrane-cleaving signal peptide peptidase (SPP), thus promoting the release of core protein from the ER membrane [66]. The region of the polyprotein downstream of NS2 is processed by two overlapping HCV-encoded proteinases. As cleavage of the structural region of the polyprotein is mediated exclusively by cellular proteinases, it would be extremely difficult to develop inhibitors of these processes that have a sufficient therapeutic window for clinical applications. Conversely, the virus-encoded proteinases constitute attractive targets doEthe development of antiviral agents.

## NS2-3 proteinase

The NS2-NS3 junction is cleaved intramolecularly by a zinc-dependent proteinase consisting of NS2 and the N-terminal serine proteinase domain of NS3 [67,68]. Strikingly, the NS2-3 proteinase activity is totally independent of the catalytic activity of the NS3 serine proteinase, yet the NS3 serine proteinase domain cannot be replaced by other polypeptides [69]. The NS2 region, conversely, shares no obvious sequence homology to known proteolytic enzymes.--Furthermore, it is highly hydrophobic and is associated with membranes in infected cells [69]. As the NS2-3 proteinase activity is stimulated by zinc ions and inhibited by chelating agents [67,70], it was tentatively classified as a metalloproteinase, a hypothesis that initially gained acceptance. Biochemical and structural data have subsequently shown that the NS3 serine proteinase domain contains a tightly bound zinc ion that is required for its structural integrity. (see below). The zinc dependence of the NS2-3 proteinase activity could therefore be related to the role of this metal ion in stabilizing the fold of NS3 and not to its participation in the catalytic process. Site-directed mutagenesis experiments, aimed at identifying the residues involved in the catalysis of the NS2/NS3 cleavage, have shown that Cys 993 and His952, contained within NS2, are required for NS2/NS3 processing [67]. This observation suggested that Cys 993 and His 952 might be the catalytic dyad of a novel cysteine proteinase [71].

- The search for inhibitors of the NS2/NS3 cleavage reaction has been hampered by the hydrophobic nature of the protein and by the autocatalytic nature of the cleavage. Recently, scientists have managed to express a recombinant NS2-NS3 precursor in the form of a defined minimal domain, devoid of membrane-anchoring sequences, which is still capable of performing the processing reaction in vitro [72,73]. Experiments have been performed on the purified enzymes utilizing classical proteinase inhibitors or mechanism-based inhibitors, such as "peptide aldehydes or peptide hydroxamic acids (specific for cysteine or metallo-proteinases respectively). However, such experiments have failed to further elucidate the NS2-NS3 catalytic process. Interestingly, peptides derived from NS4A, a cofactor for the NS3-4A serine proteinase, were found to potently inhibit the NS2-3 proteinase in vitro [72,74]. Unfortunately, because of their peptidic nature and rather large molecular weight, these peptides are not considered leads for the development of drug candidates. The purified, recombinant precursors, as well as surrogate cell-based assays [75], will now be used for large-volume screening campaigns aimed at the discovery of novel inhibitors of NS2-3 enzymatic activity.


## NS3-4A proteinase

The NS3 protein is a component of a heterodimeric serine proteinase that requires the noncovalently- associated viral protein NS4A for optimal catalytic activity [76]. Accordingly, it is often referred to as. the NS3-4A proteinase. The

virus-encoded components of the HCV replicase complex [77]. Hence, tampering with the processing kinetics or even abolishing certain cleavage events is likely to impair viral replication. In light of the success of proteinase inhibitors in controlling HIV infection, and because serine proteinases are traditionally viewed as tractable targets by medicinal chemists, many academic and industrial research groups have initiated programs aimed toward the identification of potent and selective inhibitors of the NS3 proteinase.

NS3 is a multifunctional protein that contains a serine proteinase domain in its $\sim 180 \mathrm{~N}$-terminal amino acids. The remainder of the protein encompasses an KNA helicase. The NS3 proteinase belongs structurally to the trypsin superfamily but is unique in requiring a noncatalytic, structural zinc atom and a second viral protein as a cofactor [78] (Fig. 4A). The proteinase cofactor, NS4A, is a relatively small protein, consisting of only 54 residues. The first $\sim 20$ residues of NS4A are highly hydrophobic and are believed to be involved in membrane anchoring of the NS3-4A proteinase/helicase complex. The function of the hydrophilic 20 C-terminal residues of the cofactor is presently unknown, whereas the central residues of NS4A, amino acids 21-34, were shown to interact directly with NS3 and to be absolutely required for the enhancement of its serine proteinase activity [79]. The structural zinc ion is coordinated by residues located opposite to the active site. Bound zinc is believed to play an essential structural role, as its removal was shown to lead to unfolding and precipitation of the protein [80].

Interfering with zinc or NS4A binding would be a strategy to inhibit the NS3dependent serine proteinase activity. Targeting these sites selectively with small, drug-like molecules is currently viewed as extremely difficult, however. Of the possible mechanisms of inhibition of the NS3 proteinase, the one that holds the most promise is inhibition of substrate binding. The' NS3-dependent cleavage sites of the HCV polyprotein have the consensus sequence Asp/Glu-(Xaa) ${ }_{4}$-Cys/ $\mathrm{Thr}\left[\mathrm{Ser} / \mathrm{Ala}-(\mathrm{Xaa})_{2}\right.$-Leu/Trp/Tyr, with cleavage occurring after cysteine or threonine [81]. Analysis of the cleavage kinetics of different peptide substrates has shown that the minimum length required for a synthetic substrate is a decamer incorporating all of these conserved features and spanning six amino acids upstream to four amino acids downstream of the P1-P1' cleavage site. We follow the nomenclature of Schechter and Berger [82] in designating the cleavage sites as P6-P5-P4-P3-P2-P1 . ..P1'-P2'-P3'-P4'-, with the scissile bond between P 1 and $\mathrm{Pl}^{\prime}$ and the C -terminus of the substrate on the prime side. The rather unusual requirement for large peptide substrates can be explained through the structural analysis of the substrate-binding site as revealed by the three-dimensional structure of the enzyme; the substrate-binding channel is strongly cationic, solvent-exposed, and relatively featureless [76]. Selective recognition of the substrate is derived from a series of weak interactions that are distributed along an extended contact surface and that involve all of the evolutionarily conserved features of the cleavage site sequences. This architecture has made the design of potent, small molecular weight inhibitors challenging. Despite this anticipated difficulty, compounds that block replication of HCV replicons in cell culture have been repogt 583 ]- Ehe antiviral Effect af an NS3 proteinase inhibitor; termed

BILN-2061, has recently been shown in early, proof-of-concept clinical trials [84,85].

As described below, a number of peptide-based or peptidomimetic inhibitors have been developed for the NS3-4A proteinase. Most of these inhibitors fall in one of three classes: (1) substrate analogues, (2) inhibitors con aining a covalent serine trap, and (3) product-like inhibitors. In addition, a few nonpeptidic small molecule inhibitors have been recently reported.

## Substrate analogues

Landro and coworkers [86] were the first to report peptide-based inhibitors of the NS3-4A proteinase. In substrate specificity studies, these authors have identified $\mathrm{Pl}^{\prime}$ substitutions with the amino acids proline, tetrahydroisoquino-line-3-carboxylic acid (Tic) or pipecolinic acid (Pip), respectively, that abolished cleavage but retained a high affinity of the corresponding peptides for the proteinase. The decapeptide Glu-Asp-Val-Val-Lẹu-Cys-Tic-Nle-Ser-Tyr was reported to be a potent, competitive inhihitor of the NS3-4A proteinase. Recently, Ingallinella et al further explored the residues corresponding with the $\mathrm{P}^{\prime}$ portion of the noncleavable substrate analogues in order to optimize binding to the substrate binding cleft [87]. Their effort led to a substrate-derived peptide inhibitor of the NS3-4A proteinase with the amino acid sequence Asp-(D)Glu-Leu-Ile-Cha-Cys-Pro-Cha-Asp-Leu. This peptide displayed a more than three orders of magnitude increase in potency relative to the starting peptide. Although a great deal of selectivity and potency can be obtained through the design of substrate analogues, their peptidic nature and relatively large molecular weight limits cell-membrane permeability and bioavailability, thus preventing their employment in clinical trials.

## Serine-trap inhibitors

Serine proteinase inhibitors can typically be developed by derivation of the known substrate by replacing the scissile amide bond with an electrophilic "warhead" able to form a covalent adduct with the catalytic serine residues [88]. Compounds of this mechanistic class are often referred to as "transitionstate analogues", or "serine-trap inhibitors." Several pharmaceutical groups have reported a series of electrophile-based inhibitors, which have included alpha-keto amides, boronic acids, hydrazinoureas, and alpha-keto acids [88-91]. This approach has led to potent, selective peptide-based inhibitors: Selected examples of NS3-4A serine proteinase inhibitors from the recent scientific and patent literature that fall into this class are illustrated in Fig. 5 (peptide alpha-keto amide, compund 1) [92]; peptide alpha -keto acid, compound 2) [93]; and peptide boronic acid, compound 3) [94]. Compounds' of this class have greatly contributed to a better understanding-of the requirements for efficient inhibition of the NS3-4A proteinase. Electrophile-based inhibitors may be undesirable in_aIPO OELHI setinical howevergecause pfthein $\begin{gathered}\text { Bherent chemical reactivity. }\end{gathered}$

A
NS3-4A Proteinase: Serine-trap Inhibitors


B
NS3-4A Proteinase: Product-like Inhibitors


C
NS3-4A Proteinase: Non-peptide Inhibitors


Fig. 5. Chemical structures of selected inhibitors of the NS3-4A. proteinase activity. (A) Serine trap inhibitors, (B) Product-like inhibitors, (C) Non-peptide inhibitors.

## Product analogues

The NS3 proteinase is susceptible to feedback inhibition by the N -terminal products released from the polyprotein substrate after enzymatic cleavage [95,96] ]. The hallmark of protease N -terminal products and product-based inhibitors is the presence of a free carboxylic acid on the C-terminal Pl residue. This carboxylic group is liberated by the cleavage of the peptide bond and is believed to establish crucial and unique interactions with the enzyme-active site. This hypothesis is
enzyme-product complex. In this case, the C-terminal threonine of the NS3 helicase domain, which represents the N-terminal product of the NS3-N4A cleavage event, was found occupying the active site of the proteinase domain [97]. The significance of this pronounced product feedback inhibition with respect to polyprotein processing or viral replication is presently unknown. Based on the abservation of the product inhibition phenomenon, two groups have systematically modified the natural amino acids in these product inhibitors in ordcr to oblair highly potent hexapeptide inhibitors of the NS3-4A proteinase [98,99] (Fig. 5, compounds 4 and 5). The C-terminal carboxylic acid plays a critical role in determining the affinity and selectivity of product-based inhibitors of the NS3-4A proteinase and was exploited as an active-site anchor to develop a new generation of potent, selective tripeptide acid and peptidomimetic product-based inhibitors [83,100] (Fig. 5, compounds 6 and 7). Macrocyclic peptidomimetic compounds in this series represented by compound 7 have been reported to inhibit the HCV-1b and HCV-la proteases with inhibition constant values in the low nanomolar range [83]. Submicromolar concentrations of these compounds were inhibitory in both a cell-based NS3-dependent reporter as well as replicon assays. A compound of this class, BILN-2061, was, furthermore, well tolerated and showed a substantial antiviral effect in early clinical trials [84,85].

## Nonpeptide inhibitors

The limitations of peptides and peptide derivatives as drugs are well documented [101]. Therefore, concurrent with reducing the size and peptide nature of the various inhibitors just described, effort's to discover nonpeptidic inhibitors were also made. Selected examples of a rhodanine derivative [102] (compound 8) and a bisbenzimidazole derivative [103] (compound 9) are shown in Fig. 5. The detailed mechanism of these inhibitors and their potential to inhibit HCV replication in cell-culture or animal models remains to be established before considering these compounds as potential clinical candidates.

## The viral replication contplex

The exact composition of the viral replicase complex is not known. It is often assumed that all of the viral nonstructural proteins are present in a membranebound ribonucleoprotein complex termed the "replication complex." Two enzymatic activities have been identified that are likely to be involved directly in genomic RNA replication: an NTPase/helicase activity residing in the C-terminal two thirds of NS3 and an RdRP activity residing in NS5B.

## NS3 helicase inhibitors

The HCV NS3 protein contains a RNA helicase domain in the C-terminal 500 amino acids [104].. This region of NS3 contains an Asp-Glu-Cys-His (DECH) motif that identifies it as a member of the DEXH subfamily of DEAD (Asp-Glu-

unwinding duplex RNA; the energy required for the unwinding reaction is believed to be generated by the hydrolysis of nucleoside triphosphates. Nucleic acid-stimulated NTPase activity has been shown to be an additional property of the NS3 helicase. The NS3 helicase activity is presumably involved in the resolution of double-stranded. replicative intermediates generated during the, replication of the HCV RNA genome. A role for RNA helicases in modulating RNA-protein interactions is also èmerging, however [106]. The thrcc-dimensional structure of the NS3 helicase domain has been determined by various groups, both as an isolated domain (Fig. 4B) and in the context of the full-length NS3-NS4A complex [107-109] (Fig. 4C). The three-dimensional structure of the isolated helicase domain was also obtained as a complex with nucleic acid.. Three subdomains are recognizable in the helicase portion of NS3. The cleft betweèn domains I and II. forms the nucleotide-binding site, whereas the interfaces between III and domains I and II are predominąntly involved in nucleic acid recognition and binding. The proteinase and helicase domains are separated and connected by a single protein strand. This structural segregation is consistent with functional studies showing that the isolated domains retain their respective 'catalytic activities'. The role of the NS4A component with respect to the helicase activity of the NS3-NS4A complex is currently debated. It has been suggested that NS4A is an inhibitor of helicase activity that may cause a switch between helicase and proteinase activities [110]. But more recently, it has been proposed that NS4A may instead be necessary for the helicase to restrict its activity to RNA, and not DNA, duplexes [111].

A few small-molecule inhibitors of the NS3 helicase with activity in vitro have been reported in the patent literature and some examples are shown in Fig. 6: a thiodiazonium derivative [112] (compound 10), a pyrimidine derivative [113] (compound 11), and a bis-benzimidazole derivative "[114] (compound 12). The inhibitory mechanism and specificity of these compounds are unclear at present. It is worth pointing out that, unlike viral proteinases and polymerases, replicative helicases are not. among the targets of approved antiviral drugs [115,116]. Inhibitors of a replicative helicase encoded by a DNA virus have been recently shown to display antiviral activity against herpesviruses in model systems, however $[117,118]$. The efficacy of viral helicase inhibitors in a clinical setting remains to be established.

## NS5B RNA-dependent RNA polymerase

The NS5B gene product is the viral RdRP [65]. This enzyme is required for both of the RNA synthesis steps necessary for viral replication: the synthesis of the negative-stranded RNA intermediate, complementary to the viral genome, and the synthesis of positive-stranded RNA genomes complementary to the negative-stranded intermediate. Obviously, inhibition of this pivotal enzymatic activity would lead to suppression of HCV replication in infected cells. The enzymatic reaction catalyzed by NS5B, RNA-dependent RNA synthesis, is moreover a reafgion not nogmally sarrie out in noninfected cells [119]. It is

A
NS3 Helicase Inhibitors


B
NS5B RNA-dependent RNA Polymerase Inhibitors


Fig. 6. (A) Chemical structures of selected inhibitors of the NS3 helicase activity. (B) Chemical structures of selected inhibitors of the NSSB RNA-dependent RNA polymerase activity.
therefore possible that specific inhibitors of this enzyme could be found that block HCV replication with negligible associated toxicity.

The NS5B gene was originally predicted to encode the viral RdRP based on the conserved Gly-Asp-Asp (GDD) signature found in its sequence [1]. The corresponding protein was then expressed in a variety of recombinant forms and shown to possess RdRP, enzymatic activity in the absence of any viral or cellular cofactors [120]. The recent determinatiorr of the crystal structure of NS5B by three different laboratories has confirmed the similarity between the HCV RdRP and other polymerases, but it has also revealed some important differences [121-123]. The NS5B structure folds to form a large cleft where the nucleic acid template can be accommodated (Fig. 4D). The shape of the protein, like that of other polynucleotide polymerases, has been compared with that of a half-opened right hand.- The subdomains that define the base and walls of the cleft are denoted palm, fingers, and thumb, respectively. The residues responsible for the nucleotidyl transfer reaction are found within the palm domain that, in the case of RdRPs; contains an Asp-(Xaa) $)_{4}$-Asp motif and the signature GDD motif. The first aspartate of each motif provides the carboxylate side-chains required for ligation of the two

conserved in virtually all polymerases; comparison of their three-dimensional structure reveals a conserved "two-metal-ion" catalytic center that is required for the catalysis of a phosphoryl transfer reaction at the polymerase active site [124]. In contrast with cellular and most other viral polymerases of known structure, the fingers and thumb subdomains are tightly connected in the HCV polymerase and are therefore not free to change conformation independently of each other. This unique property leads in turn to the formation of an enclosed active site tunnel in which the RNA template, the nascent RNA strand, and the nucleotide substrate can be accommodated with only minor conformational changes.

The replication of single-stranded RNA requires that the polymerase possess either some primase activity or, alternatively, that the enzyme use a specific primer, often an RNA or a protein, to initiate the elongation reaction. In this respect, a distinctive feature of the RNA polymerase of HCV is its capability of de novo, primer independent initiation of genome RNA replication. In fact, recent biochemical studies have shown that purified C-terminally deleted forms of recombinant NS5B are capable of primer independent, de novo initiation of RNA synthesis on selected templates [125,126]. According to the de novo initiation model of RNA polymerization, complementary RNA synthesis is initiated at the genome $3^{\prime}$ end by a nucleotide triphosphate rather than by a nucleic acid or a protein primer. Initiation must.then be followed by RNA elongation, termination of polymerization and release of the nascent strand. It is generally accepted that de novo RNA synthesis is• likely to be the mode of viral genome replication adopted by the virus in infected cells. This view has been confirmed by recent structural studies that provide the first snapshot of an initiation complex formed by viral RdRPs [17,127].

To date, all searches for candidate inhibitors of RNA synthesis have focused on the elongation step of the reaction because it is the easiest step to reproduce in the laboratory. In fact, purified recombinant NS5B is able to copy the entire HCV genome in vitro in a primer-dependent manner without additional cofactors [128]. In contrast, the de nọvo RNA synthesis reaction has been more difficult to reproduce efficiently under physiologic conditions. In particular, synthetic templates and a high concentration of guanosine triphosphate (GTP) and $\mathrm{Mn}^{++}$ have been shown to stimulate primer-independent RNA synthesis and favor this process over primer-dependent synthesis. The development of assays based on de novo RNA synthesis function might pave the way to the discovery of specific drugs that selectively block the initiation step of viral replication.

## Inhibitors of the HCV polymerase

As of last year, about 30 drugs had been officially approved for antiviral indications. More than half of these drugs exploit the inhibition of a viral polymerase as the primary mechanism of action [ 115,116 ]. At least one orally, bioavailable inhibitor of the HCV RdRP, JTK-003, is being studied, moreover, in early monotherapy clinical trials on a group of 72 patients who did not respond to conventional therapy fon their hepptitisA infection [129]. Inhibitors of viral
polymerases can be classified into three categories: (1) nucleosidc (substrate) analogues, (2) nonnucleoside inhibitors (NNI), and (3) pyrophosphate (product) analogues. The detailed mechanism of action of each individual member of the various classes of antiviral agents was reviewed recently [115]. Briefly, nucleoside analogues (cyclic or acyclic) are usually phosphorylated to their corresponding nucleoside triphosphate (nucleotide) in the cytoplasm of infected cells. The nucleotide is then typically incorporated by the viral polymerase during processive nucleic acid synthesis, leading to early termination and thus inhibition of the virus life cycle. Nucleoside inhibitors of viral polymerases are used therapeutically for HIV, hepatitis B, and herpesviruses. NNI of therapeutic interest have thus far been described only for HIV-1 reverse transcriptase. These compounds bind to an allosteric site on the enzyme surface away from the enzyme-active site. The NNI binding pocket does not exist in the enzyme in the absence of inhibitor. Rather, 'when the NNI is bound to its site, it induces the formation of its own pocket, possibly distorting the precise geometry of the nearby enzyme-active site so the enzymatic function is suppressed. Lastly, the drug Foscarnet (phosphonoformic acid) is the prototypic, and the only approved, member of the pyrophosphate analogue class. These agents are thought to interact directly with the pyrophosphate-binding site of the viral polymerases [130].

In the past few years, research groups in the pharmaceutical industry have reported a number of inhibitors of NS5B enzymatic activity and several of these are undergoing preclinical development. Selected examples are reviewed below.

## Nucleoside analogues

Novel series of nucleosides that are candidates for the treatment of HCV are being developed, and some have been described in the recent patent literature [131-133]. In particular, the discovery of oral, once-daily nucleosides potentially useful for the treatment of all HCV genotypes was recently reported [134]. Among these, beta-D-2'-methyl-ribofuranosyl-guanosine (Fig. 6, compound 13) was found to be phosphorylated in cultured cells and orally bioavailable in primates [133].

Interestingly, the only nucleoside analogue that thus far was shown to be therapeutically useful against $\mathrm{HC} . \mathrm{V}$ infection is the broad-spectrum antiviral agent D-ribavirin, also a guanosine analog (1-beta-D-ribofuranosyl-1-1,2,4-triazole-3carboxamide; virazole) [135]. The mechanism of action of D-ribavirin is currently debated. Some authors have proposed that D-ribavirin triphosphate is in fact incorporated by NS5B into the nascent viral genome [136]. This would lead, in turn, to an increased error frequency of the viral polymerase that might be responsible for the antiviral activity of this agent [137]. This model has not yet been proven relevant in a clinical setting, however, and alternative mechianisms have been proposed (see below).

Recent structural work has led to the identification of both catalytic and regulatory nucleotide-binding sites in the HCV RdRP [127]. The structural details of nucleotide binding $\frac{1}{1}$ the catalygic sites may provide some guidance for the
design of novel nucleotide analogues that would be inhibitors for HCV RdRPcatalyzed RNA synthesis. The. most striking result, however, is the identification of a third nucleotide site removed from the catalytic site of HCV RdRP and occupied by GTP, but not.ATP, CTP, or UTP. The location and specificity of this third site indicates that it may be related to a particularly puzzling feature of HCV RdRP, namely its activation in vitro by high concentrations of GTP [138]. It has been suggested that this unique nucleotide-binding site could provide an attractive target for potential allosteric inhibitors of the enzymatic reaction [127].

## Non-nucleoside inhibitors

Several NS5B inhibitors have been reported in the patent literature, some of which are likely to be the subject of future clinical investigation. At press time, details about the mechanism of action of these compounds have not been' disclosed. Therefore, we will group these compounds in the NNI class based solely on their chemical structure. Selected examples of non-nucleoside inhibitors of the HCV RdRP are illustrated in Fig. 6: thiazolidine derivatives [139,140] (compounds 14 and 15); two benzimidazole derivatives [141,142] (compounds 16 and 17); a benzothiophenè derivative [143] (compound 18); a benzothiadiazine derivative [144] (compound 19); and a pyrimidine derivative [145] (compound 20). The chemical structure of JTK-003; a non-nucleoside inhibitor of the HCV polymerase under study in early clinical studies [129], has not been disclosed.

## Pyrophosphate analogues

A series of dikeio acids was reported to inhibit selectively and potently the HCV RdRP elongation activity in vitro [146]. An example of this class of compounds is given in Fig. 6 (Compound 21). The mechanism of action of this and related compounds was found to be non-coinpetitive with respect to both the RNA template and to the nucleotides. Binding of diketo acids to the HCV RdRP appears to be mediated by active-site divalent cations, such as magnesium or manganese [147]. One attractive hypothesis to explain inhibition by diketo acid compounds is that the diketo acid fragment could inhibit the RdRP activity through an interaction with the catalytic metal ions found in the enzyme-active site. A similar mechanism for the inhibition of the viral polymerase has been invoked to explain inhibition by canonical pyrophosphate analogues such as Foscarnet and phosphonoacetic acid [148]. These latter compounds are believed to act as product-like inhibitors of the polymerase reaction. Viral polymerases that are inhibited by these clässical pyrophosphate analogues include the HIV reverse transcriptase (RT) and the HBV and herpesvirus DNA polymerases [130,149]. Interestingly, differentially substituted diketo acids were characterized, with each inhibiting HIV-RT or HBV polymerase in a highly selective manner [146]. Experiments aimed at measuring the combined effect of diketo acids and Foscarnet on HCV and other viral polymerases indicated futhermore thal the two classes of inhibitors interact with
the enzymes in a mutually exclusive fashion, suggesting interaction with a common binding site, ie, the pyrophosphate binding site [147]:

Although classical pyrophosphate analogues possess well-documented antiviral activity [116] and diketo acid inhibitors of HIV integrase [150] and influenza virus transcriptase [151] have been reported to inhibit viral replication in cell culture, the efficacy of diketo acids as inhibitors of HCV replication remains to be established.

## Other nonstructural viral proteins

The nonstructural proteins NS4B and NS5A have not been assigned a replicative function. NS4B is presumed to be an integral membrane protein, and it is possibly the least-studied HCV protein. Expression of NS4B in cultured cells has been shown to induce alterations, or a membranous web, of ER-derived membranes. This web may constitute the site of HCV genome replication in infected cells [152]. NS5A is post-translationally phosphorylated on multiple serine and possibly threonine residues [153]. The kinases responsible for NS5A phosphorylation has not yet been identified. Because of the lack of protein kinase signature motifs in the viral polyprotein, it is postulated to be of cellular origin. Protein phosphorylation regulates many protein-protein as well as proteinnucleic acid interactions that are important for a varíety of biologic processes: Although NS5A hyperphosphorylation has turned out not to be essential for HCV subgenomic RNA replication in cell culture [7], it is likely that alterations of the phosphorylation state of NS5A may affect the virus life cycle in a more physiologic setting. The identification of the kinases responsible for NS5A phosphorylation may thus uncover novel therapeutic targets.

Beside a potential role in viral replication, NS5A has been proposed to modulate the induction of the host interferon-stimulated antiviral response. The suggestion was initially based on the observation of a correlation between sequence variations in a defined region of NS5A, termed interferon sensitivity determining region (ISDR), and an unfavorable response to IFN- $\alpha$ therapy in chronically infected patients [154]. The ability of NS5A to interfere with the host-innate immune response was tentatively ascribed to the direct interaction between NS5A and the double-stranded RNA-activated protein kinase PKR [155]. Thus, disrupting the interaction between NS5A and PKR may provide new avenues to increase the effectiveness of IFN therapy. These findings have remained controversial, however, and NS5A has not been shown to mediate resistance to IFN- $\alpha$ in cell lines carrying a self-replicating subgenomic HCV RNA [7]. In this setting, HCV replication was sensitive to IFN- $\alpha$ independently of whether the replicon exprẹssed an NS5A protein associated with sensitivity or resistance to the cytokine. A number of other functions have also been tentatively attributed to NS5A [156]. Some of these functions may be important for the establishment of persistent $\cdot v$ jral infection in HC - infected individuals, and further investigation in these areas is warranted 3

## Other approaches

## D-ribavirin and IMPDH inhibitors

D-ribavirin is effective in increasing sustained virologic response rates in patients with chronic HCV infection when combined with IFN- $\alpha$. Although D-ribavirin possesses antiviral activity against a number of RNA viruses, it should be pointed nut that D-ribavirin monotherapy does not lead to a decrease in HCV titers [157]. Several mechanisms have been proposed to explain the action of D-ribavirin on HCV [12]. These mechanisms include: (1) increased mutation of the virus because If the incorporation of D-ribavirin triphosphate during viral genome replication (see also RdRP section); (2) polarization of the T cell response toward a type 1 cytokine profile, favoring immune clearance of the virus; and (3). inhibition of IMPDH, a rate-limiting enzyme involved in de novo purine biosynthesis, by D-ribavirin monophosphate, leading to a reduction in intracellular GTP. Clinical studies in patients during treatment with combination therapy have revealed that control of HCV viremia is often associated with an enhanced virusspecificc T-cell response, enhanced IFN- $\alpha$ secretion [158], and possibly reduced production of proinflammatory cytokines [159]. These data are consistent with the hypothesis that D-ribavirin exerts an immunomodulatory effect favoring a Thl response [160]. In this respect, it is interesting that the L-isomer of ribavirin, termed Levovirin, can stimulate a similar Th1 cytokine pattern in vitro in the absence of any antiviral activity [161]. Because D-ribavirin in combination with IFN is effective, yet by itself has not been shown to lower virus' replication, Levovirin, which shows similar immunomodulatory activity, may provide an attractive alternative and prove less toxic. The major dose-limiting toxicity of D-ribavirin is hemolytic anemia, likely caused by accumulation of ribavirin triphosphate in, red blood cells. Levóvirin does not undergo significant intracellular phosphorylation, thus explaining its lack of direct antiviral activity, and suggesting a more favorable toxicity profile. Thus, Levovirin may turn out to have a safer profile than D-ribavirin when administered to HCV patients in combination with IFN- $\alpha$. Accordingly, exploratory phase I clinical trials for the treatment of hepatitis C including Levovirin have been initiated [162].

Viramidine (ICN-3142) is a prodrug of D-ribavirin that is activated by a liver enzyme, adenosine deaminase [163]. The drug is thus efficiently targeted to the liver and has relatively reduced uptake in red blood cells. In animal studies, it is well tolerated and results in less hemolysis than D-ribavirin. Phase I studies in humans have indicated that the drug is safe and IFN-based combination therapy studies are expected in the future [163].

Alternative inhibitors of IMPDH are also being tested for the treatment of hepatitis $C$. Other compounds that selectively inhibit this enzyme include merimepodib (VX-49.7) [164] and the immunosuppressive agent mycophenolic acid. VX-497 has a broad antiviral spectrum in vitro, and it has been demonstrated to be inhibitory in the HCV replicon assay and has an additive effect with IFN [165]. Early clinical trials in patients with chronic hepatitis $C$ have shown

VX－497 to be safe，but with no observable antiviral effect when administered alone．As in the initial ribavirin monotherapy studies，ALT reductions were also noted in some patients．A subsequent phase II study of a 4－week combined treatment with VX－497 and IFN in treatment－naïve patients indicated safety but no enhancement of IFN＇s antiviral activity［166］．Studies of longer duration are required in order to assess the antiviral activity and the sustained response rates associated with this novel combination．A phase II study of VX－497 in triple combination with pegylated IF N－$\alpha$ and ribavirin is planned［167］．In addition， more potent and specific IMPDH inhibitors might be considered as preclinical development candidates．

## Other immunostimulating agents

Histamine，acting via H 2 －type histamine receptors on phagocytic cells，sup－ presses the activity of a key＇enzyme in oxygen radical formation，the NADPH oxidase．By this mechanism，histamine protects NK cells and T cells against oxygen radical－induced dysfunction and apoptosis，and also maintains their activation by IL－2 and other lymphocyte activators［168］．The rationale for using histamine is thus its role in reversing immunosuppression caused by HCV－induced oxidative stress in．the liver．Early clinical studies of histamine dihydrochloride administration along with IFN－$\alpha$ or in combination with IFN－$\alpha$ and ribavirin， suggest that there may be improved end of treatment and sustained response rates． Ongoing trials are evaluating the safety and efficacy of the triple combination of pegylated IFN－$\alpha$ ，ribavirin，and histamine in HCV－infected patients［169］．

Thymosin alpha 1 （TA1）is a synthetic 28 －amino acid peptide derived from thymus gland extracts with broad immunostimulatory activity This molecule was originally developed for the treatment of hepatitis B infection and subsequently tested clinically in HCV patients［170－172］．TA1 is endowed with multiple biologic activities primarily directed toward immune response enhancement． Recently，TAI treatment has been suggested to act by increasing the Thl－type response，fundamental for sustained clearance of HCV ，and by decreasing the Th2－ type response，associated with persistence of viremia［173］．Two large－scale clinical studies are currently evaluating the safety and benefits of this drug in combination with pegylated IFN－$\alpha$ in HCV－infected patients who did not respond to standard therapy［174］．

Therapeutic vaccination is also being considered to enhance HCV －specific immune responses and control or eliminate HCV infection（see the article by Dis．Inchauspé and Feinstone elsewhere in this issue）．Key questions regarding therapeutic vaccination include：（1）Why can＇t the host immune response eliminate HCV in chronically infected individuals？（2）．What antigens and what route of administration would lead to HCV control／clearance？and（3）Because cytolytic mechanisms are likely required to eliminate the virus；what would be the impact of therapeutic vaccination on liver damage and disease？Answers to these questions are being actively doughty 菛any laboratories．This field is in its infancy，but at
least one clinical trial is under way using a particulate El glycoprotein subunit vaccine, which in preclinical studies, boosted the level of E1-specific antibodies and decreased liver inflammation in chronically infected chimpanzees [175]. A decrease in HCV antigen in the liver was also seen, but, remarkably, there was no effect on viremia. Although this therapy is interesting and promising, the improvement was transient and revaccination was required. Thus far, safety and immunogenicity have been demonstrated in phase I and early phase II clinical trials.

## Prospects for new HCV therapies

A myriad of new therapies for treating HCV are in various stages of preclinical and clinical development. As reviewed here, these include nucleic acid-based approaches (antisense and ribozymes), small molecule inhibitors of essential HCV-encoded enzymes (protease, helicase, and polymerase), immune modulation, and immunotherapy. As more details of the HCV life cycle are elucidated, new targets and approaches will be discovered. Drug development is difficult, expensive, and always agonizingly slow for patients in need and their physicians. Nonetheless, a broad effort has been mounted for HCV, and substantial progress has been achieved. The prospects for new HCV treatments are bright.: The next years will be very exciting as the first candidates move through clinical trials and; hopefully, into widespread clinical use.

## Acknowledgments



We are grateful to our colleagues for helpful discussions on this subject, to Drs. Holly-Hanson, Ira Jacobson, Margaret MacDonald, and Jean-Michel Pawlotsky for comments on the manuscript, and to Dr: Shihyun You for help with the figures. CMR is supported by the Greenberg Medical Research Institute and by grants from the Public Health Service (CA57973, AI24134, and AI40034). RDF is an employee of Istituto di Ricerche di Biologia Molecolare P Angeletti SpA , a company affiliated with Merck \& Co.

```
:
```


## References

[1] Choo QL, Kuo G, Wciner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science -1989;244(4902): 359-62.
[2] Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, et al. Treatment of chronic non- $\dot{A}$, non- B hepatitis with recombinant human alpha interferon. A preliminary report. N Engl J Med 1986;315(25):1575-8.
[3] McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa- 2 b alone or in combination with ribavirin as initial treatınent for chronic hepatitis C . N Engl J Med 1998;339(21):1485-92.
interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis $C$ virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998;352(9138):1426-32.
[5] Cornberg M, Wedemeyer H, Manns MP. Treatment of chronic hepatitis C with PEGylated interferon and ribavirin. Curr Gastroenterol Rep 2002;4(1):23-30.
[6] Manns MP, McHutchison JG, Gordon. SC, Rustgi VK, Shiffman M, Rcindollaı R, er al. Peginterferon alfa-2b plus ribavirin'compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis $C$ : a randomised trial. Lancet 2001;358(9286):958-65.
[7] Blight KJ, Kolykhalov AA, Rice CM. Ffficient initiation of HCV RNA teplication in cell culture. Science 2000;290(5498):1972-4.
[8] Castet V, Fournier C, Soulier A, Brillet R, Coste J, Larrey D, et al. Alpha interfcron inhibits hepatitis $\dot{C}$ virus replication in primary human hepatocytes infected in vitro. J Virol 2002;76: 8189-99.
[9] Frese M, Sclwarzle V, Barth K, Krieger N, Lohmann V, Mihm S, et al, Interferon-gamma inlibits replication of subgenomic and genomic hepatitis C virus RNAs. Hepatology 2002; 35(3):694-703.
[10] Guo JT, Bichko VV, Seeger C. .Effect of alpha interferon on the hepatitis $C$ virus replicon. J Virol 2001;75:8516-23.
[11] Neumann AU, Lam NP, Dahari H; Gretch DR, Wiley TE, Layden TJ, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 1998 282(5386):103-7.
[12] Lau JY, Tam RC, Liang TJ, Hong Z. Mechanism of action of ribavirin in the combination treatment of chronic HCV infection. Hepatology 2002;35(5):1002-9.
[13] Bartenschlager R. Lohmann V. Replication of hepatitis C virus. J Gen Virol 2000;81(Pt 7): $1631 .-48$.
${ }_{[14]}$ Lindenbach BD. Rice (YM. Flaviviridae: the viruses and their replication. In: Knipe DM, Howley PM, editurs. Fields virology, 4th edition. Philadelphia: Lippincott-Raven Publishers; 2011. p. 991-1041.
[15] Dubuisson J. Folding, assembly, and subcellular localization of the hepatisis $C$ virus glycoproteins. Cur Top Microbiol Immunol 1999;242:135-48.
[16] Flint M, Quinn ER, Levy S. In search of hepatitis C virus receptor(s). Clin Liver Dis 2001; 5(4):873-93.
[17] Butcher SJ, Grimes JM, Makeyev EV, Bamford DH, Stuart DI. A mechanism for initiating RNA-dependent RNA polymerization. Nature 2001;410(6825):235-40.
[18] Block TM, Jordan R. Iminosugurs as possible broad spectrum anti hepatitis virus agents: the glucovirs and alkovirs. Antivir Chem Chemother 2001;12(6):317-25.
[19] Filocamo G, Pacini L, Migliaccio G. Chimeric Sindbis.virus dependent upon the NS3 protease of hepatitis C virus. J Virol 1997;71:1417-27.
[20] Frolov I, McBride MS, Rice CM. cis-acting RNA elements required for replication of bovine viral diarrhea virus-hepatitis $C$ virus $5^{\prime}$ nontranslated region chimeras. RNA 1998; 4:1418-35.
[21] Lu HH, Wimmer E. Poliovirus chimeras replicating under the translational control of genetic elements of hepatitis $C$ virus reveal unusual properties of the internal ribosomal entry site of hepatitis C virus. Proc Natl Acad Sci U S A 1996;93(4):1412-7.
[22] Lohmann V, Korner F, Koch JO, Herian U, Theilmann L, Bartenschlager R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. Science 1999;285:110-3.
[23] Krieger N, Lohmann V, Bartenschlager R. Enhancement of hepatitis ${ }^{C}$ © virus RNA replication by cell culture-adaptive mutations. J Virol 2001;75:4614-24:
[24] Lohmann V, Komer F, Dobierzewska A, Bartenschlager R. Mutations in hepatitis C virus RNAs conferring cell culture adaptation. J Virol 2001;75:1437-49.
[25] Mercer DF, Schiller DE, Elliotı JF. Douglas DN, Hao C, Rinfret A, et al. Hepatitis C virus replication in mice with chimeric human livers. Nat Med 2001;7(8):927...33.
[26] Rijnbrand RCA, Lemon SM. Internal ribosome entry site-mediated translation in hepatitis C

virus replication. In: Hagedorn Ç, Rice CM, editors. Hepalitis C virus. Berlin: Springer-Verlag; 2000. p. 85-1 16.
[27] Friebe P, Lohmann V, Krieger $N$, Bartenschlager R. Sequences in the 5 ' nontranslated region of hepatitis C virus required for RNA replication. J Virol 2001;75(24):12047-57.
[28] Kim YK, Kim CS, Lee SH, Jang SK. Domains I and II in the $5^{\prime}$ nontranslated region of the HCV genome are required for RNA replication. Biouchem Biòphys Kes Commun 2002; 290(1): 105-12.
[29] Walewski JL, Keller TR, Stump DD, Branch AD. Evidence for a new hepatitis $C$ virus antigen encoded in an overlapping reading framc. RNA 2001;7(5):710-21.
[30] Xu Z, Choi J, Yen TS, Lu W, Strohecker A, Govindarajan S, et al. Synthesis of a novel hepatitis C virus protein by ribosomal frameshift. FMBC J 2001;20(14):3840-8.
[31] Iuplin A, Wood J, Evans DJ, Patel AH, Simmonds P. Thermodynamic and phylogenetic prediction of RNA secondary structures in the coding region of hepatitis C virus. RNA 2002; 8(6):824-41.
[32] Walewski JL, Gutierrez JA, Branch-Ellinıan W, Stump DD, Keller TR, Rodriguez A, et al. Mutation Master: profiles of substitutions in hepatitis $C$ virus RNA of the core, alternate reading frame, and NS2 coding regions. RNA 2002;8(5):557-71.
[33] Friebe P, Bartenschlager R. Genetic analysis of sequences in the $3^{\prime}$ nontranslated region of hepatitis C virus that are important for RNA replication. J Virol 2002;76(II):5326-38.
.[34] Yanagi M, St Claire M, Emėrson SU, Purcell RH, Bukh J. In vivo analysis' of the $3^{\prime}$ untranslated region of the hepatitis $C$ virus after in vitro mutagenesis of an infectious cDNA clone. Proc Natl Acad Sci U"S A 1999;96(5):2291-5.
[35] Ito T, Tahara SM, Lai MMC. The 3'-untranslated region of hepatitis C virus RNA enhances translation from an internal ribosomal entry site. J Virol 1998;72(11):8789-96.
[36] Michel YM, Borman AM, Paulous S, Kean KM. Eukaryotic initiation factor 4G-poly(A) binding protein interaction is required for poly $(\mathrm{A})$ tail-mediated stimulation of picornavirus internal ribosome entry segment-driven translation but not for X-mediated stimulation of hepatitis C virus translation. Mol Cell Biol 2001;21(13):4097-109.
[37] Sullenger BA, Gilboa E. Emerging clinical applications of RNA. Nature 2002;418:252--8.
[38] Alt M, Renz R, Hofschneider PH, Paumgartner G, Caselmann WH. Specific inhibition of hepatitis C viral gene expression by antisense phosphorothioate oligodeoxynucleotides. Hepatology 1995;22:707-17.
[39] Hanecak R, Brown DV, Fox•MC, Azad'RF, Furusako S, Nozaki C, et al. Antisense oligonucleotide inhibition of hepatitis C virus gene expression in transformed hepatocytes. J Virol 1996;70(8):5203-12.
[40] McCaffrey AP, Ohashi K, Meuse L, Shen S, Lancaster AM, Lukavsky PJ, et al. Determinants of hepatitis $C$ translational initiation in vitro, in cultured cells and mice. Mol Ther 2002;5(6): 676-84.
[41] Mizutani T, Kato N, Hirota M, Sugiyama K, Murakami A, Shimotohno K. Inhibition of hepatitis C virus replication by antisense oligonucleotide in culture cells. Biochem Biophys Res Commun 1995;212:906-11.
[42] Wakita T, Wands JR. Specific inhibition of hepatitis C virus expression by antisense oligodeoxynucleotides. J Biol Chem 1994;269:1420S-10.
[43] Witherell GW. ISIS-14803 (Isis Pharmaceuticals). Curr' Opin Investig Drugs 2001;2(11): 1523-9.
[44] Lieber A, Hé CY, Polyak SJ, Gretch DR, Barr D, Kay MA. Elimination of hepatitis C virus RNA in infected human hepatocytes by adenovirus-mediated expression of ribozymes. J Virol 1996;70(12):8782-91. •'
[45] Ohkawa K, Yuki N, Kanazawa Y, Ueda K, Mita E, Sasaki Y, et al. Cleavage of viral RNA and inhibition of viral translation by hepatitis $C$ virus RNA-specific hammerhead ribozyme in vitro. J Hepatol 1997;27(1):78-84.
[46] Sakamoto N, Wu CH, Wu GY. Intracellular cleavage of hepatitis C. virus RNA and inhibition of viral protein translation by hammerhead ribozymes. J Clin Invest 1996;98(12):2720-8.
[47] Welch PJ, Tritz R, Yei S, Leavitt M, Yu M, Barber J. A potential therapeutic application of hairpin ribozymes: in vitro and in vivo studies of gene therapy for hepatitis $C$ virus infection. Gene Ther 1996;3(11):994-1001.
[48] Macejak DG,.Jensen KL, Jamison SF, Domenico K, Roberts EC, Chaudhary N, et al. Inhibition of hepatitis C virus. (HCV)-RNA-dependent translation and replication of a chimeric HCV poliovirus using synthetic stabilizod ribozymes. Hepatology 2000;31(3):769-76.
[49] Lec PA, Blatt LM, Blanchard KS, Bouhana KS, Pavco PA, Bellon L, et al. Pharmacokinetics and tissue distribution of a ribozyme directed against hepatitis $C$ virus RNA following suhcutancous or intravenous administration in mice. Hepatology 2000;32(3):640-6.
[50] Macejak DG, Jensen KL, Pavco PA, Phipps KM, Heinz BA, Colacino JM, et al. Enhanced antiviral effect in cell culture of type 1 interferon and ribozymes largeting HCV RNA. J Viral Hepat 2001;8(6):400-5.
[51] Hannon GJ. RNA interference. Nature 2002;418:244-51.
[52] Elbashir SM, Harborth J, Lendeckel W, Yalcin A, Weber K, Tuschl T. Duplexes of 21 -nucleotide RNAs mediate RNA interference in cultured mammalian cells. Nature 2001;411(6836): 494-8.
[53] Lee NS, Dohjima T, Baucr G, Li H, Li MJ, Ehsani A, et al. Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells. Nat Biotechnol 2002;20(5):500--5.
[54] Novina CD, Murray MF, Dykxhoom DM, Beresford PJ, Riess J, Lee SK, et al. siRNA-directed inhibition of HIV-1 infection. Nat Med 2002;8:681-6.
[55] Jacque J-M, Triques K, Stevenson M. Modulation of HIV-1 replication by RNA interference. Nature 2002;41 8:435-8.
[56] Lawrence D. RNAi could hold promise in the treatment of HIV. Lancet 2002;359(9322):2007.
[57] Gitlin L, Karelsky S, Andino R. Short interfering RNA confers intracellular antiviral immunity in human cells. Nature 2002;418:430-4.
[58] McCaffrey AP, Meuse L, Pham T-TT, Conklin DS, Hannọn,GJ, Kay MA. RNA interference in adult mice. Nature 2002;418:38-9.
[59] Randall G, Grakoui A, Rice CM. Clearance of replicating hepatitis C virus replicon RNAs in cell culture by small interfering RNAs. Proc Natl Acad Sci USA 2003; 100(1):235-40.
[60] Baltimore D. Intracellular immunization. Nature (Lond) 1988;335:395-6.
[61] Krüger M, Beger C, Li QX , Welch PJ, Tritz R, Leavitt M, èt al. Identification of eIF2Bgammu and eIF2gamma as cofactors of hepatitis $C$ virus internal ribosome entry site-mediated translation using a functional genomics approach. Proc Natl Acad Sci U S A 2000;97(15): 8566-71.
[62] Kruger M, Beger C, Welch PJ, Barber JR, Manns MP, Wong-Staal F. Involvement of proteasome alpha-subunit PSMA7 in hepatitis C virus internal ribosome entry site-mediated translation. Mol Cell Biol 2001;21(24):8357-64.
[63] Kolykhalov AA, Mihalik K, Feinstone SM, Rice CM. Hepatitis C. virus-encoded ënzymatic activities and conserved RNA elements in the $3^{\prime}$ nontranslated region are essential for virus replication in vivo. J Virol 2000;74(4):2046-51.
[64] Lohmann V, Kioch JO, Bartenschlager R. Processing pathways of the hepatitis C virus proteins. J Hepatol 1996;24(2):11-9.
[65] Rosenberg S. Recent advaņes in the molecular biology of hepatitis C virus. J Mol Biol 2001; 313(3):451-64.
[66] McLauchlan J, Lemberg MK, Hope G, Martoglio B. Intramembrane proteolysis promotes trafficking of hepatitis C virus core protein to lipid droplets. EMBO J 2002;21(15):3980-8.
[67] Hijikata M, Mizushima H, Akagi T, Mori S, Kakiuchi N, Kato N, et al. Two distinct proteinase activities required for the processing of a putative nonstructural precursor protein of hepatitis $C$ virus. J Virol 1993;67(8):4665-75.
[68] Grakoui A, McCourt DW, Wychowski C; Feinstone SM, Rice CM. A second hepatitis C virusencoded proteinasc. Proc Natl Acad Sci U S A 1993;90(22):10583-7.
[69] Santolini E, Pacini L, Fipaldini C, Migliaccio G, Monica N. The NS2 protein of hepatitis C" virus is a transmembrane polypeptide. J Virol 1995;69(12):7461-71.
[70] Pieroni L, Santolini E, Fipaldini C, Pacini L, Migliaccio G, La Monica N. In vitro study of the NS2-- 3 protease of hepatitis C virus. J Virol 1997;71(9):6373-80.
[71] Wu Z, Yao N, Le HV', Weber PC. Mechanism of autoproteolysis at the NS2-NS3 junction of the hepatitis C virus polyprotein. Tronds Biochem Sci 1998;23(3):92-4.
[72] Thibeault D, Maurice R, Pilote L, Lamarre D, Pause A. In vitro characterization of a purified NS2/3 protease variant of hepatitis C virus. J Biul Chem 2001; 276(49):46678-84.
[73] Pullaoro M, Lahm A, Biasiol G, Brunetti M, Nardella C, Orsatti L, et al. Characterization of the hepatitis C virus NS2/3 processing reaction by using a purified precursor protein. J Virol 2001; 75(20):9939-46.
[74] Darke PL, Jacobs AR, Waxman L, Kuo LC. Inhibition of hepatitis C virus NS2/3 processing by NS4A peptides. Implications for controd of viral processing. J Biol Chem 199y;274(49): 34511-4.
[75] Whitney M, Stack JH, Darke PL, Zheng W, Terzo J, Inglese J, et al. A collaborative screening program for the discovery of inhibitors of HCV NS2/3 cis-cleaving protease activity. J Biomol Screen 2002;7(2):149-54.
[76] De Francesco R, 'Steinkuhler C. Structure and function of the hepatitis C virus NS3-NS4A serine proteinase. Curr Top Microbiol Immunol 2000;242:149-69.
[77] Failla C, Tomei L, De Francesco R. Both NS3 and NS4A are required for proteolytic processing of hepatitis C virus nonstructural proteins. J Virol 1994;68(6):3753-60.
[78] De Francesco R, Pessi A, Steinkuhler C. The hepatitis C virus NS3 proteinase: structure and function of a zinc- containing serine proteinase. Antivir Ther 1998;3(Suppl):99-109.
[79] Lin $\mathbb{C}$; Thomson JA, Rice CM: A central region in the hepatitis $C$ virus NS4A protein allows formation of an activë NS3-NS4A serine proteinase complex in vivo and in vitro. J Virol 1995;69(7):4373-80.
-[80] De Francescor R, Urbani A, Nardi MC, Tomei L, Steinkuhler C, Tramontano A. A zinc binding site in viral serine proteinases: Biochemistry 1996;35(41):13282-7.
[81] Grakoui A, McCourt DW, Wychowski C, Feinstone SM, Rice CM. Characterization of the hepatitis $C$ virus-encoded serine proteinase: determination of proteinase-dependent polyprotein cleavage sites. J Virol 1993;67(5):2832-43.
[82] Schechter I, Berger A. On the size of the active site in proteases. I. Papain. Biochem Biophys Res Commun 1967;27(2):157-62.
[83] Lamarre D, Bailey M, Bolger G, Cameron D, Cartier M, Faucher AM, et al. The discovery of BILN 2061-an orally bioavailable small molecule inhibitor of the HCV serine protease and a promising target for antiviral treatment' of hepatitis C. 'Hepatology 2002;36(Suppl. 4, Pt.2): [abstract] 464.
[84] Hinrichsen H, Benhamou Y, Hinrichsen H, Sentjens R, Reiser M, Manns MP, et al. First report on the antiviral efficacy of BILN 2061, a novel oral HCV serine protease inhibitor, in patients with chronic hepatitis C genotypé I. Hepatology 2002;36(Suppl. 4, Pt:2): [abstract 866].
[85] Benhamou Y, Hinrichsen H, Sentjens R, Reiser M, Manns MP, Forns X,'et al. Safety, tolerability and antiviral effect of BILN 2061, a novel HCV serine protease inhibitor, after oral treatment over 2 days in patients with chronic hepatitis C, genotype 1, with advanced liver fibrosis. Hepatology 2002;36(Suppl. 4, Pt.2): [abstract 563].
[86] Landro JA, Raybuck SA, Luong YP, O'Malley ET, Harbeson SL, Morgenstern KA, et al. Mechanistic role of an NS4A peptide cofactor with the truncated NS3 protease of hepatitis C virus: elucidation of the NS4A stimulatory effect via kinetic analysis and inhibitor mapping. Biochemistry 1997;36(31):9340-8.
[87] Ingallinella P, Bianchi E, Ingenito $\dot{R}$, Koch $U$, Steinkuhler $C$, Altamura S, et al. Optimization of the $\mathrm{P}^{\prime}$-region of peptide inhibitors of hepatitis $C$ virus NS3/4A protease. Biochemistry 2000; 39(42):12898-906.
[88] Wilkinson T. Hepatitis C virus: prospects for future therapies. Curr Opin Investig Drugs 2001; 2(11):1516-22.
|\$9] Pricsilley ES, Decicco CP. 1-Aminocyclopropaneboronic acịd: synthesis and incorporation into an inhibitor of hepratitis C virus NS3 protease. Org Lett 2000;2(20):3095-7.
[90] Han W, Hu Z, Jiang X, Decicco CP. Alpha-ketoamides, alpha-ketoesters and alpha-diketones as HCV NS3 protease inhibitors. Bioorg Med Chem Lett 2000;10(8):711-3.
[91] Narjes F, Brunetti M, Colarusso S, Gerlach B, Koch U, Biasiol G, et al. Alpha-ketoacids are potent slow binding inhibitors of the hepatitis C virus NS3 protease. Biochemistry 2000;39(7): 1849-61.
[92] Rabine RE, Chen SH, Lamar JE, Snyder NJ, Sun XD, Tebbe MJ, et al [inventors]; Eli Lilly and Company [assignee]. Preparation of peptidomimetic protease inhibitors. Int patent appl. WO 0218369.2002.
[93] Colarusso S, Gcrlach B, Koch U, Muraglia E, Conte I, Stansfield I, et al. Evolution, synthesis and SAR of tripeptide alpha-ketoacid inhibitors of the hepatitis C virus NS3/NS4A serine protease. Binorg Med Chem Lctt 2002;12(4):705-8.
[94] Kettner CA, Jagannathan S, Forsyth TP [inventors]; Du Pont Pharmaceuticals Company [assignee]. Preparation of peptide boronic acid inhibitors of hepatitis $C$ virus protease. Int patent appl. WO 01/02424. 2001.
[95] Steinkuhler C, Biasiol G, Brunetti M, Urbani A, Koch U, Cortese R, et al. Product inhibition of the hepatitis C virus NS3 protease. Biochemistry 1998;37(25):8899-905.
[96] Llinas-Brunct M, Bailey M, Fazal G, Goulet S, Halınos T, Laplante S, et al. Peptide-based inhibitors of the hepatitis C virus serine protease. Bioorg Med Chem Lett 1998;8(13): 1713-8.
[97] Yan Y, Li Y, Munshi S, Sardana V, Cole JL, Sardana M, et al. Complex of NS3 protease and NS4A peptide of BK strain hepatitis C virus: a 2.2 A resolution structure in a hexagonal crystal form. Protein Sci 1998;7(4):837-47.
[98] Ingallinella P, Altamurä S, Bianchi E, Taljani M, Ingenito R, Cortese R, et al.,Potent peptide inhibitors of human hepatitis C virus NS3 protease are obtained by optimizing the cleavage products. Biochemistry 1998;37(25):8906-14.
[99] Llinas-Brunet M, Bailey M, Fazal G, Ghiro E, Gorys V, Goulet S, et al. Highly potent and selective peptide-based inhibitors of the hepatitis $C$ virus serine protease: towards smaller inhibitors. Bioorg Med Chem Lett 2000;10(20):2267-70.
[100] Llinas-Brunet M, Bailey MD, Cameron D, Faucher AM, Ghiro E, Goudreau N, et al [inventors]; Boehringer Ingelhein (Canada) Ltd [assignee]. Hepatitis $C$ inhibitor tri-peptides. Int patent appl. WO 00/00954. 2000.
[101] Snith III AB, Hirschmann R, Pasternak A, Akaishi R, Guzman MC, Jones DR, et al. Design and synthesis of peptidomimetic inhibitors of HIV-1 protease and renin. Evidence for improved transport. J Med Chem 1994;37(2):215-8.
[102] Sing WT, Lee CI., Yeo SL, Lim SP, Sim MM. Arylalkylidene rhodanine with bulky and hydrophobic functional group as selective HCV NS3 protease inhibitor. Bioorg Med Chem
; Lett 2001;11(2):98-4.
[103] Yeung KS, Meanwell NA, Qiu Z, Hernandez D, Zhang S, McPhee.F, et al. Structure-activity relationship studies of a bisbenzimidazole-based, $\mathrm{Zn}(2+)$-dependent inhibitor of HCV NS3 serine protease. Bioorg Med Chem Lett 2001;11(17):2355 -9 .
[104] De Francesco R, Neddermann P, Tomei L, Steinkuhler C, Gallinari P, Folgori A. Biochemical and immunologic properties of the nonstructural proteins of the hepatitis $C$ virus: implications for development of antiviral agents and vaccines. Semin Liver Dis 2000;20(1):69-83.
[105] Tanner NK, Linder P. DExD/H box RNA helicases: from generic motors to specific dissociation functions. Mol Cell $2001 ; 8(2): 251-62$.
[106] Linder P, Tanner NK, Banrqques J. From RNA helicases to RNPases. Trends Biochem Sci 2001;26(6):339-41.
[107] Kim JL, Morgenstern KA, Griffith JP, Dwyer MD, Thomson JA, Murcko MA, et al. Hepatitis C. virus NS3 RNA helicase domain with a bound oligonucleotide: the crystal structure provides insights into the mode of unwinding. Structure 1998;6(1):89-100.
[108] Yao N, Hesson T, Cable M, Hong Z, Kwong AD, Le HV, et al. Structure of the hepatitis C virus RNA helicase doraain. Nat Struct Biol 1997;4(6):463--7.
[109] Cho HS, Ha NC, Kang LW, Chung KM, Back SH, Jang SK, et al. Crystal structure of RNA
helicase from genotype lb hepatitis. C virus. A feasible mechanism of unwinding duplex RNA. J Biol Chem 1998;273(24):15045-52.
[110] Gallinari P, Paolini C, Brennan D, Nardi C, Steinkuhler C, De Francesco R. Modulation of hepatitis $C$ virus NS3 protease and helicase activities through the interaction with NS4A. Biochemistry 1999;38(17):5620-32.
[111] Pang PS, Jankowsky E, Planet PJ, Pyle AM. The hepatitis C viral NS3 protein is a processive DNA helicase with cofactor enhanced RNA unwinding. EMBO J 2002;21(5): 1168-76.
[112] Janetka JW; Ledford BE, Mullican MD [inventors]; Vertex Pharmaceuticas, Inc. [assignee]. Pentacyclic compounds uscful as inhibiturs of hepatitis C virus NS3 helicase. US patent WO 0024725. 2000.
[113] Hale M, Maltais F, Baker C C, Janetka J, Moon YG; Suunders J, [inventors]; Vertex Pharmaceuticals, Inc. [assignee]. Pyrimidine derivative inhibitors of viral helicases. Int patent appl. WO 0107027. 2001.
[114] Diana GD, Bailey TT, Nitz TJ, [inventors]; ViroPharma, Inc. [assignee]. Piperidine derivatives, pharmaceutical compositions thercof and their use in the treatment of hepatitis $C$., Int patent appl. WO 9736554. 1997.
[115] De Clercq E. 2001 ASPET Otto Krayer Award Lecture. Molecular targets for antiviral agents. J Pharmacul Exp Ther 2001;297(1):1-10.
[116] Ihe Clercq E. Alliviral drugs: current state of the art. J Clin Virol 2001;22(1):73-89.
[117] (rute JJ, Grygon CA, Hargrive KD, Simoneau B, Faucher AM, Bolger G, et al. Herpes simplex virus helicase-promase inhibitors are active in animal models of human disease. Nat Med 2002; 8(4):386-91.
[118] Kleymann G, Fischer R, Betz UA, Hendrix M, Bender W, Schneider U, et al. New helicaseprimase inhibitors as drug candidates for the treatment of herpes simplex disease. Nat Med 2002;8(4):392-8.
[119] Ahlquist P. RNA-dependent RNA polymerases, viruses, and RNA silencing. Science 2002; 296(5571):1270-3.
[120] Behrens SE, Tomei L, De Francesco R. Identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus. EMBO J 1996;15(1):12-22.
[121] Ago H, Adachi T, Yoshida A. Yámamoto M, Habuka N, Yatsunami K, et al. Crystal structure of the RNA-dependent RNA polymerase of hepatitis C virus. Ștrict Fold Des 1999;7(11): 1417-26.
[122] Bressanelli S, Tomẹi L, Roussel A, Incitti I, Vitale RL, Mathieu M, et al. Crystal structure of the RNA-dépendent RNA polymerase of hepatitis C virus. Proc Natl Acad Sci U S A 1999;96(23): 13034-9.
[123] Lesburg CA, Cable MB, Ferrari E, Hong Z, Mannarino AF, Weber PC. Crystal structure of the RNA-dependent RNA polymerase from hepatitis $C$ virus reveals a fully encircled active site. Nat Struct Biol 1999;6(10):937-43.
[124] Brautigam CA, Steitz TA. Structural and functional insights provided by crysistal structures of DNA polymerases and their substrate complexes. Curr Opin Struct Biol 1998;8(1):54-63.
[125] Luo G, Hamatake RK, Mathis DM, Racela J, Rigat KL, Lemm J, et al. De novo initiation of RNA synthesis by the RNA-dependent RNA polymerase (NS5B) of hepatitis C virus. J Virol 2000;74(2):851-63.
[126] Zhong W, Uss AS, Ferrari E, Lau JY, Hong Z. De novo initiation of RNA synthesis by hepatitis C virus nonstructural protein 5B polymerase. J Virol 2000;74(4):2017-22.
[127] Bressanelli S, Tomei L, Rey FA, De Francesco R. Structural analysis of the hepatitis C virus RNA polymerase in complex with ribonucleotides. J Virol 2002;76(7):3482-92.
[128] Lohmann V, Korner F, Herian U, Bartenschlager R. Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity. J Virol 1997;71(11):8416-28.
[129] Pharmaceuticals on clinical development (is of May 16, 2002). Japan Tobacco Website. Available at: http://www.jti.co.jp/STI_E/IR/02/P.L.20020516_E.pdf. Accessed June 23, 2002.
[130] Crumpacker CS. Mechanism of action of foscarnet against viral polymerases. Am J Med 1992;92(2A):3S-7S.
TPO DELHI $23-06-2015$ 15:.43.
[131] Storer R [inventor]; Biochem Pharma, Inc. [assignee]. Method for the treatment or prevention of Flaviridae viral infection using nucleoside analogs. Int patent appl. WO 0132153. 2001.
[132] Wutanabe KA, Pai B [inventors]; Pharmassctt, Ltd. [assignee]. $3^{\prime}$ - or $2^{\prime}$-hydroxymethyl substituted nucleoside derivatives for treatment of hepatitis virus infections. Int patent appl. WO 0179246.2001.
[133] Sommadossi JP, Lacolln P [inventurs]; Ideinix Pharmaceuticals [assignee]. Methods and compositions for treating hepatitis C virus. Int patent appl. WO 0190121. 2001.
[134] NV08 Idenix Pharmaceuticals-Hepatitis C. Idenix Pharmaceuticals Wehsite. Availablc at: http://wwwidcnix.cou/hev.html. Accessed June 24, 2002.
[135] Shad JA, McHutchison JG. Current future therapies of hepatitis C. Clin Liver Dis 2001; 5(2):335-59.
[136] Maag D, Castro C, Hong Z, Cameron CE. Hepatitis C virus RNA-dependent RNA polymerase (NS5B) as a mediator of the antiviral activity of ribavirin. J Biol Chem 2001;276(49): 46094-8.
[137] Crotty S, Maäg D, Amold JJ, Zhong W; Lau JY, Hong Z, et al. The broad-spectrum antiviral ribonucleoside ribavirin is an RNA virus mutagen. Nat Med 2000;6(12):1375-9.
[138] Lohmann V, Overton H, Bartenschlager R. Selective stimulation of hepatitis C virus and pestivins NS5B RNA polymerase activity by GTP. J Biol Chem 1999;274(16):10807-15.
[139] Jaen JC, Piper DE, Powers JP, Walker N, Li Y [inventors]; Tularik, Inc. [assignee]. NS5B HCV polymerase inhibitors. Int patent appl. WO 0177091.2001.
[140] Fushishita T, Abe K [inventors]; Shionogi \& Co., Ltd [assignee]. Compounds having antihepatitis C.virus effect. Int patent appl. WO 0220497. 2002.
[141] Beaulieu P-L, Fazal G, Gillard J, Kukolj G, Austel V, inventors; Boehringer Ingelheim (Canada) Ltd., assignee. Viral polymerase inhibitors. Int patent appl. WO 0204425. 2002.
[142] Hashimoto H , Mizutani K , Yoshida A |inventors]; Japan•Tobacco, Inc. [assignee]. Preparation of heterocyclic compounds as remedies for hepatitis C. Int patent appl. WO 0147883. 2001.
[143] Young DC, Bailay TR [inventors]; Viropharma, Inc. [assignee]. Methods using benzothiophene compounds for treating or preventing viral infections and associated diseases, and preparation thereof. Int patent appl. WO 0018231. 2000.
[144] Dhanak D, Kaura A, Shaw A [inventors]; Smithkline Beechham Corporation [assignee]. Novel anti-infectives. Int patent appl. WO 0185172. 2001.
[145] Gardelli C,-Giuliano C, Harper S, Koch U, Narjes F, Ontoria JM, et al [inventors]; Istituto di Ricerche di Biologia Molecolare P. Angeletti, SpA [assignee]. Dihydroxypyrimidine carboxylic acids as viral polymerase inhibitors. Int patent appl. WO 0206246. 2002.
[146] Altumura S, Tomei L, Koch JO, Neuner PJS, Summa V [inventors]; Istituto di Ricerche di Biologia Molecolare P. Angeletti, SpA [assignee]. Diketoacld-derivatives as inhibitors of viral polymerases. Int patent appl. WO 0006529. 2000.
[147] De Francesco 'R, Summa V, Matassa VG, Altamura S. Novel inhibitors of hepatitis C RNAdependent RNA polymerase. Paper presented at Positive strand RNA viruses. Institut Pasteur, Paris, France, Scptember 2-5, 2001.
[148] Sundquist B, Oberg B. Phosphonoformate inhibits reverse transcriptase. J Gen Virol 1979; 45(2):273-81.
[149] Hess G, Arnold W, Meyer zum Buschenfelde KH. Inhibition of hepatitis-B-virus DNA polymerase by phosphonoformate: studies on its mode of action. J Med Virol 1980;5(4): 309-16.
[150] Hazuda DJ, Felock P, Witmer M, Wolfe A, Stillmock K, Grobler JA, et al Iṇhibitors of strand transfer that prevent integration and inhibit HIV-I replication in cells. Science 2000; 287(5453):646-50.
[151] Tomassini J, Selnick H, Davies ME, Armstrong ME, Baldwin J, Bourgeois M, et al. Inhibition of cap ( $\mathrm{m} 7 \mathrm{Gppp} \mathbf{X}_{\mathrm{X}}^{\mathrm{In}}$ )-dependent ęndonuclease of influenza virus by 4 -sụbstituted 2,4-dioxobutanoic acid compounds. Antiniicrob Agents Chemother 1994;38(12):2827-37.
[152] Egger D, Wolk B, Gosert R, Bianchi L, Blum HE, Moradpour D, et al. Expression of hepatitis

C virus proteins induces distinct membrane alterations including a candidate viral replication complex. J Virol 2002;76(12):5974-84.
[153] Reed KE, Xu J, Rice CM. Phosphorylation of the hepatitis C virus NS5A protein in vitro and in vivo: properties of the NS்5A-associated kinase. J Virol 1997;71(10):7187-97.
[154] Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, et al. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus lb infection. N Engl J Med 1996;334(2):77-81.
[155] Gale Jr MJ, Korth MJ, Tang NM, Tan SL, Họpkins DA, Dever TE, et al. Evidence that hepatitis C virus resistance to interferon is mediated through repression of the PK R protein kinase by the nonstructural 5A protein. Virology 1997;230(2):217-27.
[156] Tan SL, Katze MG. How hepatitis $C$ virus counteracts the interferon response: the jury is still. out on NS5A. Virology $2001 ; 284(1): 1-12$.
[157] Bonkovsky HL, Mehta S. Hepatitis C: a review and update. Dis Mon 2001;47(12):610-47.
[158] Fang SH, Lai MY, Hwang LH, Yang PM, Chen PJ, Chiang BL, et al. Ribavirin enhances interferon-gamma lcvels in patients with chronic hepatitis $C$ treated with interferon-alpha. J Biomed Sci 2001;8(6):484-91.
[159] Souvignet C, Zarski JP. Combination treatment for chronic hepatitis C: what is the role of ribavirin? Fundam Clin Pharmacol 200(); 14(4):321-5.
[160] Tam RC, Pai B, Bard J, Lim C, Averett DR, Phan UT, et al. Ribavirin polarizes human T cell responses towards a Type 1 cytokine profile. J Hepatol 1999;30(3):376-82.
[161] Tam RC; Ramasamy K, Bard J, Pai B, Lim C, Averett DR. The ribavirin analog ICN 17261 demonstrates reduced toxicity and antiviral effects with retention of both immunomodulatory activity and reduction of hepatitis-induced serum alanine aminotransferase levels. Antimicrob Agents Chemother 2000;44(5):1276-83.
[162] Product pipeline. Roche Company Website. Available at: http://www.roche.com/science-pipeline-detail $? \mathrm{ta}=\mathrm{all}+$ Areas $\&$ Phase $=$ Phase $+\mathrm{I} \&$ submit $=$ Show + pipeline) Accessed June 24, 2002.
[163] Hong Z. Development of viranidine: a liver-targeting prodrug of ribavirin. Presented at the 15th International Conference on Antiviral Research. Prague, Czech Republic, March 17-21, 2002.
[164] Jain J, Almquist SJ, Shlyakhter D, Harding MW. VX-497: a novel, selective IMPDH inhibitor and immunosuppressive agent. J Pharm Sci 200I;90(5):625-37.
[165] Markland•W, McQuaid TJ, Jain J, Kwong AD. Broad-spectrum antiviral activity of the IMP dehydrogenase inhibitor VX- 497: a comparison with ribavirin and demonstration of antiviral additivity with alpha interferon. Antimicrob Agents Chemother 2000;44(4):859-66.
[166] McHutchison JG, Cheung R; Shiffman ML, et al. A 4 week trial of VX 497 (an IMPDH. inhibitor) combined with interferon in previously untreated patients with chronic hepatitis $C$. Hepatology 2001;34(Suppl 1):39A.
[167] Pipeline \& Products I Antiviral (HCV). Vertex Pharmaceuticals Company Website. Available at: http://www.vpharm.com/NonEnhanced/AntiviralNonE.html. Accessed July 24, 2002.
[168] Hellstrand K. Histamine in cancer immunotherapy: a preclinical background. Semin Oncol ${ }^{--}$ 2002;29(3, Suppl 7):35-40.
[169] Ceplene for Hepatitis C virus. Maxim Pharmaceuțieals Company Website. Available at: http:// www.maxim.com/products/ceplenéhcv:html. Accessed July 24, 2002.
[170] Ancell CD, Phipps J, Young L. Thymosin alpha-1. Am J Health Syst Pharm 2001;58(10): 879-85; quiz 86-8.
[171] Kullavanuaya P, Treeprasertsuk S, Thong-Ngam D, Chaermithai K, Gonlachanvit S, Suwanagool P. The combined treatment of interferon alpha-2a and thymosin alpha 1 for chronic hepatitis $C$ : the 48 weeks end of treatment results. J.Med Assoc Thai 2001 ; 84(Suppl 1):S462-8:
[172] ZADAXIN. A safe and effective treatment for major, global life-threatening diseases. SciClone Pharaceuticals Company Website. A文ailable at: http://www.sciclone.com/Zadaxin/index.html. Accessed July 24, 2002.
[173] Andreone P, Cursaro C, Gramenzi A, Margotti M, Ferri E, Talarico S, et al. In vitro effect of
thymosin-alphal and interferon-alpha on Th1 and Th2 cytokine synthesis in patients with chronic hepatitis C. J Viral Hepat 2001;8(3):194-201.
[174] McHutchinson JG, Patel K. Future therapy of hepatitis L. Hepatology 2002;36(Suppl 1): S245-52.
[175] Depla E, Priem S, Verschoor E, Roskams T, Desmet V, Van Doorn LJ, et al. Therapeutic vaccination of chronically infected chimpanzess with the HCV E1 protein. Antivir Ther•1999;4 (Suppl 4):abstract 39.
(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
$\therefore$ (19) World Intellectual Property Organization
(43) International Publication Date 29 November 2001 (29.11.2001)


PCT

(10) International Publication Number WO 01/90121 A2.
(51) International Patent Classification;
(21) International Application Number: PCT/USO1/16671
(22) International Filing Date: 23 May 2001 (23.05.2001)
(25) Filing langrage. . $\quad$. $\quad$ English
(26) Publication Language:

English
(30) Priority Data:

60/206.585 23 May $2000(23.05 .2000)$ US
(71) Applicants for all designated States except US): NOVIRIO PHARMACEUTICALS LIMITED [ $-1 \div$ - -1 ; Walker Secretaries. Walker House, Grand Cayman (KY). UNIVERSITA DEGLI STUDI DI CAGLIARI [I TIT]; Dip. Biologia Sperimentale, Sezione di Microbiologia, Citladella Universitaria SS $554, \mathrm{Km} .4 .500, \mathrm{I}-09042$ Monscrrato (IT).
(72) Inventors; and
175) Inventors/Applicants for (/S only): SOMMADOSSI, Jean-Pierre [FR/US]; 5075 Greystone Way, Birmingham, AL 35242 (US). LaCOLLA, Pablo [IT/TT): 5 Surada no. 11. Poggio dee Mini, I-09012 Capoterra (IT).
(74) Agent: KNOWLES, Slurry, M.; King \& Spalding, 191 Peachlree Stet, Atlanta, GA 30303-: 763 (US).
(81) Designated States (national): AE, AG, AL, AM, AT, AU, $A Z, B A, B B, B G, B R, B Y, B Z, C A, C H, C N, C O, C R, C U$, $C Z, D E, D K, D M, D Z, E C, E E, E S, F I, G B, G D, G E, G H$, GM, IR, ITU, ID, IL, IN, IS, JP, KL, KO, KP, KR, KL, LL LR, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MK, ML, NO, NZ, PL, PT, KO, RU, SD, SE, SG, SI, SK, SL, TI, TM, TR, TM, TX, UR, JG, US, UL, VA, MU, IA, LW.
(84) Designated States (regional): $\triangle$ RIPO patent (GH, GM, KE, ISS, MW, MZ, SD, SL, S7., T7., UG, 7.W),' Eurasian patent ( $\mathrm{AM}, \mathrm{AL}, \mathrm{BY}, \mathrm{KG}, \mathrm{KL}, \mathrm{MD}, \mathrm{KU}, \mathrm{TJ}, \mathrm{TM}$ ), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE. IT, IU, MC, NL, PT, SE, TR), OAPI patent (BF, BI, CF, $\mathrm{CG}, \mathrm{Cl}, \mathrm{CM}, \mathrm{GA}, \mathrm{GN}, \mathrm{GW}, \mathrm{ML}, \mathrm{MR}, \mathrm{NE}, \mathrm{SN}, \mathrm{TD}, \mathrm{TG})$.

Published: -
Published: without international search report and to be republished
upon receipt of that report
For nvo-lenter codes and other abbreviations, refer to the "Gidane Notes on Codes and Abbreviations" appearing at the beginming of each regular issuc of the PCT Gazette. $\therefore$
(57) Abstract: $\Lambda$ method and composition for treating a host infected with hepatitis $C$. comprising administering an effective hepatitis (' treatment amount of a described 1', 2' or 3'-modilied nucleoside or a phamaceutically acceptable salt or prodrug thereof', is provided.

## METHODS AND COMPOSITIONS FOR TREATING HEPATITIS C VIRUS

## FIELD OF THE INVENTION

This invention is in the area of phannaceutical chemistry, and is in particular, is a compound, method and composilion for the treatment of hepatitis C virus. This application claims priority to U.S. provisional application no. 60/206,585, filed on May 23, 2000. .

## BACKGROUND OF THE INVENTION

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide. (Boyer, N. et al. J. Hepatol. 32:98-112, 2000). HCV causes a slow growing viral infection and is the major cause of cirrhosis and hepatocellular carcinoma (Di Besceglie, A. M. and Bacon, B. R., Scientific American, Oct.: 80-85, (1999); Boyer, N. et al. J. Hepatol. 32:98112,2000 ). An estimated 170 million persons are infected with HCV worldwide. (Boyer, N. et al. J. Hepatol: 32:98-112, 2000). Cirrhosis caused by chronic hepatitis C infection accounts for 8,000-12,000 deaths per year in the United States, and HCV infection is the leading indication for liver transplant.

HCV is known to cause at least $80 \%$ of posttransfusion hepatitis and a substantial proportion of sporadic acute hepatitis. Preliminary evidence also implicates HCV in many cases of "idiopathic" chronic hepatitis, "cryptogenic" cirrhosis, and probably hepatocellular carcinoma unrelated to other hepatitis viruses, such as Hepatitis B Virus.(HBV). A small proportion of healthy persons appear to be chronic. HCV carriers, varying with geography and other epidemiological factors. The numbers may substantially exceed those for HBV, though information is still preliminary; how many of these persons have subclinical chronic liver discase is unclear. (The Merck Manual, ch. 69, p. 901, 16th ed., (1992)).

IICV has been classified as a member of the virus family Flaviviridae that includes the genera flaviviruses, pestiviruses, and hapaceiviruses which includes hepatitis $C$ viruses (Rice, C. M., Flaviviridae: The viruses and their replication. In: Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, Chapter 30, 931-959, 1996). HCV is an enveloped virus containing a positive-sense single-stranded RNA genome of approximately 9.4 kb . The viral genome consists of a $5^{\prime}$ untranslated region (UTR), a.lóng open reading frame encoding a polyprotein precursor of
approximately 3011 amino acids, and a short $3^{\prime}$ UTR. The $5^{\prime}$ UTR is the most highly conserved part of the HCV genome and is important for the initiation and control of polyprotein translation. Translation of the HCV genome is initiated by a cap-independent mechanism known as internal ribosome entry. This mechanism involves the binding of ribosomes to an RNA sequence known as the internal ribosome entry site (IRES). An RNA pseudoknot structure has recently been determined to be an essential structural element of the HCV IRES. Viral structural proteins include a nucleocapsid core protein (C) and two envelope glycoproteins, E1 and E2. HCV also encodes two proteinases, a zinc-dependent metalloproteinase encoded by the NS2-NS3 region and a serine proteinase encoded in the NS3 region. These.proteinases are required for cleavage of specific regions of the precursor polyprotein into mature peptides. The carboxyl half of nonstructural protein 5, NS5B, contains the RNA-dependent RNA polymerase. The function of the remaining nonstructural proteins, NS4A and NS4B, and that of NS5A (the amino-terminal half of nonstructural protein 5) remain unknown.

A significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A. M. and Bacon, B. R., Scientific American, Oct.: 80-85, (1999)). Currently, there are two primary antiviral compounds, Ribavirin and interferon-alpha, which are used for the treatment of chronic HCV infections in humans.

## Treatment of HCV Infection with Ribivarin

Ribavirin (1- $\beta$-D-ribofuranosyl-1-1,2,4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name, Virazole (The Merck Index, 11 th edition, Editor: Budavari, S., Merck \& Co., Inc., Rahway, NJ, pl304, 1989). United States Patent No. 3,798,209 and RE29,835 disclose and claim Ribavirin. Ribavirin is structurally similar to guanosine, and has in vitro activity against several DNA and RNA viruses including Flaviviridae (Gary L. Davis. Gastroenterology 118:S104-S114, 2000).

Ribavirin reduces serum amino transferase levels to normal in $40 \%$ or patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis. Gastroenterology_118:S104S114, 2000). Thus, Ribavirin alone is not effective in reducing viral RNA levels. Additionally, Ribavirin has significant toxicity and is known to induce anemia.

## Treatment of HCV Infection with Interferon

Interferon (IFNs) are compounds that have been commercially available for the treatment of chronic hepatitis for nearly a decade. IFNs are glycoproteins produced by immune cells in response to viral infection. IFNs inhibit viral replication of many viruses, including HCV, and when used as the sole treatment for hepatitis C infection, IFN suppresses serum HCV-RNA to undetectable levels. Additionally, IFN normalizes serum amino transferase levels. Unfortunately, the effects of IFN are temporary and a sustained response occurs in only $8 \%-9 \%$ of patients chronically infected with HCV (Gary L. Davis. Gastroenterology 118:S104-S114, 2000).

## Combination of Interferon and Ribavirin

 U.S. Patent No. $5,738,845$ to Imakawa discloses the use of human interferon tau proteins for treating HCV. Other interferon-based treatments for HCV are disclosed in U.S. Patent No. $5,676,942$ to Testa et al., U.S. Patent No. 5,372,808 to Blatt et al., and U.S. Patent No. 5,849,696.The combination of IFN and Ribavirin for the treatment of HCV infection has been reported to be effective in the treatment of IFN naïve'patients (Battaglia, A.M. et al.,'Anu. Pharmacother. 34:487-494, 2000). Results are promising for this combination treatment both before hepatitis develops or when histological disease is present (Berenguer, M. et al. Antivir. Ther. 3(Suppl. 3):125-136, 1998). Side effects of combination therapy include

## Additional References Disclosing Methods to Treat HCVInfections

A number of HCV treatments are reviewed by Bymock et al. in Antiviral Chemistry \& Chemotherapy, 11:2; 79-95 (2000).

Several substrale-based N83 protease inhibitors have been identified in the -literature, in which the scissile amide bond of a cleaved substrate is replaced by an electrophile, which interacts with the catalytic serine. Attwood et al. (1998) Antiviral peptide derivatives, 98/22496; Atwood et al. (1999), Antiviral Chemistry and Chemotherapy 10.259-273; Atwood et al. (1999) Preparation and use of amino acid derivatives as anti-viral agents, German Patent Publication DE 19914474; Tung et al: (1998) Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease; WO 98/17679. The reported inhibitors terminate in an electrophile such as a moronic acid or phosphonate. LLinas-Brunet et al. (1999) Hepatitis C inhibitor peptide analogues,_.WO 99/07734. Two classes of electrophile-based inhibitors have been described, alphaketoamides and hydrazinoureas.

The literature has also described a number of non-substrate-based inhibitors. For example, evaluation of the inhibitory effects of $2,4,6$-trihydroxy-3-nitro-benzamide derivatives against HCV protease and other serine proteases has been reported. Sudo, K. et al., (1997) Biochemical and Biophysical Research Communications, 238:643-647; Judo, K. et al. (1998) Antiviral Chemistry and Chemotherapy 9:186. Using a reverse-phase HPLC assay, the two most potent compounds identified were RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a paraphenoxyphenyl group.

1 Thiazolidine derivatives have been identified as micromolar inhibitors, using a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate. Sudo, K. et al. (1996) Antiviral Research 32:9-18. Compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, was the most potent against the isolated enzyme. Two other active examples were RD 4 6205 and RD4 6193.

Other literature reports screening of a relatively small library using an ELISA assay and the identification of three compounds as potent inhibitors, a thiazolidine and two benzanilides. Kakiuchi N. et al. J. EBS Letters 421:217-220; Takeshita N. et al., Analytical Biochemistry 247:242-246, 1997. Several U.S. patents disclose protease inhibitors for the treatment of HCV. For example, U.S. Patent No. 6,004,933 to Spruce et al. discloses a class of cysteine protease inhibitors for inhibiting HCV endopeptidase 2. U.S. Patent No. 5,990,276 to Zhang et al. discloses synthetic inhibitors of hepatitis C virus NS3 protease. The inhibitor is a subsequence of a substrate of the NS3 protease or a substrate of the NS4A cofactor. The use of restriction enzymes to treat HCV is disclosed in U.S. Patent No. $5,538,865$ to Reyes el al.

Isolated from the fermentation culture broth of Streptomyces sp., Sch 68631, a phenan-threnequinone, possessed micromolar activity against HCV protease in a SDSPAGE and autoradiography assay. Chu M. et al., Tetrahedron Letters 37:7229-7232, 1996. In another example by the same authors, Sch 351633, isolated from the fungus Penicillium griscofuluum, demonstrated micromolar activity in a scintillation proximity assay. Chu M. et al., Bioorganic and Medicinal Chemistry Letters 9:1949-1952. Nanomolar potency against the HCV NS3 protease enzyme has been achieved by the design of selective inhibitors based on the macromolecule eglin c. Eglin c, isolated from leech, is a potent inhibitor of several serine proteases such as $S$. griseus proteases $A$ and $B, \alpha$-chymotrypsin, chymase and subtilisin. Qasim M.A. et al., Biochemistry 36:1598-1607, 1997.

HCV helicase inhibitors have also been reported. U.S. Patent No. 5,633,358 to Diana G.D. et al.; PCT Publication No. WO 97/36554 of Diana G.D. et al.. There are a few reports of HCV polymerase inhibitors: some nucleotide analogues, gliotoxin and the natural product cerulenin. Ferrari R. et al., Journal of Virology 73:1649-1654, 1999; Lohmann V. et al., Virology 249:108-118, 1998.

Antisense phosphorothioate oligodeoxynucleotides complementary to sequence stretches in the 5' non-coding region of the HCV, are reported as efficient inhibitors of HCV gene expression in in vitro translation and HcpG2 IICV-luciferase cell culture systems. Alt M. et al., Hepatology 22:707-717, 1995. Recent work has demonstrated that nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of the HCV RNA are effective targets for antisense-mediated inhibition of viral translation. Alt M. et al., Archives of Virology 142:589-599, 1997. U.S.

WO 01/90121
Patent No. $6,001,990$ to Wands et al. discloses oligonucleotides for inhibiting the replication of HCV. PCT Publication No. WंO 99/29350 discloses compositions and methods of treatment for hepatitis C infection comprising the administration of antiscuse oligonucleotides that are complementary and hybridizable to HCV-RNA. U.S. Pateṇt No. 5,922,857 to Han et al. disclose nucleic acids corresponding to the sequence of the pestivirus homology box $I V$ area for controlling the translation of HCV. Antisense oligonucleotides as therapeutic agents have been recently reviewed (Galderisi U. et al., Journal of Cellular Physiology 181:251-257, 1999).

Other compounds have been reported as inhibitors of IRES-dependent trouslation in HCV. Japanese Patent Publication JP-08268890 of Ikeda N et al.; Japanese Patent Publication JP-10101591 of Kai, Y. et al. Nuclease-resistant ribozymes have been targeted at the IRES and recently reported as inhibitors in an HCV-poliovirus chimera plaque assay. Maccjak D.J. et al., Hepatology 30 abstract 995, 1999. The use of ribozymes to treat HCV is also disclosed in U.S. Patent No. 6,043,077 to Barber et al., and U.S. Patent Nos. 5,869,253 and 5,610,05.4 to Draper et al.

Other patents disclose the use of immune system potentiating compounds for the treatment of HCV. For example, U.S. Patent No. 6,001,799 to Chretien et al. discloses a method of treating hepatitis C in non-responders to interferon treatment by administering an immune system potentiating dose of thymosin or a thymosin fragment. U.S. Patent Nos. 5,972,347 to Eder et al. and 5,969,109 to Bona et al. disclose antibody-based treatments for treating HCV.
U.S.Patent No. 6,034,134 to Gold et al. discloses certain NMDA receptor agonists having immunodulatory, antimalarial, anti-Borna virus and anti-Hepatitis C activities. The disclosed NMDA receptor agonists belong to a family of 1 -amino-alkylcyclohexanes. U.S. Patent No. 6,030,960 to Morris-Natschke et al. discloses the use of certain alkyl lipids to inhibit the production of hepatitis-induced antigens, including those produced by the HCV virus. U.S. Patent No. 5,922,757 to Chojkier et al. discloses the use of vitamin E and other antioxidants to treat hepatic. disorders including HंCV. U.S. Patent No. 5,858,389 to Elsherbi et al. 'discloses the use of squalene for treating hepatitis C. U.S. Patent No. $5,849,800$ to Smith et al discloses the use of amantadine for treatment of Hepatitis C. U.S. Patent No. $5,846,964$ to Ozeki et al. discloses the use of bile acids for treating HCV. U.S.

WO 01/90121
PCT/US01/16671
Patent No. 5,491,135 to Blough et al. discloses the use of N-(phosphonoacetyl)-L-aspartic acid to treat flaviviruses such as HCV.

Other compounds proposed for treating HCV include plant extracts (U.S. Patent No. 5,837,257 to. Tsai et al., U.S. Patent No. 5,725,859 to Omer et al., and U.S. Patent No. $6,056,961$ ), piperidenes (U.S. Patent No. 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Patent No. 5,633,388 to Diana et al.), polyadenylic acid derivatives (U.S. Patent No. 5,496,546 to Wang et al.), 2',3'-dideoxyinosine (U.S. Patent No. 5,026,687 to Yarchoan et al.), benzimidazoles (U.S. Patent No. 5,891,874 to Colacino et al.).

In light of the fact that the hepatitis C virus has reached epidemic levels worldwide, and has tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat hepatitis C that has low toxicity to the host.

Therefore, it is an object of the present invention to provide a compound, method and composition for the treatment of a host infected with hepatitis C virus.

## SUMMARY OF THE INVENTION

Compounds, methods and compositions for the treatment of hepatitis $C$ infection are described that include an effective hepatitis $C$ treatment amount of a $\beta$ - $D$ - or $\beta$-L-nucleoside of the Formulas (I) - (XVIII); or a pharmaceutically acceptable salt or prodrug thereof.

In a first principal embodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(I)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl);

WO 01/90121
PCT/US01/16671
sulfonate ester imcluding alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{\mathfrak{4}}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selccted from the group consisting of $H$, straight chained, brâniched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a second principal embodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(II)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are indejendently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $R^{3}$ is independently $H$ or phosphate; and $Y$ is hydrogen, bromo, chloro, fluoro, iodo, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;

PCT/US01/16671
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a third principal embodiment, a compound of Formula III, or a phamaceutically acceptable salt or prodrug thereof, is provided:

wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $\mathrm{H} ;$ phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a "peptide; a cholesterol; or other 'pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, jodo, $O R^{4}, N R^{4} R^{5}$ or $S R^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $O R^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a fourth principal embodiment, a compound of Formula N ; or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(IV)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); i sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;

Y is hydrogen, promo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl,CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a fifth principal embodiment, a compound of Formula $V$, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(V)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmäceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and $Y$ is hydrogen, bromo, chloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a sixth principal embodiment, a compound of Formula VI, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(VI)

WO 01/90121
PCT/US01/16671
wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substiluents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $R^{3}$ is independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a seventh principal embodiment, a compound selected from Formulas VII, VIII and IX, or a pharmaceutically acceptable șalt or prodrug thereof, is provided:

(VII)

(VII)

(IX)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acčeptable leaving 'group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $R^{3}$ is independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, 2-Br-ethyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $-\mathrm{O}($ lower alkyl $),-\mathrm{O}(\text { alkenyl })_{\imath} \mathrm{CF}_{3}$, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), $-\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a eighth principal embodiment, a compound of Formulas X, XI and XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(XI)
(X)

(XII)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate ' (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}$ (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
${ }_{\text {, }} \mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}{ }^{3}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl $),-\mathrm{O}($ acyl), $-\mathrm{O}($ lower -acyl), $-\mathrm{O}($ alkyl $),-$ O (lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2} ;-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a ninth principal embodiment a compound selected from Formulas XIII, XIV and XV , or a pharmaceutically acceptable salt or prodrug thereof, is provided:

wherein: $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

(XIV)

(XV)

Base is a purine or pyrimidine base asidefined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl), -

In a tenth principal embodiment the invention provides a compound of Formula XVI, or a pharmaceutically acceptable salt or prodrug thereof:


IPO DELHI 23-06-2015 15:444

WO 01/90121
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{l}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acẏl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a ${ }_{\text {, phospholipid; }}$ an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{\prime}$ or $R^{2}$ is independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), -O (acyl), -O (lower acyl), -O (alkyl), -O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), -NH (acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2} ;$
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acy })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine; bromine or iodine; alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a pi bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a eleventh principal embodiment the invention provides a compound of Formula XVII, or a pharmaceutically acceptable salt or prodrug thereof:

(XVI)

WO 01/90121
PCT/US01/16671
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in wive is capable of providing a compound wherein $\mathrm{R}^{1}$ or $\mathrm{R}^{2}$ is independently H or phosphate;
$R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), -NH (acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), - O (alkyl), - O (lower alkyl), - O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$. and $\mathrm{R}^{10}$ can come together to form a pi bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In an twelfth principal enibodiment, the invention'provides a compound of Formula XVIII, or a pharmaceutically acceptable salt or prodrug thereof:

(XVIII)

Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a .peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ or $\mathrm{R}^{2}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}(l o w e r ~ a l k y l), ~-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl) amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $R^{7}$ and $R^{9}$, or $R^{8}$ and $R^{9}$ can come together to form a pi bond; X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

The $\beta$-D- and $\beta$-L-nucleosides of this invention may inhibit HCV polymerase activity. Nucleosides can be screened for their ability to inhibit.HCV polymerase activity in vitro according to screening methods sett forth more particularly herein. One can readily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.

In one embodiment the efficacy of the anti- HCV compound is measured according to the concentration of compound necessary to reduce the plaque number of the virus in vitro, according to methods set forth more particularly herein, by $50 \%$ (i.e. the compound's

WO 01/90121
PCT/US01/16671
$\mathrm{EC}_{50}$ ). In preferred embodiments the compound exhibits an $\mathrm{EC}_{50}$ of less than $25,15,10,5$, or 1 micromolar.

In another embodiment, the active compound can be administered in combination or alternation with another anti- HCV agent. In combination therapy, an effective dosage of two or more agents are administered together, whereas during alternation therapy an effective dosage of each agent is administered serially. The dosages will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to .those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include:

Antiviral Research 32:9-18, 1996), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4. 6205 and RD4 6193;
(5) Thiazolidines and benzanilides identified in Kakiuchi N. et al. J. EBS Letters 421:217-220; Takeshita N. et al. Analytical Biochemistry 247:242-246, 1997;
(6) A phenan-threnequinone possessing activity against HCV protease in a SDSPAGE and autoradiograph assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Chi M, et al., Tetrahedron Letter's 37:7229-7232, 1996), and Sch 351633, isolated from the fungus Penicillium griscofuluum; which demonstrates activity in a scintillation proximity assay (Chi M. et al., Bioorganic and Medicinal Chemistry Letters 9:1949-1952);
(7) Selective NS3 inhibitors based on the macromolecule algin c , isolated from leech (Qasim M.A. et al., Biochemistry 36:1598-1607, 1997);
(8) HCV helicase inhibitors (Diana G.D. et al., Compounds, compositions and methods for treatment of hepatitis C, U.S. Patent No. 5,633,358; Diana G.D. et al., ' Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment. of hepatitis C, PCT WO 97/36554);
(9) HCV polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. et. al. Journal of Virology 73:1649-1654, 1999), and the natural product cerulenin (Lohmann V. et al., Virology 249:108-118, 1998);
(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the $5^{\prime}$ non-coding region (NCR) of the HCV (Alt M. et al., Hepatology 22:707-71.7, 1995), or nucleotides 326-348 comprising the 3 ' end of the NCR and nucleotides 371-388 located in the core coding region of the IICV RNA (Alt M. et al., Archives of Virology 142:589-599, 1997; Galderisi U. et al., Journal. of. Cellular Physiology 181:251-257, 1999);
(11) Inhibitors of IRES-dependent translation (Ikeda $N$ et al., Agent for the prevention and treatment of hepatitis C, Japanese Patent Publication JP-08268890; Kai Y. et al. Prevention and treatment of viral diseases, Japanese Patent Publication JP10101591);
(12) Nuclease-resistant ribozymes (Maccjak D.J. et al., Hepatology 30 abstract 995, 1999); and
(13) Other miscellancous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold et al.), alkyl lipids (U.S. Patent No. 5,922,757 to Chojkier et al.), vitamin E and other antioxidants (U.S. Patent No. 5,922,757 to Chojkier et al.), squalene, amantadine, bilc acids (U.S. Patent No. $5,846,964$ to Ozeki et al.), N-(phosphonoacelyl)-L-aspartic acid, (U.S. Patent No. $5,830,905$ to Diana et al.), benzenedicarboxamides (U.S. Patent No. 5,633,388 to Diana et al.), polyadenylic acid derivatives (U.S, Patent No. 5,496,546 to Wang et al.), 2', $3^{\prime}$-didenxyinosine (U.S. Patent No. 5,026,687 to Yarchoan et al.), and benzimidazoles (U.S. Patent No. 5,891,874 to Colacino et al.).

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 provides the structure of various non-limiting examples of nucleosides of the present invention, as well as other known nucleosides, FIAU and Ribavirin, which are used as comparative examples in the text.

Figure 2 is a line graph of the pharmacokinetics (plasma concentrations) of $\beta-D-2^{\prime}$ -$\mathrm{CH}_{3}$-riboG administered to six Cynomolgus Monkeys over time after administration.

Figure 3a and 3b are line graphs of the pharmacokinetics (plasma concentrations) of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG administered to Cynomolgus Mönkeys either intravenously (3a) or orally (3b) over time after administration.

## DETAILED DESCRIPTION OF THE INVENTION

The invention as disclosed herein is a compound, method and composition for the treatment of hepatitis $C$ in humans or other host animals, that includes administering an effective HCV treatment amount of a $\beta$-D- or $\beta$-L-nucleoside as described herein or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier. The compounds of this invention either possess antiviral (i.e., anti-HCV) activity, or are metabolized to a compound that exhibits such activity.

In summary, the present invention includes the following features:
(a) $\beta$-D- and $\beta$-L-nucleosides, as described herein, and pharmaceutically acceptable salts and prodrugs thereof;
(b) $\beta$-D- and $\beta$-L-nucleosides as described herein, and pharmaceutically acceptable salts and prodrugs thereof for use in the treatment or prophylaxis of an HCV infection, especially in individuals diagnosed as having an HCV infection or being at risk for becoming infected by HCV;
(c) use of these $\beta$-D- and $\beta$-L-mucleosides, and phamaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for treatment of an HCV infection;
(d) pharmaceutical formulations comprising the $\beta$-D. or $\beta$-L-nucleosides 'or phamaceutically acceptable salts or prodrugs thereof together with a pharnaceutically acceptable carrier or diluent;
(e) $\quad \beta$-D- and $\beta$-L-nucleosides as described herein substantially in the absence of enantiomers of the described nucleoside, or substantially isolated from other chemical entities;
(f) processes for the preparation of $\beta$-D- and $\beta$-L-nucleosides, as described in more detail below; and
(g) processes for the preparation of $\beta$-D- and $\beta$-L-nucleosides substantially in the absence of enantiomers of the described nucleoside, or substantially isolated from other chemical entities.

## I. Active Compound, and Physiologically Acceptable Salts and Prodrugs Thereof

In a first principal embodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino .acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently $H$ or phosphate;

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate (preferàbly $H$ );
$\mathrm{X}^{1}$ is H ;
$\mathrm{X}^{2}$ is H or $\mathrm{NH}_{2}$; and ${ }^{+}$
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{NH}_{2}$ or OH .

In a second principal embodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(II):
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ or $R^{3}$ is independently $H$ or phosphate; and

Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group. consisting of H , straight chained, branched or_cyclic-alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate (preferably $H$ );
$\mathrm{X}^{1}$ is H ;
$\mathrm{X}^{2}$ is H or $\mathrm{NH}_{2}$; and

## WO 01/90121

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{NH}_{2}$ or OH .
In a third principal embodiment, a compound of Formula III, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

wherein:
(III)
$R^{1}, R^{2}$ and $R^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently $H$ or phosphate; and

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl); or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula III, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate (preferably $H$ );
$\mathrm{X}^{1}$ is H ;

WO 01/sul2

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{NH}_{2}$ or OH .
In a fourth principal embodiment,, a compound of Formula IV , or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(IV)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;

Y is hydrogen, bromo, chloro; fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula IV, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate (preferably H );
$\mathrm{X}^{1}$ is H or $\mathrm{CH}_{3}$; and

WO 01/90121
Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{NH}_{2}$ or OH .
In a fifth principal embodiment, a compound of Formula V, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently, H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized .phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently $H$ or phosphate; and

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula $V$, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently H or phosphate (preferably $H$ );
$\mathrm{X}^{1}$ is H or $\mathrm{CH}_{3}$; and
Y is hydrogen, promo, chloro, fluor, jodo, $\mathrm{NH}_{2}$ or OH .

In a sixth principal embodiment, a compound of Formula VI, or a pharmaceutically acceptable salt or prodrug thereof, is provided: ••

(VI) wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more sübstituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1} ; R^{2}$ or $R^{3}$ is independently $H$ or phosphate; and Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO -alkyl, CO -aryl, CO -alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula VI, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate (preferably $H$ );
$\mathrm{X}^{1}$ is H or $\mathrm{CH}_{3}$; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{NH}_{2}$ or OH .

In a seventh principal embodiment, a compound selected from Formulas VII, V.III and IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(VII)

(VIII)

(IX)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $R^{3}$ is independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, 2-Br-ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), $-\mathrm{O}($ alkyl $)$, -O(lower alkyl), -O(alkenyl), $\mathrm{CF}_{3, \text { : }}$ chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}\left(\right.$ (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
In a first preferred subembodiment, a compound of Formula YII, VIII or IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula VII, VIII or IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein; ${ }^{\circ}$.
$R^{1}, R^{2}$ and $R^{3}$ are hydrogens;
$R^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a third preferred subembodiment, a compound of Formula VII, VIII or IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$R^{6}$ is alkyl; and
X is O .
In a eighth principal embodiment, a compound of Formula X, XI or XII, or a pharmaceutically acceptable salt or prodrig thereof, is provided:

(X)

(XI)

(XII)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other
pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}$ (lower acyl), -O (alkyl), -O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), - $\mathrm{O}($ alkyl $),-$ O (lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { loweralkyl })_{2},-\mathrm{N}(\mathrm{acyl})_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a first preferred subembodiment, a compound of Formula X, XI or XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a second preferred' subembodiment, a compound of Formula X, XI or XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are hydrogen;
$R^{6}$ is alkyl; and

- X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ of $\mathrm{CH}_{2}$.

In a third preferred subembodiment, a compound of Formula X, XI or XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;

1
IPO DELHI 23-06-2015.15:440

WO 01/90121
PCT/US01/16671
$\mathrm{R}^{6}$ is alkyl; and
X is O .
In even more preferred subembodiments, a compound of Formula XI, or its pharmaceutically acceptable salt or prodrug, is provided:
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, -triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino. acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ or $\mathrm{R}^{2}$ is independently $H$ or phosphate.

In a ninth principal embodiment a compound selected from Formula XIII, XIV or XV , or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(XIII)

(XIV)

(XV)
wherein:
Base is a purine or pyrimidine base as defined herein;

WO 01/90121
PCT/US01/16671
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described.in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carhohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), $-\mathrm{O}($ lower acyl); - O (alkyl), - $\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), -NH (acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a first preferred subembodiment, a compound of Formula XIII, XIV or XV, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a second preferred subembodinient, a compound of Formula XIII, XIV or XV, or a pharmaceutically acceptable salt or prodrug thereof, iş provided wherein:
' Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are hydrogens;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a third preferred subembodiment, a compound of Formula XIII, XIV or XV, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;

WO 01/90121
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$R^{6}$ is alkyl; and
X is O .
In a tenth principal embodiment the invention provides a compound of Formula XVI, or a pharmaceutically acceptable salt or prodrug thereof:

(XVI)
, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; ar peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, promo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), -NH (acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O (alkyl), -O(lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine;

## WO 01/90121

PCT/US01/16671
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a pi bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a first preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylaikyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$, alkyl, alkenyl, alkynyl, Br-vinyl, $\mathrm{O}^{-}$ alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1). Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including 反ower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, includinig a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $\mathrm{R}^{6}$ is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a third preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a-purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, promo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$, alkyl, alkenyl, alkynyl, Br-vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are H ; and (6) X is O , $\mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$. ,

In a fourth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$ or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chioro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) : $R^{7}$ and $R^{9}$ are independently $\mathrm{OR}^{2}$, alkyl, alkenyl, alkynyl, Br-vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or dí(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\cdot \mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O .

In a fifth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$ or phosphate (including
monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as ${ }^{\circ}$ described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently II or phosphate; (3) $R^{6}$ is alkyl; (4) $K^{7}$ and $R^{9}$ are independently $O R^{1}$; (5) $R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a sixth preferred subembodiment, a compound of Formula XVI, or its phamaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in viva is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a seventh preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$. is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$, alkyl (including lower alkyl), alkenyl,

WO 01/90121
PCT/US01/16671
alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyi (including. lower alkyl), chlorine, bromine or iodine; and (6) X is O .

In a eighth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester, including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}^{1}$.

In a ninth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, díphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Bri-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $R^{9}$ are independently $O R^{2}$; (5) $R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is O .

In a tenth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or
pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or 'phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphatc prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl; wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkeniyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, Oalkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$.

In an eleventh preferred subembodiment; a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a twelfth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a-purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are.hydrogen; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a thirteenth preferred subembodiment, a. compound of Formula XVI, or its pharnaceutically acceptable salt or prodrug; is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is atkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$; (5) $R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O .

In a fourteenth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided im which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl;
(4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is O .

In even more preferred subembodiments, a compound of Formula XVI, or its (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is butyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ is hydrogen and $R^{9}$ 25 pharmaceutically acceptable salt or prodrug, is provided in which:
(1) Base is adenine;
(2) $R^{1}$ is hydrogen;
(3) $R^{6}$ is methyl;
(4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is guanine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is O ;
(1) Base is cytosine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is O
(1) Base is thymine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is uracil; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $\dot{R}^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is phosphate; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$; .
(1) Base 'is adenine; (2) $\mathrm{R}^{1}$ is hydrogen; (3) $\mathrm{R}^{6}$ is ethyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is propyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; is hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydtoxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $S$;
(1) Base is adënine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$. are hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is $\mathrm{SO}_{2}$;

WO 01/90121
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $\mathrm{CH}_{2}$;

In a eleventh principal embodiment the invention provides a compound of Formula XVII, or a pharmaceutically acceptable salt or produg thereof:

(XVII) ${ }^{\circ}$
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ is $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a -carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), - NH (acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br-vinyl'; $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O (alkyl), -O(lower alkyl), -O(allkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a pi bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a first preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)-amino; (5) $\mathrm{R}^{10}$ is- H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl suffonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is , independently H or phosphate; (3) ${ }_{1} \mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $R^{9}$ are independently $O R^{2}$; (5) $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a third preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or
wo 01/90121

## PCT/USU1/16671

pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl; wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a. cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{l}$ is independently $H$ or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)-amino; (5) $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is O .

In a fourth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including 'monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, promo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a fifth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is
optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ ; and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$. is H , alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is O .

In a sixth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino; or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{10}$ is H ; and (6) X is O .

In a seventh preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stạbilized phosphate prodrug); acyl (including lower acyl); alkyl: (including' lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3)
wo 01/90121
PCT/US01/16671
$\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H ; and (6) X is O .

In an eighth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base ace defined herein; (2) $R^{1}$ is independently II or phosplate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, alkyl (including. lower alkyl), alkenyl, alkynyl, Bi-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)-amino; (5) $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, hromine or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a ninth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$. are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a tenth preferred. subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}_{2} \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In even more preferred subembodiments, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which:
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is guanine; (2) $\dot{R}^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) X is O ;
(1) Base is cytosine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is O ;
(1) Base is thymine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is O ;
IPO DELHI $23-05-201515: 44^{44}$

## WO (1/ $1 / 0121$

PCT/US01/16671
(1) Base is uracil; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is phosphate; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is ethyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is propyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is butyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $\odot$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $S$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is $\mathrm{SO}_{2}$; or
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is $\mathrm{CH}_{2}$

In an twelfth principal embodiment the invention provides a compound of Formula XVIII, or a pharmaceutically acceptable salt or prodrug thereof:

(XVIII)
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl,

## 127

WO 01/90121
PCT/US01/16671
wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in yivo is capable of providing a compound wherein $R^{1}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, lower alkylanino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $R^{7}$ and $R^{9}$, or $R^{8}$ and $R^{9}$ can come together to form a pi bond;

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a first preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided'in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl); chlorine, bromine or iodine; and .(6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or mote substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable. leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di-(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a third preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(lower-alkyl)amino; (4) $\mathrm{R}^{7}$ and $R^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2 i}$ or $\mathrm{CH}_{2}$.

In a fourth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prođrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is

WO 01/90121 optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an aniṇo acid; a carbohydrate; a peptide; a cholesterol; or other pharmaccutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}{ }^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{N}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) $X$ is $O$..

In a fifth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a' phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a sixth preferred: subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a. stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3)
$R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O .

In a seventh preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$; phosphate (including munophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower allcyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower.alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl; chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H ; and (6) X is O .

In an eighth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $R^{7}$ and $R^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a ninth preferred subembodiment, a. compound of Formula XVIII, or its pharmaceutically acceptable salt or-prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ arelindependently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a tenth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or

WO (1)/90121
PCT/US01/16671
pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$; (5) $R^{8}$ is $H$; and (6) $X$ is $O$.

In even more preferred subembodiments, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which:
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is guanine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is cytosine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}_{\mathrm{i}}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is thymine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is uracil; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl: (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $k^{1}$ is phosphate; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\dot{\mathrm{R}}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is ethyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is $\dot{\mathrm{O}}$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is propyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $\dot{R}^{1}$ is hydrogen; (3) $R^{6}$. is butyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $S$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{\mathrm{B}}$ is hydrogen; and (6) X is $\mathrm{SO}_{2}$; or
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is $\mathrm{CH}_{2}$.

The $\beta$-D- and $\beta$ - L-nucleosides of this invention may inhibit HCV polymerase activity. Nucleosides can be screened for their ability to inhibit HCV polymerase activity in ivitro according to screening methods set forth more particularly herein. One can readily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.

In one embodiment the efficacy of the anti-IICV compound is measured according to the concentration of compound necessary to reduce the plaque number of the virus in vitro, according to methods set forth more particularly herein, by $50 \%$ (ie. the compound's $\mathrm{EC}_{50}$ ). In preferred embodiments the compound exhibits an $\mathrm{EC}_{50}$ of less than 15 or 10 micromolar, when measured according to the polymerase assay described in Ferrari et al., Jul. of Vir.; 73:1649-1654, 1999; Ishii et al., Hepatology, 29:1227-1235,1999; Lohmann et al., Jul. of Bio. Chem., 274:10807-10815, 1999; or Yamashita et al, Jul. of Bio: Chem., 273:15479-15486, 1998.

The active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and a compound that has been alkylated or acylated at the 5 '-position or on the purine or pyrimidine base (a type of "pharmaceutically acceptable prodrug"). Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the salt or prodrug and testing its antiviral activity according to the methods described herein, or other methods known to those skilled in the art.

## II. Definitions

The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of typically $\mathrm{C}_{1}$ to $\mathrm{C}_{10}$, and specifically includes methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, $t$-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl; cyclohexyl,

## WO 01/90121

cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups. Moieties with which the alkyl group can be substituted are selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

The term lower alkyl, as used herein, and unless otherwise specified, refers to a $C_{1}$ to $\mathrm{C}_{4}$ saturated straight, branched, or if appropriate, a cyclic (for example, cyclopropyl) alkyl group, including both substituted and unsubstituted forms. Unless otherwise specifically stated in this application, when alkyl is a suitable moiety, lower alkyl is preferred. Similarly, when alkyl or lower alkyl is a suitable moiety, unsubstituted alkyl or lower alkyl is preferred.

The term alkylamino or arylamino refers to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "protected" as used herein and unless otherwise defined refers to a group that is added to an oxygen; nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis.

The term aryl, as used herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl, and preferably phenyl. The term includes both substituted and unsubstituted moieties. The aryl group can be substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid; phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The term alkaryl or alkylaryl refers to an alkyl group with an aryl substituent. The term aralkyl or arylalkyl refers to an aryl group with an alkyl substituent.

The term halo, as used herein, includes chloro, bromo, iodo, and fluors:

The term purine or pyrimidine base includes, but is not limited to, adenine, $\mathrm{N}^{6}$ alkylpurines, $\mathrm{N}^{6}$-acylpurines (wherein acyl is $\mathrm{C}(\mathrm{O})$ (alkyl, aryl, alkylaryl, or arylalkyl), $\mathrm{N}^{6}$ benzylpurine, $\mathrm{N}^{6}$-halopurine, $\mathrm{N}^{6}$-vinylpurine, $\mathrm{N}^{6}$-acetylenic purine, $\mathrm{N}^{6}$-acyl purine, $\mathrm{N}^{6}$-hydroxyalkyl purine, $\mathrm{N}^{6}$-thioalkyl purine, $\mathrm{N}^{2}$-alkylpurines, $\mathrm{N}^{2}$-alkyl-6-thiopurines, thymine, cytosine, 5 -fluorocytosine, 5 -methylcytosine, 6 -azapyrimidine, including 6 -azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5 -halouracil, including 5 -fluorouracil, $C^{5}$-alkylpyrimidines, $C^{5}$-benzylpyrimidines, $C^{5}$-halopyrimidines, $C^{5}$-vinylpyrimidine, $C^{5}$ acetylenic pyrimidịne, $C^{5}$-acyl pyrimidine, $C^{5}$ hydroxyalkyl purine, $C^{5}$-amidopyrimidine, $\mathrm{C}^{5}$-cyanopyrimidine, $\mathrm{C}^{5}$-nitropyrimidine, $\mathrm{C}^{5}$-aminopyrimidine, $\mathrm{N}^{2}$-alkylpurines, $\mathrm{N}^{2}$-alkyl-6-thiopurines, 5 -azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, $t$-butyldimethylsilyl, and $t$-butyldïphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term acyl refers to a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from straight, branched, or cyclic alkyl or lower alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with chloro, bromo, fluoro, iodo, $\mathrm{C}_{1}$ to $\mathrm{C}_{4}$ alkyl or $\mathrm{C}_{1}$ to $\mathrm{C}_{4}$ alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate. ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group. The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is a lower alkyl.

As used hercin, the term "substantially free of" or "substantially in the absence of" refers to a nucleoside composition that includes at leașt 85 or $90 \%$ by weight, preferably $.95 \%$ to $98 \%$ 'by weight, and even more preferably $99 \%$ to $100 \%$ by weight, of the designated enantiomer of that nucleoside. In a preferred embodiment, in the methods and compounds of this invention, the compounds are substantially free of enantiomers.

Similarly, the term "isolated" refers to a nucleoside composition that includes at least 85 or $90 \%$ by weight, preferably $95 \%$ to $98 \%$ by weight, and even more preferably $99 \%$ to $100 \%$ by weight, of the nucleoside, the remainder comprising other chemical species or enantiomers.

The term "independently" is used herein to indicate that the variable which" is independently applied varies independently from applicaliun to application. Thus, in a compound such as $R$ "XYR", wherein $R$ " is "independently carbon or nitrogen," both $R$ " can be carbon, both R " can be nitrogen, or one R " can be carbon and the other R " nitrogen.

The term host, as used herein, refers to an unicellular or multicellular organism in which the virus'can replicate, including cell lines and animals, and preferably a human. Alternatively, the host can be carrying a part of the hepatitis C viral genome, whose replication or function can be altered by the compounds of the present invention. The term host specifically refers to infected cells, cells transfected with all or part of the HCV genome and animals, in particular, primates (including chimpanzees) and humans. In most. animal applications of the present invention, the host is a human patient. Veterinary applications, in certain indications, however, are clearly anticipated by the present invention (such as chimpanzees).

The term' "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a nucleoside compound which, upon administration to a patient, provides the nucleoside compound. Pharmaceutically. acceptable salits include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable ; salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art. Pharmaceutically acceptable. prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active
compound. The compounds of this invention possess antiviral activity against HCV, or are metabolized to a compound that exhibits such activity.

## III. Nucleotide Salt or Prodrug Formulations

In cases where compounds are sufficiently basic or acidic to form stable nontoxic .acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, $\alpha$-ketoglutarate, and $\alpha$-glycerophosphate; Suitable inorganic salts may also be formed, including, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable $\left.\right|_{\text {acid }}$ affording a physiologically acceptable anion. Alkali metal (for exanple, sodium, potassium or lithium) or alkaline eatth metal (for example calcium) salts of carboxylic acids can also be made.

Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can'replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Mariy are described in R. Jones and N . |Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

The active nucleoside can also be provided as a $5^{\prime}$-phosphoether lipid or a $5^{\prime}$-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L.S., N. Iyer, E. Leake, A. Raben, Modest E.K., D.L.W., and C. Piantadosi. 1990. 'Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation." AIDS Res. Hum. Retro Viruses. 6:491-501; Piantadosi, C., J. Marasco C.J., S.L. Morris-Natschke, K.L. Meyer, F. Gumus, J.R. Surles,

WO 01/90121
PCT/US01/16671
K.S. Ishaq, L.S. Kucera, N. Iyer, C.A. Wallen, S. Piantadosi, and E.J. Modest. 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity.". J. Med. Chem. 34:1408.1414; Hosteller, K.Y'., D.D. Richman, D.A. Carson, L.M. Stuhmiller, G.M. T. van Wijk, and H. van den Bosch. 1992. "Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 3'deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3,-deoxythymidine." Antimicrob. Agents Chemother. 36:2025.2029; Hosetler, K.Y., L.M. Stuhmiller, H.B. Letting, H. van den Bosch, and D.D. Richman, 1990. "Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." J. Biol. Chem. 265:61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituent that can be covalently incorporated into the nucleoside, preferably at the $5^{\prime}-\mathrm{OH}$ position of the nucleoside or lipophilic preparations, include U.S. Patent Nos. 5,149,794 (Sep. 22, 1992, Yatvin et al.); 5,194,654 (Mar. 16, 1993, Hosteler et al., 5,223,263 (Tune 29, 1993, Hosteler et al.); 5,256,641 (Oct. 26, 1993, Yatvin et al.); 5,411,947 (May 2, 1995, Hostetler et al.); 5,463,092 (Oct. 31, 1995, Ilostetler et al.); 5,543,389 (Aug. 6, 1996, Yatvin et al.); 5,543,390 (Aug. 6, 1996, Yatvin et al.); 5,543,391 (Aug. 6, 1996, Yatvin et al.); and 5,554,728 (Sep. 10, 1996; Basava et al.); all of which are incorporated herein by reference. Foreign patent applications that disclose lipophilic substituent s that can be attached to the nucleosides of the present invention, or lipophilic preparations, include WO 89/02733, W0 90/00555, W0 91/16920, W0 91/18914, W0 93/00910, W0 94/26273, W0 96/15132, EP •0 350 287, EP 93917054.4, and W0 91/19721.

## IV. Combination and Alternation Therapy

It has been recognized that drug-resistant variants of HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against HCV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is
typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include:
(1) an interferon and/or ribavirin (Battaglia, A.M. et. al., Ann. Pharmacother. 34:487494, 2000); Berenguer, M. et al. Antivir. Ther. 3(Suppl. 3):125-136, 1998);
(2) Substrate-based NS3 protease inhibitors (Attwood et al., Antiviral peptide derivatives, PCT WO 98/22496, 1998; Attwond et al., Antiviral Chemistry and Chemotherapy 10.259-273, 1999; Atwood et al., Preparation and use of amino acid derivatives as anti-viral agents, German Patent Publication DE 19914474; Ting et al. Inhibitors of serine proteases, particularly hepatitis. C virus. NS3 protease, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a moronic acid or phosphonate. Llinas-Brunet et al, Hepatitis $C$ inhibitor peptide analogues, PCT WO 99/07734.
(3) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives(Sudo K.' et al., Biochemical and Biophysical Research Communications, 238:643-647, 1997; Sudo K. et al. Antiviral Chemistry and Chemotherapy 9:186, 1998), including RD3-4082. and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group;
(4) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Ludo K. et al., Antiviral Research 32:9-18, 1996), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;
(5) Thiazolidines and benzanilides identified in Kakiuchi N: et al. J. EBS Letters 421:217-220; Takeshita N. et ail. Analytical Biochemistry 24.7:242-246, 1997;
(6) A phenan-threnequinone possessing activity against HCV protease in a SDSPAGE and autoradiograph assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Thu M. et al., Tetrahedron Letters 37:7229-7232, 1996), and Sch 351633, isolated from the fungus Penicillium griscofulumin; which demonstrates activity in a scintillation proximity assay (Thu M. et al., Bioorganic and Medicinal Chemistry Letters 9:1949-1952);
(7) Selective NS3 inhibitors based on the macromolecule elgin c , isolated from leech (Qasim M.A. et all., Biochemistry 36:1598-1607, 1997);
(8) HCV helicase inhibitors (Diana G.D. et al., Compounds, compositions and methods for treatinent of hepatitis C, U.S. Patent No. 5,633,358; Diana G.D. et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C, PCT WO 97/36554);
(9) HCV polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. ct al. Journal of Virology 73:1649-1654, 1999), and the natural product cerulenin (Lohmann V. et al., Virology 249:108-118, 1998);
(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the $5^{\prime}$ non-coding region (NCR) of the HCV (Alt M. et al., Hepatulogy 22:707-717, 1995), or nucleotides 326-348 comprising the 3 ' end of the NCR and nucleotides 371-388 located in the core coding region of the ICV RNA (Alt M. et al., Archives of Virology 142:589-599, 1997; Galderisi U. et al., Journal of Cellular Physiology 181:251-257, 1999);
(11) Inhibitors of $\operatorname{RES}$-dependent translation (Ikeda $N$ et al., Agent for the prevention and treatment of Kepatitis C, Japanese Patent Publication JP-08268890; Kai Y. et al. Prevention aind treatment of iiral diseases, Japanese Patent Publication JP10101591);
(12) Nuclease-resistant ribozymes. (Maccjak D.J. et al., Hepatology 30 abstract 995, 1999); and
(13) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. 6,034, 134 to Gold et al.), alkyl lipids (U.S. Patent No. 5,922,757 to Chojkier et al.), vitamin E and other antioxidants (U.S. Patent No. 5,922,757 to Chojkier et al.), squalene, amantadine, bile acids (U.S. Patent No. $5,846,964$ to Ozeki et al.), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Patent No. 5,830,905 to Diana et äl.), benzenedicarboxamides (U.S. Patent No. 5,633,388 to Diana et al.), polyadenylic acid derivatives (U.S. Patent No. 5,496,546 to Wang' et al.), $2^{\prime}, 3^{\prime}$-dideoxyinosine (U.S. Patent No. 5,026,687 to Yarchoan et al.), and benzimidazoles (U.S. Patent ${ }_{\text {i }}$ No. 5, 891,874 to Colacino et al.).


IPO DELHI 23-05-2015.15:448

## V. Pharmaceutical Compositions

Hosts, including humans, infected with HCV, or a gene fragment thereof, can be treated by adininistering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. :The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

A preferred dose of the compound for HCV will be in the range from about 1 to 50 $\mathrm{mg} / \mathrm{kg}$, preferably 1 to $20 \mathrm{mg} / \mathrm{kg}$, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent nucleoside to be delivered. If the salt or prodrug exhibits activity in itself, the 'effective dosage, can be estimated as above using the weight of the salt or prodrug, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg , preferably 70 to 1400 mg of active ingredient per unit dosage form. A oral dosage of $50-1000 \mathrm{mg}$ is usually convenient.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.2 to $70 \mu \mathrm{M}$, preferably aboüt 1.0 to $10 \mu \mathrm{M}$. This nay be achieved, for example, by the intravenous injection of a 0.1 to $5 \%$ solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. . It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only: and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipient and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium slearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. •

If administered intravenously, preferred carriers are physiological saline_or phosphate buffered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulate delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen; polyorthoesters and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation.

Liposomal suspensions (including liposomes 'targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carrier. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipids) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

## VI. Processes for the Preparation of Active Compounds

The nucleosides of the present invention can be synthesized by any means known in the art. In particular, the synthesis of the present nucleosides can be achieved by either alkylating the appropriately modified sugar, followed by glycosylation or glycosylation followed by alkylation of the nucleoside. The following non-limiting embodiments illustrate some general methodology to obtain the nucleosides of the present invention.

## A. General Synthesis of 1'-C-Branched Nucleosides

1'- C-Branched ribonucleosides of the following structure:

61
wherein BASE is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}{ }^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynÿl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), - O (lower alkyl), - O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2} ;$
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a pi bond;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including mcthanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ or $\mathrm{R}^{2}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is an alkyl, chloro-, bromo-, fluoro-, or iodo-alkyl (ie. $\mathrm{CF}_{3}$ ), alkenyl, or alkynyl (ie. allyl); and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$
can be prepared by one of the following general methods.

## 1) Modification from the lactone

The key starting material for this process is an appropriately substituted lactone. The lactone can be purchased or can be prepared by any known means including standard epimerization, substitution and cyclization techniques. The lactone can be optionally

WO 01/00121
PCT/US01/16671
protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991. The protected lactone can then be coupled with a suitable coupling agent, such as an organometallic carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or $R^{6}$ $\mathrm{SiMe}_{3}$ in TBAF with the appropriate non-protic solvent at a suitable temperature, to give the 1'-allkylated sugar.

The optionally activated sugar can then be coupled to the BASE by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nuoleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a' silylated base with a lewis acid, such as tin tetrachloride, titanium tetrachloride or trimethylsilyltriflate in the appropriate solvent at a suitable temperature.

Subsequéntly, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by, Grecne et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the 1 '-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 1. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective 0 Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'OH can be reduced with a suitable reducing agent. 'Optionally, the 2 '-hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction.

## Scheme 1



## 2. Alternative method for the preparation of 1'- C-branched nucleosides

I

The key starting material for this process is an appropriately substituted hexose. The hexose can be purchased or can be prepared by any known means including standard epimerization, such as alkaline treatment; substitution and coupling techniques. The hexose can be selectively protected to give the appropriate hexa-furanose, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum. Press, 1994.

The 1'-hydroxyl can be optionally activated to a suitable leaving group such as an acyl group or a chloro, bromo, fluors, ido via acylation or halogenation, respectively. The optionally activated sugar can then be coupled to the BASE by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a lewis acid, such as tin tetrachloride, titanium tetrachloride or trimethylsilyltriflate in the appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base with the presence of trimethylsilyltriflate.

The 1'- $\mathrm{CH}_{2}-\mathrm{OH}$, if protected, can be selectively deprotected by methods well known in the art. The resultant primary hydroxyl can be functionalized to yield various C-branched nucleosides. For example, the primary hydroxyl can be reduced to give the methyl, using a suitable reducing agent. Alternatively, the hydroxyl can be activated prior to reduction to facilitate the reaction; i.e. via the Barton reduction. In an alternate embodiment, the primary hydroxyl can be oxidized to the aldehyde, then coupled with a carbon nucleophile, such as a Grignard reagent, an organolithium, Tithium dialliylcopper or $\mathrm{R}^{6}-\mathrm{SiMe}_{3}$ in '1'BAF with the appropriate non-protic solvent at a suitable temperature.

In a particular embodiment, the l'-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 2. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'OH can be reduced with a suitable reducing agent. Optionally, the $2^{\prime}$-hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction.

## Scheme 2



In addition, the L-enantiomers corresponding to the compounds of the invention can be prepared following the same gencral methods ( 1 or 2 ), beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.
B. General Synthesis of 2'-C-Branched Nucleosides

2'-C-Branched ribonucleosides of the following structure:

wherein BASE is a purine or pyrimidine base as defined herein;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $R^{7}$ and $R^{9}$, or $R^{7}$ and $R^{10}$ can come together to form a pi bond;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl; wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other phamaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ or $\mathrm{R}^{2}$ is independently FI or phosphate;
$\mathrm{R}^{6}$ is an alkyl, chloro-, bromo-, fluoro-, iodo-alkyl (i.e. $\mathrm{CF}_{3}$ ), alkenyl, or alkynyl (i.e. allyl); and

## X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$

can bo prepared by one of the following general methods.

## 1. Glycosylation of the nucleobase with an appropriately modified sugar

The key starting material for this process is an appropriately substituted sugar with a $2^{\prime}-\mathrm{OH}$ and $2^{\prime}-\mathrm{H}$, with the appropriate leaving group (LG), for example an acyl group or a
chloro, bromo, fluor or jodo. The sugar can be purchased or can be prepared by any known means including standard epimerization, substitution, oxidation and reduction techniques. The substituted sugar can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the $2^{\prime}$-modified sugar. Possible oxidizing agents arc Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine $\mathrm{Cr}(\sqrt[V]{ })$ oxide, Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, $\mathrm{MnO}_{2}$, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, $\mathrm{Cl}_{2}-$ pyridine, $\mathrm{H}_{2} \mathrm{O}_{2}$-ammonium molybdate, $\mathrm{NaBrO}_{2}$ - $\mathrm{CAN}, \mathrm{NaOCl}$ in HOAc , copper chromite, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum $t$-butoxide with another ketone) and $N$-bromosuccinimide.

Then coupling of an organometallic carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or $\mathrm{R}^{6}-\mathrm{SiMe}_{3}$ in TBAF with the ketone with the appropriate non-protic solvent at a suitable temperature, yields the 2 '-alkylated sugar. The alkylated sugar can be optionally protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The optionally protected sugar can then be coupled to the BASE by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a lewis acid, such as tin tetrachloride, titanium tetrachloride or trimethylsilyltriflate in the appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base with the presence of trimethylsilyltriflate.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the $2^{\prime}$-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 3. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-

WO 01/90121
PCT/US01/16671
OH can be reduced with a suitable reducing agent. Optionally, the $2^{\prime}$-hydroxyl can be activated to facilitate reduction; ie. via the Barton reduction.

## Scheme 3




## 2. Modification of a pre-formed nucleoside

The key starting material for this process is an appropriately substituted nucleoside with a $2^{\prime}-\mathrm{OH}$ and $2^{\prime}-\mathrm{H}$. The nucleoside can be purchased or can be prepared by any known means including standard coupling techniques. The nucleoside can be optionally protected with suitable protecting groups, preferably with acyl or silyl groups, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The appropriately protected nucleoside can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the $2^{\prime}$-modified sugar. Possible oxidizing agents. are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's' reagent (dipyridine $\mathrm{Cr}(\mathrm{Vl})$ oxide, . Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, $\mathrm{MnO}_{2}$,
ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, $\mathrm{Cl}_{2}$-pyridine, $\mathrm{H}_{2} \mathrm{O}_{2}$-ammonium molybdate, $\mathrm{NaBrO}-\mathrm{CAN}, \mathrm{NaOCl}$ in HOAc, copper chromite, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum $t$-butoxide with another ketone) and N - bromosuccinimide.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by GreeneGreene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the $2^{\prime}$-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 4. Alternatively, deoxyribo-nucleoside is desired. To obtain these nuclcosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then-the-2?OH can be reducied with a suitable reducing agent. Optionally, the $2^{\prime}$-hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction.

## Scheme 4



In another embodiment of the invention, the L-enantiomers are desired. Therefore, the L-enantiomers can be corresponding to the compounds of the invention can be prepared following the same foregoing general methods, beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

## C. General Synthesis of $3^{\prime}$ : C -Branched Nucleosides

3'-C-Brancked ribonucleosides of the following structure:
wherein BASE is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $O \mathrm{R}^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower
acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, -NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\stackrel{R}{8}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or;iodine;
alternatively, $R^{7}$ and $R^{9}$, or $R^{8}$ and $R^{9}$ can come together to form a pi bond;
$R^{1}$ and $R^{2}$ are indcpendently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ or $R^{2}$ is independently $H$ or phosphate;
$\mathrm{R}^{6}$ is an alkyl, chloro-, fluoro-, bromo-, iodo-alkyl (i.e. $\mathrm{CF}_{3}$ ), alkenyl, or alkynyl (i.e. allyl); and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$
can be prepared by one of the following general methods.

## 1. Glycosylation of the nucleobase with an appropriately modified sugar

The key starting material for this process is an appropriately substituted sugar with a $3^{\prime}-\mathrm{OH}$ and $3^{\prime}-\mathrm{H}$, with the appropriate leaving group (LG), for example an acyl group or a chloro, bromo, fluoro, iodo. The sugar can be purchased or can be prepared by any known means including standard epimerization, substitution, oxidation and reduction techniques. The substituted sugar can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 3 '-modified sugar.' Possible oxidizing agents are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine $\mathrm{Cr}(\mathrm{V} \cdot \mathrm{I})$ oxide; Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, $\mathrm{MnO}_{2}$, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, $\mathrm{Cl}_{2^{-}}$ reagent (aluminum $t$-butoxide with another ketone) and $N$-bromosuccinimide.

Then coupling of an organometallic carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or $\mathrm{R}^{6}-\mathrm{SiMe}_{3}$ in TBAF with the ketone with the appropriate non-protic solvent at a suitable temperature, yields the 3'-C-branched sugar. The 3'-C-branched sugar can be optionally protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The optionally protected sugar can then be coupled to the BASE by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a lewis acid, such as tin tetrachloride, titanium tetrachloride on trimethylsityltriflate in the appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base with the presence of trimethylsilyltriflate.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the $3^{\prime}$-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 5. Alternatively, deoxyribonucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the $2^{\prime}-\mathrm{OH}$ can be reduced with a suitable reducing agent. Optionally, the 2'-hydroxyl can be activated to facilitate reduction; ie. via the Barton reduction.

## Scheme 5



## 2. Modification of a pre-formed nucleoside

The key starting material for this process is an appropriately substituted nucleoside with a $3^{\prime}-\mathrm{OH}$ and $3^{\prime}-\mathrm{H}$. 'The nucleoside can be purchased or can be prepared by any known means including standard coupling techniques. The nucleoside can be optionally protected with suitable protecting groups, preferably with acyl or silyl groups, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John: Wiley: and Sons, Second Edition, 1991.

The appropriately protected nucleoside can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 2 '-modified sugar. Possible oxidizing agents are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine Cr(VI) oxide, Corey's reagent (pyridinium chlorochromate), pyridinium :dichromate, acid dichromate, 'potassium permanganate, $\mathrm{MnO}_{2}$, ruthenium tetroxide, phase transfer catalysts such

WO 01/ע0121
as chromic acid or permanganate supported on a polymer, $\mathrm{Cl}_{2}$-pyridine, $\mathrm{H}_{2} \mathrm{O}_{2^{-}}$ ammonium molybdate, $\mathrm{NaBrO}_{2}-\dot{\mathrm{CAN}}, \mathrm{NaOCl}$ in HOAc , copper chromite, copper oxide, Raney nićkel, pàlladium acetate, Meerwin-Pondorf-Verley reagent (aluminum $t$-butoxide with another ketone) and $N$-bromosuccinimide.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by GreeneGreene et al. Protective Croups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular 'embodiment, the $3^{\prime}$-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 6. Alternatively, deoxyribunucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991 , and then the $2^{\prime}-\mathrm{OH}$ can be reduced with a suitable reducing agent. Optionally, the 2'-hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction.

Scheme 6


In another embodiment of the invention, the L-enantiomers are desired. Therefore, the L-enantiomers can be corresponding to the compounds of the invention can be prepared following the same foregoing general methods, beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

## Examples

Example 1: Preparation of 1'-C-methylriboadenine via 6-amino-9-(1-deoxy- $\beta$-Dpsicofuranosyl)purine

As another plternative method of preparation, the title compound could also be prepared according to a published procedure (J. Farkas, and F. Sorm, "Nucleic acid components and their analogues. XCIV. Synthesis of 6 -amino-9-(1-deoxy- $\beta$-Dpsicofuranosyl)purine", Collect. Czech. Chem. Commun. 1967, 32, 2663-2667. J. Farkas", Collect. Czech. Chem. Commun. 1966, 31, 1535) (Scheme 7).

Scheme 7


In a similar manner, but using the appropriate sugar and pyrimidine or purine bases, the following nucleosides of Formula I are prepared.

(I)
wherein:


| WO 01/90121 |  |  | /us |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{R}^{\text {P }}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| monophosphate | H | H | H | H | NH-methyl |
| monophosphate | H | H | H. | H | NH -ethyl |
| monophosphate | ${ }^{-}$ | H | H | H | OH |
| monophosphate | H | H | H | HI | O-acetyl |
| monophosphate | H | H | H | H | OMe |
| monophosphato | II | H | H | H. | OEt |
| monophosphate | H | H | H | H | O-cyclopropyl |
| monophosphate | H | H | H | H | SH |
| monophosphate | H | H | H | H. | SMe |
| monophosphate | H | H | H | H | SEt |
| monophosphate | H | H | H | H | S-cyclopropyl |
| monophosphate | H | H | H | H | F |
| monophosphate | H, | H | H | H | Cl |
| monophosphate | H | H | H | H | Br |
| monophosphate | H. | H | $\mathrm{H}^{\text {: }}$ | H | I |
| diphosphate. | H | H | H | H | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | H | NH-acetyl |
| diphosphate. | H | H | H | H | NH-cyclopropyl |
| diphosphate | H | H | H | Hi | NH-methyl |
| diphosphate | H | H | H | H | NH-ethyl |
| diphosphate | H | H | H | H | OH |
| diphosphate | H | H | H | H | O-acetyl |
| diphosphate- - | H | H | H | H | OMe |
| diphosphate | H | H | H | H | OEt |
| diphosphate | H | H- | H | H | O-cyclopropyl |
| diphosphate | H | H | H | H | SH |
| diphosphate | H | H | H | H | SMe |
| diphosphate | H | H | H | H | SEt |
| diphosphate | H | H | H | H | S-cyclopropyl |
| diphosphate | H | H | H | H | F |
| diphosphate | H | H | H | H | Cl |



| W0 01/90121 |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$. | $\mathbf{X}^{2}$ | $\mathbf{Y}$. |
| triphosphate | triphosphate | triphosphate | H | H | NH-cyclopropyl |
| triphosphate | triphosphate | triphosphate | H | H | OH |
| triphosphate | triphosphate | triphosphate | H | H | F |
| triphosphate | triphosphate | triphosphate | H | H | Cl |
| H | H | H | F | H | $\mathrm{NH}_{2}$ |
| H | H: | H | F | H | NH-cyclopropyl |
| H | H | H | F | H | OH |
| H | H | H | F | H | F |
| H | H | H | F | H | Cl |
| H | H | H | Cl | H | $\mathrm{NH}_{2}$ |
| H | H | H | - Cl | H | NH-cyclopropyl |
| H | H | H | Cl | H | OH |
| H | H | H | Cl | H. | F |
| H | H | H | Cl | H | Cl |
| H | H | H | $\stackrel{\mathrm{Br}}{ }$ | H | $\mathrm{NH}_{2}$ |
| H | H | H | Br | H | NH-cyclopropyl |
| H | H | H | Br | H | OH |
| H | H | H | Br | H | F |
| H | H | H | Br | H | Cl |
| H | H | H | $\mathrm{NH}_{2}$ | H | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{NH}_{2}$ | H | NH-cyclopropyl |
| H | H | H | $\mathrm{NH}_{2}$ | H | OH |
| H | H | H | $\mathrm{NH}_{2}$ | H | F |
| H | H | H | $\mathrm{NH}_{2}$ | H | Cl |
| H | H | H | SH | H | $\mathrm{NH}_{2}$ |
| H | H | $\mathrm{H}_{3}$ | SH | H | NH-cyclopropyl |
| H | H | H | SH | H | OH |
| H | H | H | 'SH | H | F |
| H | H | H | SH | H | Cl |
| acetyl | H | H | H, | H | $\mathrm{NH}_{2}$ |
| acetyl | H | H | H | H | NH-cyclopropyl |


| WO 01/90121 |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\overline{\mathbf{R}^{2}}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y . |
| acetyl | H | H | H | H | OH |
| acetyl | H | H | H | H | F |
| acetyl | H | H | H | H | Cl |
| acctyl | H | H | - | H | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | H | NH-cyclopropyl |
| acotyl | H | II | F | H | OH |
| acetyl | H | H | F | H. | F |
| acetyl | H | H | F | H | Cl |
| H | acetyl | acetyl | H | H. | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | H | NH-cyclopropyl |
| H | acetyl | acetyl | H | H | OH |
| H | acetyl | acetyl | H | H | F |
| H | acctyl | acetyl | H: | H | Cl |
| acetyl | acetyl | acctyl | H | H | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | H. | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | H | OH |
| acetyl | acetyl | acetyl | H | H | F |
| acetyl | acetyl | acetyl | H | H | Cl |
| monophosphate | acetyl | acetyl | H | H | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | H. | H | NH-cyclopropyl |
| monophosphate | acetyl | acetyl | H | H | OH |
| monophosphate | acetyl | acetyl | H | H | F |
| monophosphate | acetyl | acetyl | H | H | Cl |
| diphosphate | acetyl | acetyl | H | H. | $\mathrm{NH}_{2}$ |
| diphosphate | acetyl | acetyl | H | H | NH-cyclopropyl |
| diphosphate | acctyl | acetyl | H | H | OH |
| diphosphate | acetyl | acetyl | H | H | F |
| diphosphate | acctyl | acetyl | H | H | Cl |
| triphosphate | acetyl | acetyl | H | H | $\mathrm{NH}_{2}$ |
| triphosphate | acctyl | acetyl | H | H | NH-cyclopropyl |
| triphosphate | acetyl | acetyl | H | H | OH |



| WO 01/90121 |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1 \times}$ | $\mathrm{X}^{2}$ | Y |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SH |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SMe |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | F |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | I |
| diphosphate | H | H | II | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-methyl |
| diphosphate | ${ }^{+}$ | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-acetyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | OMe |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | OEt |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-cyclopropyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SH |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SMe |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |
| diphosphate - | H | H | H | $\mathrm{NH}_{2}$ | F |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | I .: |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-methyl. |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |

WO 01/90121 $\because \cdot$ PCT/US01/16671




167
WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$. | . $\mathbf{x}^{6}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | Cl | NH-ethyl |
| H | H | HI | H | Cl | NH-acetyl |
| H | H | H | H | Cl | OH |
| H | H | H | H | Cl | OMe |
| H | H | H | H | Cl | OEt |
| H | H | H | H | Cl | O-cyclopropyl |
| H | H | H | H | Cl | O-acetyl |
| H | H | H | H | Cl | SH |
| H | H | H | H | Cl - | SMe |
| H | H | H | H | Cl | SEt |
| H | H | H | H | Cl | S-cyclopropyl |
| monophosphate | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| monophosphate | H | H | H | Cl | NH-acetyl |
| monophosphate | H | H | H | Cl | NH-cyclopropyl |
| monophosphate, | H | H | H | Cl | NH-methyl |
| monophosphate | H | H | H | Cl | NHF-ethyl |
| monophosphate | H | H | H | Cl | OH |
| monophosphate | $\mathrm{H}^{\prime}$ | H | H | Cl | O-acetyl |
| monophosphate | H | H | $\mathrm{H}_{1}$ | Cl | OMe |
| monophosphate | H | H | H | Cl | OEt |
| monophosphate | H | H | H | Cl | O-cyclopropyl |
| monophosphate | H | H | H | Cl | SH |
| monophosphăte. | H | H | H | Cl | SMe |
| monophosphate ${ }^{\text {' }}$ | H | H | H | Cl | SEt |
| monophosphate | H | H | H | Cl | S-cyclopropyl |
| diphosphate | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | Cl | NH-acetyl |
| diphosphate | H | H | H | Cl | NH-cyclopropyl |
| diphosphate | H | H | H | Cl | NH-methyl |
| diphosphate | H | H | H | Cl | NH-ethyl |
| diphosphate | H | H | H | Cl | OH |



WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | F | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | F | Cl | NH-cyclopropyl |
| H | H | H | F | Cl | OH |
| H | H | H | Cl | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | Cl | Cl | NH-cyclopropyl |
| H | H | H | Cl | Cl | OH |
| H | H | H | Br | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | Br | Cl | NH-cyclopropyl |
| H | H | H | Br | Cl | OII |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | NH-cyclopropyl |
| H | H | H. | $\mathrm{NH}_{2}$ | Cl | OH |
| H | H | H | SH | Cl | $\mathrm{NH}_{2}$. |
| H | H | H | SH | Cl | NH-cyclopropyl |
| H | H | H | SH | Cl | OH |
| acetyl | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| acetyl | H | H | H. | Cl | NH-cyclopropyl |
| acetyl | H. | H | H | Cl | OH |
| acetyl | H | H | F | Cl | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | Cl | NH-cyclopropyl |
| acetyl | H | H | F | Cl | OH |
| H | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | Cl | NH-cyclopropyl |
| H | acetyl | acetyl | H | Cl | OH |
| acetyl | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| acctyl | acetyl | acetyl | H | Cl | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | Cl | OH |
| monophosphate | acetỳl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | $\cdot \mathrm{H}$ | Cl | NH-cyclopropyl |
| monophosphate | acetyl | acetyl | H | Cl | OH |
| diphosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |


| WO 01/90121 |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| diphosphate | acetyl | acetyl | H | Cl | NH-cyclopropyl |
| diphosphate | acetyl | acetyl | H | Cl | OH |
| triphosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| triphosphate | acetyl | acetyl | H. | Cl | NH-cyclopropyl |
| triphosphate | acetyl | acctyl | ${ }^{\mathrm{H}}$. | Cl | OH |
| H | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | H | Cl | NH-cyclopropyl |
| H | H | H | H | Cl | OH |
| Iİ | H | H | H | Br | $\mathrm{NH}_{2}$ |
| H | H | H | H | Br | NH-cyclopropyl |
| H | H | H | H | Br | OH |

Alternatively, the following nucleosides of Formula IV are prepared, using the appropriate sugar and pyrimidine or purine bases.

(IV)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | H |
| H | H | H | H | $\mathrm{NH}_{2}$ |
| H | H | H | H | NH-cyclopropyl |
| H | H | H | H | NH-methyl |
| H | H | H | H | NH-ethyl |
| H | H | H | H | NH-acetyl |

WO 01/90121
PCT/US01/16671

| $\mathrm{R}^{\mathbf{1}}$. | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | OH |
| H | H | H | H | OMe |
| H | H | H | H | OEt |
| H | H | H | H | O-cyclopropyl - |
| H | H | H | H | O-acetyl |
| H | H | H | H | SH |
| H | H | H | H | SMe |
| H | H. | H | H | SEt |
| H | H | H | H | S-cyclopropyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ |
| monophosphate | H | H | H | NH-acetyl |
| monophosphate | H | H | H | NH-cyclopropyl |
| monophosphate | H | H | H | NH-methyl |
| monophosphate | H | H | H | NH-ethyl |
| monophosphate | H | H | H | OH |
| monophosphate | H | H | H | O-acetyl |
| inonophosphate | H | H | H | OMe |
| monophosphate | H | H | H | OEt |
| monophosphate | H | H | H | O-cyclopropyl |
| monophosphate | H | H | H | SH |
| monophosphate | H | H | H | SMe |
| monophosphate | H | H | H | SEt |
| monophosphate | H | H | H | S-cyclopropyl |
| diphosphate | H ! | H | H | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | NH-acetyl |
| diphosphate | H | H | H . | NH-cyclopropyl- |
| diphosphate | H | H | H | NH-methyl |
| diphosphate | H | H | H | NH-ethyl |
| diphosphate | H | H | H | OH |
| diphosphate. | H | H | H | O-acetyl |
| diphosphate 1 | H | H | H | OMe |




WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | $\mathbf{Y}$ |
| :--- | :--- | :--- | :--- | :--- |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| triphosphate | acetyl | acetyl | H | NH -cyclopropyl |
| triphosphate | acetyl | acetyl | H | OH |

Alternatively, the following nucleosides of Formula VII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(VII)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ : | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H . | H | $\mathrm{CH}_{3}$ | 0 | $2,4-0-$ <br> Diacetyluracil |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| H | H | $\mathrm{H}^{+}$ | $\mathrm{CH}_{3}$ | 0 | $2,4-0-$ <br> Diacetylthymine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetỳl)cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil... |
| H | H | H | $\mathrm{CH}_{3}$ | S | $2,4-0-$ <br> Diacetyluraci |
| H | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |

WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2,4-0- <br> Diacetylthymine |
| H | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| H | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 4-(N-mono- acetyl)cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | S | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | S | Uracil |
| H | H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O- <br> Diacetyluracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $2,4-\mathrm{O}$ <br> Diacetylthym |
| moriophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| -monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,Ndiacetyl)cytosine |
| monophosphate | II | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | $2,4-0-$ <br> Diacetyluracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-0- <br> Diacetylthym |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | H - | H | $\mathrm{CH}_{3}$ | S | 4-(N-monoacetyl)cytosine |


| WO) 01/90121 |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{R}^{1}$. | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | $4-\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $2,4-0-$ <br> Diacetyluracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-0- <br> Diacetylthymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono- <br> acetyl)cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N- <br> diacetyl)cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-0- <br> Diacetyluracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O- <br> Diacetylthym |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $2,4-0-$ <br> Diacetyluracil |
| triphosphate , | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 2,4-O- <br> Diacetylthymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| triphosphate | H. | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |

WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Basc |
| :--- | :--- | :--- | :--- | :--- | :--- |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono- <br> acetyl)cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 4 -(N,N- <br> diacetyl)cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | Uracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| triphosphate | H | $\cdot$ | H | $\mathrm{CH}_{3}$ | S |


| WO 01/90121 |  |  |  |  | PCT/US01/16671 |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\begin{aligned} & \text { 4-(N-mono- } \\ & \text { acetyl)cytosine } \end{aligned}$ |
| monophosphate | monophosphate. | monophosphate | $\mathrm{CF}_{3}$ | S | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| munuphosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | $4-\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| acctyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | S | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| acctyl | acetyl | acetyl | 2-bromovinyl | 0 | $\begin{aligned} & \text { 4-(N,N- } \\ & \text { diacetyl)cytosine } \end{aligned}$ |
| acetyl | acetyl | acetyl | 2-bromovinyl | S | 4-(N,Ndiacetyl)cytosine |
| H | H | ${ }^{\prime \prime}$ | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2-(N,N-diacetyl)- } \\ & \text { guanine } \end{aligned}$ |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acctyl <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroguanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 6-(N,N-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoroadenine |
| H | II | H | $\mathrm{CH}_{3}$ | 0 | adenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)- <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 6-0-acetyl <br> guanine |

WO 01/9()121
PCT/US01/16671


WO 01/90121
PCT/US01/16671

| R ${ }^{1}$. | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | H | $\overline{\mathrm{CH}_{3}}$ | S | 2,8-difluoro- <br> adenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)- <br> guanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acelyl <br> guanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | $\begin{aligned} & \text { 6-(N,N-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoroadenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | adenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)- <br> guanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl <br> guanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S. | 8 -fluoroguanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | guanine |
| diphosphate | H | H | $\overline{\mathrm{CH}_{3}}$ | S | 6-(N,N-diacetyl)- <br> adenine |
| diphosphate , | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8 -fluoroadenine |
| diphosphate | $\mathrm{H} \quad \ddots$ | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoroadenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)- <br> guanine |




Alternatively, the following nucleosides of Formula VIII are prepared, using the appropriate sugar and pyrimidine or purine bases.


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: |
| H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| H. | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| H | H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| H | H | $\mathrm{CH}_{3}$ | S : | 4-(N,N-diacetyl)cytosine |
| H | H | $\mathrm{CH}_{3}$ | S | Uracil |
| H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0. | 2,4-O-Diacetylthymine |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | Cytosine ... |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 : | 4-(N-mono-acetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |



WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N-monu-acetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Uracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Hypoxanthine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Thymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 . | Cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 5-Fluorouracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S. | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |


| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| acetyl | acety] | 2-bromovinyl | 0 | 4-(N,N-diacetyl)cytosi |  |
| acetyl | acetyl | 2-bromovinyl | S | 4-(N,N-diacetyl)cytosis |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)-guani |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl guanine |  |
| II | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |  |
| H | H | $\mathrm{CH}_{3}$ | $0^{\circ}$ | yuanine |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | 6-( $\mathrm{N}, \mathrm{N}$-diacetyl)-adeni |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroadenine |  |
| H | H | $\mathrm{CH}_{3}$ | 0 : | 2,8-difluoro-adenine |  |
| ${ }^{\text {H }}$ | H | $\mathrm{CH}_{3}$ | O | adenine |  |
| H | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)-guan |  |
| H | H | $\mathrm{CH}_{3}$. | S | 6-O-acetyl guanine |  |
| H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroguanine |  |
| H | H | $\mathrm{CH}_{3}$ | S. | guanine |  |
| H | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)-adeni |  |
| H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |  |
| H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |  |
| H | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro-adenine |  |
| H | H | $\mathrm{CH}_{3}$ | S | adenine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)-guani |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl guanine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 : | guanine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 6-(N,N-diacetyl)-adeni | ne |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoro-adenine - |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | 0 | adenine |  |


| WO 01/90121 |  |  |  | PCT/US0 | 6671 |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{\text {T }}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | X | Base |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)-guan |  |
| monophosphate | H | $\mathrm{CH}_{3}$. | S | 6-O-acetyl guanine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 8-fluoroguanine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | guanine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)-aden | ne |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |  |
| monophosphate. | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro-adenine |  |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | adenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)-guan | ne |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl guanine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroguanine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | guanine |  |
| diphosphate | H. | $\mathrm{CH}_{3}$ | 0 | 6-(N,N-diacetyl)-ader | ne |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoro-adenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | 0 | adenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)-guan |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl guanine |  |
| diphosphate -.. | H | $\mathrm{CH}_{3}$. | S | 8 -fluoroguanine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | guanine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)-aden |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro-adenine |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | adenine |  |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)-guan |  |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl guanine |  |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroguanine |  |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | guanine |  |

WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | R ${ }^{2}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | 6-(N,N-diacetyl)-adeni |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0. | 8-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoro-adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | 0 | adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2-(N;N-diacetyl)-guani |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl guanine |
| triphosphate | H | $\mathrm{CrH}_{3}$ | S. | 8-fluoroguanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | -guanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)-adeni |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro-adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2-(N,N-diacetyl)-guani |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 6-O-acetyl guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8-fluoroguanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 6-(N,N-diacetyl)-adeni |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,8-difluoro-adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-(N,N-diacetyl)-guanin |
| monophosphate | monophosphate: | $\mathrm{CF}_{3}$ | S | 6-O-acetyl guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S ! | 8-fluoroguanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 6-(N,N-diacetyl)-adenin |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,8-difluoro-adenine |

WO 01M0121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{\mathbf{2}}$ | $\mathrm{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | adenine |  |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | guanine |  |
| acetyl | acetyl | - $\mathrm{CF}_{3}$ | S | guanine |  |
| acetyl | acety! | 2-bromovinyl | O | guanine |  |
| acetyl | acetyl | $\begin{aligned} & \text { 2-bromo- } \\ & \text { vinyl } \end{aligned}$ | S | guanine | . |

Alternatively, the following nucleosides of Formula IX are prepared, using the appropriate sugar and pyrimidine or purine bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| H | $\mathrm{CH}_{3}$ | 0. | Cytosine |
| H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | O | Uracil |
| H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil. |
| H | $\mathrm{CH}_{3}$ | S | Hypoxanthine. |
| H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |

WO 01/90121

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | S | Thymine |
| H | $\mathrm{CH}_{3}$ | S | Cytosine |
| H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | S | Uracil |
| H | S | 5-Fluorouracil |  |
| monophosphate | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CH}_{3}$ | O | Hypoxanthinc |
| monophosphate | $\mathrm{CH}_{3}$ | O | 2,4-O-Diăcetylthymine |
| monophosphate | $\mathrm{CH}_{3}$ | O | Thymine |
| monophosphate | $\mathrm{CH}_{3}$ | O | Cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | O | Uracil $\cdot$ |
| monophosphate | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CH}_{3}$ | S | Thymine |
| monophosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytos |
| monophosphate | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| diphosphate | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| diphosphate | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| diphosphate | $\mathrm{CH}_{3}$ | O | Thymine |
| diphosphate | $\mathrm{CH}_{3}$ | O | Cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |  |



WO 01~0121

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophnsphate | $\mathrm{CF}_{3} \quad \therefore$ | S. | 4-(N-miono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3} \quad$. | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3} \quad$. | S | Uracil. |
| monophosphate | $\mathrm{CF}_{3}$ | $\mathrm{CF}_{3}$ | S |
| acetyl | O | 5-Fluorouracil |  |
| acetyl | $\mathrm{CF}_{3}$ | 4-(N,N-diacetyl)cytosine |  |
| acetyl | 2-bromo-vinyl | S | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | S | 4-(N,N-diacetyl)cytosine |

Alternatively, the following nucleosides of Formula XVI are prepared, using the appropriate sugar and pyrimidine or purine bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{R}^{\mathbf{8}}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{\mathbf{1 0}}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | H | H | O | 2,4-O-Diacetyluracil | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | O | Hypoxanthine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | O | 2,4-O-Diacetylthymine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | O | Thymine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | O | Cytosine | OH | Me |
| H |  | $\mathrm{CH}_{3}$ | H | H | O | 4-(N-mono-acetyl)cytosine | OH |
| H | Cl | Me |  |  |  |  |  |

WO 01/90121
PCT/US01/16671


WO 01/90121
PCT/US01/16671


WO 01/90121 $\dot{C}$ PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{R}^{8}$ | $\mathbf{X}$ | Base $\quad \mathbf{R}^{10}$ | $\mathbf{R}^{9}$ |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 4-(N-mono-acetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 4-(N,N-diacetyl)cytosine | $\mathrm{OH}_{1}$ | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | Uracil | $\mathrm{OH}^{\prime}$ | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 5-Fluorouracil | $\mathrm{OH}_{4}$ | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 2,4-O-Diacetyluracil | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Hypoxanthine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 2,4-O-Diacetylthymine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Thymine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 4-(N-mono-acetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 4-(N,N-diacetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Uracil | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 5-Fluorouracil | OH | Me |
| acetyl | $\mathrm{CH}_{3}$ | H | H | O | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | H | H | S | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | H | O | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | H | S | 4-(N,N-diacetyl)cytosine | H | Br |

Example 2: Preparation of 2'-C-methylriboadenine
The title compound was prepared according to a published procedure (R.E. HarryO'kuru, J.M. . Smith, and M.S. Wolfe, "A short, flexible route toward 2'-C-branched ribonucleosides", J.Org. Chem. 1997, 62, 1754-1759) (Scheme 8).

## Scheme 8



WO 01/90121
PCT/US01/16671
(a) Dess-Martin periodinane; (b) $\mathrm{MeMgBr} / \mathrm{TiCl}_{4}$; (c) $\mathrm{BzCl}, \mathrm{DMAP}^{2} \mathrm{Et}_{3} \mathrm{~N}$; (d) bis(trimethylsilyl)acetamide, $\mathrm{N}^{6}$-benzoyl adenine, TMSOTf; (e) $\mathrm{NH}_{3} / \mathrm{MeOH}$

In a similar manner, but using the appropriate sugar and pyrimidine or purine bases, the following nucleosides of Formula $\Pi$ are prepared.

(II)
wherein:


| WO 01/90121 |  |  |  | PCT/US01/16671 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| H | H | H | H | H | Br |  |
| H | H | H | H | H | I |  |
| monophosphate | H | H | H | H | $\mathrm{NH}_{2}$ |  |
| monophosphate | H | H | H | H | NH-ac | Ctyl |
| monophosphate । | H | H | H | II. | NH-cy | yclopropyl |
| monophosphate | H | H | H | H | NH-m | 'ethyl |
| monophosphate | H | H | H | H | NH-et | hyl: |
| monophosphate | H | H | H | H | OH |  |
| monophosphate | H | H | H | H | O-ace |  |
| monophosphate | H | H | H | H | OMe |  |
| monophosphate | H | H | H | H | OEt |  |
| monophosphate | H | H | H | H | O-cyc | lopropyl |
| monophosphate | H | H | H. | H | SH |  |
| monophosphate | H | H | H | H | SMe |  |
| monophosphate | II | H | H | H | SEt |  |
| nionophosphate | 11 | H | H | H | S-cycl | lopropyl |
| monophosphate | H | H | H | H | F |  |
| monophosphate | H | H | H | H | Cl |  |
| monophosphate | H | H | H | H | Br |  |
| monophosphate | H | H | H | H | I |  |
| diphosphate | H | H | H | H | $\mathrm{NH}_{2}$ |  |
| diphosphate | H | H | H | H | $\mathrm{NH}-\mathrm{ac}$ |  |
| diphosphate | H | H | H | H | $\mathrm{NH}-\mathrm{cy}$ | clopropyl |
| diphosphate | H | H | H | H | NH-mi | lethyl |
| diphosphate | H | H | H | H | NH-et | hyl |
| diphosphate | H | H | H | H | OH |  |
| diphosphate | H | H | H | H | O-acet |  |
| diphosphate | H | H | H | H | OMe |  |
| diphosphate | H | H | H | H | OEt |  |
| diphosphate | H | H | H | H | O-cyc | lopropyl |
| diphosphate | H | H | H | H | SH |  |

WO 019012!
PCT/US01/1667.1

| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathbf{X}^{2}$ | Y |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | H | H | H | H | SMe |  |
| diphosphate | II | H | H | H. | SEt |  |
| diphosphate | H | H | H | H | S-cyclopropyl |  |
| diphosphate | H | H | H | H | F |  |
| diphosphate | H | H | H | H | Cl |  |
| diphosphate | H | H | H | H | Br |  |
| diphosphate | H | H | H | H | I |  |
| triphosphate | H | H | H | H | $\mathrm{NH}_{2}$ |  |
| triphosphate | H | H | ${ }_{4}$ | H | NH-acetyl |  |
| triphosphate | H | H | H | H | NH-cyclopropyl |  |
| triphosphate | H | H | H | H | NH-methyl |  |
| triphosphate | H | H | H | H | NH-ethyl |  |
| triphosphate | H | H | H | H | OH |  |
| triphosphate | H | H | H | H | OMe |  |
| triphosphate | H | H | H | H | OEt |  |
| triphosphate | H | H | H | H | O-cyclopropyl |  |
| triphosphate | H | H | H | H | O-acetyl |  |
| triphosphate | H | H | H | H | SH |  |
| triphosphate | H | H | H | H | SMe |  |
| triphosphate | H | H | H | H | SEt |  |
| triphosphate | H | H | H | H | S-cyclopropyl |  |
| triphosphate | H | H | H | H | F |  |
| triphosphate | H | H | H | H | Cl |  |
| triphosphate | H | H. | H. | H | Br |  |
| triphosphate | H | H | H | H | I |  |
| monophosphate | monophosphate | monophosphate | H | H | $\mathrm{NH}_{2}$ |  |
| monophosphate | monophosphate | monophosphate | H | H | NH-cyclopropyl |  |
| monophosphate | monophosphate | monophosphate | H | H | OH |  |
| monophosphate | monophosphate | monophosphate | H | H | F |  |
| monophosphate | monophosphate | monophosphate - | H: | H |  |  |
| diphosphate | diphosphate | diphosphate | H | H | $\mathrm{NH}_{2}$ |  |


| WO 01/90121 : |  |  |  | PCT/US01/16671 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| diphosphate | diphosphate | diphosphate | H | H | NH-cyclopropyl |  |
| diphosphate | diphosphate | diphosphate | H | H | OH |  |
| diphosphate | diphosphate | diphosphate | H | H | F |  |
| diphosphate | diphosphate | diphosphate | H | H | Cl |  |
| triphosphate | triphosphate | triphosphatc | H | H | $\mathrm{NH}_{2}$ |  |
| triphosphate | triphosphate | triphosphate | H | H | NH-cyclopropyl |  |
| triphosphate | triphosphate | triphosphate | H | H | OH |  |
| triphosphate | triphosphate | triphosphate | H | H | F |  |
| triphosphate | triphosphate | triphosphate | H | H | Cl |  |
| H | H | H. | F | H | $\mathrm{NH}_{2}$ |  |
| H | H | H. | F | H | NH-cyclopropyl |  |
| H | H | H | F | H | OH |  |
| H | H | H | F | H | F |  |
| H | H | H | F | H | Cl |  |
| H | H | H | Cl | H | $\mathrm{NH}_{2}$ |  |
| H | H | H | Cl | H | NH-cyclopropyl |  |
| H | H | H | Cl | H | OH |  |
| H | H | H | Cl | H | F |  |
| H | H | H | Cl | H | Cl |  |
| H | H | H | Br | H | $\mathrm{NH}_{2}$ |  |
| H | H | H | Br | H | NH-cyclopropyl |  |
| H | H | H | Br | H | OH |  |
| H | H | H | Br | H | F |  |
| H | H | H | Br | H | Cl |  |
| H | H | H | $\mathrm{NH}_{2}$ | H | $\mathrm{NH}_{2}$ |  |
| H | H | H | $\mathrm{NH}_{2}$ | H | NH-cyclopropyl |  |
| H | H | H | $\mathrm{NH}_{2}$ | H | OH |  |
| H | H | H | $\mathrm{NH}_{2}$ | H |  |  |
| H | H | H | $\mathrm{NH}_{2}$ | H | Cl |  |
| H | H | 'H | SH | H | $\mathrm{NH}_{2}{ }^{-}$ |  |
| H | H. | H | SH | H | NH-cyclopropyl |  |




| W0 01 190121 |  |  | PCT/US01/16671 |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathbf{X}^{2}$ | Y |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | O-ace | tyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OMe |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OEt |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | O-cyc | lopropyl |
| monophosphate | H | H | - H | $\mathrm{NH}_{2}$ | SH |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SMe |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyc | opropyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | F |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Cl |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | I |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{a}$ | etyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-m | Iethyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-et | thyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-ace | tyl |
| diphosphate ... | H | H | H | $\mathrm{NH}_{2}$ | OMe |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$. | OEt |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-cyc | lopropyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SH |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SMe |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyc | lopropyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | F |  |
| diphosphate , | H | H | H | $\mathrm{NH}_{2}$. | Cl |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | I |  |

WO 01/90121
PCT/US01/16671




| WO 01/90121 |  |  |  | PCT/US01/16671 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathbf{X}^{2}$ | Y |  |
| H | H | H | H | Cl | H |  |
| H | H | H | H | Cl | H |  |
| H | H | H | H | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | H | Cl | NH-c | yclopropyl |
| H | H | H | II | Cl . | NH-m | methyl |
| H | H | H | H | Cl | $\mathrm{NH}-\mathrm{e}$ | thyl |
| H. | H | H | H | Cl | $\mathrm{NH}-\mathrm{a}$ | cetyl |
| H | H | H | H | Cl | OH |  |
| H | H | H | H | Cl | OMe |  |
| H | H | H | H | Cl | OEt |  |
| H | H | H | H | Cl | O-cyc | 'lopropyl |
| H | H | H | H | Cl | O -ace |  |
| H | H | H | H | Cl | SH |  |
| H | H | H | H | Cl | SMe |  |
| H | H | H | H | Cl | SEt |  |
| H | H | H | H | Cl | S-cyc | lopropyl |
| monophosphate | H | H. | H | Cl | $\mathrm{NH}_{2}$ |  |
| monophosphate | H | H | $\dot{\mathrm{H}}$ | Cl | $\mathrm{NH}-\mathrm{a}$ | cetyl |
| monophosphate | H | H | H | Cl | NH-c | yclopropyl |
| monophosphate | H | H | H | Cl | NH-m | methyl |
| monophosphate | H | H | H | Cl | NH -et | thyl |
| monophosphate | H | H | H | Cl | OH |  |
| monophosphate | H | H | H | Cl . | O-ace |  |
| monophosphate | H | H | H | Cl | OMe |  |
| monophosphate | H | H | H | Cl | OEt |  |
| monophosphate | H | H | H | Cl | O-cyc | lopropyl |
| monophosphate | H | H | H | Cl | SH |  |
| monophosphate | H | H | H | Cl | SMe |  |
| monophosphate | H | H | H | Cl | SEt |  |
| monophosphate | H | H | H | Cl | S-cye | lopropyl |
| diphosphate | H. | H | H | Cl | $\mathrm{NH}_{2}$ |  |



WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$. | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathbf{X}^{2}$ | Y |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | diphosphate | diphosphate | H | Cl | NH-cyclopropyl |  |
| diphosphate | diphosphate | diphosphate | H | Cl | OH |  |
| triphosphate | triphosphate | triphosphate | H | Cl | $\mathrm{NH}_{2}$ |  |
| triphosphate | triphosphate | triphosphate | H | Cl | NH-cyclopropyl |  |
| triphosphate | triphosphate | triphosphate | H | Cl | OH |  |
| H | H | H | F | Cl | $\mathrm{NH}_{2}$ |  |
| H | II | H | F | Cl | NH-cyclopropyl |  |
| H | H | H | F | Cl | OH |  |
| H | H | H | Cl | $\mathrm{Cl}^{+}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | Cl | Cl | NH-cyclopropyl |  |
| H | H | H | Cl | Cl | OH |  |
| H | H | H | Br | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | Br | Cl | NH-cyclopropyl |  |
| H | H | H | Br | Cl | OH |  |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | NH-cyclopropyl |  |
| H | H | H : | $\mathrm{NH}_{2}$ | Cl | OH | . |
| H | H | H | SH | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | SH | Cl | NH-cyclopropyl |  |
| H | H | H. | SH | Cl | OH |  |
| acetyl | H | H | H | Cl | $\mathrm{NH}_{2}$ |  |
| acetyl | H | H | H | Cl . | NH-cyclopropyl |  |
| acetyl | H | H | H | Cl | OH |  |
| acetyl | H | H | F | Cl | $\mathrm{NH}_{2}$ |  |
| acetyl | H | H | F | Cl | NH-cyclopropyl |  |
| acetyl | H | H | F | Cl | OH |  |
| H | .acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| H | acetyl | acetyl | H | Cl | NH-cyclopropyl |  |
| H | acetyl | acetyl | H | Cl | OH |  |
| acetyl | acetyl | acetyl | H: | Cl | $\mathrm{NH}_{2}{ }^{-}$ |  |
| acetyl | acetyl | acetyl | . H | Cl | NH-cyclopropyl |  |

WO 01/90121
PCT/US01/16671

| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| acetyl | acetyl | acetyl | H | Cl | OH |  |
| monophosphate | acetyl | acetyl | II | Cl | $\mathrm{NH}_{2}$ |  |
| monophosphate | acetyl | acetyl | H | Cl | NH-cy | clopropyl |
| monophosphate | acetyl | acetyl | H | Cl | OH |  |
| diphosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| diphosphate | acetyl | acetyl | H | Cl | NH-cy | clopropyl |
| diphosphatc | acetyl | acetyl | H | Cl | OH |  |
| triphosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| triphosphate | acetyl | acetyl | H | Cl | NH-cyclopropyl |  |
| triphosphate | acetyl | acetyl | H | Cl | OH |  |
| H | H | H | H | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | $\cdot \mathrm{H}$ | Cl | NH-cyclopropyl |  |
| H | H | H | H | Cl | OH |  |
| H | H | H | H | Br | $\mathrm{NH}_{2}$ |  |
| H | H | H | H | Br | NH-cy | clopropyl |
| H | H | H | H | Br | OH |  |

Alternatively, the following nucleosides of Formula $V$ are prepared, using the appropriate sugar and pyrimidine or purine bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{\mathbf{2}}$ | $\mathbf{R}^{1}$ | $\mathbf{Y}$ | . |  |
| :--- | :--- | :--- | :--- | :--- | :--- |
| H | $\mathrm{H}_{\ddots}$ | H | H | H |  |
| H | H | H | H | $\mathrm{NH}_{2}$ |  |

WO 01/90121

| WO 01/90121 . . ${ }^{\text {PCT/US01/16 }}$ |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{\text {I }}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathbf{Y}$ \| |
| H | H | H | H | NH-cyclopropyl |
| H | H | H | H | NH-methyl |
| H | H | H | H | NH -ethyl |
| H | H | H | H | NH-acetyl |
| H | H | H | H | OH |
| H | H | H | 'H | OMe |
| H | H | H | H | OEt |
| H | H | H | H | O-cyclopropyl |
| H | H | H | H | O-acetyl |


| WO 01/90121 |  |  | PCT/US01/160 |  |
| :---: | :---: | :---: | :---: | :---: |
| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | Y |
| diphosphate | H | H | H | NH-ethyl |
| diphosphate | H | H | H | OH |
| diphosphate | H | H | H | O-acetyl |
| diphosphate | H | H | H | OMe |
| diphosphate | H | H | H | OEt |
| diphosphate | H | H | H | O-cyclopropyl |
| diphosphate | H | H | H | SH |
| diphosphate | H | H | H | SMe |
| diphosphate | H | H | H | SEt |
| diphosphate | H | H | H | S-cyclopropyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | H | NH-acetyl |
| triphosphate | H | H | H | NH-cyclopropyl |
| triphosphate | H | H | H | NH-methy! |
| triphosphate | H | H | H | NH-ethyl |
| triphosphate | H | H | H | OH |
| triphosphate | H | H | H | OMe |
| triphosphate | H | H | H | OEt |
| triphosphate | H | ${ }^{\mathrm{H}}$ | H | O-cyclopropyl |
| triphosphate | H | H | H | O-acetyl |
| triphosphate | H | H | H | SH |
| triphosphate | H | H | H | SMe |
| triphosphate | H | H | H | SEt |
| triphosphate | H | H | H | S-cyclopropyl |
| monophosphate | monophosphate | monophosphate• | H | $\mathrm{NH}_{2}$ |
| monophosphate | monophosphate | monophosphate | H | NH-cyclopropyl |
| monophosphate | monophosphate | monophosphate | H | OH |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ |
| diphosphate | diphosphate | diphosphate | H | NH-cyclopropyl |
| diphosphate | diphosphate | diphosphate | H | OH |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ |


| WO 01/90121 ${ }^{\text {Pr }}$ |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| $\mathrm{R}^{\text {I }}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | Y |
| triphosphate | triphosphate | triphosphate | H | NH-cyclopropyl |
| triphosphate | triphosphate | triphosphate | H | OH |
| H | H | H | F | $\mathrm{NH}_{2}$. |
| H | H | H | F | NH-cyclopropy ${ }^{1}$ |
| H | H | H | F | OH |
| H | H | H | Cl | $\mathrm{NH}_{2}$ |
| H | H | II | Cl | NH-cyclopropyyl |
| H | H | H | Cl | OH |
| H | H | H | Br | $\mathrm{NH}_{2}$ |
| H | H | H | $\cdot \mathrm{Br}$ | NH-cyclopropyl |
| H | H | H | Br | OH |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | $\mathrm{NH}_{2}$ | OH |
| H | 11 | H | SH | $\mathrm{NH}_{2}$ |
| H | H | H | SH | NH-cyclopropyl |
| H | H | H | SH | OH |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ |
| acetyl | H | H | H | NH-cyclopropy ${ }^{1}$ |
| acetyl | H | H | H | OH |
| acetyl . $\because$. | H | H | ${ }_{5}$ | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | NH-cyclopropyl |
| acetyl | H | H | F | OH |
| H | àcetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | NH-cyclopropyl |
| H | acetyl | acetyl. | H | OH |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | 'H | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | OH |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ - |
| monophosphate | acetyl | acetyl | H | NH-cyclopropyl |

WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{\text {T }}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| monophosphate | acety! | acetyl | H | OH |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| diphosphate | acetyl | acetyl | H | NH-cyclopropyl |
| diphosphate | acetyl | acetyl | H | OH |
| triphosphate | acetyl | acetyl | II | $\mathrm{NH}_{2}$ |
| triphosphate | acetyl | acetyl | H | NH-cyclopropyl |
| triphosphate | acetyl | acetyl | H | OH |

Alternatively, the following nucleosides of Formula X are prepared, lusing the appropriate sugar and pyrimidine or purine bases.

(X)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | $2,4-0-$ <br> Diacetylur |  |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanth | thine |
| H | $\mathrm{H}$ | H | $\mathrm{CH}_{3}$ | 0 | $2,4-0-$ <br> Diacetylth | thymine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |  |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |  |
| H | H' | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono acetyl)cyto | no- |
| H | H | H | $\mathrm{CH}_{3}$ | $0$ | $4-(\mathrm{N}, \mathrm{~N}--$ <br> diacetyl)cy | cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |  |

WO 01/90121
PCT/US01/16671


WO 01/90121
PCT/USU1/16671

| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 4-(N-monoacetyl)cytosine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & 4-(\mathrm{N}, \mathrm{~N}- \\ & \text { diacetyl) } \end{aligned}$ | cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Uracil |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $2,4-\mathrm{O}-$ <br> Diacetylu | racil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxan | thine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $2,4-0-$ <br> Diacetylt | thymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 4-(N-mont } \\ & \text { acetyl)cytt } \end{aligned}$ | $\begin{aligned} & \text { no- } \\ & \text { nosing } \end{aligned}$ |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 4-(N,N- } \\ & \text { diacetyl) } \mathrm{c} \end{aligned}$ | ytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |  |
| diphosphate _. | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorou | racil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-0- <br> Diacetylu |  |
| diphosphate | II | H | $\mathrm{CH}_{3}$ | S | Hypoxant | thine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | $2,4-0-$ <br> Diacetylth | hym |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2,4-O- } \\ & \text { Diacetyluracil } \end{aligned}$ |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |  |

WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-0- <br> Diacetylthymine |
| triphosphate | H | $\mathrm{H}_{7}$ | $\mathrm{CH}_{3}$ | 0 | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-N $\vdots$ <br> diacetyl)cytosine  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | $\begin{array}{\|l\|l\|} \hline \text { 2,4-0- } \\ \text { Diacetyluracil } \end{array}$ |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypexanthine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O- <br> Diacetylthymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate. | monophosphate | monophosphate | . $\mathrm{CF}_{3}$ | 0 | $\begin{array}{\|l\|} \hline 2,4-\mathrm{O}- \\ \text { Diacetyluracil } \end{array}$ |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 . | Hypoxanthine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-0- <br> Diacetylthymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Thymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Cytosine |
| monophosphate | monophosphate | monophosphate | $\dot{\mathrm{CF}_{3}}$ | $\bigcirc$ | 4-(N-monoacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 4-(N,N- diacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate . | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 5-Fluorouracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $2,4-\mathrm{O}-$ <br> Diacetyluracil |

WO 01M0121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\begin{array}{\|l\|l} \hline 2,4-\mathrm{O}- & \\ \text { Diacetylthymine } \end{array}$ |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | monophosphiate | monophosphate | .$^{-} \mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-monoacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N- diacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | $\bigcirc$ | 4-(N,N- diacetyl)cytosine |
| acetyl | acety! | acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N- <br> diacetyl)cytosine |
| acetyl | acetyl | acetyl | 2-bromovinyl | 0 | 4-(N,N- diacetyl) cytosine |
| acetyl | acetyl | acetyl | 2-bromovinyl | S | $4-(\mathrm{N}, \mathrm{N}-$  <br> diacetyl) cytosine  |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{array}{\|l\|} \hline \text { 2-(N,N-diacetyl)- } \\ \text { guanine } \end{array}$ |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| H | H | H | $\mathrm{CH}_{3}$ | O | $\begin{array}{\|l\|l\|} \hline 6 \text {-(N,N-diacetyl)- } \\ \text { adenine } & \cdots \end{array}$ |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | $0$ | 2,8-difluoro- <br> adenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | adenine |

WO 01/90121
PCT/US01/16671


WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)- <br> adenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoroadenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2-(N,N-diacetyl)- } \\ & \text { guanine } \end{aligned}$ |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |  |
| diphosphate | H | 'H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-(N,N-diacetyl)adenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |  |
| diphosphate | H. | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | 2,8-difluoro'adenine |  |
| diphosphate | II | H | $\mathrm{CH}_{3}$ | 0 | adenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)- <br> guanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl <br> guanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluorroguanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | guanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S. | 6-(N,N-diacetyl)- <br> adenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8 -fluoroadenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro- <br> adenine |  |


| WO 01/90121 |  | $2.20$ |  |  | PCT/US01/16671 |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  |
| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)- <br> guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \hline \text { 6-O-acety } \\ & \text { guanine } \end{aligned}$ |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | guanime |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 6-(N,N-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| triphosphate | $\mathrm{H}^{\prime}$ | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2-(N,N-diacetyl)- } \\ & \text { guanine } \end{aligned}$ |
| triphosphate | $\mathrm{H}$ | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \text { 6-O-acety } \\ & \text { guanine } \end{aligned}$ |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroguanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ . | S | 6-(N,N-diacetyl)adenine |
| triphosphate | H. | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8 -fluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2-(N,N-diacetyl)guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | $\text { 6-O-acety } 1$ <br> guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{ClF}_{3}$ | 0 | 8-fluoroguanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | guanine |



Alternatively, the following nucleosides of Formula XI are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XI)
wherein:


223

| WO 01/90121 |  |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| R | R ${ }^{2}$ | R | R ${ }^{6}$ | X | Base |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacety | cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylu | racil |
| monophosphate | H | $\mathrm{H}_{1}$ | $\mathrm{CH}_{3}$ | S | Hypoxanthine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylt | ymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 4-(N-monoacetyl)cytosine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl | cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Uracil |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylu |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylt | ymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl) | cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylu | racil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | ${ }_{5}$ S | 2,4-O-Diacetylt | ym |
| diphosphate | H. | H | $\mathrm{CH}_{3}$ | S | Thymine |  |

WO 01/90121
PCT/US01/16671


WO 01/90121
PCT/US01/16671


Alternatively, the following nucleosides of Formula XII are prepared, using the appropriate sugar and pyrimidine or purine bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| H | $\mathrm{CH}_{3}$ | O | Thymine |
| H | $\mathrm{CH}_{3}$ | O | Cytosine |
| H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | O | Uracil |
| H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |



WO 01/90121


WO 01/90121

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| monophosphate | $\mathbf{C F}$ | $\mathbf{O}$ | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | O | 5-Fluorouracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacctylthymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphatc | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | $\mathrm{CF}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | O | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | S | 4-(N,N-diacetyl)cytosine |

Alternatively, the following nucleosides of Formula XVII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XVII)
wherein:

| $\mathbf{R}^{\Gamma}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{9}$ | $\mathbf{R}^{10}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | H | O | 2,4-O-Diacetyluracil | NHAc | Me |
| H | $\mathrm{CH}_{3}$ | H | O | Hypoxanthine | NH 2 | Me |
| H | $\mathrm{CH}_{3}$ | H | O | 2,4-O-Diacetylthymine | NHAc | Me |
| H | $\mathrm{CH}_{3}$ | H | O | Thymine | $\mathrm{NH2}$ | Me |

WO 01/90121
PCT/US01/16671


WO 01/90121
PCT/US01/16671


WO 01/90121 PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | X | Base | $\mathbf{R}^{9}$ | $\mathrm{R}^{10}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 2,4-O-Diacetylthymine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | Thymine | NIL | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | Cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 4-(N-mono-acetyl)cytosine | $\mathrm{NH}^{2}$ | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 4-(N,N-diacetyl)cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | Uracil | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 5-Fluorouracil | $\mathrm{NH}^{2}$ | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 2,4-O-Diacetyluracil | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | Hypoxanthine | NH2 | Me |
| monophosphate. | $\mathrm{C}^{\text {F }}$ | H | S | 2,4-O-Diacetylthymine | NH2 | Me |
| monophosphate | $\mathrm{C}^{\text {F }}$ | H | S | Thymine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | Cytosine | $\mathrm{NH}^{2}$ | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 4-(N-mono-acetyl)cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 4-(N,N-diacetyl)cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | Uracil | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 5-Fluorouracil | NH2 | Me |
| acetyl | $\mathrm{CH}_{3}$ | H | 0 | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | H | S | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | 0 | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | S | 4-(N,N-diacetyl)cytosine | H | Br |

## Example 3: Preparation of 3'-C-methylriboadenine

The title compound can be prepared according to a published procedure (R.F. Nutt, M.J. Dickinson, F.W. Holly, and E. Walton, "Branched-chain sugar nucleosides. M. 3'-Cmethyladenine ", J.Org. Chem. 1968, 33, 1789-1795) (Scheme 9).

## Scheme 9


(a) $\mathrm{RuO}_{2} / \mathrm{NaIO}_{4}$; (b) $\mathrm{MeMgI} / \mathrm{TiCl}_{4}$; (c) $\mathrm{HCl} / \mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$; (d) $\mathrm{BzCl} /$ pyridine; (e) AcBr , $\mathrm{HBr} / \mathrm{AcOH}$; (f) chloromercuri-6-benzamidopurine; (g) $\mathrm{NH}_{3} / \mathrm{MeOH}$.

In a similar manner, but using the appropriate sugar and pyrimidine or purine bases, the following nucleosides of Formula III are prepared. •

(III)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{\mathbf{1}}$ | $\mathbf{X}^{2}$ | $\mathbf{Y}$ |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| H | H | H | H | H | H | H |
| H | H | H | H | H | NH $_{2}$ |  |
| H | H | H | H | H | NH-cyclopropyl |  |
| H | H | H | H | H | NH-methyl |  |
| H | H | H | H | H | NH-ethyl |  |
| H | H | H | H | NH-acetyl |  |  |
| H | H | H | H. | OH |  |  |




235

| W0 01/90121 |  |  | PCT/US01/16671 |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| triphosphate | H | H | H | H | F |  |
| triphosphate | H | H | H | H | Cl |  |
| triphosphate | H | H | H | H | Br |  |
| triphosphate | H | H | H | H | I |  |
| monophosphate | monophosphate | monophosphate | H | H | $\mathrm{NH}_{2}$ |  |
| monophosphate | monophosphate | monophosphate. | H | H | NH-cyclopropyl |  |
| monophosphate | monophosphate | monophosphate | H | H | OH |  |
| monophosphate | monophosphate | monophosphate | H | H | F |  |
| monophosphate | monophosphate | monophosphate | H | H | Cl |  |
| diphosphate | diphosphate | diphosphate | H | H | $\mathrm{NH}_{2}$ |  |
| diphosphate | diphosphate | diphosphate | H | H | NH-cyclopropyl |  |
| diphosphate | diphosphate | diphosphate | H | H | OH |  |
| diphosphate | diphosphate | diphosphate | H | H | F |  |
| diphosphate | diphosphate | diphosphate | H | H | Cl |  |
| triphosphate | .triphosphate | triphosphate | H | H | $\mathrm{NH}_{2}$ |  |
| triphosphate | Iriphosphate | triphosphate | H. | H | NH-cyclopropyl |  |
| triphosphate | triphosphate | triphosphate | H | H | OH |  |
| triphosphate | triphosphate | triphosphate | H | H | F |  |
| triphosphate | triphosphate | triphosphate | H | H | Cl |  |
| H | H | H | . F | H | $\mathrm{NH}_{2}$ |  |
| H | H | H | F | H | NH-cyclopropyl |  |
| H | H | H | F | H | OH |  |
| H | H | H | F | H | F |  |
| H | H | H | F | H | Cl |  |
| H | H | H | Cl | H | $\mathrm{NH}_{2}$ |  |
| H | H | H | Cl | H | NH-cyclopropyl |  |
| H | H | H | Cl | H | OH |  |
| H | H | H . | Cl | H | F |  |
| H | H | H | Cl | H | Cl |  |
| H | H | H | Br | H | $\mathrm{NH}_{2}$ |  |
| H | H | H | Br | H | NH-cyclopropyl |  |

$$
236
$$

WO 01/90121
PCT/US01/16671


WO 01/90121
PCT/USU1/16671




| $\mathrm{R}^{\text {I }}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |  |
| H | H | H | H | $\mathrm{NH}_{2}$ | F |  |
| H | H | H | H | $\mathrm{NH}_{2}$ | Cl |  |
| H | H | H | H | $\mathrm{NH}_{2}$ | Br |  |
| H | H | II | H | $\mathrm{NH}_{2}$ | I |  |
| monophosphate! | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |  |
| monophosphate | H | $\mathrm{H}^{\prime}$ | II | $\mathrm{NH}_{2}$ | NH-cyclopropyl |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-m | nethyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH- |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | O -acetyl |  |
| mionophosphate | H | H | H | $\mathrm{NH}_{2}$ | OMe | . |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OEt |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | O-cyćlopropyl |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SH |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SMe |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | F |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Cl |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |  |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | I |  |
| diphosphate : | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-methyl |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-acetyl |  |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | OMé |  |



| W0 01/90121 |  |  |  | PCT/US01/16671 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{\mathbf{1}}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| monophosphate | monophosphate | monophosphate | H | $\mathrm{NH}_{2}$ | F |  |
| monophosphate | monophosphate | monophosphate | H | $\mathrm{NH}_{2}$ | Cl |  |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| diphosphate | diphosphate | diphosphate | $\cdot \mathrm{H}$ | $\mathrm{NH}_{2}$ | NH-c | clopropyl |
| diplosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | OH |  |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | F |  |
| diphosphate | diphosphate | diphosphatc | H | $\mathrm{NH}_{2}$ | Cl |  |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | -...... |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | NH-C | clopropyl |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | OH |  |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | F |  |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | Cl |  |
| II | H | H | F | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | F | $\mathrm{NH}_{2}$ |  | clopropyl |
| H | H | H | F | $\mathrm{NH}_{2}$ | OH |  |
| H | H | H | F | $\mathrm{NH}_{2}$ | F |  |
| H | I | H | F | $\mathrm{NH}_{2}$ | Cl |  |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | Cl | $\mathrm{NH}_{2}$ |  | clopropyl |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | OH |  |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | F |  |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | Cl |  |
| H | H | H | Br | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | Br | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| H | H | H | Br | $\mathrm{NH}_{2}$ | OH |  |
| H | $\mathrm{H} \quad$ | H | Br | $\mathrm{NH}_{2}$ | F |  |
| H | H | H | Br | $\mathrm{NH}_{2}$ | Cl |  |
| H | H | H. | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}{ }^{-}$ | OH: |  |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | F |  |


| WO 01/90121 |  | $241$ |  |  |  | 116671 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | PCT/US01/ |  |  |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | Cl |  |
| H | H | II | SH | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | SH | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| H | H | H | SH | $\mathrm{NH}_{2}$ | OH |  |
| H | 15 | H | SH | $\mathrm{NH}_{2}$ | F |  |
| H | H | H | SH | $\mathrm{NH}_{2}$ | Cl |  |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}-$ | cyclopropyl |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | OH |  |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | F |  |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | Cl |  |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | NH-c | cyclopropyl |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | OH |  |
| acety] | H | H | F | $\mathrm{NH}_{2}$ | F |  |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | Cl |  |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| H | acety] | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}-$ | yclopropyl |
| H | acetyl | acstyl | H | $\mathrm{NH}_{2}$ | OH |  |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |  |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |  |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-c | yclopropyl |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | OH |  |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}{ }^{\circ}$ | F |  |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |  |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\overline{\mathrm{OH}}$ |  |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F - |  |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |  |


| WO 11/90121 |  |  | PCT/US01/16671 |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ - | $\mathrm{NH}_{2}$ |  |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| diphosphate | acetyl | acetyl | H. | $\mathrm{NH}_{2}$ | OH |  |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |  |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$. | Cl |  |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}-\mathrm{c}$ | clopropyl |
| triphosphate | acetyl | acctyl | H | $\mathrm{NH}_{2}$ | OH |  |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |  |
| triphosphate | acetyl | acctyl | H | $\mathrm{NH}_{2}$ | Cl |  |
| H | H | H | H | Cl | H |  |
| H | II | H | H | Cl | H |  |
| II | H | H | H | Cl | $\mathrm{NHH}_{2}$ |  |
| H | H | H | H | Cl | NH-c | yclopropyl |
| H | H | H | H | Cl | NH-m | nethyl |
| H | H | H | H | Cl | $\mathrm{NH}-\mathrm{e}$ |  |
| H | H | H | H | Cl | $\mathrm{NH}-\mathrm{a}$ |  |
| H | H | H | H | Cl | OH |  |
| H | H | H | : H | Cl | OMe |  |
| H | H | H | H | Cl | OEt |  |
| H | H | H | H | Cl | O-cyc | lopropyl |
| H | H | H | H | Cl | O-ace | tyl |
| H | H | H | H | Cl | SH |  |
| H | H | H | H | Cl | SMe |  |
| H | H | H | H | Cl | SEt |  |
| H | H | H | H | Cl | S-cyc | lopropyl |
| monophosphate | H | H | H | Cl | $\mathrm{NH}_{2}$ |  |
| monophosphate | H | H | H | Cl | $\mathrm{NH}-\mathrm{a}$ | cetyl |
| monophosphate | H | H | H | Cl | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| monophosphate | H | H | H | Cl | $\mathrm{NH}-\mathrm{m}$ | ethyl |
| monophosphate | H | H | H | Cl | $\mathrm{NH}-\mathrm{e}$ | hyl |



WO 01/90121

| WO 01/90121 |  |  | PCT/US01/16671 |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | . $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |  |
| triphosphate | H | H | H | Cl | O-cy | lopropyl |
| triphosphate | H | H | H | Cl | $\mathrm{O}-\mathrm{ac}$ |  |
| triphosphate | H | H | H | Cl | SH |  |
| triphosphate | H | H | H | Cl | SMe |  |
| triphosphate | H | H | H | Ci | SEt |  |
| triphosphate | H | H | H | C1 | S-cy | clopropyl |
| monophosphate | monophosphate | monophosphate | H | Cl | $\mathrm{NH}_{2}$ |  |
| monophosphate | monophosphate | monophosphate | H | Cl | NH-8 | rinpropyl |
| monophosphate | monophosphate | monophosphate | H | Cl | OH |  |
| diphosphate | diphosphạte | diphosphate | H | Cl | $\mathrm{NH}_{2}$ |  |
| diphosphate | diphosphate | diphosphate | H | Cl | NH-c | clopropyl |
| diphosphate | diphosphate | diphosphate | H | Cl | OH |  |
| triphosphate | triphosphate. | triphosphate | H | Cl | $\mathrm{NH}_{2}$ |  |
| triphosphate | triphosphate | triphosphate | H | Cl | NH | clopropyl |
| triphosphate | triphosphaté | triphosphate | H | Cl | OH |  |
| H | H | H | F | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | F | Cl | NH-c | cyclopropyl |
| H | H | H | F | Cl | OH |  |
| H | H | H | Cl | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | Cl | Cl | $\mathrm{NH}-\mathrm{c}$ | clopropyl |
| H | H | H | Cl | Cl | OH |  |
| H | H | H | Br | CI | $\mathrm{NH}_{2}$ |  |
| H | H | H | Br | Cl | NH-c | clopropyl |
| H | H | H | Br | Cl | OH |  |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{Cl}^{\text {}}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | $\mathrm{NH}_{2}$ | Cl : | NH-c | yclopropyl |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | OH |  |
| H | H | H | SH | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | SH | Cl | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| H | H | H | SH | Cl | OH |  |
| acetyl | H | H | H | Cl | $\mathrm{NH}_{2}$ |  |

IPO DELHI 23-06-2015•15:45


| $\mathrm{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | $\mathbf{Y}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| acety] | H | H | H | Cl | NH-cyclopropyl |  |
| acetyl | H | H | H | Cl | OH |  |
| acetyl | H | H | F | Cl | $\mathrm{NH}_{2}$ |  |
| acetyl | H | H | F | Cl | NH-c | yclopropyl |
| acetyl | H | H | F | Cl | OH |  |
| H | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| H | acetyl | acetyl | H | Cl | NH-cyclopropyl |  |
| H | acetyl | acetyl | H | Cl | OH |  |
| acetyl | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| acetyl | acetyl | acetyl | H | Cl | NH-cyclopropyl |  |
| acetyl | acetyl | acetyl | H | Cl | OH |  |
| monophosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| monophosphate | acoty | actyl | II | Cl | NH-cyclopropyl |  |
| monónophosphate | acetyl | 'acetyl | H | Cl | $\mathrm{OH}^{-1}$ |  |
| diphosphate | acety] | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| diphosphate | acetyl | acetyl | H | Cl | NH-cyclopropyl |  |
| diphosphate | acetyl | acetyl | . H | Cl | OH |  |
| triphosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |  |
| triphosphate | acetyl | acetyl. | H | Cl | $\mathrm{NH}-\mathrm{c}$ | yclopropyl |
| triphosphate | acetyl | acetyl | H | Cl | OH |  |
| H | II | H | H | Cl | $\mathrm{NH}_{2}$ |  |
| H | 11 | H | H | Cl | NH-cyclopropyl |  |
| H | H | H | H | Cl | OH |  |
| H | H | H. | H | Br | $\mathrm{NH}_{2}$ |  |
| H | H | H | H | Br | NH-cyclopropyl |  |
| H | H | H | H | Br . | OH |  |

Alternatively, the following nucleosides of Formula VI are prepared, using the appropriate sugar and pyrimidine or purine bases.

(VI)
wherein:


WO 01/90121
PCT/US01/16671


| WO 01,90121 |  |  | 67 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{\mathbf{T}}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | Y |  |
| triphosphate | H | H | H | SH |  |
| triphosphate | H | H | H | SMe |  |
| triphosphate | H | H | H | SEt |  |
| triphosphate | H | H | H | S-cyclopropyl |  |
| monophosphate, | monophosphate | monophosphate | H | $\mathrm{NII}_{2}$ |  |
| monophosphate | monophoșphate | monophosphate | H | NH-cyclopropy |  |
| monophosphate | monophusplate | monophosphate | H | OH |  |
| diphosphate | diphosphate | diphnsphate. | H | $\mathrm{NH}_{2}$ |  |
| diphosphate | diphosphate | diphosphate | H | NH-cyclopropy |  |
| diphosphate | diphosphate | diphosphate | H | OH |  |
| triphosphate | triphosphate. | triphosphate | H | $\mathrm{NH}_{2}$ |  |
| triphosphate | triphosphate | triphosphate | H | NH-cyclopropy |  |
| triphosphate | triphosphate | triphosphate | H | OH |  |
| H | H | H | F | $\mathrm{NH}_{2}$ |  |
| H | H | H | F | NH-cyclopropis |  |
| H | H | H | F | OH |  |
| H | H | H | Cl | $\mathrm{NH}_{2}$ |  |
| H | H | H | Cl | NH-cyclopropy |  |
| H | H | H | Cl | OH |  |
| H | H | H | Br | $\mathrm{NH}_{2}$ |  |
| H | H | H | Br | NH-cyclopropi' |  |
| H | H | H | Br | OH |  |
| H | H | - H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |  |
| H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropy |  |
| H | H | H | $\mathrm{NH}_{2}$ | OH |  |
| H | H | H | SH | $\mathrm{NH}_{2}$ | - |
| H | H | H | SH | NH-cyclopropy |  |
| H | H | H | SH | OH | , |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ |  |
| acetyl | H | H | H | NH-çyclopropy |  |
| acetyl | H | H | H | OH |  |

WO 01/90121
PCT/US01/16671

| $\cdot \mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | X ${ }^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ |
| acetyl | H | $\dot{\mathrm{H}}$ | F | NH-cyclopropy ${ }^{1}$ |
| acetyl | H | H | F | OH |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | NH-cyclopropyl |
| H | acetyl | acetyl | H | OH |
| acetyl | acety! | acetyl | II | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | OH |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | H | NH-cyclopropyl |
| monophosphate | acetyl | acetyl | H | OH |
| diphosphate | acetyl | aectyl | H | - $\mathrm{HH}_{2}$ |
| diphosphate | acety] | acety! | H | NH-cyclopropyl |
| diphosphate | aicetyl | acetyl | H | OH |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| triphosphate | accty] | acetyl | H | NH-cyclopropyl |
| triphosphate | acetyl | acetyl | H | OH |

Alternatively, the following nucleosides of Formula XIII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XIII)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | -2,4-O- <br> Diacety |  |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | Нуроха | thine |




IPO DELHI 23-06-2015.15:450.


253
WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | $\begin{aligned} & \text { 4-(N-mono- } \\ & \text { acety1)cytosinc } \end{aligned}$ |
| monophosphate | monophosphate | -monophosphate | $\mathrm{CF}_{3}$ | 0 | $\begin{array}{l\|l} \hline 4-(\mathrm{N}, \mathrm{~N}- & \\ \text { diacetyl)cytosine } \end{array}$ |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | monophosphate ${ }^{\text {P }}$ | nionophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O- <br> Diacetyluracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate. | monophosphate | $\mathrm{CF}_{3}$ | S | $2,4-0-$ <br> Diacetylthymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | monophosphate | munuphosphatc | $\mathrm{Cr}_{3}$ | S | Cylosine |
| monophosphate | monophosphate | monophosphate | ${ }^{-} \mathrm{CF}_{3}$ | S | 4-(N-monoacetyl)cytosine |
| monophosphate | monophosphatc | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N- diacetyl) cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monophosphate | monophosphate. | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | $\begin{array}{l\|l} \hline 4-(\mathrm{N}, \mathrm{~N}- \\ \text { diacetyl) cytosine } \end{array}$ |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | S | $4-(\mathrm{N}, \mathrm{N}-$ <br> diacetyl) cytosine |
| acetyl | acetyl | acetyl | 2-bromovinyl | 0 | 4-(N,N- diacetyl) cytosine |
| acetyl | acetyl | acetyl | $\begin{aligned} & \text { 2-bromo- } \\ & \text { vinyl } \end{aligned}$ | S | $4-(\mathrm{N}, \mathrm{N}-$ diacetyl) cytosine |
| H |  | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)- <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 6-0-acetyl <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroguanine |


| WO 01900121 |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 6-(N,N-diacctyl)- } \\ & \text { adenine } \end{aligned}$ |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2,8-difluoro- } \\ & \text { adenine } \end{aligned}$ |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | adenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \text { 2-(N,N-diacetyl)- } \\ & \text { guanine } \end{aligned}$ |
| H | H | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \text { 6-O-acetyl } \\ & \text { guanine } \end{aligned}$ |
| H | H | H | $\mathrm{CIF}_{3}$ | 3 | 8 -fluoroguaniine |
| H | H | H | $\mathrm{CH}_{3}$ | $S$ | guanine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)adenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \text { 2,8-diflubro- } \\ & \text { adenine } \end{aligned}$ |
| H | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | H | H | $\overline{\mathrm{CH}_{3}}$ | $\bigcirc$ | 2-(N,N-diacetyl)guanine |
| monophosphate | $\mathrm{H}$ | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | O | $\begin{aligned} & 6-(\mathrm{N}, \mathrm{~N} \text {-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |

255

WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoro- <br> adenine |  |
| monophosphate | H. | H | $\mathrm{CH}_{3}$. | 0 | adenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)- <br> guanine |  |
| monophosphate | H | If | $\mathrm{CH}_{3}$ | S | 6-O-acetyl <br> guanine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroguanine |  |
| morophosphate | H | H | $\mathrm{CH}_{3}$ | S | guanine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)- <br> adenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |  |
| monophosphate | H. | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,S-difluoro- <br> adenine |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{array}{\|l\|} \hline \text { 2-(N,N-diacetyl)- } \\ \text { guanine } \end{array}$ |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | ${ }^{8}$-fluoroguanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{array}{\|l} \hline \text { 6-(N,N-diacetyl)- } \\ \text { adenine } \end{array}$ |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoroadenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoroadenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | adenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | $S$ | $\begin{array}{\|l} \hline 2-(\mathrm{N}, \mathrm{~N}-\text { diacetyl)- } \\ \text { guanine } \end{array}$ |  |


| WO 01/90121 |  |  |  |  | PCT/US01/16671 |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base | , |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-O-acet <br> guaninc |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoro | guanine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | guanine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \text { 6-(N,N-d } \\ & \text { adenine } \end{aligned}$ | diacetyl)- |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroa | adenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroa | adenine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,8-diflu adenine |  |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2-(N,N-C } \\ & \text { guanine } \end{aligned}$ | diacetyl)- |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 6-O-acet } \\ & \text { guanine } \end{aligned}$ |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8 -fluoro | guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 6- } \mathrm{N}, \mathrm{~N}-\mathrm{d} \\ & \text { adenine } \end{aligned}$ | diacetyl)- |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoro | adenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroa | Idenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 2,8-diflu <br> adenine |  |
| triphosphate | II | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2-(N,N-d } \\ & \text { guanine } \end{aligned}$ | diacetyl)- |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | $\begin{array}{\|l\|} \hline \text { 6-O-ace } \\ \text { guanine } \end{array}$ |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluorog | guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | guanine |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | $\begin{array}{\|l\|} 6-\mathbb{N}, \mathrm{N}-\mathrm{c} \\ \text { adenine } \end{array}$ | diacetyl)- |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroa | adenine |

WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroa | adenine |
| triphosphate | H | $\mathrm{H}$ | $\cdot \mathrm{CH}_{3}$ | S : | 2,8-diflu <br> adenine |  |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | $\begin{aligned} & \text { 2-(N,N-d } \\ & \text { guanine } \end{aligned}$ | diacetyl)- |
| monophosphate | monophosphate | monophosphatc | $\mathrm{CF}_{3}$ | 0 | 6-O-acct <br> guanine |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8-fluo | anine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | guanine |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | $\bigcirc$ | $\begin{aligned} & \hline 6-(\mathrm{N}, \mathrm{~N}-\mathrm{d} \\ & \text { adenine } \end{aligned}$ | diacetyl)- |
| monophosphatc | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2 -fluoro | adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8 -fluoro | adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,8-diflu <br> adenine |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | adenine |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\begin{array}{\|l\|} \hline \text { 2-(N,N-d } \\ \text { guanine } \end{array}$ | diacetyl)- |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\begin{array}{l\|} \text { 6-O-acet } \\ \text { guanine } \end{array}$ |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8 -fluoro | annine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | guanine |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\begin{array}{\|l\|} \hline 6-(\mathrm{N}, \mathrm{~N}-\mathrm{d} \\ \text { adenine } \end{array}$ | diacetyl)- |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-fluoro | adenine |
| monophosphate | monophosphate | monophosphate - | $\mathrm{CF}_{3}$ | S | 8 -fluoroa | adeninie |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $2,8 \text {-diflu }$ <br> adenine |  |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | adenine |  |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | O | guanine |  |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | S | guanine |  |

WO 01F00121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| acetyl | acetyl | acetyl | 2-bromo- <br> vinyl | $\mathbf{O}$ | guanine |  |
| acetyl | acetyl | acetyl | 2-bromo- <br> vinyl | S | guanine |  |

Alternatively, the following nucleosides of Formula XIV are prepared, using the appropriate sugar and pyrimidine or purine bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{6}$ | X | Base |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |  |
| H | H | $\mathrm{CH}_{3}$. | 0 | 2,4-O-Diacetylthymine |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |  |
| H | H | $\mathrm{CH}_{3}$ | 0. | Cytosine |  |
| H | H. | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |  |
| H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |  |
| H | ${ }^{\prime}$ | $\mathrm{CH}_{3}$ | 0 | Uracil |  |
| H | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |  |
| H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |  |
| H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |  |
| H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |  |
| H | H | $\mathrm{CH}_{3}$ | S | Thymine |  |
| H | H. | $\mathrm{CH}_{3}$ | S | Cytosine |  |
| H | $\mathrm{H}^{+}$ | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosin |  |

WO 01/90121
PCT/US0116671



WO 01/90121
P.CT/US01/16671
$\mathbf{R}^{1}$
I

| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4 -(N-mono-acetyl)cytosine |  |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |  |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |  |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil | - |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | O | 4-(N,N-diacetyl)cytosine |  |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |  |
| acetyl | acetyl | 2-bromo- <br> vinyl | O | 4-(N,N-diacetyl)cytosine |  |
| acetyl | acetyl | 2-bromo- <br> vinyl | S | 4-(N,N-diacetyl)cytosine |  |

Alternatively, the following nucleosides of Formula $X V$ are prepared, using the appropriate sugar and pyrimidine or purine bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| H | $\mathrm{CH}_{3}$ | O | Thymine |
| H | $\mathrm{CH}_{3}$ | O | Cytosine |
| H | $\mathrm{CH}_{3} \quad \vdots$ | O | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| H | $\mathrm{CH}_{3} \cdot$. | O | Uracil. |

262
WO 01/90121

- PCT/US01/16671


263



WO 0190121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| monophosphate | $\mathrm{CF}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | O | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | O | 5-Fluorouracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate $!$ | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| atelyl | $\mathrm{CF}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | O | 4-(N,N-diacetyl)cytosine |
| ácetyl | 2-bromo-vinyl | S | 4-(N,N-diacetyl)cytosine |

Alternatively, the following nuclcosides of Formula XVIII are prepared, using the appropriate sugar and pyrimidine or purińe bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{4}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{8}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | OH | O | 2,4-O-Diacetyluracil | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | O | Hypoxanthine | H | Me |
| H |  | $\mathrm{CH}_{3}$ | OH | O | 2,4-O-Diacetylthymine | H |

WO 01/90121




WO 01/90121
PCT/US01/16671

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{8}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | Hypoxanthine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | $\cdot$ | OH | O | 2,4-O-Diacetylthymine | H |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | Thymine | Me |  |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | Cytosine , | H | Me |
| monophosphate | $\mathrm{Cr}_{3}$ | OH | O | 4-(N-mono-acetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | 4-(N,N-diacetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH. | O | Uracil | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | 5-Fluorouracil | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 2,4-O-Diacetyluracil | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Hypoxanthine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 2,4-O-Diacetylthymine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Thymine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 4-(N-mono-acetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 4-(N,N-diacetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Uracil | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 5-Fluorouracil | H | Me |
| acetyl | $\mathrm{CH}_{3}$ | OH | O | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | S | 4-(N,N-diacetyl)cytosine | H | Br |

## VII. Anti-Hepatitis C Activity

Compounds can exhibit anti-hepatitis C activity by inhibiting HCV polymerase, by inhibiting other enzymes needed in the replication cycle, or by other pathways. A number of assays have been published to assess these activities. A general method that assesses the gross increase of HCV virus in culture is disclosed in U.S: Patent No. 5,738,985 to Miles et al. In vitro assays have been reported in Ferrari et al., Jul. of Sir., 73:1649-1654, 1999; Ishii et al., Hepatology, 29:1227-1235,1999; Lohmann et al., Jul. of Bio. Chem., 274:1080710815, 1999; and Yamashita et al, Jul. of Bio. Chem., 273:15479-15486, 1998..-

WO 97/12033, filed on September 27, 1996, by Emory University, listing C. Hagedorn and A. Reinoldus as inventors, and which claims priority to U.S.S.N. 60/004,383,
filed on September 1995, describes an HCV polymerase assay that can be used to evaluate the activity of the compounds described herein. Another HCV polymerase assay has been reported by Bartholomeusz, et al., Hepatitis C virus (HCV) RNA polymerase assay using cloned HCV non-structural proteins; Antiviral Therapy 1996:1(Supp 4) 18-24.

Screens that measure reductions in kinase activity from HCV drugs are disclosed in U.S. Patent No. 6,030,785, to Katze et bl., U.S. Patent No. 6,010,848 to Delvecchio et al, and U.S. Patent No. 5,759,795 to Jubin et al. Screens that measure the protease inhibiting activity of proposed HCV drugs are disclosed in U.S. Patent No. 5,861,267 to Su et al, U.S. Patent No. 5,739,002 to De Francesco et al, and U.S. Patent No. 5,597,691 to Houghton ot al.

## Eximple 4: Phosphorylation Assay of Nucleoside to Active Triphosphate

To determine the cellular metabolism of the compounds, HepG2 cells were obtained from the American Type Culture Collection (Rockville, MD), and were grown in $225 \mathrm{~cm}^{2}$ tissue culture flasks in minimal essential medium supplemented with non-essential amino acids, $1 \%$ penicillin-streptonycin. The medium was renewed every three days, and the cells were subcultured once a week. After detachment of the adherent monolayer with a 10 minute exposure to 30 mL of trypsin-EDTA and three consecutive washes with medium, confluent HepG2 cells were seeded at a density of $2.5 \times 10^{6}$ cells per well in a 6 -well plate and exposed to $10 \mu \mathrm{M}$ of $\left.{ }^{3} \mathrm{H}\right]$ labeled active compound ( $500 \mathrm{dpm} / \mathrm{pmol}$ ) for the specified time periods. The cells were maintained at $37^{\circ} \mathrm{C}$ under a $5 \% \mathrm{CO}_{2}$ atmosphere. At the selected time points, the cells were washed three times with ice-cold phosphate-buffered saline (PBS). Intracellular active compound and its respective metabolites were extracted by incubating the cell pellet ovemight at $-20^{\circ} \mathrm{C}$ with $60 \%$ methanol followed by extraction with an additional $20 \mu \mathrm{~L}$ of cold methanol for one hour in an ice bath. The extracts were then combined, dried under gentle filtered air flow and stored at $-20^{\circ} \mathrm{C}$ until HPLC analysis. The preliminary results of the HPLC analysis are tabulated in Table 1.


## Example 5: Bioavailability Assay in Cynomolgus Monkeys

Within 1 week prior to the study initiation, the cynomolgus monkey was surgically implanted with a chronic venous catheter and subcutaneous venous access port (VAP) to facilitate blood collection and underwent a physical examination including hematology and serum chemistry evaluations and the body weight was recorded. Each monkey (six total), received approximately 250 uCi of ${ }^{3} \mathrm{H}$ activity with each dose of active compound, namely $\beta$-D-2'- $\mathrm{CH}_{3}-\mathrm{riboG}$ at a dose level of $10 \mathrm{mg} / \mathrm{kg}$ at a dose concentration of $5 \mathrm{mg} / \mathrm{mL}$, either via an intravenous bolus ( 3 monkeys, IV), or via oral gavage ( 3 monkeys, PO). Each dosing syringe was weighed before dosing to gravimetrically determine the quantity of formulation administered. Urine samples were collected via pan catch at the designated intervals (approximately $18-0$ hours pre-dose, $0-4,4-8$ and $8-12$ hours post-dosage) and processed. Blood samples were collected as well (pre-dose, $0.25, .0 .5,1,2,3,6,8,12$ and 24 hours post-dosage) via the chronic tenous catheter and VAP or. from a peripheral vessel if the chronic venous catheter procedure should not be possible. The blood and urine samples were analyzed for the maximum concentration ( $\mathrm{C}_{\max }$ ), time when the maximum concentration was achieved ( $\mathrm{T}_{\max }$ ), area under the curve (AUC), half life of the dosage concentration ( $\mathrm{T}_{1 / 2}$ ), clearance (CL), steady state volume and distribution $\left(\mathrm{V}_{\mathrm{ss}}\right)$ and bioavailability ( F ), which are tabulated in Tables 2 and 3, and graphically illustrated in Figures 2 and 3, respectively.

Table 2: Oral Bioavailability in Monkeys

|  | Dose <br> $(\mathrm{mg})$ | AUS <br> $(\mathrm{ng} / \mathrm{mL} \times \mathrm{h})$ | Norm AUC <br> $(\mathrm{ng} / \mathrm{mL} \times \mathrm{h} / \mathrm{mg})$ | Mean Norm AUC <br> $(\mathrm{ng} / \mathrm{mL} \times \mathrm{h} / \mathrm{mg})$ | $\mathrm{F}(\%)$ |
| :--- | :---: | :---: | :---: | :---: | :---: |
| IV Monkey 1 | 46.44 | 13614 | 293.2 |  |  |
| IV Monkey 2 | 24.53 | 6581 | 268.3 |  |  |
| IV. Monkey 3 | 20.72 | 6079 | 293.4 | 284.9 |  |
| PO Monkey 1 | 29.04 | 758 | 26.1 |  |  |
| PO Monkey 2 | -30.93 | 898 | 29.0 |  |  |
| PO Monkey 3 | 30.04 | 1842 | 61.3 | 38.8 | 13.6 |

Table 3: Experimental Pharmacokinetics of $\beta-\mathrm{D}^{\prime} \mathbf{2}^{\prime}-\mathrm{CH}_{3}$-riboG in Cynomolgus


Example 6: Bone Marrow Toxicity Assay

Human bone marrow cells were collected from normal healthy volunteers and the mononuclear population was separated by Ficoll-Hypaque gradient centrifugation as described previously by Sommadossi J-P, Carlisle R. "Toxicity of 3'-azido-3'deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine for normal human hematopoietic progenitor cells in vitro" Antimicrobial Agents and Chemotherapy 1987; 31:452-454; and Sommadossi J- Pं, Schinazi RF, Thu CK, Xie M-Y. "Comparison of cytotoxicity of the $(-)$ - and $(+)$-enantiomer of $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-thiacytidine in normal human bone marrow progenitor cells". Biochemical Pharmacology 1992; 44:1921-1925. The culture assays for CFU-GM and BFU-E were performed using a bilayer soft agar or methylcellulose method. Drugs were diluted in tissue culture medium and filtered. After 14 to 18 days at $37^{\circ} \mathrm{C}$ in a humidified atmosphere of $5 \% \mathrm{CO}_{2}$ in air, colonies of greater than 50 cells were counted using an inverted microscope. The results in Table 4 are presented as the percent inhibition of colony formation in the presence of drug compared to solvent control cultures.

Table 4: Human Bone Marrow Toxicity CFU-GM and BFU-E Clonogenic Assays

|  | ${ }^{\text {IC }}{ }_{50}$ in $\mu \mathrm{M}$ |  |
| :---: | :---: | :---: |
|  | CFU-GM | BFU-E |
| ribavirin | $\sim 5$ | $\sim 1$ |
| $\beta$-D-2'-CH3 -riboA | $>100$ | $>100$ |
| $\beta-\mathrm{D}^{\prime}-\mathrm{CH}_{3}$-riboU | $>100$ | $>100$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboC | $>10$ | $>10$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboG | $>10$ | $>100$ |

## Example 7: Mitochondria Toxicity Assay

HepG2 cells were cultured in 12 -well plates as described above and exposed to various concentrations of drugs as taught by Pan-Zhou X-R, Tui L, Thou X-J, Sommadossi J-P, Darley-Usmer VM. "Differential effects of antiretroviral nucleoside analogs on mitochondrial function in HopG2: cells" Antinierob Agents Cheinuther 2000; "44:490́-303. Lactic acid levels in the culture medium after 4 day drug exposure was measured using a Boehringer lactic acid assay kit. Lactic acid levels were normalized by cell number as measured by hemocytometer count. The preliminary results from this assay are tabulated in Table 5.

Table 5: Mitochondrial Toxicity Study (L-lactic acid assay)

|  | Conc. $(\mu \mathrm{M})$ | lactate (m g/10 ${ }^{6}$ cell) | $\%$ of Control |
| :---: | :---: | :---: | :---: |
| Control |  | 2.18 | 1 |
| FIAU | 10 | 3.73 | 170.4 |
| $\beta$-D-2'-CH3-riboC | 1 | 2.52 | 115.3 |
| - | 10 | 2.36 | 107.9 |
|  | $\frac{50}{}$ | 2.26 | 103.4 |
|  | 100 | 2.21 | 101.2 |



FLA

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboC

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention, will be obvious to those skilled in the art from the foregoing detailed description of the invention.

## We Clain:

1. A compound of Formula I:

(I)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
2. A compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino. acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and .
$Y$ is hydrogen, bromo, chloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and $R^{4}$ and $R^{5}$ are independently_hydrogen,_acyl_(including-lower-acyl)-or-alkyl-(ineluding but not limited to methyl, ethyl, propyl and.cyclopropyl).
3. A compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group. which when administered in vive is

WO 01/90121
capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, promo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
4. A compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{\prime}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{l}$ is selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

## WO 01/00121

5. A compound of Formula $V$ :

(V)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including-a-phospholipid;-an-amino-acid;-a-carbaliydrate; a peptide; ar cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro; fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{\prime}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
6. A compound of Formula VI:


IPO. DELHI 23-06-201515:465

## WO 01/90121

or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{\prime}$ is selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and_ $R^{5}$ are_independently-hydrogen,-acyl-(ineluding-lower-acyl),or-alkyl-(including but not limited to methyl, ethyl, propyl and cyclopropyl).
7. A compound selected from Formulas VII, VIII and IX:


or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in-vivo is

## WO 01/ 0121

PCT/US01/16671
capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2-Br-ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O (lower acyl), -O(alkyl), - O(lower alkyl), O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}\left(\right.$ lower alkyl),$-\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
8. A compound of Formulas X, XI and XII:

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate,
 (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which-when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O} \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O (lower acyl), -O(alkyl), O (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkÿl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{1}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyll), $-\mathrm{O}(\mathrm{lower}$ acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

WO 01/90121
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
9. A compound selected from Formulas XIII, XIV and XV:

(XIII)


or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaccutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), -O (acyl), -O (lower acyl), -O(alkyl), O (lower alkyl), -O (alkenyl), chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $) ;-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and ' X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
10. A compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable salt thereof, wherein:

Base is a purine or pyrimidine base as defined herein; $R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphósphate, triphosphatc, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including akkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl) $)=\mathrm{O}($ acyl), $-\mathrm{O}\left(\right.$ lower aryl), $-\mathrm{O}($ alkyl) $)=\left(\right.$ (lower alkyl), -O (alkenyl), chlorine, brominc, iodinc, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
11. A compound of Formula XVII:

(XVTI)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl
(including low cr alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in viva is capable of providing a conipound wherein $R^{\prime}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), O (lower alkyl); -O(alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), $-\mathrm{O}($ acyl $)$, - $\mathrm{O}\left(\right.$ lower acyl), $, \mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl $),-\mathrm{O}($ alkenyl $)$, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2} ;$
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl) chlorine, bromine, or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
12. A compound of Formula XVIII:

(XVII)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including' lower acyl);-alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl; wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or

## WO 01/90121

PCT/US01/16671
other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), O (lower alkyl), -Ó(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NII (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
13. A compound of the structure:

14. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
15. A compound of the structure:

or a pharmaceutically acceptable salt thereof.

WO 01/90121
16. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
17. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
18. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
19. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
20. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
21. A compound of the structure:

or a phammaceutically acceptable salt thereof.
22. A compound of the structure:

or a pharmaceutically acoeptable salt thereof.
23. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
24. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
25. The compound as described in any of the preceding clainis $1-24$, wherein the said compound is in the form of a dosage unit.
26. The compound as described in claim 187, wherein the dosage unit contains 10 to 1500 mg of said compound.
27. The compound as described in claim 187 or 188 , wherein said dosage unit is a tablet or capsule.
28. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula I:

(I)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkýl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogeni, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
29. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C -virus in a host, comptising an effective amount of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, (riphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesteroi; or other pharmaceutically ácceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2 \cdot}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chlóro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
30. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen; bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{\prime}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

TPO DELHI 23-06-2015.15:406
31. A pharmaceutical composition for the trealment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{j}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

IPO DELHI $23-06-2015 \cdot 15: 46$
32. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula $V$ :

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
33. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula VI:

(VI)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylaikyl suifonyl including methanesulfonyl and benzyl; whercin the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \dot{\mathrm{R}}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{\prime}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
34. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formulas VII, VII or IX:

(VII)

(VIII)


209

or a phannaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyi, Br -vinyl, 2-Br-ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(liower alk'yl), :O(alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
35. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula X, XI or XII:

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
Base is a purine or pyrimidine base as.defined herein;
$R^{1}, R^{2}$ and $R^{\prime 3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabjlized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid,

WO 01/90121
PCT/US01/16671
including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}(\mathrm{acyl}),-\mathrm{O}($ lower acyl), -O(alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, flụoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alky! (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
36. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula XIII, XIV or XV:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $), ~ \mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}(\mathrm{acyl}),-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chloro, bromó, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
37. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula XVI:

(XVI)
for a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
Base is a purine or pyrimidine base as defined herein; $\mathrm{R}^{1}$ and $\mathrm{R}^{2 \cdot}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\dot{\mathrm{R}^{2}}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O(lower acyl), -O(alkyl), O(lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{\prime}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O (lower acyl), -O (alkyl), - O (lower alkyl), -O (alkenyl), chlorine, bromine, iedine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2}$ or $-\mathrm{N}(\text { acyl })_{2}$;
$R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
38. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula XVII:

(XVII)
or_a pharmactutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:

Buse is a purinu or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro; iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), $-\mathrm{O}\left(\right.$ lower acyl), -O (alkyl), - $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl); chlörine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acy })_{2}$; $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;

WO 01/90121
PCT/US01/16671
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
39. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula XVIII:

(XVIII)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate; diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

## wo 01/90121

PCT/US01/16671
40. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
41. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective, amount of a compound of structure:

or a pharmaceutically accepṭable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
42. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof; together with a pharmaceutically acceptable carrier or diluent.
43. A pharmaccutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically. acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
44. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
45. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable canier or diluent.

IPO DELHI 23-06-2015.15:45
46. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable çarziè or-diluent
47. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
48. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carricr or diluent.

WO 01/90121
PCT/US01/16671
49. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $\mid C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaccutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
50. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
51. A pharmaceutical composition tor the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

IPO DELHI 23-06-2015 15:46

WO (11/90121
PCT/US01/16671
52. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $\mathbb{C}$ virus in a host, comprising an effective amount of a compound of Formula I:

$\because \cdot$
(I)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
53. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula II:

(I)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently. $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionality substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other phannaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
$Y$ is hydrogen, promo, chloro, fluor, ido, $O R^{4}, N R^{4} R^{5}$ or $S R^{44}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$, or $\mathrm{SR}^{4}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

IPO DELHI 23-06-2015 15:A20

WO 01/90121
54. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$.are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

WO $11 / 90121$
PCT/US01/16671
55. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agentṣ, wherein: -
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate.prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid; including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptablè leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$Y$ is hydrogén, bromo, chloro; fluoro, iodo, $\left(R^{4}, N R^{4} R^{5}\right.$ or $S R^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl; CO-aryl; CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
56. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula V:

(V)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized $\overline{\mathrm{p}}$ hosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonatc ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
57. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula VI:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (inclúding monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{\prime}$ is selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
58. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula VII, VIII or IX:




IPO DELHI 23-06-2015 15: A24
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2-Br-ethyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}\left(\right.$ alkyl), ' ${ }^{\prime} \mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), - O (alkyl), -O (lower alkyl), -O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
59. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula X., XI or Y II;

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $\mathbb{R}^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with

## WO 11/90121

PCT/US01/16671
one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which whon administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}($ acyl $) 2$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl $),-\mathrm{O}($ acyl), -O (lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-$ $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
60. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula XIII, XIV or XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is

WO 01/90121
PCT/US01/16671
capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\dot{\mathrm{C}}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}(l o w e r ~ a c y l),-\mathrm{O}($ alkyl $),-$ $\mathrm{O}(l o w e r ~ a l k y l), ~-\mathrm{O}\left(\right.$ alkenyl), chloro, bromo; fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
61. A pharmaceutical composition for the trealment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula XVI:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, whorein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in yivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, $\mathrm{O}\left(\right.$ lower alkyl), - O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl); -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$;

PCT/US01/16671
WO 01/9012
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
62. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of Formula XVII:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, of a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, whercin the phenyl group is optionally substitated with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceitically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl $),-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), O (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$; $R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyll, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\dot{\text { alk }} \dot{\mathrm{l}} \mathrm{l}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O (lower acyl), $-\mathrm{O}\left(\right.$ alkyl), $-\mathrm{O}\left(\right.$ löwer alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2}, .-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
63. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of Formula XVIII:

(XVIII)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmáceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), -O(alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $O \mathrm{R}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
64. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
65. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
66. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
67. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other untivirally effective agents.
68. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
69. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a componnd of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
70. A pharmaceutical composition for the treatrnent or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effeclive agents.
71. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound.of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents:
72. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, cómprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
73. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
74. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis $C$ virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
75. A pharmaceutical composition for the treatment or prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more-other antivirally effective agents.
76. The pharmaceutical composition as described in any of the preceding claims 28-75, wherein the said compound is in the form of a dosage unit.
77. The pharmaceutical composition as described in claim 76, wherein the dosage unit contains 10 to 1500 mg of said compound.
78. The pharmaceutical composition as described in claim 75 or 76 , wherein said dosage unit is a tablet or capsule.
79. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective amount of a compuinit $u f$ Formula 1 :

(I)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
80. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, wherein: .
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphatc, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluors, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $S R^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl; CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$. are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

IPO DELHI 23-06-201.5 15: 4B

WO 11/90121
PCT/US01/16671
81. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, ${ }^{\circ} \mathrm{CO}$-alkyl, CO-aryl, CO-àlkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to, methyl, ethyl, propyl and cyclopropyl).
82. A method for the treatment or prophylaxis of a Hepatitis $C$. virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independeintly $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; $Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

IPO OELHI 25-06-2015 15:40
83. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula V:

(V)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO -alkyl, CO -aryl, CO -alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

WO 01/90121
PCT/US01/16671
84. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula VI:

(VI)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is. capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ is selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
85. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula VII, VIII or IX:

$$
!
$$

## WO $01 / 90121$


(VI)

(VII)

(IX)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H :or phosphate;
$R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyi, Br -vinyl, 2-Br-ethyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl 1 ), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
86. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula X , XI or XII:

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;

WO 01/90121
PCT/US01/16671
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaping group which when administered in vive is capable of providing a compound whercin $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, aikenyi, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O(acyl); - $\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), "- O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, . NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
87. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XIII, XIV or XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein; .
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with

WO 01/50121
PCT/US01/16671
one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acy })_{2}$; and $\overline{\mathrm{X}}$ is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
88. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antijyirally effective amount of a compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable sall thereof, wherein:
Base is a purine or pyrimidinc base as defined herein; $R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl•group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen; hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}($ acyl $)$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), $-\mathrm{O}\left(\right.$ lower acyl), -O (alkyl), $-\mathrm{O}\left(\right.$ lower alkyl), $-\mathrm{O}\left(\right.$ alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a bond; and.
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
89. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVI:

(XVII)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate; or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy,: alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}(l o w e r ~ a l k y l),-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, $\mathrm{O}\left(\right.$ lower alkyl), -O(alkeņ́yl), chloro, bromo, fluoro, ịodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}(l o w e r ~ a l k y l),-\mathrm{O}$ (acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), $-\mathrm{O}\left(\right.$ alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2} ;$
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
90. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVIII:


- (XVDI)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized. phosphate prodrug); acyl (including lower acyl); alky] (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $\mathrm{O}\left(\right.$ lower alkyl), $-\mathrm{O}\left(\right.$ alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{2}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

91. A method for the treatment-or'prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
92. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
93. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
94. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure;

or a pharmaceutically acceptable sált thereof.
95. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
96. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the stiucture:

or a pharmaceutically acceptable salt thereof.
97. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound 'of the structure:

or a pharmaceutically acceptable salt thereof.
98. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
99. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
100. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
101. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective. amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
102. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.

WO 01/90121
PCT/US01/16671
103. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula I:

(I).
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
104. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other untivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalky! sulfonyl including methanesulfonyl and benzyl; wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharnaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluor, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propel and cyclopropyl).
105. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, in combination or altemation with one or more other antivirally effective agents, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosplate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
106. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, whereini:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester ịncluding alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; $Y$ is hydrogen, bromo, chloro, fluoro, iodo, $O R^{4}, N R^{4} R^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyil, propyl and cyclopropyl).

IPO DELHI 23-05-2015.15:252
107. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering ant anti-virally effective amount of a compound of Formula V :

(V)
or a pharmaceutically acceptable salt thereof, in combination or alteration with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; all amino acid; a carbohydrate; a peptide; a cholesterol; or other phamaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \dot{\mathrm{NR}}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{\prime}$ is selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

WO 01/90121
PCT/US01/16671
108. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula VI:

(VI)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbolydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
109. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula VII, VIII or IX:

IPO DELHI 23-05-2015. 15:454

WO 01/90121

(VII)

(VIII)

(IX)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including-menophoophate, dipliusphiate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2- Br -ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluors, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, . NH (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}{ }^{\circ}$.
110. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula X , XI or XII:


(XII)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:

Hase is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ arc independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate produy); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with onc or more substituents às described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable-leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently II or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), O (lower alkyl), O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyanie, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
111. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XIII, XIV or XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purinc or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (inclúding monophosphate, diphosphate, triphosphate, oi a stabilized phosphate prodrug); acyl (including lower acyl); alkyl
(including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl lincluding methanesulfonyl and benzyl; wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alky1-(including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl) $),-\mathrm{O}($ lower acyl), $-\mathrm{O}(\mathrm{alkyl})$, O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
112. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an anti-virally effective-amount of a compound of Formula XVI:

(XVI)
or a phamaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); açyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate;

PCT/US01/16671
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl), -O (alkyl), -O(lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl); $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{lowcr}$ alkyl), -O (acyl), - O (lower acyl), . O (alkyl), - O (lower alkyl), - O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}($ acyl $), \mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\mathrm{acyl})_{2}$; $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
113. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVII:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents, as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}(a l k y l)$, O (lower alkyl), -O (alkenyl), chloru, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O(lower acyl), - O (alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $\cdots \mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
114. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVII:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O (alkyl), -
$\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), - $\mathrm{N}\left(\right.$ lower alkyl) $2 ;-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyh, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
115. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
116. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or $u$ pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
117. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
$i$
118. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
119. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
120. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
121. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
122. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:


or a pharmaceutically acceptable salt thereof, in combination or alternation -with one or more antivirally effective agents.
123. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
124. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
125. A method for the treatment or prophylaxis of a Hepatitis $C$ virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof; in combination or alternation with one or more antivirally effective agents.

IPD DELHI 23-06-2015 15:45
126. A method for the treatment or prophylaxis of a Hepatitis C virus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
127. Method of treatment as described in any of the preceding claims 79-126, wherein the said compound is in the form of a dosage unit.
128. Method of treatment as deșcribed in claim 127, wherein the dosage unit contains 10 to 1500 mg of said compound.
129. Method of treatment as described in claim 127 or 128 , wherein said dosage unit is a tablet or capsule.
130. A use of a compound of Formula I:

(I)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl
and benzyl; wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{\prime}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; Y is hydrogen, promo, chloro, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently. selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO:alkyl, CO -aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
131. A use of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, jodo, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
132. A use of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphatc, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically, acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, biome, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl); or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
133. A use of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, for the treatment ar -prophylaxis of $a$ hoot infected with the Hepatitis C virus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate 'ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; $Y$ is hydrogen, bromo, chloro, fluoro, ido, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluors, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\overline{\mathrm{R}^{5}}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
134. A use of a compound of Formula V:

(V)

IPO DELHI 23-06-2015:15:47
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C.virus, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized' phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, promo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl; ethyl, propyl and cyclopropyl).

## 135. A use of a compound of Formula VI:


(VI)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\ddot{\mathrm{R}}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid,

## 350

WO 01/90121
PCT/US01/16671
including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromó, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}{ }^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
136. A use of a compound selected from Formulas VII, VIII and IX:

(VII)

(VIII)

(IX)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionaliy substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2-Br-ethyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), - O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$,
138. A use of a compound selected from Formulas XIII, XIV and XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alky] (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $\mathrm{R}^{1} ; \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $), '-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl); $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\dot{\mathrm{N}}(\mathrm{acyl})_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
139. A use of a compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the 'phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which whon administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{O} \dot{\mathrm{R}}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), $-\mathrm{O}\left(\right.$ lower acyl), -O (alkyl), $-\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl); chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
140. A use of a compound of Formula XVI:

(XVII)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
Base is a purine or pyrimidine base as defined herein;

WO 01/90121
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\dot{\mathrm{O}}$ (acyl), $-\mathrm{O}($ lower acyl), -O (alkyl), O (lower alkyl), - - (alkenyl), chloró, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), - O (acyl), $-\mathrm{O}\left(\right.$ lower acyl), $-\mathrm{O}\left(\right.$ alkyl), -O (lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (inclüding lower alkyl), chlorine, bromine, or iodine; allernatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$. or $\mathrm{CH}_{2}$.

## 141. A use of a compound of Formula XVIII:


(XVII)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with
one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in'vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently $H$ or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl $),-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl $),-\mathrm{O}($ alkyl $)$, O (lower alkyl); -O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
142. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
143. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the 'treatment or prophylaxis of a host infected with the Hepatitis C virus.
144. A use of a compound of the structure:

or a pharmaceeutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
145. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
146. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.

## WO $11 / 90121$

147. A use of a compound of the structure:


or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $\dot{C}$ virus.
148. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
149. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
150. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
151. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
152. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
153. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
154. A use of a compound of Formula I:

(I)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
$\because$ 155. A use of a compound of Formula Il:

(II)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a hostinfected with the Hepatitis C virus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalikyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an annino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are is independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

WO 01/90121
156. A use of a compound of Formula III:

(III)
or a plarmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of $a$ host infected with the Hepatitis $C$ virus, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl-group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-allkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

WO 01/9012!
PCT/US01/16671
157. A use of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other: pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; Y is hydrogen, promo, chloro, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propel and cyclopropyl).
158. A use of a compound of Formula $V$ :

(V)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein: $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl. (including lower acyl); alkyl (including lower alkyl); sulfonate ester including. alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluors, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl); or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
159. A use of a compound of Formula VI:

(VI)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid,

IPO DELHI 23-06-2015 15:472
including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyàlkyl; chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
160. A use of a compound selected from Formulas VII, VIII and IX:

(VII)

(VIII)

(IX)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl' group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharnaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyll), -O(alkyl), -O (lower alkyl), -O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2} ;-\mathrm{N}(\text { acyl })_{2}$; and

WO 01/90121
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$ :
161. A use of a compound of Formulas $\mathbf{X}, \mathrm{XI}$ and XII :

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereoof, in the manupfacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), . O(acyl); -O(lower acyl), $-\mathrm{O}\left(\right.$ alkyl), $-\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}($ acy l$),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

IPO DELHI 23-96-2015. 15:474

## 366

WO 01/90121
162. A use of a compound selected from Formulas XIII, XIV and XV:

(XII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; :an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, O (lower alkyl), $\cdot \mathrm{O}$ (alkenyl), chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\mathrm{acyl})_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
163. A use of a compound of Formula XVI:

(XVI) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl); - $\mathrm{O}($ alkyl $),-$ O (lower alkyl), -O(alkenyl), chloro, bromo, fluors, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower } \cdot \text { alkyl })_{2},-\mathrm{N}($ acyl $) 2$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}(l o w e r ~ a l k y l), ~-O(a c y l)$, -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
164. A use of a compound of Formula XVII:

(XVII)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphatc, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an àmino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ açyl), -O (lower acyl), -O (alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}{ }^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O\{lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl); chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$ :
$\mathrm{R}^{14}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
165. A use of a compound of Formula XVIII:

(XVII)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus, wherein:

Base is a purine or pyrimidine base as defined herein;'
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with
one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}(l o w e r ~ a c y l), ~-O(a l k y l),-$ O (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;"
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{\dagger}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
166. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
167. A use of a compound of the' structure:

or a pharmaceutically acceptabie salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
168. A use of a compound of the structure:

or a pharmaceütically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
169. A use of a compound of the structure:

or a pharmaceutically acceptable sall thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
170. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
171. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
172. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
173. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a niedicament for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.

WO 01/90121
PCT/US01/16671
174. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
175. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
176. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis $C$ virus.
177. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the Hepatitis C virus.
178. Use of the compound as described in any of the preceding claims 130-177, wherein the said compound is in the form of a dosage unit.
179. Use of the compound of claim 101, wherein the dosage unit contains 178 to 1500 mg of said compound.
180. Use of the compound of claim 178 or 179 , wherein said dosage unit is a tablet or capsule.

$\beta-\mathrm{D}-\mathrm{2}^{\prime}-\mathrm{CH}_{3}-$-riboA

$\beta-\mathrm{D}-\mathrm{Z}^{\prime}-\mathrm{CH}_{3}$-ńboG


$\beta$-D-2' $-\mathrm{CH}_{3}$-riboc

$\beta$-D-2' $-\mathrm{CH}_{3}$-riboU

$\beta$-D-1' $-\mathrm{CH}_{3}$-riboA



FIAU




$\beta$-D-1'- $\mathrm{CH}_{3}$-riboG


Ribavirin


$\beta$-D-2' $-\mathrm{CH}_{3}$-riboT
Chemical Structure of Illustrative Nucleosides FIG. 1

IPO DELHE 23-06-2015 SUSTITÜT A7


TPO DELHI 23-GB-2G15 $\frac{15: 47}{S U B S I T U T E ~ S H E E T ~(R U L E ~ 26) ~}$



Screening Phamacokinetics of $\beta$-D-2' $-\mathrm{CH}_{3}$-riboG in Cynomolgus Monkeys

FIG.3b

## ORLGSNAL-YOL-I

# BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI 

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN I'HE MA'IIER OF a pre-grant representation under Section 25(1)

AND
IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND
IN THE MATTER OF:

INDIA CARES
VS.

Pharmasset, Inc.
... RESPONDENTS/APPLICANTS

## PRE-GRANT OPPOSITION BY INDIA CARES

Volume -II of IV
(Page Nos. 377 to 678)

| S. No. | Particulars | Page No. |
| :--- | :--- | :--- |
|  | $\frac{\text { Annexure-4 }}{\text { Copy of WO 2001/92282 }}$ | $377-678$ |

# BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI 

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND
IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472. (Published as WO 2005/003147).

AND
IN THE MATTER OF:

INDIA CARES

VS.

Pharmasset, Inc.
... RESPONDENTS/APPLICANTS

## PRE-GRANT OPPOSITION BY INDIA CARES

## Volume-II of IV

(Page Nos. 377 to 678 )

| S. No. | Particulars | Page No. |
| :--- | :--- | :--- |
| . | $\frac{\text { Annexure-4 }}{\text { Copy of WO 2001/92282 }}$ | $377-678$ |

Dated this $23^{\text {rd }}$ day of June, 2015.

To,
The Controller of Patents
The Patent Office, Delhi
(19) World Intellectual Property Organization International Bureau
(43) International Publication Date

6 December 2001 ( 06.12 .2001 )


PCT

## 

(10) International Publication Number WO 01/92282 A2
(51) International Patent Classification${ }^{\top}$ :

C07H 19/00
(21) International Application Number: "PCT/US01/16687
(22) International Filing Date: 23 May 2001 (23.05.2001)
(25) Filing Language; .' . English
(26) Publication Language: ' . . English
(30) Priority Data:

60/207,674 26 May $2000(26.05 .2000)$ US 60/283.276 $11 \Delta$ april 2001 (11.04.2001) US
(71) Applicants for all designated. States except (IS): NOVIRIO PHARMACEUTICALS LIMITED [ -1 ]; Walker Secretaries, Walker IIouse, Grand Cayman (KY). UNIVERSITA DEGLI STUDI DI CAGLIARI [TT/IT];
. Dip. Biologia Sperimentale, Sezione di Microbiologia, Cittadella Universitaria• SS $554, \mathrm{Km}$ : $\mathbf{4} .500$, I-09(42 Monserrato (IT).
(72) Inventors; and
(75) Inventors/Applicants (for US only): SOMMADOSSI, Jean-Pierre [FRNIS]; 5075 Greystone Way, Birmingham, AL 35242 (US). LACOLLA, Pablo [I'T/I']; 5 Strada no. 11, Poggio de Mini, I-09012 Capoterra (IT).
(74) Agent: KNOWLES, Sherry, M.; King \& Spalding, 191 Peachtree Street, Atlanta, GA 30303-1763 (US).
(81) Designated. States (national): $\mathrm{AE}, \mathrm{AG}, \mathrm{AL}, \mathrm{AM}, \mathrm{AT}, \mathrm{AU}$, $A Z, B A, B B, B G, B R, B Y, B Z, C A, C H, C N, C O, C R, C U$, $C Z, D E, D K, D M, D Z, E C, E E, E S, F I, G B, G D, G E, G H$, GM, IR, ITU, ID, IL, IN, IS, JP, KL, KG, KP, KR, KL, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MK, MR, NO, NZ, PL, PT, RD, RU, SD, SE, SG, SI, SK, GL, TJ, TM, TR, TI, TR, JA, JG, US, UT, VN, YU, RA, ZN.
(84) Designated States (regional): ARIPO patent (GH, GM, KE, IS, MW, M7, SD, SI, S7, T7, UG, 7W), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, 'TJ, ' CM ); European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, I, I, MC, NT, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, BN, GO, ML, MR, NE, SN, 'TD, 'LG).

## Published:

---. without international search report and to be republished upon receipt of that report

For twol-letter codes and other abbreviations, refer to the "Quidance Notes on Codes and Abbreviations" appearing at the beginming of each regular issue of the PCT Gazette.
(57) Abstract: A method ally composition for treating a host infected with flavivirus or pestivirus comprising administering an
 salt or prodiug thereof, is provided.

# METHODS AND COMPOSITIONS FOR TREATING FLAVIVIRUSES AND PESTIVIRUSES 

## FIELD OF THE INVENTION

This invention is in the area of pharmaceutical chemistry, and in particular, is a compound, method and composition for the treatment of flaviviruses and pestiviruses: This application claims priority to U.S. provisional application no. 60/207,674, filed on May 26, 2000 and U.S. provisional application no. 60/283;276; filed on April 11, 2001.

## BACKGROUND OF THE INVENTION

Pestiviruses and flaviviruses belong to the Flaviviridae family of viruses along with hepatitis $C$ virus. The pestivirus' genus' includes bovine viral diarrhea virus ( $B V D V$ ), classical swine fever virus (CSFV, also called hog cholera virus) and border disease virus (BDV) of sheep (Moennig; V..et al. Adv. Sir. Res. 1992, 41, 53-98). Pestivirus infections of domesticated livestock (cattle, pigs and sheep) cause significant economic losses worldwide. BVDV causes mucosal disease in cattle and is of significant economic importance to the livestock industry (Meyers, G. and Thill, H.-J., Advances in Virus Research, 1996, 47, 53118; Moennig V., et al, Adv. Fir. Res. 1992, 4l, 53-98).

Human pestiviruses have not been as extensively characterized as the animal pestiviruses. However, serological surveys indicate considerable pestivirus exposure in humans. Pestivirus infections in man have been implicated in several diseases including congenital brain injury, infantile gastroenteritis and chronic diarrhea in human immunodeficiency virus (HIV) positive patients. M. Giangaspero et al., Arch. Virol. Suppl., 1993, 7, 53-62; M. Giangaspero ct al., Int. J. Std. Aids, 1993, 4 (5): 300-302.

The flavivirus genus includes more than 68 members separated into groups on the basis of serological relatedness (Calisher et al., J. Gen. Viol, 1993, 70, 37-43). Clinical symptoms vary and include fever, encephalitis and hemorrhagic fever. Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, 1996, Chapter 31, 931-959. Flaviviruses of global concern that are associated with human disease include the dengue hemorrhagic fever viruses (DHF), yellow fever virus, shock syndrome and Japanese encephalitis virus. Halstead, S. B., Rev. Infect.

Dis., 1984, 6, 251-264; Halstead, S. B. 2 Science, 239:476-481, 1988; Monath, T. P., New Eng. J. Med., 1988, 319, 641-643.

Examples of antiviral agents that have been identified as active against the flavivirus or pestiviruses include:
(1) interferon and ribavirin (Battaglia, A.M. et al, Ann. Pharmacother, 2000, 34, 487494); Berenguer, M. et al. Antivir. Ther., 1998, 3 (Suppl: 3), 125-136);
(2) Substrate-based NS3 protease inhibitors (Attwood et al., Antiviral peptide derivatives, PCT WO 98/22496, 1998; Atwood et al., Antiviral Chemistry and Chemotherapy 1999, 10, 259-273; Atwood et al., Preparation and use of amino. acid derivatives as antiviral agents, German Patent Pub. DE 19914474; Ting et al. Inhibitors of serine proteases, particularly hepatitis $C$ virus NS3 protease, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in in electrophile such as a boronic acid or phosphonate (Llinas-Brunet et al, Hepatitis C inhibitor peptide analogues, PCT WO 99/07734).
(3) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives (Sudo K. et al., Biochemical and Biophysical Research Communications, 1997, 238, 643-647; Sudo ${ }^{\circ}$ K. et al. Antiviral Chemistry and Chemotherapy, 1998 2 9, 186), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-. phenoxyphenyl group;
(4) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. et al., Antiviral Research, 1996, 32, 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;
(5) Thiazolidines and benzanilides identified in Kakiuchi N. et al. J. EBS Letters 421, 217-220; Takeshita N. et al. Analytical Biochemistry, 1997, 247, 242-246;
(6) A phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Chi M. et al., Tetrahedron Letters, 1996, 37, 7229-7232), and Sch 351633, isolated from the fungus Penicillium griscofuluum, which demonstrates

WO 01/92282
activity in a scintillation proximity assay (Chu M. et al., Bioorganic and Medicinal Chemistry Letters 9, 1949-1952);
(7) Selective NS3 inhibitors based on the macromolecule elgin c , isolated from leech (Qasim M.A. et al., Biochemistry, 1997, 36, 1598-1607);
(8) Helicase inhibitors (Diana G.D. ct cal., Compounds, compositions and methods for treatment of hepatitis C, U.S. Pat. No. 5,633,358; Diana G.D. et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C, PCT WO 97/36554);
(9) Polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. et al. Journal of Virology, 1999, 73, 1649-1654), and the natural product cerulenin (Lohmann V. et al., Virology, 1998, 249; 108-118);
(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the $5^{\prime}$ non-coding region (NCR) of the virus (Alt M. et al., Hepatology, 1995, 22, 707-717), or nucleotides 326-348 comprising the 3 ' end of the NCR and nucleotides 371-388 located in the core coding region of the ICV. RNA (Alt M. et al., Archives of Virology, 1997, 142, 589-599; Galderisi U. et al., Journal of Cellular Physiology, 1999, 181, 251-257);
(11) Inhibitors of IRES-dependent translation (Ikeda N et al., Agent for the prevention and treatment of hepatitis C, Japanese Patent Pub. JP-08268890; Kai Y. et al. Prevention and treatment of viral diseases, Japanese Patent Pub. JP-10101591);
(12) Nuclease-resistant ribozymes (Maccjak, D. J. et al., Hepatology 1999, 30, abstract 995); and
(13) Other miscellaneous :compounds including 1 -amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold et al.), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier et al.), vitamin E and other antioxidants (U.S. Pat. No. 5,922,757. to Chojkier et al.), squalene, amantadine, bile acids (U.S. Pat. No. 5,846,964 to Ozeki et al.), N -(phosphonoacetyl)-L-aspartic acid, (U.S. Pat. No. 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diana et al.), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546 to. Wang et āl.), 2',3'dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan et al.), and benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino et al.).

TPO DELHE 23-06-2015 15:49

In view of the severity of diseases associated with pestiviruses and flaviviruses, and their pervasiveness in animal and man, it is an object of the present invention to provide a compound, method and composition for the treatment of a host infected with flavivirus or pestivirus.

## SUMMARY OF THE INVENTION

Compounds, methods and compositions for the treatment of a host infected with a flavivirus or pestivirus infection are described that includes an effective treatment amount of a $\beta$-D- or $\beta$-L-nucleoside of the Formulas (I) - (XVII), or a pharmaceutically acceptable salt or prodrug thereof.

In a first principal embodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(I)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are- independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{l}, R^{2}$ or $R^{3}$ is independently H or phosphate;

Y is hydrogen, promo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, $\mathrm{CO}_{\mathrm{i}}$ aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a second principal embodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof; is provided:

(II)
wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and
$Y$ is hydrogen, promo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a third principal embodiment, a compound of Formula III, or a pharmaceutically acceptable salt or prodrug thereof, is provided:


(III)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrig); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in wivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a fourth principal embodiment, a compound of Formula IV, or a pharmaceutically acceptable salt or prodrug thereof, is provided:


6
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given hercin; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, COalkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a fifth principal embodiment, a compound of Formula V , or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(V)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; : cholesterol; or other pharmaceutically acceptable leaving
group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, COalkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a sixth principal embodiment, a compound of Formula VI; or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(VI)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester inclading alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in $\ddot{v} \boldsymbol{v} o$ is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, COalkyl, CO-aryl, CO-alkoxyalkyl, chioro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a seventh principal embodiment, a compound selected from Formulas VII, VIII and IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(VII)

(VIII)

(IX)
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a sțabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, 2-Br-ethyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), -O (lower alkyl), -O(alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { fower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a eighth principal embodiment, a compound of Formulas X, XI and XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(X)

(XI)

(XII)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are, independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in . wive is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -
 alkyl), -O(alkenyl), chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), $-\mathrm{NH}($ acyl), N (lower alkyl) $2,-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), -O(alkyl), -O(lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a ninth principal embodiment a compound selected from Formulas XII, XIV and XV , or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(XII)

(XIV)

(XV)
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino
acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;
$R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), -O (alkyl), -O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}\left(\text { ạcyl }^{2}\right)_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
In a tenth principal embodiment thie invention provides a compound of Formula XVI, or a pharmaceutically acceptable salt or prodng thereof:

(XVI)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosplate (including monophosphate, diphosphate, triphosphate, or-a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a pliospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceütically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ or $R^{2}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), $-\mathrm{O}(\mathrm{alkyl}),-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iudo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, - NH (lower alkyl), -NH (acyl), N (lower alkyl) $)_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \bigcirc($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), - O (alkyl), -O(lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, -NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{7}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\dot{R}^{10}$ can come together to form a pi bond; and

X is $\mathrm{O}, \mathrm{S}^{\mathrm{S}} \mathrm{SO}_{2}$ or $\mathrm{CH}_{3}$.
In a eleventh principal embodiment the invention provides a compound of Formula XVII, or a pharmaceutically acceptable salt or prodrug thereof:

(XVII)
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, ora stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an anino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ or $R^{2}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinỵl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a pi bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In an twelth principal embodiment, the invention provides a compound of Formula XVIII, or a pharmaceutically acceptable salt or prodrug thereof:

(XVIII)
wherein:
Base is a purine or 'pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ or $\mathrm{R}^{2}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl; Brvinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}$ (lower alkyl), -O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a pi bond; X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

The $\beta$-D- and $\beta$-L-nucleossides of this invention may inhibit flavivinus or pestivirus polymerase activity. These nucleosides can be assessed for their ability to inhibit flavivirus or pestivirus polymerase activity in vitro according to standard screening methods.

In one embodiment the efficacy of the anti-flavivirus or pestivirus compound is measured according to the concentration of compound necessary to reduce the plaque number of the virus in vitro, according to methods set forth more particularly herein, by $50 \%$ (i.e. the compound's $\mathrm{EC}_{50}$ ): In preferred embodiments the compound exhibits an $\mathrm{EC}_{50}$ of less than 15 or preferably, less than 10 micromolar in vitro.

In another embodiment, the active compound can be administered in combination or alternation with another anti-flavivirus or pestivirus agent. In combination therapy, effective dosages of two or more agents are administered together, whereas during altemation therapy an effective dosage of each agent is administered serially. The dosages will depend on absorption, inaetivation and excretioh rates of the drug as well as other factors known to those of skill in the art. It is to be-noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions:

HCV is a member of the Flaviviridae family; however, now, HCV has been placed in a new monotypic genus, hepacivirus. Therefore, in one embodiment, the flavivirus or pestivirus is not HCV .

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include:
(1) an interferon and/or ribavirin (Battaglia, A.M. et al., Ann. Pharmacother. 34:487494, 2000); Berenguer, M. et al. Antivir. Ther. 3(Suppl. 3):125-136, 1998);
(2) Substrate-based NS3 protease inhibitors (Attwood et al., Antiviral peptide derivatives, PCT WO 98/22496, 1998; Attwood et al., Antiviral Chemistry and Chemotherapy 10.259-273, 1999; Atwood et al., Preparation and use of amino acid derivatives as anti-viral agents, German Patent Publication DE 19914474; Ting et al. Inhibitors of serine proteases; particularly hepatitis C virus NS3 protease, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate. Llinas-Brunet et al, Hepatitis C' inhibitor peptide analogues, РCTT WO 99/07734.
(3) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives(Sudo K. et al., Biochemical and Biophysical Research Communications, 238:643647, 1997; Suds K. et al. Antiviral Chemistry and Chemotherapy 9:186, 1998), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group;
(4) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. et al., Antiviral Research 32:9-18, 1.996), especially compound RD-1-62.50, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;
(5) Thiazolidines and benzanilides identified in Kakiuchi N. et al. J. EBS Letters 421:217-220; Tákeshita N. et al. Analytical Biochemistry 247:242-246, 1997;
(6) A phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Chu M. et al., Tetrahedron Letters 37:7229-7232, 1996), and Sch 351633, isolated from the fungus Penicillium griscofuluum; which demonstrates activity in a scintillation proximity assay (Chụ M. et al., Bioorganic and Medicinal Chemistry Letters 9:1949-1952);
(7) Selective NS3 inhibitors based on the macromolecule algin c, isolated from leech (Qasim M.A. et al., Biochemistry 36:15.98-1607, 1997);
(8) Helicase inhibitors (Diana G.D. et al., Compounds, compositions and methods for treatment of hepatitis C, U.S. Patent No. 5,633,358; Diana G.D. et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis $C, \mathrm{PCT}$ WO 97/36554);
(9) Polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. et al. Journal of Virology 73:1649-1654, 1999), and the natural product cerulenin (Lohmann V. et al., Virology 249:108-118, 1998);
(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the $5^{\prime}$ non-coding region (NCR) of the virus (Alt M. et al., Hepatology 22:707-717, 1995), or nucleotides 326-348 comprising the $3^{\prime}$ end of the NCR and nucleotides 371-388 located in the core coding region of the IICV RNA (Alt M. et al., Archives of Virology 142:589-599, 1997; Galderisi U. et al., Journal of Cellular Physiology 181:251-257, 1999);
(11) Inhibitors of IRES-dependent translation (Ikeda N et al., Agent for the prevention and treatment of hepatitis C, Sapanese Patent Publication, JP-08268890; Kai Y. et al. Prevention and treatment of viral diseases, Japanese Patent Publication JP-10101591);
(12) Nuclease-resistant ribozymes. (Maccjak D.J. et al., Hepatology 30 abstract 995, 1999); and
(13) Other miscellaneous compounds including 1 -amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold et al.), alkyl lipids (U.S. Patent No. 5,922,757 to Chojkier et al.), vitamin E and other antioxidants (U.S. Patent No. 5,922,757 to Chojkier et al.), squalene, amantadine, bile aciḍs (U.S. Patent No. 5,846,964 to Ozeki et al.), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Patent No: 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Patent No. 5,633,388 to Diana et al.), polyadenylic acid derivatives (U.S.'. Pateṇt No. 5,496,546 to Wang et al.), 2', $3^{\prime}$-dideoxyinosine (U.S. Patent No. 5,026,687 to Yarchoan et al.), and benzimidazoles (U.S. Patent No. 5,891,874 to Colacino et al.).

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 provides the structure of various non-limiting examples of nucleosides of the present invention, as well as other known nucleosides, FIAU and Ribavirin, which are used as comparative examples in the text.

Figure 2 is a line graph of the pharmacokinetics (plasma concentrations) of $\beta$-D-2'-$\mathrm{CH}_{3}$-riboG administered to Cynomolgus Monkeys over time after administration:

Figure 3a and 3b are line graphs of the pharmacokinetics (plasma concentrations) of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG administered to Cynomolgus Monkeys either intravenously (3a) or orally (3b) over time after adininistration.

Figure 4 depicts line graphs of the results of the cell protection assay of $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}-$ riboG against BVDV.

Figure 5 depicts line graphs of the results of the cell protection assay of ribavirin against BVDV.

Figure 6 are line graphs of the cell protection assay of $\beta-D-2^{\prime}-\mathrm{CII}_{3}-$ riboG, $\beta-\mathrm{D}-2^{\prime}$ -$\mathrm{CH}_{3}$-riboC, $\beta$-D-2'- $\mathrm{CH}_{3}$-riboU, $\beta$-D-2'- $\mathrm{CH}_{3}$-riboA and ribavirin.

Figure 7 are line graphs of the results of the plaque reduction assay for $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}-$ riboU, $\beta$-D-2'- $\mathrm{CH}_{3}$-riboC and $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG.

Figure 8 is an illustration of plaque reduction based on increasing concentrations of $\beta$-D-2'-CHI-riboU.

Figure 9 is a line graph of the results of the yield reduction assay for $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}-$ riboG, depicting a $4 \cdot \log$ reduction at $9 \mu \mathrm{M}$.

Figure 10 is an illustration of the yield reduction.based on increasing concentrations of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboC.

## - DETAILED DESCRIPTION OF THE INVENTION

The invention as disclosed herein is a compound, method and composition for the treatment of pestiviruses and flaviviruses in humans and other, host animals, that includes the administration of an effective flavivirus or pestivirus treatment amount of an $\beta$-D- or $\beta$-Lnucleoside as described herein' or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier. The compounds of this invention either possess antiviral (i.e., anti-flavivirus or pestivirus) activity, or are metabolized to a compound that exhibits such activity.

In summary, the present invention includes the following features:
(a) $\beta$-D- and $\beta$-L-nucleosides, as described herein, and pharmaceutically acceptable salts and prodrugs thereof;
(b) $\quad \beta$-D- and $\beta$-L-nucleosides as described herein, and pharmaceutically acceptable salts and prodrugs thereof for use in the treatment or prophylaxis of a flavivirus or pestivirus infection, especially in individuals diagnosed as having a flavivirus or pestivirus infection or being at risk for becoming infected by flavivirus or pestivirus;
(c) use of these $\beta$-D- and $\beta$-L-nucleosides, and pharmaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for treatment of a flavivirus or pestivirus infection;
(d) pharmaceutical formulations comprising the $\beta$-D- and $\beta$-L-nucleosides or pharmaceutically acceptable salts or prodrugs thereof together with a pharmaceutically acceptable carrier or diluent;
(e) $\beta$-D- and $\dot{\beta}$-L-mucleosides as described herein substantially in the absence of enantiomers of the described nucleoside, or substantially isolated from other chemical entities;
(f) processes for the preparation of $\beta$-D- and $\beta$-L-nucleosides, as described in more detail below; and
(g) processes for the preparation of $\beta$-D- and $\beta$-L-nucleosides substantially in the absence of enantiomers of the described nucleoside, or substantially isolated from other chemical entities. -

Flaviviruses included within the scope of this invention are discussed generally in Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, Chapter 31, 1996. Specific flaviviruses include, without limitation: Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Larigat, Louping ill, Meaban, Modoc, ${ }^{\bullet}$ Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, Royal Farm, Ruṣsian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tenbbusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, West Nile, Yaounde, Yellow fever, and Zika.

Pestiviruses included within the scope of this invention are discussed generally in Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, Chapter 33, 1996. Specific pestiviruses include, without limitation: bovine viral diarrhea viras ("BVDV"), classical swine fever virus ("CSFV," also called hog cholera virus), and borider disease virus ("BDV").

## 1. Active Compound, and Physiologically Acceptable Salts and Prodrugs Thereof

In a first principal embodimenl, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(I)
wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H , phosphate (including mono-, di- or triphosphate and a stabilized plosphate prodrug); acyl (including lower acyl); alkyl (including lower alkýl); sulfonate ester inicluding alkyl or arylalikyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herẹin; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $R^{3}$ is independently H or phosphate;

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate (preferably $H$ );
$\mathrm{X}^{1}$ is H ;
$\mathrm{X}^{2}$ is H or $\mathrm{NH}_{2}$; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{NH}_{2}$ or OH .
In a second principal embodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(II)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and.
$Y$ is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate (preferably $H$ ); $\mathrm{X}^{1}$ is H ;
$\mathrm{X}^{2}$ is H or $\mathrm{NH}_{2}$; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{NH}_{2}$ or OH .
In a third principal embodiment, a compound of Formula III, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(III)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including. lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administcred in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula III, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate (preferably H );
$\mathrm{X}^{\mathrm{l}}$ is H ;
$\mathrm{X}^{2}$ is H or $\mathrm{NH}_{2}$; and
Y is hydrogen, promo, chloro, fluoro, ido, $\mathrm{NH}_{2}$ or OH .
In a fourth principal embodiment, a compound of Formula $I V$; or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(IV)
wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H , phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ or $R^{3}$ is independently H or phosphate;
$Y$ is hydrogen, promo, chloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, COalkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula IV, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate (preferably $H$ );
$\mathrm{X}^{1}$ is H or $\mathrm{CH}_{3}$; and
Y is hydrogen, bromo, chloro, fluoro, jodo, $\mathrm{NH}_{2}$ or OH .
In a fifth principal embodiment, a compound of Formula V , or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(V)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluors, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluors, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula V, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate (preferably $H$ );
$\mathrm{X}^{1}$ is H or $\mathrm{CH}_{3}$; and
Y is hydrogen, bromo, chloro, fluoro, jodo, $\mathrm{NH}_{2}$ or OH .
In a sixth principal embodiment, a compound of Formula VI, or a pharmaceutically acceptable salt or prodnug thereof, is provided:

(V)
wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is 'optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a c̣holesterol; or other pharnaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $R^{1}, R^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, jodo, $O R^{4}, N R^{4} R^{5}$ or $S R^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, COalkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluors, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{5}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

In a preferred subembodiment, a compound of Formula VI, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate (preferably H );
$\mathrm{X}^{1}$ is $\mathrm{H}^{\text {or }} \mathrm{CH}_{3}$; and

Y is hydrogen, bromo, chloro, fluor, ido, $\mathrm{NH}_{2}$ or OH .
In a seventh principal embodiment, a compound selected from Formulas VII, VIII and IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(VII)

(VIII)

(IX)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; 'a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, 2-Br-ethyt; -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), $\mathrm{CF}_{3}$, chloro, promo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
In a first preferred subembodiment; a compound of Formula VII, VIII or IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently hydrogen or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula VII, VIII or IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are hydrogens;
$R^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a third preferred subembodiment, a compound of Formula VII, VIII or IX, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is O .
In a eighth principal embodiment, a compound of Formula X, XI or XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(X)

(XI)

(XII)
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in. vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$. or $\mathrm{R}^{3}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl $),-\mathrm{O}($ acyl), -O (lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2} ;$
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), -NH(acyl), $\mathrm{N}(\text { loweralkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a first preferred subembodiment, a compound of Formula X, XI or XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a second preferred subembodiment, a compound of Formula $\mathrm{X}, \mathrm{XI}$ or XII, or a pharmaceutically acceptable salttor prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{l}, R^{2}$ and $R^{3}$ are hydrogens;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a third preferred subembodiment, a compound of Formula X, XI or XII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is O .

In even more preferred subembodiments, a compound of Formula XI, or its pharmaceutically acceptable salt or prodrug, is provided:

(XI)
wherein:
Base is a purine or pyrimidine base as defined herein; optionally substituted with an amine or cyclopropyl (e.g., 2-amino, 2,6-diamino or cyclopropyl guanosine); and
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent s as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ or $R^{2}$ is independently H or phosphate.

In a ninth principal embodiment a compound selected from Formula XIII, XIV or XV , or a pharmaceutically acceptable salt or prodrug thereof, is provided:

(XIII)

(XIV)

(XV)
wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl
and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ or $\mathrm{R}^{3}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, $\mathrm{Br}-$ vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), - O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), $-\mathrm{NH}($ acyl), -$-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a first preferred subembodiment, a compound of Formula XII, XIV or XV, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein; $R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate; $\mathrm{R}^{6}$ is alkyl; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula XIII, XIV or XV, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are hydmogens;
$\mathrm{R}^{6}$ is alkyl; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a third preferred subembodiment, a compound of Formula XIII, XIV or XV, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently hydrogen or phosphate;
$\mathrm{R}^{6}$ is alkyl; and
X is O .

In a tenth principal embodiment the invention provides a compound of Formula XVI, or a pharmaceutically acceptable salt or prodrug thereof:

(XVI)
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$, and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl. or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}($ lower alkyl), -O(alkeńyl), chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), -NH (acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\mathrm{acyl})_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O (alkyl), $-\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a pi bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a first preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ is independently.H or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$, alkyl, alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{\prime}$ is independently $H$ or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically, acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O -alkenyl, chloro, promo, fluoro, ido, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a third preferred subembodiment, a compound of Formula XVI, or its .pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or
arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O -alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$, alkyl, alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a fourth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, . riphosphate, or a.stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl, alkenyl, alkynyl, Br -vinyl, hydroxy, O -alkyl, O -alkenyl, chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$, alkyl, alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O .

In a fifth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{\prime}$ is independently $H$ or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl' or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a
cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{1}$; (5) $R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a sixth preferred subembodiment, a compound of Formula XVI, or its pharmaccutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl. including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a seventh preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1), Base is a purine or pyrimidine base as defined herein; (2) $R^{l}$ is independently $H$ or phosphate (including monophosphate, diphosphate, triphospliate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; ad cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O -alkenyl; chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) $X$ is $O$.

In a eighth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or
pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$ or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a ninth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{\prime}$ is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) $X$ is $O$.

In a tenth preferred subembodiment, a compound of Formula XVI, or its pharmaccutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{\prime}$ is independently $H$ or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a
cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl,. Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is O .

In an eleventh preferred subembodiment, a compound of. Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$ or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluors, ido, $\mathrm{NO}_{2}$, amino, loweralkylumino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a twelfth preferred. subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O, S, S_{2}$, or $\mathrm{CH}_{2}$.

In a thirteenth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{4}$ are independently $O R^{2}$; (5) $R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O .

In a fourteenth preferred subembodiment, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$.

In even more preferred subembodiments, a compound of Formula XVI, or its pharmaceutically acceptable salt or prodrug, is provided in which:
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is guanine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) X is O ;
(1) Base is cytosiue; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is thymine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is uracil; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5). $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is phosphate; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is ethyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is propyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R!$ is hydrogen; (3) $R^{6}$ is butyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ is hydrogen and $R^{9}$ is hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ and $R^{10}$ are hydrogen; and (6) X is S ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is $\mathrm{SO}_{2}$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are hydrogen; and (6) X is $\mathrm{CH}_{2}$;

In a eleventh principal embodiment the invention provides a compound of Formula XVII, or a pharmaceutically acceptable salt or prodrug thereof:

(XVII)
wherein:
Base is a purine or pyrimidine başe as defined herein;
$\mathrm{R}^{1}$ is H ; phosphaté (including monophosphate, diphosphate; triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phóspholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently H or phosphate;
$\cdot \mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), $-\mathrm{O}($ alkyl $),-\mathrm{O}$ (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), - $\mathrm{NH}($ acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), -O (acyl), -O (lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acy })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyt), chlorine, bromine, or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ cain come together to form a pi bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a first preferred subembodiment, a compound of Formula XVIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl
(including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkyniyl, Bi vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{10}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine-or pyrimidine base as defined herein; (2) $R^{l}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyll); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an aminq acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, luweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a third preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined hercin; (2) $R^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a
cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $R^{9}$ are independently hydrogen, $\dot{O}^{\circ} R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Brvinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, löweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is O .

In a fourth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{l}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as $\dot{\text { described }}$ in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a fifth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$
and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is O .

In a sixth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one.or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lover alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{10}$ is H ; and (6) X is O .

In a seventh preferred subembodiment, a compound of Formula XVII, or its pharnaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{l}$ is independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including ar phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, ànino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $R^{9}$ are independently $O R^{2}$; (5) $R^{10}$ is $H$; and (6) $X$ is $O$.

In an eighth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4)
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)-amino; (5) $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl); chlorine, bromine or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a ninth preferred subembodiment, a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O -alkyl, O -alkenyl, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{K}^{7}$ and $\mathrm{K}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a tenth preferred subembodiment, a compound of Formula XVIl, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently H or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$. and $R^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{10}$ is H ; and (6) X is.O, $\mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In even more preferred "'subembodinents, a compound of Formula XVII, or its pharmaceutically acceptable salt,or.prodrug, is provided in which:
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is guanine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is cytosine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is O ;
(1) Base is thymine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is uracil; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is phosphate; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is ethyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is propyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is butyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is O ;
(1) Base is adeninc; (2) $R^{\prime}$ is hydogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{10}$ is hydrogen; and (6) $X$ is $S$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogent; and (6) X is $\mathrm{SO}_{2}$; or
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{10}$ is hydrogen; and (6) X is $\mathrm{CH}_{2}$.

In an twelfh principal embodiment the invention provides a compound of Formula XVIII, or a pharmaceutically acceptable salt or prodrug thereof:

(XVII)
wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Brvinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), $-\mathrm{O}($ alkyl), $-\mathrm{O}($ lower
alkyl), -O(alkenyl), chloro, bromo; fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), -NH (acyl), $\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl' (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, lower alkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a pi bond;
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
In a first ipreferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided. in which: (1); Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including metrianesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently hydrogen, $O \dot{R}^{2}$, alkyl (including lower alkyl); alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a second preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$
is alkyl (including lower alkyl), alkenyl, ạlkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, amino, loweralkylamino or di-(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a third preferred subembodiment, a compound of Formula XVIII, or its, pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(lower-alkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a fourth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\dot{\mathrm{OR}}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Brvinyl, O-alkenyl, chlorine, $\cdot \cdot$ bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or

WO 11 N22*2
PCT/US01/16687
di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O .

In a fifth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate; (3) $\mathrm{R}^{6}$. is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a sixth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$ is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl);- sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) $\dot{X}$ is $O$.
'In a seventh preferred subembodiment,' a compound of Formula XVII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $\mathrm{R}^{1}$. is independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl
(including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2} ;$ amino, loweralkylamino, or di(loweralkyl)amino; (5) $\mathrm{R}^{8}$ is H ; and (6) X is O .

In an eighth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, hydroxy, O -alkyl, O -alkenyl, chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}$, amino, loweralkylamino or di(loweralkyl)amino; (4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

In a ninth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $\mathrm{OR}^{2}$; (5) $\mathrm{R}^{8}$ is H ; and (6) X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.

In a tenth preferred subembodiment, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) $R^{1}$ is independently $H$ or phosphate; (3) $R^{6}$ is alkyl; (4) $R^{7}$ and $R^{9}$ are independently $O R^{2}$; (5) $R^{8}$ is $H$; and (6) $X$ is $O$.

In even more preferred subembodiments, a compound of Formula XVIII, or its pharmaceutically acceptable salt or prodrug, is provided in which:
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is guanine; (2) $R^{1}$ is hydrogen; (3). $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is cytosine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is thymine; (2) $R^{1}$ is hydrogen;
(3) $R^{6}$ is methyl;
(4) $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$; •
(1) Base is uracil; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is phosphate; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$; •
(1) Base is adenine; (2). $R^{1}$ is hydrogen; (3) $R^{6}$ is ethyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is propyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is O ;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is butyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $O$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $R^{8}$ is hydrogen; and (6) $X$ is $S$;
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is $\mathrm{SO}_{2}$; or
(1) Base is adenine; (2) $R^{1}$ is hydrogen; (3) $R^{6}$ is methyl; (4) $R^{7}$ and $R^{9}$ are hydroxyl; (5) $\mathrm{R}^{8}$ is hydrogen; and (6) X is $\mathrm{CH}_{2}$.

The $\beta$-D- and $\beta$-L-nucleosides of this invention belong to a class, of anti-flavivirus or pestivirus agents that may inhibit flavivirus or pestivirus polymerase activity. Nucleosides can be screened for their ability to inhibit flavivirus or pestivirus polymerase activity in vitro according to screening methods set forth more particularly herein. One can readily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.

In one embodiment the efficacy of the anti-flavivirus or pestivirus compound is measured according to the concentration of compound necessary to reduce the plaque number of the virus in vitro, according to methods set forth more particularly herein, by $50 \%$ (i.e. the compound's $\mathrm{EC}_{50}$ ). In preferred embodiments the compound exhibits an $\mathrm{EC}_{50}$ of less than 15 or 10 micromolar.

IPO DELHI 23-06-2015 15:49

HCV is a member of the Flaviviridae family; however, now, HCV has been placed in a new monotypic genus, hepacivinus. Therefore, in one embodiment, the flavivirus or pestivirus is not HCV .

The active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and a compound, which has been alkylated or acylated at the 5 '-position, or on the purine or pyrimidine base (a type of "pharmaceutically acceptable prodrug"). Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the salt or prodrug and testing its antiviral activity according to the methods described herein, or other methods known to those skilled in the art.

## II. Deflnitions

The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of typically $\mathrm{C}_{1}$ to $\mathrm{C}_{10}$, and specifically includes methyl, trifluoromethyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, $t$-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups. Moieties with which the alkyl group can be substituted are selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

The term lower alkyl, as used herein, and unless otherwise specified, refers to a $\mathrm{C}_{1}$ to $\mathrm{C}_{4}$ saturated straight, branched, or if appropriate, a cyclic (for example, cyclopropyl) alkyl group, including both substituted and unsubstituted forms. Unless otherwise specifically stated in this application, when alkyl is a suitable moiety, lower alkyl is preferred. Similarly, when alkyl or lower alkyl is a suitable moiety, unsubstituted alkyl or lower alkyl is preferred.

The term alkylamino or arylamino refers to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "protected", as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to thosé skilled in the art of organic synthesis.

The term aryl, as used hercin, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl, and preferably phenyl. The teim includes both substituted and unsubstituted moieties. The aryl group can be substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The term alkaryl or alkylaryl refers to an alkyl group with an aryl substituent. The term aralkyl or arylalkyl refers to an aryl group with an alkyl substituent.

The term halo, as used herein, includes chloro, bromo, iodo, and fluoro.
The term purine or pyrimidine base includes, but is not limited to, adenine, $\mathrm{N}^{6}$ alkylpurines, $\mathrm{N}^{6}$-acylpurines (wherein acyl is $\mathrm{C}(\mathrm{O})$ (alkyl, aryl, alkylaryl, or arylalkyl), $\mathrm{N}^{6}$. benzylpurine, $\mathrm{N}^{6}$-halopurine, $\mathrm{N}^{6}$-vinylpurine, $\mathrm{N}^{6}$-acetylenic purine, $\mathrm{N}^{6}$-acyl purine, $\mathrm{N}^{6}$-hydroxyalkyl purine, $\mathrm{N}^{6}$-thioalkyl purine; $\mathrm{N}^{2}$-alkylpurines, $\mathrm{N}^{2}$-alkyl-6-thiopurines, thymine, cytosine, 5 -fluorocytosine, 5 -methylcytosine, 6 -azapyrimidine, including 6 azacytosine, $2-$ and/or 4 -mercaptopyrmidine, uracil, 5 -halouracil, including 5 -fluorouracil, $C^{5}$-alkylpyrimidines, $C^{5}$-benzylpyrimidines, $C^{5}$-halopyrimidines, $C^{5}$-vinylpyrimidine, $C^{5}$ acetylenic pyrimidine, $C^{5}$-acyl pyrimidine, $C^{5}$-hydroxyalkyl purine, $C^{5}$-amidopyrimidine, $C^{5}$ cyanopyrimidine, $C^{5}$-nitropyrimidine, $C^{5}$-aminopyrimidine, $N^{2}$-alkylpurines, $N^{2}$-alkyl-6thiopurines, 5 -azacytidinyl, 5 -azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolo-pyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6 -diaminopurine, and 6 -chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to, those skilled in the art, and include trimethylsilyl, dimethylhexylsilyi, $t$-butyldimethylsilyl and $t$-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl. Alternatively, the purine or pyrimidine base can optionally substituted such that it forms a viable prodrug,
which can be cleaved in vivo. Examples of appropriate substituent include acyl moiety, an amine or cyclopropyl (e.g., 2-amino, 2,6-dianino or cyclopropyl guanosine).

The term acyl refers to a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from straight, branched, or cyclic alkyl or lower alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, $\mathrm{C}_{1}$ to $\mathrm{C}_{4}$ alkyl or $\mathrm{C}_{1}$ to $\mathrm{C}_{4}$ alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethylt -butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group. The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is lower alk gl.

As used herein, the term "substantially free of" or "substantially in the absence of" refers to a nucleoside composition that includes at least 85 or $90 \%$ by weight, preferably $95 \%$ to $98 \%$ by weight, and even more preferably $99 \%$ to $100 \%$ by weight, of the designated enantiomer of that nucleoside. In a preferred embodiment, in the methods and compounds of this invention, the compounds are substantially free of enantiomers.

Similarly, the term "isolated" refers to a nucleoside composition that includes at least 85 or $90 \%$ by weight, preferably $95 \%$ to $98 \%$ by weight, and even more preferably $99 \%$ to $100 \%$ by weight, of the nucleoside, the remainder comprising other chemical species or enantiomers.

The term "independently" is used herein to indicate that the variable, which is independently applied, varies independently from application to application. Thus, in a compound such as $R$ "XYR", wherein $R$ " is "independently carbon or nitrogen," both $R$ " can be carbon, both $R$ " can be nitrogen, or one $R$ " can be carbon and the other $R$ " nitrogen.

The term host, as used herein, refers to an unicellular or multicellular organism in which the virus can replicate, including cell lines and animals, and preferably a human. Alternatively, the host can be carrying a part of the flavivirus or pestivirus genome, whose replication or function can be altered by the compounds of the present invention. The term host specifically refers to infected cells, cells transfected with all or part of the flavivirus or pestivirus genome and animals, in particular, primates (including chimpanzees) and humans. In most animal applications of the present invention, the host is a human patient: Veterinary
applications, in certain indications, however, are clearly anticipated by the present invention (such as chimpanzees).

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a nucleoside compound which, upon administration to a patient, provides the nucleoside compound. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts, include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and imaynesium, among numerous other acids well known in the pharmaceutical att: Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include coinpounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound. The compounds of this invention possess antiviral activity against flavivirus or pestivirus, or are metabolized to a compound that exhibits such activity.

## III. Nucleotide Salt or Prodrug Formulations

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may-be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, $\alpha$ ketoglutarate, and $\alpha$-glycerophosphate. Suitable inorganic salts may also be formed, including, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well . known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogen on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

The active nucleoside can also be provided as a 5'-phosphoether lipid or a 5'-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L.S., N. Iyer, E. Leake, A. Raben, Modest E.K., D.L.W., and C. Piantadosi, "Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation," AIDS Res. Hum. Retro Viruses, 1990, 6, 491-501; Piantadosi, C., J. Marasco C.J., S.L. Morris-Natschke, K.L. Meyer, F. Gumus, J.R. Surles, K.S. Ishaq, L.S. Kucera, N. Iyer, C.A. Wallen, S. Piantadosi, and E.J. Modest, "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity," J. Med. Chem., 1991, 34, 1408-1414; Hosteler, K.Y., D.D. Richman, D.A. Carson, L.M. Stuhmiller, G.M. T. van Wijk, and H . van den Bosch, "Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6G cells by 3 '-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3,-deoxythymidine," Antimicrob. Agents Chemother., 1992, 36, 2025-2029; Hostler, K.Y., L.M. Stulmiller, H.B. Lenting, H. van den Bosch, and $\mathrm{D}_{\mathrm{i}} \mathrm{D}$. Richman, "Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." J. Biol. Chem., 1990, 265, 61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituent that can be covalently incorporated into the nucleoside, preferably at the $5^{\prime}-\mathrm{OH}$ position of the nucleoside or lipophilic preparations, include U.S. Patent Nos. 5,149,794 (Sep. 22, 1992, Yatvin et al.); 5,194,654 (Mar. 16, 1993, Hosteler et al., 5,223,263 (June 29, 1993, Hosteler et al.); 5,256,641 (Oct. 26, 1993, Yatvin et al.); 5,411,947 (May 2, 1995, Hosteler et al.); 5,463,092 (Oct. 31, 1995, Hosteler et al.); 5,543,389 (Aug. 6, 1996, Yatvin et al.); 5,543,390 (Aug. 6, 1996, Yatvin et al.); 5,543,391 (Aug. 6, 1996, Yatvin et al.); and 5,554,728 (Sep. 10, 1996; Basava et al.), all of which are incorporated herein by reference. Foreign patent applications that disclose lipophilic substituent that can be attached to the nucleosides of the
present invention, or lipophilic preparations, include WO 89/02733, W0 90/00555, wo 91/16920, W0 91/18914, W0 93/00910, W0.94/26273, W0 96/15132, EP 0350 287, EP 93917054.4, and W0 91/19721.

## IV. Combination and Alternation Therapy

It has been recognized that drug-resistant variants of viruses can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against flavivirus or pestivirus infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different nutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution or other parameter of the drug can be altered by such combination or alternation therapy: In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

Nonlimiting examples of antiviral agents that can be used in combination or alternation with the compounds disclosed herein include:
(1) an interferon and/or ribavirin (Battaglia, A.M. et al., Ann. Pharmacother. 34:487494, 2000); Berenguer, M. et al. Antivir. Thar. 3(Suppl. 3):125-136, 1998);
(2) Substrate-based NS3 protease inhibitors (Attwood et al., Antiviral peptide derivatives, PCT WO 98/22496, 1998; Attwood et al., Antiviral Chemistry and Chemotherapy 10.259-273, 1999; Attwood et al., Preparation and use of amino acid derivatives as anti-viral agents, German Patent Publication DE 19914474; Rung et al. Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as. a moronic acid or phosphonate. Llinas-Brunet et al, Hepatitis C inhibitor peptide analogues, PCT WO 99/07734.
(3) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives(Sudo K. et al., Biochemical and Biophysical Research Communications, 238:643647, 1997; Sudo K. et al. Antiviral Chemistry and Chemotherapy 9:186, 1998), including

RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group;
(4) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. et al., Antiviral Research 32:9-18, 1996), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;
(5) Thiazolidines and benzanilides identified in $\cdot$ Kakiuchi N. et al. J. EBS Letters 421:217-220; Takeshita N. et al. Analytical Biochemistry 247:242-246, 1997;
(6) A phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Chu M. et al., Tetrahedron Letters 37:7229-7232, 1996), and Sch 351633, isolated from the fungus Penicillium griscofuluum, which demonstrates activity in a scintillation proximity assay (Thu M. et al., Bioorganic and Medicinal Chemistry Letters .9:1949-1952);
(7) Selective NS3 inhibitors based on the macromolecule elvin c , isolated from leech (Qasim M.A. et al., Biochemistry 36:1598-1607, 1997);
(8) Helicase, inhibitors (Diana G.D. et al., Compounds, compositions and methods for treatmem of hepatitis C, U.S. Patent No. 5,633,358; Diana G.D. et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis $C$, PCT WO 97/36554);
(9) Polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. et al. Journal of Virology 73:1649-1654, 1999), and the natural product cerulenin (Lohmann V. et al., Virology 249:108-118, 1998);
(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the $5^{\prime}$ non-coding region (NCR) of the virus (Alt M. et al., Hepatology 22:707-717, 1995), or nucleotides 326-348 comprising the $3^{\prime}$ end of the NCR and nucleotides 371-388 located in the core coding region of the IICV RNA (Alt M. et al., Archives of Virology 142:589-599, 1997; Galderisi U. et al., Journal of Cellular Physiology 181:251-257, 1999);
(11) Inhibitors of IRES-dependent translation (Ikeda Net al., Agent for the prevention and treatment of hepatitis C, Japanese Patent Publication JP-08268890; Kai Y. et al. Prevention and treatment. of viral diseases, Japanese Patent Publication JP-10101591);
(12) Nuclease-resistant ribozymes. (Maccjak D.J. et al., Hepatology 30 abstract 995, 1999); and
(13) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. $6,034,134$ to Gold et al.), alkyl lipids (U.S. Patent No. 5,922,757 to Chojkier et al.), vitamin E and other antioxidants (U.S. Patent No. 5,922,757 to Chojkier et al.), squalene, amantadine, bile acids (U.S. Patent No. 5,846,964 to Ozeki et al.), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Patent No. 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Patent No. 5,633,388 to. Diana et al.), polyadenylic acid derivatives (U.S. Patent No. 5,496,546 to Wang et al.), 2',3'-dideoxyinosine (U.S. Patent Nu. 5,026,687 to Yarchoan et al.), and benzimidazoles (U.S. Patent No. 5,891,874 to Colacino et al.).

## V. Pharmaceutical Compositions

Host, including humans, infected with flavivirus or pestivirus, or a gene fragment thereof can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

A preferred dose of the compound for flavivirus or pestivirus infection will be in the range from about $i_{1}$ to $50 \mathrm{mg} / \mathrm{kg}$, preferably 1 to $20 \mathrm{mg} / \mathrm{kg}$, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent nucleoside to be delivered. If the salt or prodrug exhibits activity in itself, the effective dosage can be estimated as above using the weight of the salt or prodrug, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg , preferably 70 to 1400 mg of active ingredient per unit dosage form. A oral dosage of $50-1000 \mathrm{mg}$ is usually convenient.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.2 to $70 \mu \mathrm{M}$, preferably about 1.0 to 10
$\mu \mathrm{M}$. This may be achieved, for example, by the intravenous injection of a 0.1 to $5 \%$ solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judginent of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipient and used in the form of tablets, troches or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty: oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be -inixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or méthyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated•delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen; polyorthoesters and polylactic acid. Methods for preparation of such fonnulations will be apparent to those skilled in the art. The materials can also be obtained commercialiy from Alza Corporation.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

## VI. Processes for the Preparation of Active Compounds

The nucleosides of the present invention can be synthesized by any means known in the art. In particular, the synthesis of the present nucleosides can be achieved by either alkylating the appropriately' modified sugar, followed by glycosylation or glycosylation followed by alkylation of the nucleoside. The following non-limiting embodiments illustrate some general methodology to obtain the nucleosides of the present invention.

## A. General Synthesis of 1'-C-Branched Nucleosides :

1'-C-Branched ribonucleosides of the following structure:

wherein BASE is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O (lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, -NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a pi. bond;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate;
$R^{6}$ is an alkyl, halogeno-alkyl ( $i_{1}^{\prime}, e^{\circ} \cdot C_{3}$ ), alkenyl, or alkynyl (i.e. allyl); and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$
can be prepared by one of the following general methods.

## 1) Modification from the lactone.

The key starting material for this process is an appropriately substituted lactone. The lactone can be purchased or can be prepared by any known means including standard epimerization, substitution and cyclization techniques. The lactone can be optionally protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991. The protected lactone can then be coupled with a suitable coupling agent, such as an organometallic carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or $\mathrm{R}^{6}-\mathrm{SiMe}_{3}$ in TBAF with the appropriate non-protic solvent at a suitable temperature, to give the $1^{\prime}$-alkylated sugar.

The optionally activated sugar can then be coupled to the BASE by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a lewis acid, such as tin tetrachloride, titanium tetrachloride or trimethylsilyltriflate in the appropriate solvent at a suitable temperature.

Subsequently, the nucleọside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular' embodiment, the l'-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 1. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene 'et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'OH can be reduced with a suitable reducing agent. Optionally, the 2'-hydroxyl can be activated to facilitate reduction; ie. via the Barton reduction.

IPO DELHI 23-05-2015 15: 49

Scheme 1




## 2. Alternative method for the preparation of 1'-C-branched nucleosides

The key starting material for this process is an appropriately substituted hexose. The hexose can be purchased or can be prepared by any known means including standard epimerization (e.g. via alkaline treatment), substitution and coupling techniques. The hexose can be selectively protected to give the appropriate hexa-furanose, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994:

The 1'-hydroxyl can be optionally activated to a suitable leaving group such as an acyl group or a halogen via acylation or halogenation, respectively. The optionally activated sugar can then be coupled to the BASElby methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a lewis acid, such as tin tetrachloride, titanium tetrachloride or trimethylsilyltriflate in the appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base with the presence of trimethylsilyltriflate.

The 1'- $\mathrm{CH}_{2}-\mathrm{OH}$, if protected, can be selectively deprotected by methods well known in the art. The resultant, primary hydroxyl can be functionalized to yield various C -branched nucleosides. For example, the primary hydroxyl can be reduced to give the methyl, using a suitable reducing agent: Alternatively, the hydroxyl can be activated prior to reduction to facilitate the reaction; i.e. via the Barton reduction. In an alternate embodiment, the primary hydroxyl can be oxidized to the aldehyde, then coupled with a carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or $\mathrm{R}^{6}-\mathrm{SiMe}_{3}$ in TBAF with the appropriate non-protic solvent at a suitable temperature.

In a particular embodiment, the 1'-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 2. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'OH can be reduced with a suitable reducing agent. Optionally, the 2 ' hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction.


In addition, the L-enantiomers corresponding to the compounds of the invention can be prepared following the same general methods ( 1 or 2 ), beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

## B. General Synthesis of 2'-C-Branched Nucleosides

2'-C-Branched ribonucleosides of the following structure:

wherein BASE is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O(acyl), -O(lower acyl), - O (alkyl), -O (lower alkyl), $-\mathrm{O}\left(\right.$ alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a pi bond;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is an alkyl, halogeno-alkyl (i.e. $\mathrm{CF}_{3}$ ), alkenyl, or alkynyl (i.e. allyl); and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$
can be prepared by one of the following general methods:

## 1. Glycosylation of the nucleobase with an appropriately modified sugar

The key starting material for this process is an appropriately substituted sugar with a $2^{\prime}-\mathrm{OH}$ and $2^{\prime}-\mathrm{H}$, with the appropriate leaving group (LG), for example an acyl group or a
halogen. The sugar can be purchased or can be prepared by any known means including standard epimerization, substitution, oxidation and reduction techniques. The substituted sugar can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 2 '-modified sugar. Possible oxidizing agents are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine $\operatorname{Cr}(\mathrm{VI})$ oxide, Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, $\mathrm{MnO}_{2}$, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, $\mathrm{Cl}_{2}$-pyridine, $\mathrm{H}_{2} \mathrm{O}_{2}$ ammonium molybdate, $\mathrm{NaBrO}_{2}-\mathrm{CAN}, \mathrm{NaOCl}$ in HOAc , copper chromite, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum $t$-butoxide with another ketone) and $N$-bromosuccinimide.

Then coupling of an organometallic carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or $\mathrm{R}^{6}-\mathrm{SiMe}_{3}$ in TBAF with the ketone with the appropriate non-protic solvent at a suitable temperalure, yields the 2 '-alkylated sugar. The alkylated sugar can be optionally protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The optionally protected sugar can then be coupled to the BASE by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base, with a lewis acid, such as tin tetrachloride, titanium tetrachloride or trimethylsilyltriflate in the appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base with the presence of trimethylsilyltriflate.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the 2 -C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 3. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-

OH can be reduced with a suitable reducing agent. Optionally, the $2^{\prime}$-hydroxyl can be activated to facilitate reduction; ie. via the Barton reduction. .

## Scheme 3



## 2. Modification of a pre-formed nucleoside

The key starting material for this process is an appropriately substituted nucleoside with a $2^{\prime}-\mathrm{OH}$ and $2^{\prime}-\mathrm{H}$. The nucleoside can be purchased or can be prepared by any known means including standard coupling techniques. The nucleoside can be optionally protected with suitable protecting groups, preferably with acyl or silyl groups, by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The appropriately protected nucleoside can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the $2^{\prime}$-modified
sugar: Possible oxidizing agents are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine $\mathrm{Cr}(\mathrm{VI})$ oxide, Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, $\mathrm{MnO}_{2}$, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, $\mathrm{Cl}_{2}$-pyridine, $\mathrm{H}_{2} \mathrm{O}_{2}$-ammonium molybdate, $\mathrm{NaBrO}_{2}$ - $\mathrm{CAN}, \mathrm{NaOCl}$ in HOAc , copper chromite, copper oxide, Randy nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum $\hat{t}$-butoxide with another ketone) and $N$-bromosuccinimide.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by GreeneGreene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the 2 '-C-branched ribonucleoside is desired. The synthesis of a ribonuclcoside is shown in Scheme 4. Alternatively, deoxyribo-nucleoside is desired. 'To obtain these nucleosides, the formed ribonucleoside can optionally be protected by -methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'OH can be reduced with a suitable reducing agent. Optionally, the 2 '-hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction.

## Scheme 4



In another embodiment of the invention, the L-enantiomers are desired. Therefore, the L-enantiomers can be corresponding to the compounds of the invention can be prepared following the same foregoing general methods, beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

## C. General Synthesis of 3'-C-Branched Nucleosides

3'-C-Branched ribonucleosides of the following structure:

wherein BASE is a purine or pyrimidine base as defined herein; $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br-vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \bigcirc($ lower alkyl); - O (acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a pi bond;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including numupliosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}$ is independently H or phosphate;
$\mathrm{R}^{6}$ is an alkyl, halogeno-alkyl (ie. $\mathrm{CF}_{3}$ ), alkenyl, or alkyniyl (ie. allyl); and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$
can be prepared by one of the following general methods.

## 」 Glycosylation of the mucleobase with an appropriately modified sugar

The key starting material for this process is an appropriately substituted sugar with a $3^{\prime}-\mathrm{OH}$ and $3^{\prime}-\mathrm{H}$, with the appropriate leaving group (LG), for example an acyl group or a halogen. The sugar can be purchased or can be prepared by any known means including standard epimerization, substitution, oxidation and reduction techniques. The substituted sugar can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the $3^{\prime}$-modified sugar. Possible oxidizing agents are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine $\mathrm{Cr}(\mathrm{VI})$ oxide, Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, $\mathrm{MnO}_{2}$, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, $\mathrm{Cl}_{2}$-pyridine, $\mathrm{H}_{2} \mathrm{O}_{2}$ ammonium molybdate, $\mathrm{NaBrO}_{2}-\mathrm{CAN}, \mathrm{NaOCl}$ in HOAc , copper chromite, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum $t$-butoxide with another ketone) and N -bromosuccinimide.

Then coupling of an organometallic carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or $\mathrm{R}^{6}-\mathrm{SiMe}_{3}$ in TBAF with the ketone with the appropriate non-protic solvent at a suitable temperature, yields the 3 '-C-branched sugar. The $3^{\prime}$-C-branched sugar can be optionally protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene el al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The optionally protected sugar can then be coupled to the BASE by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994: For example, an acylated sugar can be coupled to a silylated base with a lewis acid, such as tin tetrachloride, titanium tetrachloride or trimethylsilyltriflate in the appropriate solvent at a suitable temperature. Alternatively.. a halo-sugar can be coupled to a silylated base with the presence of trimethylsilyltriflate.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John .Wiley and Sons, Second Edition, $1991^{\circ}$.

In a particular embodiment, the $3^{\prime}$-C-branched ribonucleoside is desired: The synthesis of a ribonucleoside is shown in Scheme 5. Alternatively, deoxyribo-nucleoside is

PCT/US01/16687
desired. 'To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'OH can be reduced with a suitable reducing agent. Optionally, the 2 '-hydroxyl can be activated to facilitate reduction; ie. via the Barton reduction.

## Scheme 5



## 2. Modification of a pre-formed nucleoside

The key starting material for this process is an appropriately substituted nucleoside with a $3^{\prime}-\mathrm{OH}$ and $3^{\prime}-\mathrm{H}$. The nucleoside can be purchased or can be prepared by any known means including standard coupling techniques. The nucleoside can be optionally protected with suitable protecting groups, preferably with acyl or silyl groups, by methods well -known to those skilled in the art, as taught by Greene et al. Protective Groups in .Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The appropriately protected nucleoside can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the $2^{\prime}$-modified
sugar. Possible oxidizing agents are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine $\mathrm{Cr}(\mathrm{VI})$ oxide, Corey's reagent (pyridinium chlorochromate), pyridinium dicfromate, acid dichromate, polassium permanganate, $\mathrm{MnO}_{2}$, ruthenium tetroxidé, phase transfer catalysts such as chromic àcid or permanganate supported on a polymer, $\mathrm{Cl}_{2}$-pyridine, $\mathrm{H}_{2} \mathrm{O}_{2}$-ammonium molybdate, $\mathrm{NaBrO} \mathrm{O}_{2}$ - $\mathrm{CAN}, \mathrm{NaOCl}$ in HOAc , copper chromite, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum $t$-butoxide with another ketone) and $\dot{N}$-bromosuccinimide.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Oryauic Synthesis; John Wiley and Sons, Second Edition, 1991:

In a particular embodiment, the $3^{\prime}$-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 6. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'OH can be reduced with a suitable reducing agent. Optionally, the 2 '-hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction.

Scheme 6


In another embodiment of the invention, the L-enantiomers are desired. Therefore, the L-enantiomers can be corresponding to the compounds of the invention can be prepared following the same foregoing general methods, beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

## - EXAMPLES

## Example 1: Preparation of 1'-C-methylriboadenine via 6-amino-9-(1-deoxy- $\bar{\beta}-\mathrm{D}$ psicofuranosyl)purine

The title compound could also be prepared according to a published procedure (J. Farkas, and F. Sorn, "Nucleic acid components and their analogues. XCIV. Synthesis of 6-amino-9-(1-deoxy- $\beta$-D-psicofuranosyl)purine" Collect. Czech. Chem. Commiun. 1967, 32, 2663-2667; J. Farkas", Collect. Czech. Chem. Commun. 1966, 31, 1535) (Scheme 7).

## Scheme 7




In a similar manner, but using the appropriate sugar and pyrimidine or purine bases, the following nucleosides of Formula I are prepared.

(I)
wherein:


| $\mathbf{R}^{1}$ | R ${ }^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | H | H | H | NH-ethyl |
| monophosphate | H | H | H | H | OH |
| monophosphate | H | H | H | H | O-acetyl |
| monophosphate | H | H | H | H | OMe |
| monophosphate | H | H | H . | $\overline{\mathrm{H}}$ | OEt |
| monophosphate | H | H | H | H | O-cyclopropyl |
| monophosphate | H | H | H | H | SH |
| monophosphate | H | H | H | H | SMe |
| monophosphate | H | H | H | H | SEt |
| monophosphate | H | H | H | H | S-cyclopropyl |
| monophosphate | H | H | H | H | F |
| monophosphate | H | H | H | H | Cl |
| monophosphate | H | H | H | H | Br |
| monophosphate | H | H | $\cdot \mathrm{H}$ | H | I |
| diphosphate | H | H | H | H | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | H | NH-acetyl |
| diphosphate | H | H | H | H | NH-cyclopropyl |
| diphosphate | H | H | H | H | NH-methyl |
| diphosphate | H | H | H. | H | NH-ethyl |
| diphosphate | H | H | H | H | OH |
| diphosphate | H | H | H | H | O-acetyl |
| diphosphate | H | H | H | H | OMe |
| diphosphate | H | H | H | H | OEt |
| diphosphate | H | H | H | H | O-cyclopropyl |
| diphosphate | H | H | H | H | SH |
| diphosphate | H | H | H | H | SMe |
| diphosphate | H | H | H | H | SEt |
| diphosphate | H | H | H | H | S-cyclopropyl |
| diphosphate | H | H | H | H | F |
| diphosphate | H | H | H | H | Cl |
| diphosphate | H | H | H | H | Br |


| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | H | H | H | H |  |
| triphosphate | H | H | H | H | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | H | H | NH-acetyl |
| triphosphate | H | H | H | H | NH-cyclopropyl. |
| triphosphate | H | H | H | H | NH-methyl |
| triphosphate | H | H | H: | H | NH-ethyl |
| triphosphate | H | H | H | H. | OH |
| triphosphate | H | H | H | H | OMe |
| triphosphate | H | H | H | H | OEt |
| triphosphate | H | H | H | H | O-cyclopropyl |
| triphosphate | H | H | H | H | O-acetyl |
| triphosphate | H | H | H | H | SH |
| triphosphate | H | H | H, | H | SMe |
| triphosphate | H | H | H | H | SEt |
| triphosphate | H | H | H | H | S-cyclopropyl |
| triphosphate | H | H | H | H | F |
| triphosphate | H | H | H | H | Cl |
| triphosphate | H | H | H | H | Br |
| triphosphate | H | H | H | H | I |
| monophosphate. | monophosphate | monophosphate | H | H | $\mathrm{NH}_{2}$ |
| monophosphate | monophosphate | monophosphate | H | H | NH-cyclopropyl |
| monophosphate | monophosphate | monophosphate | H | H | OH |
| monophosphate | monophosphate | monophosphate | H | H | F |
| monophosphate | monophosphate | monophosphate | H | H | Cl |
| diphosphate | idiphosphate | diphosphate | H | H | $\mathrm{NH}_{2}$ |
| diphosphate | diphosphate | diphosphate | . H | H | NH-cyclopropyl |
| diphosphate | diphosphate | diphiosphate | H | H | OH |
| diphosphate | diphosphate | diphosphate | H | H | F |
| diphosphate | diphosphate | diphosphate | H | H | Cl - |
| triphosphate | triphosphate | triphosphate | H | H | $\mathrm{NH}_{2}$ |
| triphosphate | triphosphate | triphosphate | H | H | NH-cyclopropyl |




## IPO DELHI 23-06-2015 15:49

| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$. | $\mathrm{X}^{\mathbf{2}}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| triphosphate | acetyl | acetyl | H | H | Cl |
| H | H | H | H | $\mathrm{NH}_{2}$ | H |
| H | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | H | $\mathrm{NH}_{2}$ | NH-methyl |
| H | H | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |
| H | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |
| H | H | H | H | $\mathrm{NH}_{2}$. | OH |
| H | H | $\overline{\mathrm{H}}$ | H | $\mathrm{NH}_{2}$ | OMe |
| H | H | H | H | $\mathrm{NH}_{2}$ | OEt |
| H | H | H | H | $\mathrm{NH}_{2}$ | O-cyclopropyl |
| H | H | H | H | $\mathrm{NH}_{2}$ | O-acetyl |
| H | H | H | H | $\mathrm{NH}_{2}$ | SH |
| H | H | H | H | $\mathrm{NH}_{2}$ | SMe |
| H | H | H | H | $\mathrm{NH}_{2}$ | SEt |
| H | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |
| H | H | H | H | $\mathrm{NH}_{2}$ | F |
| H | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | H | $\mathrm{NH}_{2}$ | Br |
| H | H | H | H | $\mathrm{NH}_{2}$ | I |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-methyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | O-acetyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OMe |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OEt - |
| monophosphate | H | H | H, | $\mathrm{NH}_{2}$ | O-cyclopropyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SH |




| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$, | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | F | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H. | H | H | Cl | $\mathrm{NH}_{2}$ | OH |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | F |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | Br | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | Br | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | Br | $\mathrm{NH}_{2}$ | OH |
| H | H | H | Br | $\mathrm{NH}_{2}$ | F |
| H | H. | H | Br | $\mathrm{NH}_{2}$ | ${ }^{\text {Cl }}$ |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | $\mathrm{H}_{1}$ | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | OH |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | F |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | SH | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | SH | $\mathrm{NH}_{2}$ | NH -cyclopropyl |
| H | H | H | SH | $\mathrm{NH}_{2}$ | OH |
| H | H | H | SH | $\mathrm{NH}_{2}$ | F |
| H | H | H | SH | $\mathrm{NH}_{2}$ | Cl |
| acetyl | H. | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | OH |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | F |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| acetyl | H | H | F. | $\mathrm{NH}_{2}$ | OH - |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | F |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | Cl |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$. | OH |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | OH |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |
| monophosphate | acetyl | acetyl | $\stackrel{\mathrm{H}}{\square}$ | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | OH |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | OH |
| diphosphate | acetyl | acetyl | H. | $\mathrm{NH}_{2}$ | F |
| diphosphate . - | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| triphosphate | acetyl | acety | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | OH |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | H | Cl | H |
| H | H | H | H | Cl | H |
| H | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | H | Cl | NH-cyelopropyl |
| H | H | H | H | Cl | NH-methyl |
| H | H | H | H | Cl | NH-ethyl |

PCT/US01/16687

| $\mathbf{R}^{1}$ | R ${ }^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | Cl | NH-acetyl |
| H | H | H | H | Cl | OH |
| H | H | H | H | Cl | OMe |
| H | H | H | H | Cl | OEt |
| H | H | H | H | Cl | O-cyclopropyl |
| H | II | H | . H | Cl | O-acetyl |
| H | H | H | H | Cl | SH |
| H | H | H | H | Cl | SMe |
| H | H | H | H | Cl | SEt |
| H | H | H | H | Cl | S-cyclopropyl |
| monophosphate | H. | H | H | Cl | $\mathrm{NH}_{2}$ |
| monophosphate | H | H | H | Cl | NH-acetyl |
| monophosphate | H | H | H | Cl | - NH -cyclopropyl |
| monophosphate | H. | H | H | Cl | NH-methyl |
| monophosphate | H | H | H. | Cl | NH-ethyl |
| monophosphate | H | H | H | Cl | OH |
| monophosplate | H | H | H | Cl | O-acetyl |
| monophosphate | H | H | H | Cl | OMe |
| monophosphate | H | H | H | Cl | OEt |
| monophosphate | H | H | H | Cl | O-cyclopropyl |
| monophosphate | H | H | H | Cl | SH |
| monophosphate | H | H | H | Cl | SMe |
| monophosphate | H | H | H | Cl | SEt |
| monophosphate | H | H | H | $\mathrm{Cl}^{\circ}$ | S-cyclopropyl |
| diphosphate | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | Cl | NH-acetyl |
| diphosphate | H | H | H | Cl | NH-cyclopropyl |
| diphosphate | H | H | H | Cl | NH-methyl |
| diphosphate | H | H | H | Cl | NH-ethyl |
| diphosphate | H | $\cdot \mathrm{H}$ | H | Cl | OH |
| diphosphate | H | H | H | Cl | O-acetyl |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathbf{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | H | H | H | Cl | OMe |
| diphosphate | H | H | H | Cl | OEt |
| diphosphate | H | H | H | Cl | O-cyclopropyl |
| diphosphate | H. | H | H | Cl | SH |
| diphosphate | H | H | H | Cl | SMe |
| diphosphate | H | H | H | Cl | SEt |
| diphosphate | H | H | H | Cl | S-cyclopropyl |
| triphosphate | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | H | Cl | NH -acetyl |
| triphosphate | H | H | H | Cl | NH-cyclopropyl |
| triphosphate | H | H | H | Cl | NH-methyl |
| triphosphate | H | H | H | Cl | NH-ethyl |
| triphosphate | H | H | H. | Cl | OH |
| triphosphate | H | H | H | Cl | OMe |
| triphosphate | H | H | H | Cl | OEt |
| triphosphate | H | H | H | Cl | O-cyclopropyl |
| triphosphate | H | H | H! | Cl | O-acetyl |
| triphosphate | H | H | H | Cl | SH |
| triphosphate | H | H | H | Cl | SMe |
| triphosphate .- | H | H | H | Cl | SEt |
| triphosphate | H | H | H | Cl | S-cyclopropyl |
| monophosphate | monophosphate | monophosphate | H | Cl | $\mathrm{NH}_{2}$ |
| monophosphate | monophosphate | monophosphate | H | Cl | NH-cyclopropyl |
| monophosphate | monophosphate | monophosphate ${ }^{\text {' }}$ | H | Cl | OH |
| diphosphate | diphosphate | diphosphate | H | Cl | $\mathrm{NH}_{2}$ |
| diphosphate | diphosphate | diphosphate | H | Cl | NH-cyclopropyl |
| diphosphate | diphosphate | diphosphate | H | Cl | OH |
| triphosphate | triphosphate | triphosphate | H | Cl | $\mathrm{NH}_{2}$ |
| triphosphate | triphosphate | triphosphate | H | Cl . | NH-cyclopropyl |
| triphosphate | triphosphate | triphosphate | - H | Cl | OH |
| H | H | $\mathrm{H}_{i}$ | F | Cl | $\mathrm{NH}_{2}$ |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{\text {1 }}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | F | Cl | NH-cyclopropyl |
| H | H | H | F. | Cl | OH |
| H | H | H | Cl | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | Cl | Cl | NH-cyclopropyl |
| H | H | H | Cl - | Cl | OH |
| II | H | H | Br | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{Br}{ }^{1}$ | Cl | NH-cyclopropyl |
| H | H | H | Br | Cl | $\overline{\mathrm{OH}}$ |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | NH-cyclopropyl |
| H | H | H | $\mathrm{NH}_{2}$ | Cl | OH |
| H | H | H | SH | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | SH | Cl | NH-cyclopropyl |
| H | H | H | SH | Cl | OH |
| acetyl | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| acetyl | H | H | H | Cl | NH-cyclopropyl |
| acetyl | H | H | H | Cl | OH |
| acetyl | H | H | F | Cl | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | Cl | NH-cyclopropyl |
| acetyl | H | H | F | Cl | OH |
| H | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | Cl | NH-cyclopropyl |
| H | acetyl | acetyl | H | Cl | OH |
| acetyl | acetyl. | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | Cl | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | Cl | OH |
| monophosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | H | Cl | NH-cyclopropyl |
| monophosphate | acetyl | acetyl | H | Cl | OH |
| diphosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| diphosphate | acetyl | acetyl | H | Cl | NH-cyclopropyl |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{\mathbf{3}}$ | $\mathbf{X}^{2}$ | $\mathbf{Y}$ |
| :--- | :--- | :--- | :--- | :--- | :--- |
| diphosphate | acetyl | acetyl | H | Cl | OH |
| triphosphate | acetyl | acetyl | H | Cl | $\mathrm{NH}_{2}$ |
| triphosphate | acetyl | acetyl | H | Cl | NH -cyclopropyl |
| triphosphate | acetyl | acetyl | H | Cl | OH |
| H | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | H | Cl | NH -cyclopropyl |
| H | H | H | H | Cl | OH |
| H | H | H | H | Br | $\mathrm{NH}_{2}$ |
| H | H | H | H | Br | NH -cyclopropyl |
| H | H | H | H | Br | OH |

Alternatively, the following nucleosides of Formula IV are prepared, using the appropriate sugar and pyrimidine or. purine bases.

(IV)
wherein:

| $\mathbf{R}^{\mathbf{1}}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{\mathbf{1}}$ | $\mathbf{Y}$ |
| :--- | :--- | :--- | :--- | :--- |
| H | H | H | H | H |
| H | H | H | $\cdot$ H $^{\bullet}$ | $\mathrm{NH}_{2}$ |
| H | H | H | H | NH-cyclopropyl |
| H | H | H | H | NH-methyl |
| H | H | H | H | NH-ethyl |
| H | H | H | H | NH-acetyl |
| H | H | H | H | OH |




| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| H | H | H | Cl | $\mathrm{NH}_{2}$ |
| H | H | H | Cl | NH-cyclopropyl |
| H | H | H | Cl | OH |
| H | H | H | Br | $\mathrm{NH}_{2}$ |
| H | H | H | Br | NH-cyclopropyl |
| H | H | H | Br | OH |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | - $\mathrm{NH}_{2}$ | OH |
| H | H | H | SH . | $\mathrm{NH}_{2}$ |
| H | H | H | SH | NH-cyclopropyi |
| H | H | H | SḢ | OH |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ |
| acetyl | H | H | H | NH-cyclopropyl |
| acetyl | H | H | H | OH |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ |
| acetyl | H | $\stackrel{\text { H }}{ }$ | F | NH-cyclopropyl |
| acetyl | H | H | F | OH |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | NH-cyclopropyl |
| H | acetyl | acetyl | H | OH |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | OH |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| monophosphate. | acetyl | acetyl | H | NH-cyclopropyl |
| monophosphate | acetyl | acety ${ }^{\text {l }}$ | H | OH |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| diphosphate | acetyl | acetyl | H | NH-cyclopropyl |
| diphosphate | acetyl | acetyl | H | OH |
| triphosphate | acetyl | acetyl | H . | $\mathrm{NH}_{2}$ |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | . | $\mathbf{R}^{3}$ | $\mathbf{X}^{1} \cdot$ |
| :--- | :--- | :--- | :--- | :--- |
| Iriphosphate | acetyl $\quad .$. | acetyl | H | NH-cyclopropyl |
| triphosphate | acetyl $\quad$. | acetyl | H | OH |

Alternatively, the following nucleosides of Formula VII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(VII)
wherein:




PCT/US01/16687



IPO DELHI 23-96-2015 15:49

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | II | H | $\mathrm{CH}_{3}$ | S | guanine |
| H | $\mathrm{H}$ | H. | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \hline \text { 6-(N,N-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro- <br> adenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | H | FF. | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-(N,N-diacetyl)- <br> adenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroadenine |
| monophosphate | H | H | $\overline{\mathrm{CH}_{3}}$ | 0 | 2,8-difluoro- <br> adenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | adenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$. | S | 2-(N,N-diacetyl)- <br> guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 8 -fluoroguanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}{ }^{\text {. }}$ | S | 6-(N,N-diacetyl)- <br> adenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |



| $\mathrm{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| triphosphate | H- | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 6-(N,N-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| triphosphate | H | H | $\mathrm{CH}_{3}$ : | 0 | 2-fluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoro- <br> adenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $\begin{aligned} & \text { 2-(N,N-diacetyl)- } \\ & \text { guanine } \end{aligned}$ |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl <br> guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroguanine |
| triphosphate | H. | H | $\mathrm{CH}_{3}$ | S | guanine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)- <br> adenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| triphosphate | $\mathrm{H}$ | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro- <br> adenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2-(N,N-diacetyl)- <br> guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}{ }^{\text {' }}$ | 0 | 6-O-acetyl guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8-fluoroguanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | guanine |
| monophosphate | monophosphate. | monophosphate | $\mathrm{CF}_{3}$ | 0 | 6-(N,N-diacetyl)- <br> adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2-fluoroadenine |

IPO DELHI 23-06-2015 15:50

| $\mathbf{R}^{\text {I }}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8-fluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2,8-difluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-(N,N-diacetyl)guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\begin{aligned} & \text { 6-O-acetyl } \\ & \text { guanine } \end{aligned}$ |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8-fluoroguanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}{ }^{\text {. }}$ | S | $\begin{aligned} & \text { 6-(N,N-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-fluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8 -fluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,8-difluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | adenine |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | guanine |
| acetyl | .acetyl | acetyl | $\mathrm{CF}_{3}$ | S | guanine |
| acetyl | àcetyl | acetyl | 2-bromovinyl | 0 | guanine |
| acetyl | acetyl | acetyl | 2-bromovinyl | S | guanine |

Alternatively, the following hucleosides of Formula VIII are prepared, using the appropriate sugar and pyrimidine or purine bases.

$$
i
$$


(VIII)
wherein


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | Uracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Thymine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | H | $\mathrm{CH}_{3}^{\prime}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Thymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Uracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | $\cdot$ |
| diphosphate | H | 5-Fluorouracil |  |  |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| diphosphate | H | S | U | Uracil |

WO 01/92282
PCT/US01/16687

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| triphosphate | II | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 2;4-O-diacethylthymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | Thymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| triphosphate | H | $\mathrm{CII}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | Uracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Uracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Hypoxanthine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Thymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Uracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 5-Fluorouracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\cdot$ 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |




| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- |
| diphosphatc | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro-adenine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 2-(N,N-diacetyl)-guanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 6-O-acetyl guanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 8-fluoroguanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | guanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 6-(N,N-diacetyl)-adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 2-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 8-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 2,8-difluoro-adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)-guanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl guanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 8-fluoroguanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | guanine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)-adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoro-adenine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2-(N,N-diacetyl)-guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 6-O-acetyl guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 8-fluoroguanine |
| monophosphate | moluphosphate | $\mathrm{CF}_{3}$ | O | guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 6-(N,N-diacetyl)-adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 8-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2,8-difluoro-adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-(N,N-diacetyl)-guanine |


| $\mathbf{R}^{\mathbf{1}}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 6-O-acetyl guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8-fluoroguanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | guanine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 6-(N,N-diacetyl)-adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8-fluoroadenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,8-difluoro-adenine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | adenine |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | O | guanine |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | S | guanine |
| acetyl | acetyl | 2-bromu- <br> vinyl | O | guanine |
| acetyl | acetyl | 2-bromu- <br> vinyl | S | guanine |

Alternatively, the following nucleosides of Formula IX are prepared, using the appropriate sugar and pyrimidine or purine buses.

(IX)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| H | $\mathrm{CH}_{3}$ | O | Thymine. |
| H | $\mathrm{CH}_{3}$ | O | Cytosine |

WO 01/92282
PCT/US01/16687


| $\mathbf{R}^{\text {1 }}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: |
| diphosphate | $\mathrm{CH}_{3}$ | $\bigcirc$ | 2,4-O-Diacetyluracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Thymine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| diphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| diphosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| diphosphate | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Thymine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| triphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| triphosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphospahate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| triphospahate | $\mathrm{CH}_{3}$ | S | Thymine |
| triphospahate | $\mathrm{CH}_{3}$ | S | Cytosiné |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-0-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Hypoxanthine |
| monophosphate | ${ }^{\circ} \mathrm{CF}_{3}$ | 0 | 2,4-O-Diacetylthymine |


| R ${ }^{1}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytos |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate | $\mathrm{C}_{1} \mathrm{~F}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | 0 | 4-(N,N-diacetyl) cytosine |
| acetyl | 2-bromo-vinyl | S | 4-(N,N-diacetyl)cytosine |

Alternatively, the following nucleusides of Formula XVI are prepared, using the appropriate sugar aṇ̀d pyrimidińe or purine bases.

(XVI)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{R}^{8}$ | $\mathbf{X}$ | Base $\cdot$ | $\mathbf{R}^{10}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| $\mathrm{H}_{.}$ | $\mathrm{CH}_{3}$ | H | H | O | 2,4-O-Diacetyluracil | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | O | Hypoxanthine | OH | Me |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{R}^{8}$. | X | Base | $\mathbf{R}^{10}$ | $\mathbf{R}^{9}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| H | $\mathrm{CH}_{3}$ | H | H | 0 | 2,4-O-Diacetylthymine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | 0 | Thymine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | 0 | Cytosine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | 0 | 4-(N-mono-acetyl)cytosine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | 0 | 4-(N,N-diacetyl)cytosine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | 0 | Uracil | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | 0 | 5-Fluorouracil | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | 2,4-O-Diacetyluracil | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | Hypoxanthine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | 2,4-O-Diacetylthymine | OH | - Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | Thymine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | Cytosine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | 4-(N-mono-acetyl)cytosine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | 4-(N,N-diacetyl)cytosine | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | Uracil | OH | Me |
| H | $\mathrm{CH}_{3}$ | H | H | S | 5-Fluorouracil | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | 0 | 2,4-O-Diacetyluracil | OH | Me. |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | 0 | Hypoxanthine | OH | Me |
| monophosplate | $\mathrm{CH}_{3}$ | H | H | 0 | 2,4-O-Diacetylthymine | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H. | 0 | Thymine : | OH | Me |
| monophosplate | $\mathrm{CH}_{3}$ | H | H | 0 | Cytosine | OH | Me |
| monophosplate | $\mathrm{CH}_{3}$ | H | H | 0 | 4-(N-mono-acetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | 0 | 4-(N,N-diacetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | $\overline{\mathrm{H}}$ | H | 0 | Uracil | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | 0 | 5-Fluorouracil | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | S | 2,4-O-Diacetyluracil | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | S | Hypoxanthine | OH | Me |
| monophosphate. | $\mathrm{CH}_{3}$ | H | H | S | 2,4-O-Diạcetylthymine | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | S | Thymine | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | S | Cytosine | OH | Me |
| monophosphate | $\mathrm{CH}_{3}$ | H | H | S | 4-(N-mono-acetyl)cytosine | OH | Me |



| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{R}^{8}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{10}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 2,4-O-Diacetyluracil | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | Hypoxanthine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 2,4-O-Diacetylthymine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | Thymine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | Cytosine $\cdot$ | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 4-(N-mono-acetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 4-(N,N-diacetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | Uracil | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | O | 5-Fluorouracil | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 2,4-O-Diacetyluracil | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Hypoxanthine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 2,4-O-Diacetylthymine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Thymine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 4-(N-mono-acetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 4-(N,N-diacetyl)cytosine | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | Uracil | OH | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | H | S | 5-Fluorouracil | OH | Me |
| acetyl | $\mathrm{CH}_{3}$ | H | H | O | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | H | H | S | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | H | O | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | H | S | 4-(N,N-diacetyl)cytosine | H | Br |

## Example 2: Preparation of 2'-C-methylriboadenine

The title compound was prepared according to a published procedure (R.E. HarryO'kuru, J.M. Smith, and M.S. Wolfe, "A short, flexible route toward 2'-C-branched ribonucleosides", J.Org. Chem. 1997, 62, 1754-1759) (Scheme 8).

Scheme 8

(a) Dess-Martin periodinane; (b) $\mathrm{MeMgBr} / \mathrm{TiCl}_{4}$; (c) $\mathrm{BzCl}, \mathrm{DMAP}^{2} \mathrm{Et}_{3} \mathrm{~N}$; (d) bis(trimethylsilyl)acetamide, $\mathrm{N}^{6}$-benzoyl adenine, TMSOTf; (e) $\mathrm{NH}_{3} / \mathrm{MeOH}$

In a similar manner, but using the appropriate sugar and pyrimidine or purine bases, the following nucleosides of Formiula II are prepared.

(II)
wherein:

| $\mathbf{R}^{\mathbf{1}}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{\mathbf{1}}$ | $\mathbf{X}^{2}$ | $\mathbf{Y}$ |
| :--- | :--- | :--- | :--- | :--- | :--- |
| H | H | H | H | H | H |
| H | H | H | H | H | NH $_{2}$ |
| H | H | H | H | H | NH-cyclopropyl |
| H | H | H | H | H | NH-methyl |
| H | H | H | H | H | NH-ethyl |
| H | H | H | H | H. | NH-acetyl |
| H | H | H | H | H | OH |
| H | H | H | H | H | OMe |
| H | H | H | H | H | OEt |

PCT/US01/16687

| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathbf{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | H | O-cyclopropyl |
| H | H | H | H | H | O-acetyl |
| H | H | H | H | H | SH |
| H | H | H | $\mathrm{H}^{+}$ | H | SMe |
| H | H | H | H | H | SEt |
| H | H | H | H | H | S-cyclopropyl |
| H | H | H | H | H | F |
| H | H | H | H | H | Cl |
| H | H | H | H | H | Br |
| H | H | H | H | H | I |
| monophosphate | H | H | H | H | $\mathrm{NH}_{2}$ |
| monophosphate | H | H | H | H | NH-acetyl |
| monophosphate | H | H | H | H | NH-cyclopropyl |
| monophosphate | H. | H | H | H | NH-methyl |
| monophosphate | H | H | H | H | NH-ethyl |
| monophosphate | H | H | H | H | OH |
| monophosphate | H | H | H | H | O-acetyl |
| monophosphate | H | H | H | H | OMe |
| monophosphate | H | H | H | H | OEt |
| monophosphate | H | $\mathrm{H}_{4}$ | H | H | O-cyclopropyl |
| monophosphate | H | H | H | H | SH |
| monophosphate | H | H | H | H | SMe |
| monophosphate | H | H | - H . | H | SEt |
| monophosphate | H | H | H | H. | S-cyclopropyl |
| monophosphate | H | H | H | H | F |
| monophosphate | H | H | H | H | Cl |
| monophosphate | H | H | $\stackrel{\mathrm{H}}{ }$ | H | Br |
| monophosphate | H. | H | H | H | I |
| diphosphate | H | H | H | H | $\mathrm{NH}_{2}$ : |
| diphosphate | H | H | H | H | NH-acetyl |
| diphosphate | H | H | H | H | NH-cyclopropyl |


| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | $\mathbf{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | H | H | H | H | NH-methyl |
| diphosphate | H | H | H | H | NH -ethyl |
| diphosphate | H | H | H | H | OH |
| diphosphate | H | H | H | H | O-acetyl |
| diphosphate | H | H. | H | H | OMe |
| diphosphate | H | H | H | H | OEt |
| diphosphate | H | H | H | H | O-cyclopropyl- |
| diphosphate | H | H | H | H | SH |
| diphosphate | H | H | H | H | SMe |
| diphosphate | H | $\mathrm{H}_{\mathrm{i}}$ | H | H | 'SEt |
| diphosphate | H | H | H | H | S-cyclopropyl |
| diphosphate | H | H | H | H | F |
| diphosphate | H | H | H | H | Cl |
| diphosphate | H | H | H | H | Br |
| diphosphate | H | H | H | H | I |
| triphosphate | H | H | H | H | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | $\mathrm{H}$ | H | NH-acetyl |
| triphosphate | H | H | H | H | NH-cyclopropyl |
| triphosphate | H | H | H. | H | NH-methyl |
| triphosphate | H | H | H | H | NH-ethyl |
| triphosphate | H | H | H | H | OH |
| triphosphate | $\stackrel{H}{\mathrm{H}}$ | H | H | H | OMe |
| triphosphate | H | H | H | H | OEt |
| triphosphate | H | H | H | H | O-cyclopropyl |
| triphosphate | H | H | H | H | O-acetyl |
| triphosphate | H | H | H | H | SH |
| triphosphate | H | H | H | H | SMe |
| triphosphate | H | H | H | H | SEt |
| triphosphate | H | H | H | H | S-cyclopropyl |
| triphosphate | H | H | H | H | F |
| triphosphate | H | H | H | H | Cl |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| triphosphate | H | H | H | H | Br |
| triphosphate | H | H | $\stackrel{H}{+}$ | H | I |
| monophosphate | monophosphate | monophosphate | H | H | $\mathrm{NH}_{2}$ |
| monophosphate | monophosphate | monophosphate | H | H | NH-cyclopropyl |
| monophosphate | monophosphate | monophosphate | H | H | OH |
| monophosphate | monophosphate | monophosphate | H | H | F |
| monophosphate | monophosphate | monophosphate | H | H | Cl |
| diphosphate | diphosphate | diphosphate | H | H | $\mathrm{NH}_{2}$ |
| diphosphate | diphosphate | diphosphate | H | H | NH-cyclopropyl |
| diphosphate | diphosphate | diphosphate | H | H | OH |
| diphosphate | diphosphate | diphosphate | H | H | F |
| diphosphate | diphosphate | diphosphate | H | H | Cl |
| triphosphate | triphosphate - | triphosphate | H | H | $\mathrm{NH}_{2}$ |
| triphosphate | triphosphate | triphosphate | H: | H | NH-cyclopropyl |
| triphosphate | triphosphate | triphosphate | H | H | OH |
| triphosphate | triphosphate | triphosphate | H | H | F |
| triphosphate | triphosphate | triphosphate | H | H | Cl |
| H | H | H | F | H | $\mathrm{NH}_{2}$ |
| H | H | H | F | H | NH-cyclopropyl |
| H | H | H | F | H | OH |
| H | H | H | F | H | F |
| H | H | H | F | H | Cl |
| H | H | H | - Cl | H | $\mathrm{NH}_{2}$ |
| H | H | H | Cl | H | NH-cyclopropyl' |
| H | H | H | $\mathrm{C}]$ | H | OH |
| H | H | H | Cl | H | F |
| H | H | H | Cl | H | Cl |
| H | H | H | Br | H | $\mathrm{NH}_{2}$ |
| H | H | H | Br . | H | NH-cyclopropyl |
| H | H | H | Br | H | OH |
| H | H | H | $\stackrel{\mathrm{Br}}{ }$ | H | F |





| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | H | ${ }^{\text {H }} \mathrm{H}$ | H | $\mathrm{NH}_{2}$ | SH |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SMe |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |
| diphosphate | H | $\mathrm{H}_{9}$ | H | $\mathrm{NH}_{2}$ | F |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | I |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| triphosphate | H | H | $\stackrel{H}{4}$ | $\mathrm{NH}_{2}$ | NH-methyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | OMe |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | OEt |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-cyclopropyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-acetyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | SH |
| triphosphate | H | H | . ${ }^{+}$ | $\mathrm{NH}_{2}$ | SMe |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | F |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ | I |
| monophosphate | monophosphate | monophosphate. | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| monophosphate | monophosphate | monophosphate | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| monophosphate | monophosphate | monophosphate | H | $\mathrm{NH}_{2}$ | OH |
| monophosphate | monophosphate | monophosphate | H | $\mathrm{NH}_{2}$ | F |
| monophosphate | monophosphate | monophosphate | H | $\mathrm{NH}_{2}$ | Cl |






WO 01/92282
PCT/US01/16687



Alternatively, the following nucleosides of Formula V are prepared, using the appropriate sugar and pyrimidine or purine bases.

IPO DELHT 25-06-2015•15:50

(V)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{\mathbf{1}}$ | $\mathbf{Y}^{*}$ |
| :--- | :--- | :--- | :--- | :--- |
| H | H | H | H | H |
| H | H | H | H | NH $_{2}$ |
| H | H | H | H | NH-cyclopropyl |
| H | H | H | NH-methyl |  |
| H | H | H | H | H. |
| H | NH-ethyl |  |  |  |
| II | H | H | NH-acetyl |  |
| H | H | H | H | OH |
| H | H | H | H | OMe |
| H | H | H | H | O-cyclopropyl |
| H | H | H | O-acetyl |  |
| H | H | H | SH |  |
| H | H | SMe |  |  |
| H | H | H | H | S-cyclopropyl |
| H | H | H | NH 2 |  |
| monophosphate | H | H | NH-acetyl |  |
| monophosphate | H | H | H | NH-cyclopropyl |
| monophosphate | H | H | H. | NH-methyl |
| monophosphate | H | H | H | NH-ethyl |
| monophosphate | H | H | H |  |
| monophosphate | H | H | H | O-acetyl |
| monophosphate | H | H |  |  |


| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | H | H | OMe |
| monophosphate | H | H | H | OEt |
| monophosphate | H | H | H | O-cyclopropyl |
| monophosphate | H | H | H | SH |
| monophosphate | H | H | H | SMe |
| monophosphate | H | H | H | SEt |
| monophosphate | H | H | $\cdot \mathrm{H}$ | S-cyclopropyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | NH-acetyl |
| diphosphate | H | H | H | NH-cyclopropyl |
| diphosphate | H | H | H | NH-methyl |
| diphosphate | H | H | H | NH-ethyl |
| diphosphate | H | H | H | OH |
| diphosphate | H | H | H | O-acetyl |
| diphosphate | H | H | H | OMe |
| diphosphate | H | H | H | OEt |
| diphosphate | H | H | H | O-cyclopropyl |
| diphosphate | H | H | H | SH |
| diphosphate | H | H | H | SMe |
| diphosphate | H | H | H | SEt |
| diphosphate | H | H | H | S-cyclopropyl |
| triphosphate | H | H | H | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | H | NH-acetyl |
| triphosphate | H | H | H | NH-cyclopropyl |
| triphosphate | H | H | H | NH-methyl |
| triphosphate | H | H | H• | NH-ethyl |
| triphosphate | H | H | H | OH |
| triphosphate | H | H | H | OMe |
| triphosphate | H | H | H | OEt |
| triphosphate | H | H | H | O-cyclopropyl |
| triphosphate | H | H | H | O-acetyl |



WO 01/92282

| $\mathbf{R}^{1}$ | R ${ }^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | NH-cyclopropyl |
| acetyl | H | H | F | OH |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | NH-cyclopropyl |
| H | , acetyl | acetyl | H | OH |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | OH |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | H | NH-cyclopropyl |
| monophosphate | acetyl | acetyl | H | OH |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| diphosphate | acetyl | acetyl | H | NH-cyclopropyl |
| diphosphate | acetyl | acetyl | H | OH |
| triphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| triphosphate | acetyl | acetyl | H | NH-cyclopropyl |
| triphosphate | acetyl | acetyl | H | OH |

Alternatively, the following nucleosides of Formula X are prepared, using the appropriate sugar and pyrimidine or purine bases.

' X )
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\cdot$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6} \quad:$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| H | $\mathrm{H} \cdot \cdot$ | H | $\mathrm{CH}_{3}$ | O | $2,4-\mathrm{O}$ <br> Diacetyluracil |  |



| $\mathbf{R}^{\text {T }}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | II | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| monophosphate | H' | H | $\mathrm{CH}_{3}$ | 0 | $4-\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$. | 0 | 5-Fluorouracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O- <br> Diacelyluracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate |  | $\mathrm{H}$ | $\mathrm{CH}_{3}$ | S | 2,4-O- <br> Diacetylthym |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \text { 4-(N-mono- } \\ & \text { acetyl)cytosine } \end{aligned}$ |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 4-(N,N- <br> diacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | $\mathrm{H}$ | H | $\mathrm{CH}_{3}$. | 0 | $2,4-0$ <br> Diacetyluracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-0- <br> Diacetylthymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| diphosphate | H | $\mathrm{H}^{\prime}$ | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $4-\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |


| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | $2,4-0$ <br> Diacetyluracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O- <br> Diacetylthym |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-0 <br> Diacetyluracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| triphosphate | H |  | $\mathrm{CH}_{3}$ | 0 | 2,4-O- <br> Diacetylthymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| triphosphate | H | If | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $4-\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| triphosphate | H | H | ${ }^{1} \mathrm{CH}_{3}$ | 0 | Uracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| triphosphate | H | $\mathrm{H}$ | $\mathrm{CH}_{3}$ | S | $2,4-0-$ <br> Diacetyluracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosphate | H | H | $\overline{\mathrm{CH}_{3}}$ | S | $2,4-0-$ <br> Diacetylthymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | moriophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-0- <br> Diacetyluracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Hypoxanthine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-0 <br> Diacetylthymine |


| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Thymine |
| monophosphate | monophosphate | nwoophosphate | $\mathrm{CF}_{3}$ | 0 | Cytosine |
| manophosphate | monophosphate | monophosphatc | $\mathrm{CF}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N,N- <br> diacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | monophosphate | .ronophosphate | $\mathrm{CF}_{3}$ | S | $2,4-\mathrm{O}-$ <br> Diàcetyluracil |
| monophosphate | mionophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-0- <br> Diacetylthymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-monoacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monwphosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | S. | 4-(N,N- <br> diacetyl)cytosine |
| acetyl | acetyl | acetyl | 2-bromovinyl | 0 | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| acetyl | acetyl | acetyl | 2-bromovinyl | S | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)- <br> guanine |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | $\bar{H}^{\text {' }}$ | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| H | H | H | $\mathrm{CH}_{3}$. | 0 | guanine |
| H | H | H | $\overline{\mathrm{CH}_{3}}$ | 0 | 6-(N,N-diacetyl)- <br> adenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 2-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 2,8-difluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | adenine |
| H | H. | H | $\mathrm{CH}_{3}$ | S | 2-(N,N-diacetyl)guanine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 6-O-acetyl <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroguanine |
| H | H | H | $\mathrm{CH}_{3}$ | S | guanine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 6-(N,N-diacetyl)adenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| H | $\mathrm{H}$ | H | $\mathrm{CH}_{3}$ | S | 2,8-difluoroadenine |
| H | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2-(N,N-diacetyl)guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}{ }^{\text {}}$ | 0 | 6-O-acetyl <br> guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |
| monophosphate | $\mathrm{H}$ | H | $\mathrm{CH}_{3}$ | 0 | guanine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 6-(N,N-diacetyl)- <br> adenine |




| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | $\begin{aligned} & \text { 6-(N,N-diacetyl)- } \\ & \text { adenine } \end{aligned}$ |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2-fluoroadenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 8-fluoroadenine |
| triphosphate | H | $\mathrm{H}$ | $\mathrm{CH}_{3}$ | S | 2,8-difluoro- <br> adenine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2-(N,N-diacetyl)- <br> guanine |
| monophosphate. | monophosphate | moriophosphate | $\mathrm{CF}_{3}$ | 0 | 6-O-acetyl <br> guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8-fluoroguanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | $6 \text {-(N,N-diacetyl) }$ <br> adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2-fluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 8-fluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,8-difluoro- <br> adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-(N,N-diacetyl)- <br> guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 6-O-acetyl <br> guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8 -fluoroguanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | guanine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $6 \text {-(N,N-diacetyl)- }$ <br> adenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2-fluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 8-fluoroadenine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,8-difluoroadenine |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- | :--- |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | adenine |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | O | guanine |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | S | guanine |
| acetyl | acetyl | acetyl | 2-bronio- <br> vinyl | O | guanine |
| acetyl | acetyl | acetyl | 2-bromo- <br> vinyl | S | guanine |

Alternatively, the following nuclcosides of Formula XI are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XI)
wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{7}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- | :--- |
| H | H | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| H | H | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| H | H | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| H | H | H | $\mathrm{CH}_{3}$ | O | Thymine |
| H | H | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| H | H | . | H | $\mathrm{CH}_{3}$ | O. |
|  | 4-(N-mono- <br> acetyl)cytosine |  |  |  |  |
| H | H | . | H | $\mathrm{CH}_{3}$ | O |
| H | H | H | $\mathrm{CH}_{3}$ | O | Uracil |
| H | H | H | $\mathrm{CH}_{3}$ | O | 5-Fluacorouracil |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |  |


| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{7}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| H | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| H | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosin |
| H | H | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| H | H | H | $\mathrm{CH}_{3}$ | S | Uracil |
| H | H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
|  |  |  | $\mathrm{CH}_{3}$ |  |  |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosinc |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 4-(N-monoacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | H | H | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | H | H. | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylurac |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{4}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- | :--- |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | Thymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono- <br> acetyl)cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | Uracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacctyluracil |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthym |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono- |
|  |  | H |  | . | acetyl)cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytos |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | Uracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthym |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | O | 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | O | Hypoxanthine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | O | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | O | Thymine |


| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{7}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | 0 | Cytosine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | 0 | 4-(N-monoacetyl)cytòsine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| monophosphate | monóphosphate | Br | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | 4-(N-monoacetyl)cytosine |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytos |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monophosphate | Br | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | NO2 | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| acetyl | acetyl | NO2 | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| acetyl | acetyl | NO2 | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| acetyl | acetyl | NO2 | 2-bromo <br> vinyl | $\mathrm{S}$ | 4-(N,N-diacetyl)cytosine |

Alternatively, the following nucleosides of Formula XII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XII)
wherein:

| $\mathbf{R}^{\text {I }}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: |
| H | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| H | $\overline{\mathrm{CH}_{3}}$ | 0 | 2,4-O-Diacetylthymine |
| H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| H | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | 0 | 4-( $\mathrm{N}, \mathrm{N}$-diacetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| H | $\mathrm{CH}_{3}$ | S | Thymine |
| H | $\mathrm{CH}_{3}$ | S | Cytosine |
| H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | S | Uracil |
| H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| monophosphate - | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Thymine . . |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil ' |
| monophosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CH}_{3}$ | S | Thymine |


| $\mathrm{R}^{1}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: |
| monophosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | S | 4-(N-mono-aceetyl)cytosirie |
| monophosphate | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| diphosphato | $\mathrm{CH}_{3}$ | 0 | 2,4.n-Dias.etylthymine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Thymine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | '0 | 4-(N-mono-acetyl)cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil, |
| diphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| diphosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| diphosphate | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Thymine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Cytosine . |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| triphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil - . |
| triphosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |


| $\mathrm{R}^{1}$ | $\mathbf{R}^{6}$. | X | Base |
| :---: | :---: | :---: | :---: |
| triphosphate | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| monophosplate | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | 0 | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | S | 4-(N,N-diacetyl)cytosine |

Alternatively, the following nucleosides of Formula XVII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XVII)
wherein:



| $\mathbf{R}^{1}$ | $\mathrm{R}^{6}$ | R ${ }^{\text {r }}$ | X | Base | $\mathbf{R}^{9}$ | $\mathrm{R}^{10}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| triphosphate | $\mathrm{CH}_{3}$ | H | S | 2,4-O-Diacetylthymine | NH2 | Me |
| triphosphate | $\mathrm{CH}_{3}$ | H | S | Thymine | NH2 | Me |
| triphosphate | $\mathrm{CH}_{3}$ | H | S | Cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 2,4-O-Diacetyluracil | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | Hypoxanthine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H. | 0 | 2,4-O-Diacetylthymine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H: | 0 | Thymine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | Cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 4-(N-mono-ȧctyl)cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 4-(N,N-diacetyl)cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | Uracil | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | 0 | 5-Fluorouracil | NTH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 2,4-O-Diacetyluracil | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | Hypoxanthine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H. | S | 2,4-O-Diacetylthymine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | Thymine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | Cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 4-(N-mono-acetyl)cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 4-(N,N-diacetyl)cytosine | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | Uracil | NH2 | Me |
| monophosphate | $\mathrm{CF}_{3}$ | H | S | 5-Fluorouracil | NH2 | Me |
| acetyl | $\mathrm{CH}_{3}$ | H | 0 | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | H | S | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | 0 | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | S | 4-(N,N-diacetyl)cytosine | H | Br |

## Example 3: Preparation of 3'-C-methylriboadenine

The title compound can be prepared according to a published procedure (R.F.,Nutt, M.J. Dickinson, F.W. Holly, and E. Walton, 'Branched-chain sugar nucleosides. II. 3'-Cmethyladenine ", J.Org. Chem. 1968, 33, 1789-1795) (Scheme 9).

## Scheme 9


(a) $\mathrm{RuO}_{2} / \mathrm{NaIO}_{4}$; (b) $\mathrm{MeMgI} / \mathrm{TiCl}_{4}$; (c) $\mathrm{HCl} / \mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$; (d) $\mathrm{BzCl} /$ pyridine; (e) AcBr , $\mathrm{HBr} / \mathrm{AcOH}$; (f) chloromercuri-6-benzamidopurine; (g) $\mathrm{NH}_{3} / \mathrm{MeOH}$.

In a similar manner, but using the appropriate sugar and pyrimidine or purine bases, the following nucleosides of Formula III are prepared.

(III)
wherein:

| $\mathbf{R}^{\mathbf{1}}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{\mathbf{1}}$ | $\mathbf{X}^{2}$ | $\mathbf{Y}$ |
| :--- | :--- | :--- | :--- | :--- | :--- |
| H | H | H | H | H | H |
| H | H | H | H | H | H |
| H | H | H $_{2}$ |  |  |  |
| H | H | H : | H | NH-cyclopropyl |  |
| H | H | H | H | H | NH-methyl |
| H | H | H | H. | NH-ethyl |  |
| H | H | H | H | H | NH-acetyl |







| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |
| H | H | H | H | $\mathrm{NH}_{2}$ | F |
| H | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | H | $\mathrm{NH}_{2}$ | Br |
| H | H | H | H | $\mathrm{NH}_{2}$ | I |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-acetyl |
| monophosphate | H. | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| monophosphate | H | H | H: | $\mathrm{NH}_{2}$ | NH-methyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | O-acetyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | OMe |
| monophosphate | H | H | H. | $\mathrm{NH}_{2}$ | OEt |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | O-cyclopropyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SH |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SMe |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | SEt |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | S-cyclopropyl |
| -monophosphate | H | H | H | $\mathrm{NH}_{2}$ | F |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | Br |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ | I |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH -acetyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | NH-methyl |
| diphosphate | ${ }_{\mathrm{H}}$ | H | H | $\mathrm{NH}_{2}$ | NH-ethyl |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | OH |
| diphosphate | H | H | H | $\mathrm{NH}_{2}$ | O-acetyl |
| diphosphate | H | $\mathrm{H}^{\text {t }}$ | H | $\mathrm{NH}_{2}$ | OMe |



WO 01/92282

| $\mathbf{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | Imonophosphate | H | $\mathrm{NH}_{2}$ | F |
| monophosphate | monophospliate | monophosphate | H | $\mathrm{NII}_{2}$ | Cl |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | OH |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | F |
| diphosphate | diphosphate | diphosphate | H | $\mathrm{NH}_{2}$ | Cl |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| triphosphate | triphosphate | triphosphate | H | $\mathrm{NH}_{2}$ | OH |
| triphosphate | triphosphate | triphosphate | ${ }^{\mathrm{H}}$ | $\mathrm{NH}_{2}$ | F |
| triphosphate | triphosphate | triphosphate | H: | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | F | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | F | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | F | $\mathrm{NH}_{2}$ | OH |
| H | H | H | F | $\mathrm{NH}_{2}$ | F |
| H | H | H | F | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | $\mathrm{Cl}^{\circ}$ | $\mathrm{NH}_{2}$ | OH |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | F |
| H | H | H | Cl | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | Br | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | Br | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | Br | $\mathrm{NH}_{2}$ | OH |
| H | H | H | Br . | $\mathrm{NH}_{2}$ | F |
| H | H | H | Br | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | OH |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | F |


| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| H | H | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ | Cl |
| H | H | H | SH | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| H | H | H | SH | $\mathrm{NH}_{2}$ | NH-cyclopropyl- |
| H | H | H | SH | $\mathrm{NH}_{2}$ | OH |
| H | H | H | SH | $\mathrm{NH}_{2}$ | F |
| H | H | H | SH | $\mathrm{NH}_{2}$ | Cl |
| acetyl | H | H | H: | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | OH |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | F |
| acetyl | H | H | H | $\mathrm{NH}_{2}$ | Cl |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | OH |
| acetyl | H | H | F | $\mathrm{NH}_{2}$ | F |
| acety! | H | H | F | $\mathrm{NH}_{2}$ | Cl |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$. | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | OH |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |
| H | acetyl | acetyl. | H. | $\mathrm{NH}_{2}$ | Cl |
| acetyl | ácetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| acetyl | acety! | acetyl | H | $\mathrm{NH}_{2}$ | OH |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | NH-cyclopropyl |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | OH |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | F |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ | Cl |



| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{X}^{1}$ | $\mathrm{X}^{2}$ | Y |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | H | H | H | Cl | OH |
| monophosphate | H | H | H | Cl | O-acetyl |
| monophosphate | H | H | H | Cl | OMe |
| monophosphate | - H | H | H | Cl | OEt |
| monophosphate | H | H | H | Cl | O-cycloprupyl |
| monophosphate | H | H | H | Cl | SH |
| monophosphate | H | H | H | Cl | SMe |
| monophosphate | H | H | H | Cl | SEt |
| monophosphate | H | H | H | Cl | S-cyclopropyl |
| diphosphate | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| diphosphate | H | H | H | Cl | NH-acetyl |
| diphosphate | H | H | H | Cl | NH-cyclopropyl |
| diphosphate | H | H | H | Cl | NH-methyl |
| diphosphate | H | $\mathrm{H}$ | H | Cl | NH-ethyl |
| diphosphate | H | H | H | Cl | OH |
| diphosphate | H | H | H | Cl | O-acetyl |
| diphosphate | H | H | H | Cl | OMe |
| diphosphate | H | H | H | Cl | OEt |
| diphosphate | H | H | H | Cl | O-cyclopropyl |
| diphosphate | H | H | H | Cl | SH |
| diphosjhate | H | H |  | Cl | SMe |
| diphosphate | H | H | H | Cl | SEt |
| diphosphate | H | H | H | Cl | S-cyclopropyl |
| triphosphate | H | H | H | Cl | $\mathrm{NH}_{2}$ |
| triphosphate | H | H | H | Cl | NH-acetyl |
| triphosphate | H | H | H | Cl | $\mathrm{NH}-\mathrm{cyclopropyl}$ |
| triphosphate | H | H | H | Cl | NH-methyl |
| triphosphate | H | H | H | Cl | NH-ethyl |
| triphosphate | H | H | H . | Cl | OH |
| triphosphate | H | H | H | Cl | OMe |
| triphosphate | H | H | H | Cl - | OEt |




Alternatively, the following nucleosides of Formula VI arc prepared, using the appropriate sugar and pyrimidine or purine bases.

(VI)
wherein:

| $\mathrm{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| H | H | H | H | H |
| H | H | H | H | $\mathrm{NH}_{2}$ |
| H' | H | H | H | NH-cyclopropyl |
| H | H | H | H | NH-methyl |
| H | H | H | H | NH-ethyl |
| H | H | H | H | NH-acetyl |
| H | H | H | H | OH |
| H | H | H | H | OMe |
| H | H | H | H | OEt |
| H | H | H | H | O-cyclopropyl |
| H | H | H | H | O-acetyl |
| H | H | H | H | SH |
| H | H | H | H | SMe |
| H | H | $\mathrm{H}!$ | H | SEt |
| H | H | H | H | S-cyclopropyl |
| monophosphate | H | H | H | $\mathrm{NH}_{2}$ |
| monophosphate | H | H | H | NH-acetyl |
| monophosphate | H. | H | H | NH-cyclopropyl |
| monophosphate | H | H | H | NH1-methyl |
| monophosphate | H | H | H | NH-ethyl |
| monophosphate | H | H | H | OH |
| monophosphate | H | H | H | O-acetyl |

WO 11/92282
PCT/US01/16687


WO 01/92282


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{X}^{1}$ | Y |
| :---: | :---: | :---: | :---: | :---: |
| acctyl | H | H | F | $\mathrm{NH}_{2}$ |
| acetyl | H | H | F | NH-cyclopropyl |
| acetyl | H | H | F | OH |
| H | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| H | acetyl | acetyl | H | NH-cyclopropyl |
| II | acetyl | acetyl | H. | OH |
| acetyl | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| acetyl | acetyl | acetyl | H | NH-cyclopropyl |
| acetyl | acetyl | acetyl | H | OH |
| monophosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| monophosphate | acetyl | acetyl | H: | NH-cyclopropyl |
| monophosphate | acetyl" | acetyl | H | OH |
| diphosphate | acetyl | acetyl | H | $\mathrm{NH}_{2}$ |
| diphosphate | acetyl ... | acetyl. | H | NH-cyclopropyl |
| diphosphate | acetyl | acetyl | H | OH |
| triphosphate | acetyl . | acetyl | H. | $\mathrm{NH}_{2}$ |
| triphosphate | acetyl | acetyl | H | NH-cyclopropyl |
| triphosphate | acetyl | acetyl | H | OH |

Altematively, the following nucleosides of Formula XIII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XIII)
wherein

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}:$ | $\mathbf{X}$ | Base. |
| :--- | :--- | :--- | :--- | :--- | :--- |
| H | H | H <br> $\vdots$ | $\mathrm{CH}_{3}$ | O | 2,4-O- <br> Diacetyluracil |
| H | H | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |



[^1]

| $\mathbf{R}^{T}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | $2,4-0$ <br> Diacetylthym |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| tripliosphate | H- | H | $\mathrm{CH}_{3}$ | 0 | 2,4-0 <br> Diacetyluracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ : | 0 | 2,4-0- <br> Diacetylthymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 4-(N-monoacetyl)cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | Uracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | 2,4-O- <br> Diacetyluracil |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | $2,4-0-$ <br> Diacetylthymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O- <br> Diacetyluraci] |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Hypoxanthine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O- <br> Diacetylthymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Thymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Cytosine |

WO 01/92282
PCT/US01/16687

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 4-(N-mono- acetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | Uracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O- <br> Diacetyluracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-0- <br> Diacetylthymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$. | S | Cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | $\begin{aligned} & \text { 4-(N-mono- } \\ & \text { acetyl)cytosine } \end{aligned}$ |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N- <br> diacetyl)cytosine |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| acetyl | acetyl | acetyl | $\mathrm{CF}_{3}$ | S | $4-\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| acetyl | acetyl | acetyl | $\begin{aligned} & \text { 2-bromo- } \\ & \text { vinyl } \end{aligned}$ | 0 | $4-(\mathrm{N}, \mathrm{~N}-$ <br> diacetyl)cytosine |
| acetyl | acetyl | acetyl | $\begin{aligned} & \text { 2-bromo- } \\ & \text { vinyl } \end{aligned}$ | S | 4-(N,N- <br> diacetyl)cytosine |
| H | H | $\mathrm{H}$ | $\mathrm{CH}_{3}$ | $\bigcirc$ | 2-(N,N-diacetyl) <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 6-O-acetyl <br> guanine |
| H | H | H | $\mathrm{CH}_{3}$ | 0 | 8-fluoroguanine |






## IPO DELHI 23-06-2015 15:572

| $\mathbf{R}^{\text {r }}$ | $\mathbf{R}^{\mathbf{2}}$. | $\mathbf{R}^{3}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- | :--- |
| acetyl | acetyl | acetyl <br> $\cdot$ | 2-bromon <br> vinyl | O | guanine <br> . |
| acetyl | acetyl $\cdot$ | $\cdot$ | acetyl | $\cdot$ | 2-bromo- <br> vinyl |

Alternatively, the following nucleosides of Formula XIV are prepared, using the appropriate sugar and pyrimidine or purine bases.

wherein:

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- |
| H | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| H | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| H | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| H | H | $\mathrm{CH}_{3}$ | O | Thymine |
| H | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| H | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| H | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| H | H | $\mathrm{CH}_{3}$ | O | Uracil |
| H | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| H | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| H | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| H | H | $\mathrm{CH}_{3}$ | S | 2;4-O-Diacetylthymine |
| H | H | $\mathrm{CH}_{3}$ | S | Thymine |
| H | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosin |  |
| H | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- |
| H | H | $\mathrm{CH}_{3}$ | S | Uracil |
| H | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthym |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | Thymine |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytos |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | Uracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthym |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Thymine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Thymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | Uracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| diphosphate | H | Hypoxanthine |  |  |

IPO DELHI 23-06-2015 15:50

| $\mathbf{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- | :--- |
| diphosphate | H | CH | S | 2,4-O-Diacetylthymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | Thymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | Cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | Uracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | H | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Hypoxanthine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Thymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | O | Uracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | monophosphate | $\mathrm{EF}_{3}$ | S | Cytosine |
|  |  |  |  |  |

WO (11/92282
PCT/US01/16687

| $\mathrm{R}^{1}$ | $\mathbf{R}^{2}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: | :---: |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | 0 | 4-(N,N-diacetyl) cytosine |
| acetyl | acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| acetyl | acetyl | 2-bromo-- vinyl | 0 | 4-(N,N-diacetyl)cytosine |
| acetyl | acetyl | 2-bromovinyl | S | 4-(N,N-diacetyl)cytosine |

Alternatively, the following nucleosides of Formula $X V$ are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XV)
wherein:

| $\mathbf{R}^{\boldsymbol{1}}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetyluracil |
| H | $\mathrm{CH}_{3}$ | O | Hypoxanthine |
| H | $\mathrm{CH}_{3}$ | O | 2,4-O-Diacetylthymine <br> H |
| H | $\mathrm{CH}_{3}$ | O | Thymine |
| H | $\mathrm{CH}_{3}$ | O | Cytosine |
| H | $\mathrm{CH}_{3}$ | O | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| $\mathrm{H}^{\prime}$ | $\mathrm{CH}_{3}$ | O | Uracil |
| H | $\mathrm{CH}_{3}$ | O | 5-Fluorouracil |


| $\mathbf{R}^{\text {T }}$ | $\mathrm{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: |
| H | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| H | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| H | $\mathrm{CH}_{3}$ | S | Thymine |
| H | $\mathrm{CH}_{3}$ | S | Cytosine |
| H | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| H | $\mathrm{CH}_{3}$ | S | Uracil |
| H | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| monophosphate | $\mathrm{CH}_{3}$ | $0$ | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Thymine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| monophosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| monophosphate, | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CH}_{3}$ | S | Thymine |
| monophosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CH}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CH}_{3}$ | S | 5-Fluorouracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| diphosphate | $\mathrm{CH}_{3}$. | 0 | Thymine |
| diphosphate | $\mathrm{CH}_{3}$ | 0. | Cytosine |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | X | Base |
| :---: | :---: | :---: | :---: |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| diphosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil |
| diphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| diphosphate | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| diphosphate | $\mathrm{CH}_{3}$ | S | 2,4-0-Diacetylthymine |
| diphosphate | $\mathrm{CH}_{3}$ | S | Thymine |
| diphosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Hypoxanthine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Thymine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N-mono-acetyl)cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 4-(N,N-diacetyl)cytosine |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | Uracil |
| triphosphate | $\mathrm{CH}_{3}$ | 0 | 5-Fluorouracil. |
| triphosphate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetyluracil |
| triphosphate - | $\mathrm{CH}_{3}$ | S | Hypoxanthine |
| triphosplıate | $\mathrm{CH}_{3}$ | S | 2,4-O-Diacetylthymine |
| triphosphate | $\mathrm{CH}_{3}$ | S | Thymine |
| triphosphate | $\mathrm{CH}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Cytosine |
| monophosphate | $\mathrm{CF}_{3}{ }^{\prime}$ | 0 | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$. | 0 | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | 0 | Uracil |


| $\mathbf{R}^{\mathbf{1}}$ | $\mathbf{R}^{6}$ | $\mathbf{X}$ | Base |
| :--- | :--- | :--- | :--- |
| monophosphate | $\mathrm{CF}_{3}$ | O | 5-Fluorouracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetyluracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | Hypoxanthine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 2,4-O-Diacetylthymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Thymine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N-mono-acetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| monophosphate | $\mathrm{CF}_{3}$ | S | Uracil |
| monophosphate | $\mathrm{CF}_{3}$ | S | 5-Fluorouracil |
| acetyl | $\mathrm{CF}_{3}$ | O | 4-(N,N-diacetyl)cytosine |
| acetyl | $\mathrm{CF}_{3}$ | S | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | O | 4-(N,N-diacetyl)cytosine |
| acetyl | 2-bromo-vinyl | S | 4-(N,N-diacetyl)cytosine |

Altematively, the following nucleosides of Formula XVIII are prepared, using the appropriate sugar and pyrimidine or purine bases.

(XVIII)
wherein:

| $\mathbf{R}^{\mathbf{1}}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{8}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| H | $\mathrm{CH}_{3}$ | OH | O | 2,4-O-Diacetyluracil | H. | Me |
| H | $\mathrm{CH}_{3}$ | OH | O | Hypoxanthine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | O | 2,4-O-Diacetylthymine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH. | O | Thymine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | O | Cytosine | H | Me |


| R | $\mathbf{R}^{6}$ | R ${ }^{\text {? }}$ | X | Base | $\mathbf{R}^{8}$ | $\mathrm{R}^{9}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| II | $\mathrm{CHI}_{3}$ | OHI | 0 | 4 (N-mono-acetyl)cytosine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | 0 | 4-( $\mathrm{N}, \mathrm{N}$-diacetyl)cytosine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | 0 | Uracil | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | 0 | 5-Fluorouracil | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetyluracil | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | Hypoxanthine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetylthymine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | Thymine | H | Me |
| H | $\mathrm{CH}_{3}$ | $\mathrm{OH}^{+}$ | S | Cytosine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | 4-(N-mono-acetyl)cytosine | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | 4:( $\mathrm{N}, \mathrm{N}$-diacetyl) ${ }^{\text {cytosine }}$ | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | Uracil. | H | Me |
| H | $\mathrm{CH}_{3}$ | OH | S | 5-Fluorouracil | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | 2,4-O-Diacetyluracil | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | Hypoxanthine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | 2,4-O-Diacetylthymine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | Thymine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | Cytosine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | 4-(N-mono-acetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | 4-(N,N-diacetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | Uraçil | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | 0 | 5-Fluorouracil | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetyluracil | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | S | Hypoxanthine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetylthymine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | S | Thymine : | H | Me |
| mónophosphate | $\mathrm{CH}_{3}$ | OH | S | Cytosine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | S | 4-(N-mono-acetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | S | 4-(N,N-diacety $)$ cytosine | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | $\overline{\mathrm{OH}}$ | S | Uracil | H | Me |
| monophosphate | $\mathrm{CH}_{3}$ | OH | S | 5-Fluorouracil | H | Me |


| $\mathbf{R}^{1}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{8}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| diphosphatc | $\mathrm{CII}_{3}$ | OH | O | 2,4-O-Diacetyluracil | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | -O | Hypoxanthine | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | O | 2,4-O-Diacetylthymine | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | O | Thymine | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | O | Cytosine | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | O | 4-(N-mono-acetyl)cytosine | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | O | 4-(N,N-diacetyl)cytosine | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | O | Uracil | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | O | 5-Fluorouracil | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetyluracil | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | S | Hypoxanthine | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetylthymine | H | Me |
| dipliosphate | $\mathrm{CH}_{3}$ | OH | S | Thymine : | H | Me |
| diphosphate | $\mathrm{CH}_{3}$ | OH | S | Cytosine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | 2,4-O-Diacetyluracil | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | Hypoxanthine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | 2,4-O-Diacetylthymine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | Thymine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | Cytosine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | 4-(N-mono-acetyl)cytosine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | 4-(N,N-diacetyl)cytosine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | Uracil | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | O | 5 -Fluorouracil | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetyluracil | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | S | Hypoxanthine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | S | 2,4-O-Diacetylthymine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | S | Thymine | H | Me |
| triphosphate | $\mathrm{CH}_{3}$ | OH | S | Cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | 2,4-O-Diacetyluracil | $\mathrm{H} \cdot$ | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | Hypoxanthine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | $2,4-\mathrm{O}$-Diacetylthymine | H | Me |


| $\mathbf{R}^{\text {r }}$ | $\mathbf{R}^{6}$ | $\mathbf{R}^{7}$ | $\mathbf{X}$ | Base | $\mathbf{R}^{8}$ | $\mathbf{R}^{9}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | Thymine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | Cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | 4 -(N-mono-acetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | 4-(N,N-diacetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | Uracil | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | O | 5-Fluorouracil | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 2,4-O-Diacetyluracil | H | Mc |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Hypoxanthine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 2,4-O-Diacetylthymine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Thymine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 4-(N-mono-acetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 4-(N,N-diacetyl)cytosine | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | Uracil | H | Me |
| monophosphate | $\mathrm{CF}_{3}$ | OH | S | 5-Fluorouracil | H | Me |
| acetyl | $\mathrm{CH}_{3}$ | OH | O | 4-(N,N-diacetyl)cytosine | H | Br |
| acetyl | $\mathrm{CH}_{3}$ | OH | S | 4-(N,N-diacetyl)cytosine | H | Br |

## VII. Anti-Flavivirus or Pestivirus Activity

Compounds can exhibit anti-flavivirus or pestivirus activity by inhibiting flavivirus or pestivirus polymerase, by inhibiting other enzymes needed in the replication cycle, or by other pathways.

## EXAMPLES

The test compounds were dissolved in DMSO at an initial concentration of $200 \mu \mathrm{M}$ and then were serially diluted in culture medium.

Unless otherwise stated, baby hamster kidney (BHK-21) (ATCC CCL-10) and Dos Taurus (BT) (ATCC CRL 1390) cells were grown at $37^{\circ} \mathrm{C}$ in a humidified $\mathrm{CO}_{2}$ (5\%) atmosphere. BHK-21 cells were passage in Eagle MEM additioned of 2 mM L-glutamine,
$10 \%$ fetal bovine serum (FBS, Gibco) and Earle's BSS adjusted to contain $1.5 \mathrm{~g} / \mathrm{L}$ 'sodium bicarbonate and 0.1 mM non-essential amino acids. BT cells were passaged in Dulbecco's. modified Eagle's medium with 4 mM L-glutamine and $10 \%$ horse serum (HS, Gibco), adjusted to contain $1.5 \mathrm{~g} / \mathrm{L}$ sodium bicarbonate, $4.5 \mathrm{~g} / \mathrm{L}$ glucose and 1.0 mM sodium pyruvate. 'The vaccine strain 17D (YFV-17D) (Stamaril®, Pasteur Merieux) and Bovine Viral Diarrhea virus (BVDV) (ATCC VR-534) were used to infect BHK and BT cells, respectively, in $75 \mathrm{~cm}^{2}$ bottles. After a 3 day incubation period at $37^{\circ} \mathrm{C}$, extensive cytopathic cffect was observed. Cultures were freeze-thawed three times, cell debris were removed by centrifugation and the supernatant was aliquoted and stored at $-70^{\circ} \mathrm{C}$. YFV-17D and BVDV were titrated in BHK-21 and BT cells, respectively, that were grown to confluency in 24-well plates.

## Example 4: Phosphorylation Assay of Nucleoside to Active Triphosphate

To determine the cellular metabolism of the compounds, HepG2 cells were obtained from the American Type Culture Collection (Rockville, MD), and were grown in $225 \mathrm{~cm}^{2}$ tissue culture flasks in minimal essential medium supplemented with non-essential amino acids, $1 \%$ penicillin-streptomycin. The medium was renewed every three days, and the cells -were subcultured once a week. After detachment of the adherent monolayer with a 10 minute exposure to 30 mL ' of trypsin-EDTA and three consecutive washes with medium, confluent HepG2 cells were seeded at a density of $2.5 \times 10^{6}$ cells per well in a 6 -well plate and exposed to $10 \mu \mathrm{M}$ of [ ${ }^{3} \mathrm{H}$ ] labeled active compound ( $500 \mathrm{dpm} / \mathrm{pmol}$ ) for the specified time periods. The cells were maintained at $37^{\circ} \mathrm{C}$ under a $5 \% \mathrm{CO}_{2}$ atmosphere. At the selected time points, the cells were washed three times with ice-cold phosphate-buffered saline (PBS). Intracellular active compound and its respective metabolites were extracted by incubating the cell pellet overnight at $-20^{\circ} \mathrm{C}$ with $60 \%$ methanol followed by extraction with an additional $20 \mu \mathrm{~L}$ of cold methanol for one hour in an ice bath. The extracts were then combined, dried under gentle filtered air flow and stored at $-20^{\circ} \mathrm{C}$ until HPLC analysis. The preliminary results of the HPLC analysis are tabulated in Table 1.

Table 1


## Example 5: Bioavailability Assay in Cynomolgus Monkeys

Within I week prior to the studly initiation, the cynomolgus monkey was surgically implanted with a chronic venous catheter and subcutaneous venous access port (VAP) to facilitate blood collection and underwent a physical examination including hematology and serum chemistry evaluations and the body weight was recorded. Each monkey (six total), received approximately 250 uCi of ${ }^{3} \mathrm{H}$ activity with each dose of active compound, namely $\beta$ -D-2'- $\mathrm{CH}_{3}$-riboG at a dose level of $10 \mathrm{mg} / \mathrm{kg}$ at a dose concentration of $5 \mathrm{mg} / \mathrm{mL}$, either via an intravenous bolus ( 3 monkeys, IV), or via oral gavage ( 3 monkeys, PO). Each dosing syringe was weighed before dosing to gravimetrically determine the quantity of formulation administered. Urine samples were collected via pan catch at the designated intervals (approximately $-48-0$ hours pre-dose, $0-4,4-8$ and $8-12$ hours post-dosage) and processed. Blood samples were collected as well (pre-dose, $(0.25,0.5 ; 1,2,3,6,8,12$ and 24 hours postdosage) via the chronic venous catheter and VAP or from a peripheral vessel if the chronic venous catheter proccilure should not be possible. The blood and urine samples were analyzed for the maximum concentration ( $\mathrm{C}_{\text {max }}$ ), time when the maximum concentration was achieved ( $\mathrm{T}_{\mathrm{max}}$ ), area under the curve (AUC), half life of the dosage concentration ( $\mathrm{T}_{1 / 2}$ ), clearance ( CL ), steady state volume and distribution ( $\mathrm{V}_{\mathrm{ss}}$ ) and bioavailability ( F ), which are tabulated in Tables 2 and 3, and graphically illustrated in Figures 2 and 3, respectively.

Table 2: Oral Bioavailability in Monkeys

|  | Dose <br> $(\mathrm{mg})$ | AUG <br> $(\mathrm{ng} / \mathrm{mL} \times \mathrm{h})$ | Norm AUC <br> $(\mathrm{ng} / \mathrm{mL} \times \mathrm{h} / \mathrm{mg})$ | Mean Norm AUC <br> $(\mathrm{ng} / \mathrm{mL} \times \mathrm{h} / \mathrm{mg})$ | $F(\%)$ <br> N Monkey 1 <br> 46.44 <br> IV Monkey 2 224.53 |
| :--- | :---: | :---: | :---: | :---: | :---: |
| N Monkey 3 | 20.72 | 6581, | 293.2 |  |  |
| PO Monkey 1 | 29.04 | 758 | 268.3 |  |  |
| PO Monkey 2 | 30.93 | 898 | 293.4 | 284.9 |  |
| PO Monkey 3 | 30.04 | 1842 | 29.1 |  |  |

Table 3: Experimental Pharmacokinetics of $\beta$-De'- $\mathrm{CH}_{3}$-riboG in Cynomolgus Monkeys

|  | $I V$ | PO |
| :--- | :---: | :---: |
| Dose/Route $(\mathrm{mg} / \mathrm{kg})$ | 10 | $:$ |
| $\left(T_{\max }(\mathrm{ng} / \mathrm{mL}):\right.$ | $0945.6 \pm 1886.0$ | $217.7 \pm 132.1$ |
| $T_{\max }(\mathrm{hr})$ | $0.25 \pm 0.00$ | $2.00 \pm 1.00$ |
| $\mathrm{AUC}(\mathrm{ng} / \mathrm{mL} \times \mathrm{hr})$ | $8758.0 \pm 42.12 .9$ | $1166.0 \pm 589.6$ |
| $\mathrm{~T}_{1 / 2}(\mathrm{hr})$ | $7.9 \pm 5.4$ | $10.3 \pm 4.1$ |
| $\mathrm{CL}(\mathrm{L} / \mathrm{hr} / \mathrm{kg})$ | $1.28 \pm 0.48$ |  |
| $\mathrm{~V}_{\mathrm{ss}}(\mathrm{L} / \mathrm{kg})$ | $2.09 \pm 0.54$ |  |
| $\mathrm{~F}(\%)$ | 13.8 |  |

## Example 6: Bone Marrow Toxicity Assay

Human bone marrow cells were collected from normal healthy volunteers and the mononuclear population was separated by Ficoll-Hypaque gradient centrifugation as described previously by Sommadossi J-P, Carlisle R. "Toxicity of 3'-azido-3'deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine for normal human hematopoietic progenitor cells in vitro" Antimicrobial Agents and Chemotherapy 1987; 31:452-454; and Sommadossi J-P, Schinazi RF, Thu CK, Xe M-Y. "Comparison of cytotoxicity of the $(-)$ - and ( + )-enantiomer of 2 ', $3^{\prime}$-dideoxy- $3^{\prime}$-thiacytidine in normal human bone marrow progenitor cells" Biochemical Pharmacology 1992; 44:1921-1925. The culture assays for CFU-GM and BFU-E were performed using a bilayer soft agar or methylcellulose method. Drugs were diluted in tissue culture medium and filtered. After 14 to 18 days at $37^{\circ} \mathrm{C}$ in a humidified atmosphere of $5 \% \mathrm{CO}_{2}$ in air, colonies of greater than 50 cells were counted using an inverted microscope. The results in Table 4 are presented as the percent inhibition of colony formation in the presence of drug compared to solvent control cultures.

Table 4: Human Bone Marrow Toxicity CFU-GM and BFU-E Clonogenic Assays

| Treatment | $\mathrm{IC}_{50}$ in $\mu \mathrm{M}$ |  |
| :---: | :---: | :---: |
| CFU-GM | BFU-E |  |
| ribavirin | -5 | $\sim 1$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboA | $>100$ | $>100$ |
| $\beta-\mathrm{D}^{\prime}-\mathrm{CII}_{3}$-riboU | $>100$ | $>100$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboC | $>10$ | $>10$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboG | $>10$ | $>100$ |

## Example 7: Mitochondria Toxicity Assay

HepG2 cells were cultured in 12 -well plates as described above and exposed to various concentrations of drugs as taught by Pan-Zhou X-R, Chi L, Chou X-J, Sommadossi JP, Darley-Usmer YM: "Differential effects of antiretroviral nucleoside analogs on mitochondrial function in HepG2 cells" Antimicrob Agents Chemother 2000; 44:496-503. Lactic acid levels in the culture medium after 4 day drug exposure was measured using a Boehringer lactic acid assay kit. Lactic acid levels were normalized by cell number as measured by hemocytometer count. The preliminary results from this assay are tabulated in

## Table 5.

Table 5: Mitochondrial Toxicity Study (L-lactic acid assay)


## Example 8: Cytotoxicity Assay

Cells were seeded at a rate of between $5 \times 10^{3}$ and $5 \times 10^{4} /$ well into 96 -well plates in. growth medium overnight at $37^{\circ} \mathrm{C}$ in a hunuidified $\mathrm{CO}_{2}(5 \%)$ atmosphere. New growth medium containing serial dilutions of the drugs was then added. After incubation for 4 days, cultures were fixed in $50 \%$ TCA and stained with sulforhodamineB. The optical density was read at 550 nm . The cytotoxic concentration was expressed as the concentration required to reduce the cell number by $50 \%\left(\mathrm{C} \dot{C}_{50}\right)$. The data is tabulated in Table 6 .

Table 6: MDBK versus Human Hepatoma

| Compound | MDBK | $\mathrm{CC}_{50}, \dot{\mu} \mathrm{M}$ <br> Huh7 7 | HepG2 |
| :--- | :---: | :---: | :---: |
| $\beta$-D-2'-CH3-riboA | 20 | 40 | $50-60$ |
| $\beta$-D-2'-CH3 -riboU | $>250$ | $>250$ | $>250$ |
| $\beta$-D-2' $-\mathrm{CH}_{3}$-riboC | 100 | $>250$ | 150 |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboG | 100 | $>250$ | $>250$ |
| Ribavirin | 5 | 25 | 150 |

## Example 9: Cell Protection Assay (CPA)

The assay was performed essentially as described by Baginski, S. G.; Pevear, D. C.; Seipel, M.; Sun, S. C. C.; Benetatos, C. A.; Chunduru, S. K.; Rice, C. M. and M. S. Collett "Mechanism of action of a pestivirus antiviral compound" PNAS USA 2000, 97(14), 79817986. MDBK cells (ATCC) were seeded onto 96 -well culture plates ( 4,000 cells per well) 24 hours before use. After infection with BVDV (strain NADL, ATCC) at a multiplicity of infection (MO1) of $\left.\right|_{0: 02}$ plaque forming units (PFU) per cell, serial dilutions of test compounds were added to both infected and uninfected cells in a final concentration of $0.5 \%$ DMSO in growth medium. Each dilution was tested in quadruplicate. Cell densities and virus inocula were adjusted to ensure continuous cell growth throughout the experiment and to achieve more than $90 \%$ virus-induced cell destruction in the untreated controls after four days post-infection. After four days, plates were fixed with $50 \%$ TCA and stained with sulforhodamine B. The optical density of the wells was read in a microplate reader at 550 hm . The $50 \%$ effective concentration ( $\mathrm{EC}_{50}$ ) values were defined as the compound concentration that achieved $50 \%$ reduction of cytopathic effect of the virus. The results are tabulated in Table 7. Figures 4 and 5 provide a graphical illustration of the methodology used to arrive
at the $50 \%$ effective concentration $\left(\mathrm{EC}_{50}\right)$ values for $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboG and ribavirin. Figure 6 compares the results of the CPA for $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG, $\beta$-D-2' $-\mathrm{CH}_{3}$-riboC, $\beta$-D-2'- $\mathrm{CH}_{3}-$ riboU, $\beta$-D-2'- $\mathrm{CH}_{3}$-riboA and ribavirin

Table 7: Cell Protection Assay

|  | $\cdot \mathrm{EC}_{50}, \mu \mathrm{M}$ | $\mathrm{CC}_{50}, \mu \mathrm{M}$ |
| :--- | :---: | :---: |
| $\beta$-D-2'- $\mathrm{CH}_{3}$-riboA | 2 | 20 |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboU | 20 | $>250$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboC | 2 | 100 |
| $\beta$-D-2'-CH - riboG | 4 | 100 |
| Ribavirin | $>3$ | 5, |

## Example 10: Plaque Reduction Assay

For each compound the effective concentration was determined in duplicate 24 -well plates by plaque reduction assays. Cell monolayers were infected with $100 \mathrm{PFU} /$ well of virus. Then, serial dilutions of test compourds in MEM .supplemented with $2 \%$ inactivated serum and $0.75 \%$ of methyl cellulose were added to the monolayers. Cultures were further incubated at $37^{\circ} \mathrm{C}$ for 3 days, then fixed with $50 \%$ ethanol and $0.8 \%$ Crystal Violet, washed and air-dried. Then plaques were counted to determine the concentration to obtain $90 \%$ virus suppression and tabulated in Table 8. Figure 7 is a graphical illustration of the results from the Plaque Reduction Assay. Figure 8 is an image of BVDV plaque formation in the presence of increasing concentrations of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboU.

Table 8: Viral Suppression via Plaque Reduction Assay

|  | $\mathrm{EC}_{90}, \mu \mathrm{M}$ |
| :--- | :---: |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboA | $<3$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboU | $<81$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboC | $<9$ |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}-$ riboG | $<9$ |
|  | $\quad$, |

## Example 11: Yield Reduction Assay

For each compound the concentration to obtain a 6 -log reduction in viral load was determined in duplicate 24 -well plates by yield reduction assays. The assay was performed
as described by Baginski, S. G.; Pevear, D. C.; Seipel, M.; Sun, S. C. C.; Benetatos, C. A.; Chunduru, S. K.; Rice, C. M. and M. S. Collett "Mechanism of action of a pestivirus antiviral compound" PNAS USA 2000, 97(14), 7981-7986, with minor modifications. Briefly, MDBK cells were seeded onto 24 -well plates ( $2 \times 105$ cells per well) 24 hours before infection with BVDV (NADL strain) at a multiplicity of infection (MOI) of 0.1 PFU per cell. Serial dilutions of test compounds were added to cclls in a final concentration of $0.5 \%$ DMSO in growth medium. Each dilution was tested in triplicate. After three days, cell cultures (cell monolayers and supernatants) were lysed by three freeze-thaw cycles, and virus yield was quantified by plaque assay. Briefly, MDBK cells were seeded onto 6 -well plates ( $5 \times 105$ cells per well) 24 h beffore use. Cells were inoculated with 0.2 mL of test lysates for 1 hour, washed and overlaid with $0.5 \%$ agarose in growth medium. After 3 days, cell monolayers were fixed with $3.5 \%$ formaldehyde and stained with $1 \%$ crystal violet ( $w / v$ in $50 \%$ ethanol) to visualize plaques. The plaques were counted to determine the concentration to obtain a 6 $\log$ reduction in viral load as tabulated in Table 9. Figure 9 is a graphical illustration of the results from the Yield Reduction Assay. Figure 8 is an image of BVDV yield reduction in the presence of increasing concentrations of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboC.

Table 9: Coucentration to Obtain 6-log Reduction

|  | Conc. for 6-log Reduction $(\mu \mathrm{M})$ |
| :--- | :---: |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboU | 120 |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboG | 20 |
| $\beta$-D-2 $-\mathrm{CH}_{3}$-riboC | 20 |
| $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboA | 9 |

## Example 12: Comparative Cytotoxicity

Table 10 sumnarizes the cytoxicity of two compounds of this invention, $\beta$-D-1'- $\mathrm{CH}_{3}-$ riboA and $\beta-\mathrm{D}_{-2}$ '- $\mathrm{CH}_{3}$-riboA, in comparison to RBV ("ribavirin"), in various cell systems.

Table 10: Comparative Cytotoxicity* $\left(\mathrm{CC}_{50}\right)$

|  | BD | BK | VERO | MT-4 |
| :--- | :---: | :---: | :---: | :---: |
| $\beta$-D-1' $-\mathrm{CH}_{3}$-riboA | $>100$ | 200 | $>100$ | 18 |
| $\beta-\mathrm{D} 2^{\prime}-\mathrm{CH}_{3}$-riboA | 75 | 22 | 22 | 6.6 |
| REV | ND | 50 | 11 | ND |

* Compound concentration ( $\mu \mathrm{M}$ ) required to reduce the viability of cells by $50 \%$.

The chemical structures for $\beta-D-1$ '- $\mathrm{CH}_{3}$-riboA and $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboA are as follows:

$\beta$-D-1'- $\mathrm{CH}_{3}$-riboA

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboA

Table 11 summarizes the antiviral activity of $\beta-\mathrm{D}-\mathrm{l}^{\prime}-\mathrm{CH}_{3}$-riboA and $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}-$ riboA against several viruses within the flavivirus and pestivirus genuses.

Table 11: Comparative Antiviral Activity* ( $\mathrm{EC}_{50}$ )

|  | BVDV | YFV | PICO | VSV | HIV-1 |
| :--- | :---: | :---: | :---: | :---: | :---: |
| $\beta$-D-1'-CH3-riboA | 10 | 7.0 | 51 | $>100$ | $>18$ |
| $\beta$-D-2'-CH3-riboA | 0.1 | 0.2 | 5.0 | $>100$ | $>6.6$ |
| REV | ND | 30 | $>30$ | ND | ND |

* Compound concentration $(\mu \mathrm{M})$ required to reduce the plaque number by $50 \%$. The following virus-çell system were used: BVDC-BT, YFV-BHK, PICO (Cosxackie B1 and Polio Sabin)/VSV - Veró.

Table 12 summarizes the antiviral activity and toxicity of $\beta$-D-2'-methyl-riboG, $\beta$-D-2'-methyl-riboC and $\beta$-D-2'-methyl-riboU, against a couple of viruses within the flavivirus and pestivirus genuses.

Table 12: Comparative Antiviral Activity* ( $\mathbf{E C}_{50}$ )

|  | BVDV |  | YFV |  |
| :--- | :---: | :---: | :---: | :---: |
|  | $\mathrm{EC}_{50}{ }^{*}$ | $\mathrm{CC}_{50} * *$ | $\mathrm{EC}_{50}{ }^{*}$ | $\mathrm{CC}_{50}{ }^{* *}$ |
| $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG | -2 | $>100$ | 1.2 | 20 |
| $\beta$-D-2 ${ }^{\prime}-\mathrm{CH}_{3}$-riboC, | $\vdots 3.7$ | $>100$ | 70 | $>100$ |
| $\beta$-D-2 $2^{\prime}-\mathrm{CH}_{3}$-riboU | 20 | $>100$ | 33 | $>100$ |

* Compound concentration ( $\mu \mathrm{M}$ ) required to reduce the plaque number by $50 \%$. The following virus-cell system were used: BVDC-BT and YFV-BHK.
* Compnund concentration ( $\mu \mathrm{M}$ ) required to reduce the viability of cells by $50 \%$.

The chemical structures for $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG, $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}$-riboC and $\beta-\mathrm{D}-2^{\prime}-\mathrm{CH}_{3}-$ riboU are as follows:

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboG

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboC

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboU

Table 13 summarizes the anti-viral activity of several compounds of this invention against $B V D V$ in three different assays.

Table 13: for BVDV

| Compound | $\begin{array}{c}\text { Cell } \\ \text { Protection } \\ \left(\mathrm{EC}_{50}, \mu \mathrm{M}\right)\end{array}$ | $\begin{array}{c}\text { Plaque } \\ \text { Reduction } \\ \left(\mathrm{EC}_{90}, \mu \mathrm{M}\right)\end{array}$ | $\begin{array}{c}\text { Yield Reduction } \\ \mathrm{EC} \\ 90\end{array}, \mu \mathrm{M}$ |  |  | $\begin{array}{c}6 \log _{10} \\ \text { reduction }(\mu \mathrm{M})\end{array}$ |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | \(\left.\begin{array}{c}Cytotoxicity <br>

Huh7 cells <br>
\left(\mathrm{EC}_{50}, \mu \mathrm{M}\right)\end{array}\right]\)

WO 01/92282

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention, will be obvious to those skilled in the art from the foregoing detailed description of the invention.

IPO DELHI 23-06-2015 15:51

## We Claim:

1. A compound of Formula I:

(I)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
Y is hydrogen, bromo, chloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched -or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
2. A compound of Formula II:

(II)

WO 01/92282
PCT/US01/16687
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodıug); acyl (including lower acyl); alkyl' (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in viva is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $\mathrm{H}^{-1}$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and,
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
3. A compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is
capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propel and cyclopropyl).
4. A compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including $\frac{1}{a}$ phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; $Y$ is hydrogen, promo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
5. A compound of Formula $V$ :

(V)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methancsulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{\mathrm{l}}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
6. A compound of Formula VI:

(VI)

IPO DELHI 23-06-2015:15:51
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, K^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, promo, chloro, fluoro, ido, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO -alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluors, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
7. A compound selected from Formulas VII, VIII and IX:

(VII)

(VIII)

(IX)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein; .
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is
capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, $\dot{B} r$-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), - O (alkyl), -O (lower alkyl), -O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, ; $\mathrm{NH}\left(\right.$ lower alkyl); $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
8. A compound of Formulas X, XI and XII:

or a pharmaceutically acceptable salt thereof, wherein:
Basc is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \dot{\mathrm{O}}(\mathrm{lower}$ alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}^{\prime}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ àcyl), $-\mathrm{O}($ lower acyl $)$, -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
9. A compound selected from Formulas XIII, XIV and XV:

(XII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lòwer acyl);-alkyl (including lowier alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$R^{6}$. is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
10. A compound of Formula XVI:

(XVI) or a pharmaceutically acceptable salt thereof, wherein:

IPO OELHI: 23-06-2015 15: W1

Base is a purine or pyrimidine base as defined herein; $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower -alkyl$),-\mathrm{O}$ (acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, $\mathrm{O}\left(\right.$ lower alkyl), -()(alkenyl), chloro, bromo, fluor, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}\left(\text { acyl }_{2}\right)_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), $-\mathrm{O}($ acyl $)$, $-\mathrm{O}\left(\right.$ lower acyl), -O (alkyl), - O (lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine, or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.

## 11. A compound of Formula XVII:


(XVII)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl $\therefore \cdot$
(including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl); azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O(lower acyl), - O (alkyl), - $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2} ;-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
12. A compound of Formula XVII:

(XVIII)
or a pharmaccutically acoeptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently. $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or
other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}(l o w e r ~ a l k y l), ~-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $\mathrm{O}\left(\right.$ lower alkyl), $-\mathrm{O}\left(\right.$ alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2}, ~, ~ \mathrm{~N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chloriné, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come togetherito form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
13. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
14. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
15. A compound of the structure:

or a pharmaceutically acceptable salt thereof. -
16. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
17. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
18. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
19. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
20. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
21. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
22. A compound of the structure:

or a pharmaceutically acceptable salt thereof.

IPO DELHI $23-06-2015$ 15: ${ }^{201} 1$
23. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
24. A compound of the structure:

or a pharmaceutically acceptable salt thereof.
25. The compound as described in any of the preceding claims $1-24$, wherein the said compound is in the form of a dosage unit.
26. The compound as described in claim 187, wherein the dosage unit contains 10 to 1500 mg of said compound.
27. The compound as described in claim 187 or 188 , wherein said dosage unit is a tablet or capsule.
28. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula I:


(I)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $\dot{H}$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrig); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid;" an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate;
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl; CO-aryl, CO-alkoxyalkyl, chiloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}+\mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
29. A pharmaccutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\dot{\mathrm{R}}^{3}$ are independently H ; phosphate (including monophosphate, dịphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or-more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $O R^{4}, N R^{4} R^{5}$. or $S R^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo; $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (includirg lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
30. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluént, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with
one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and

Y is hydrogen, bromo, chloro, fluors, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and $R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propel and cyclopropyl).
31. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H , phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; $Y$ is hydrogen, bromo, chloro, fluoro, ido, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
32. A pharmaceutical composition for the treatment br prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula $V$ :

(V)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3 .}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

WO (1/1/92282
33. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula VI:

(VI)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrúg); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate. ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol;' or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
Y is hydrogen, bromo, clloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or ${ }^{i} \mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl); or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
34. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formulas VIII, VIII or IX:

(VII)


(IX)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; on amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2- Br -ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, -NH (lower alkyl), $-\mathrm{NH}($ açyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S},-\mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
35. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective anmount of a compound of Formula X, XI or XII:

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:

Base is a purine or pyrimidine base as defined herein; $R^{1}, R^{2}$ and $R^{j}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; ani amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate;
$R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}$ (álkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
36. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus int a host, comprising an effective amount of a compound of Formula XIII, XIV or XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl
(including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, $\mathrm{O}\left(\right.$ lower alkyl), - O (alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}\left(\right.$ lower alkyl) $2_{2}^{\prime}-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
37. A pharmaceutical composition for the treatment or prophylaxis of a tlavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), -
$\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluor, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), -N (lower alkyl) $)_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently. hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), - O (lower acyl); - O (alkyl), - - (lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl) })_{2}$ or $-\mathrm{N}(\text { acyl) })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{9}$ and $\mathrm{R}^{4}, \mathrm{R}^{7}$ and $\mathrm{R}^{10}, \mathrm{~K}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
38. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula XVII:'

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2^{\circ}}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl); $-\mathrm{O}($ alkyl $),-$

O (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl); $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}\left(\right.$ lower acyl), -O (alkyl), -O (lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2} ;$
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
39. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula XVIII:

(XVIII)
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently $H$; phosphate (including mọnophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chloro, bromo, fluor, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;

IPO DELHI 23-05-2015 1.5:515
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $R^{7}$ and $R^{9}$, or $R^{8}$ and $R^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
40. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
41. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a phanmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

IPO DEEHI 23-06-2015 15:51
42. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable sal thereof, together with a pharmaceutically acceptable carrier or diluent.
43. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
44. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

IPO DELHT 23-06-2015 15:51 $1^{217}$
45. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
46. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable.carrier or diluent.
47. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
48. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceulically acceptable carrier or diluent.
49. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
50. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
51. A pharmaceutical compasition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, tugether with a pharmaceutically acceptable carrier or diluent.
52. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula I:

(1)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, whercin:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodiug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaking group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; $Y$ is hydrogen, bromo, chloro, fluoro, iodo, $O R^{4}, N R^{4} R^{5}$ or $S R^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cycloprapyl).
53. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including' lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including mcthancsulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vito is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluors, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ arc independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
54. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphatc prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group oonsisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
55. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a best, comprising an effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ is selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propel and cyclopropyl).

IPO DELHI 25-06-2015 15:513
56. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula V :

(V)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, promo, chloro, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4} ; \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
57. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula VI:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesuilfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
58. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula VI, VIII or IX:

IPO DELHE 23-06-2015 15: 25 I

(VII)

(VIII)

(IX)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\overline{\mathrm{R}}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azide; cyano, alkenyl, alkynyl, Br -vinyl, 2- Br -ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), - O (alkyl), -O (lower alkyl), -O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluors, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-$ $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
59. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula X, XI or XII!

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:

Base is a purine or pyrimidine base as defined herein; $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, whercin the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving_group_which when-administered in-wive-is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $), ~-$ O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl) })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
60. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host; comprising an effective amount of a compound of Formula XIII, XIV or XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a'stabilized phosphate prodrug); acyl (including lower acyl); alkyl
(including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid; including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ O (lower alkyl), -O(alkenyl); chloro, bromo, fluor, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl) })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
61. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally-effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{\prime}$ and $R^{2}$ are independently $H$ or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, -
$\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), $-\mathrm{O}\left(\right.$ lower acyl), $-\mathrm{O}\left(\right.$ alkyl), $-\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including. lower alkyl), chlorine, bromine, or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
62. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula XVII:

or a pharmaceutically acceptable salt thereof, in conibination with one or more other antivirally-effective agents, whercin:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl. (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$
$\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azide, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl); $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $R^{7}$ and $R^{9}$, or $R^{7}$ and $R^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
63. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of Formula XVIII:

(XVII)
or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently H; phosphate (including, monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), O (lower alkyl), -O(alkenyl); chloro, bromo, fluors, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)anino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $R^{7}$ and $R^{9}$, or $R^{8}$ and $R^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
64. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
65. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
66. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
67. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
68. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of stricture:

or a pharmaceutically acceptable salt thereof, in combination with one or more other 1 antivirally effective agents.
69. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt therenf, in combination with one or more other antivirally effective agents.
70. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
71. A pharmáceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
72. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmacetutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
73. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
74. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.

IPO DELHI 23-06'-2015 15:51
75. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus or pestivirus in a host, comprising an effective amount of a compound of structure:

or a pharmaceutically acceptable salt thereof, in combination with one or more other antivirally effective agents.
76. The pharmaceutical composition as described in any of the preceding claims 28-75, wherein the said compound is in the form of a dosage unit.
77. The pharmaceutical composition as described in claim 76, wherein the dosage unit contains 10 to 1500 mg of said compound.
78. The pharmaceutical composition as described in claim, 75 or 76 , wherein said dosage unit is a tablet or capsule.
79. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula I:

(I)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently H, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower
alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other phannaceutically açceptable leaving group which when'administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chioro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or çyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl; chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and $\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
80. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate; or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when adriunistered in vivo is capable of providing a compound wherein $R^{1}, \dot{R}^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
81. A method for the treatment or prophyluxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when admiinistered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl; chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

IPO DELHI 23-05-2015. 15:51
82. A method for the trcatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{\prime}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo; fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
83. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula V:

(V)
or a pharmaceutically acceptable salt thereof, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
84. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula VI:

(VI)
or a pharmaceutically acceptable salt thereof, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate; triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
Y is hydrogen, bromo, chloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{\mathbf{\prime}}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO -alkyl, CO -aryl, CO alkoxyalkyl, chloro, promo, fluors, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
85. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula VII, VIII or IX:

(VII)

(VIII)

(IX)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when adninistered in vivo is capable of providing a compound wherein $R^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2-Br-ethyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl); - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), -O (alkyl), -O (lower alkyl), -O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}(\text { lower alkyl })_{1}-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
86. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula X, XI or XII:

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein; ;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ $\mathrm{O}(l o w e r ~ a l k y l),-\mathrm{O}\left(\right.$ alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyll $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}(l o w e r ~ a c y l)$, -O (alkyl), - O(lower alkyl), - O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
87. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Fonnula XIII, XIV or XV:

(XII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein; $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with
one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\dot{\mathrm{C}}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ O (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl),$-\mathrm{N}(\text { lower alkyl })_{2} ;-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
88. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable: salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano; alkenyl; alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { liver alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), $-\mathrm{O}\left(\right.$ lower acyl), $-\mathrm{O}\left(\right.$ alkyl), $-\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{8}$ and $R^{10}$ are independently $H$, alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
89. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVII:

(XVII)
or a pharmaceutically acceptable salt thereof, wherein: Base is a purine or pyrimidine base ás defined herein; $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is. capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, 'cyano, alkenyl; alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{lower}$ alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\Theta$ (alkyl), O (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;

PCT/US01/16687
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O(lower acyl), - O (alkyl), - O (lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\mathrm{l} \text { ( w wer alkyl) })_{2},-\mathrm{N}(\text { acyl) })_{2}$; $\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; altematively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
90. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administcring an anti-virally effective amount of a compound of Formula XVIII:

(XVIII)
or a pharmaceutically acceptable salt thereof, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including, monophosphate, diphosphate, triphosphate, or a stabilized phosphatc prodrug); acyl (including lower acyl); alkyl (including-lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}(l o w e r ~ a l k y l),-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, ${ }^{\mathrm{NO}} \mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl),NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
91. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure: .

or a pharmaccutically acceptable salt thereof.
92. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
93. A method for the treatment or prophylaxis of a flavivirus or pestivirus.infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
94. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
95. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
Y
96. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
97. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
98. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
99. A methot for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
100. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
101. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
102. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof.
103. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula I:

(I)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, ivherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally, substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in wive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; $Y$ is hydrogen, bromo, chloro, fluor, jodo, $O R^{4}, N R^{4} R^{5}$ or $S R^{4}$; $\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
104. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phösphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an aminọ acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-àlkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
105. A method for the treatment of prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound-of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein: $\quad \therefore$
$R!, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
106. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anli-virally effective amount of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$Y$ is hydrogen, bromo, chloro, fluoro, iopdo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
107. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula V:

(V)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodıug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate and

Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group coñsisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
108. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Fornula VI:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently' H or phosphate; and
Y is hydrogen, bromo; chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ is selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are.independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
109. A method for the treatinent or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula VII, VIII or IX:'

(vI)

(VII)

(IX)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vive is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2- Br -ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O (lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, ido, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, $\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}^{-}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
110. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula X, XI or XII:

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}(a l k y l)$, O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl; Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl $),-\mathrm{O}($ acyl), $-\mathrm{O}(\mathrm{lower}$ acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
111. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XIII, XIV or XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$; phosphate (including monophosphate; diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl
(including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl,
Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}(\mathrm{alkyl}),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O(acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $\mathrm{O}\left(\right.$ lower alkyl ), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
112. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized'phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate;
$R^{6}$ is hydrogen; hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $O R^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O(acyl), -O(lower acyl), - O (alkyl), $-\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2} ;$
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently H , alkyl (including lower alkyl), chlorine, bromine or iodine;
altematively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}, \mathrm{R}^{7}$ and $\mathrm{R}^{10} ; \mathrm{R}^{8}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ can come together to form a bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
113. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Formula XVII:

(XVII)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $),-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $)$, $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl), $\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl. (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}$ (lower alkyl), -O (acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), -NII(acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\dot{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
114. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an anti-virally effective amount of a compound of Forninula XVIII:

(XVIII)
or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more other antivirally effective agents, wherein:
Base is a purine or pyrimidine base as defined herein; $R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; 'an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered-in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), -
133. A use of a compound of Formula IV:

(IV)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino. acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$Y$ is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5^{\prime}}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
134. A use of a compound of Formula V:

$\mathrm{O}\left(\right.$ lower alkyl), - O (alkenyl), chloro, bromo, fluoro, ioḍ, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2}, \div \mathrm{N}(\text { acyl })_{2} ;$
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
1.15. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
116. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
117. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents:
118. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a hosi, cumprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
119. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.

IFO DELHI 23-06-2015 15: 51
120. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
121. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
122. A method for the treatuent or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
123. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable sall thereof, in combination or alternation with one or more antivirally effective agents.
124. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable sall thereof, in combination or alternation with one or more antivirally effective agents.
125. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
126. A method for the treatment or prophylaxis of a flavivirus or pestivirus infection in a host, comprising administering an antivirally effective amount of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in combination or alternation with one or more antivirally effective agents.
127. Method of treatment as described in any of the preceding claims $79-126$, wherein the said compound is in the form of a dosage unit.
128. Method of treatment as described in claim 127, wherein the dosage unit contains, 10 to 1500 mg of said compound.
129. Method of treatment as described in claim 127 or 128 , wherein said dosage unit is a tablet or capsule.
130. A use of a compound of Formula I:

(1)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower

IPO DELHI 23-06-2015 15: ${ }^{265}$
alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
Y is hydrogen, bromo, chloro, fluoro, jodo, $\left(\mathrm{R}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}\right.$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to. methyl, ethyl, propel and cyclopropyl).
131. A use of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
$\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
$Y$ is hydrogen, bromo, chlow, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$X^{1}$ and $X^{2}$ are independently selected from the group consisting of $H$, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
132. A use of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently. selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more sùbstituents as described in the definition of aryl given herein; a lipid, including a phospholipid; ain amino acid; a' carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when adninistered in vivo is capable of providing a compound wherein $R^{i}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
135. A use of a compound of Formula VI:

(VD)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyi (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid,
including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluor, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-äryl, CO-alkoxyalkyl, chloro, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
136. A use of a compound selected from Formulas VII, VIII and IX:

(VII)

(VIII)

(IX)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vino is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, 2-Br-cthyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O(lower acyl), - O (alkyl), -O (lower alkyl), -O (alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
137. A use of a compound of Fomulas $\mathrm{X}, \mathrm{XI}$ and XII:

(X)

(XI)

(XII)
or a pharmaccutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl; Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyll $),-\mathrm{O}($ lower acyl), $-\mathrm{O}(\mathrm{alkyl})$, O (lower alkyl); -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}(l o w e r ~ a l k y l), ~-~$ $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido; cyano, alkenyl, alkynyl; Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), - O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, , NH (lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower } \cdot \text { alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
138. A use of a compound selected from Formulas XIII, XIV and XV:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ $\mathrm{O}\left(\right.$ lower alkyl), -O (alkenyl), chiloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl) $,-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
139. A use of à compound of Formula XVI:

(XVI)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfornate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents. as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholestcrol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), O (lower alkyl), - O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\dot{\mathrm{N}}(\mathrm{acyl})_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independently, H , alkyl (including lower alkyl), chlorine; bromine, or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
140. A use of a compound of Formula XVII:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:
Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an anino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{\prime}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lòwer alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl), $\mathrm{O}\left(\right.$ lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are' independently hydrogen, $\mathrm{OR}^{2}$, hydróxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl)! -O(lower acyl), - - ${ }^{(a l k y l}$ ), -O(lower alkyl), - O(alkenyl), chlorine, bromine, iodine; $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}\left(\right.$ lower alkyl), $-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acy })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine; or iodine; altematively, $R^{7}$ ind $R^{y}$, or $R^{7}$ and $R^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
141. A use of a compound of Formula XVIII:

(XVIII)
or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:

Base is a purine or pyrimidinc base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with
one or more substituent as described in the definition of aryl given herein; a lipid; including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{\prime}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), -O (acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ O (lower alkyl), -O (alkenyl), chloro, tron, fungo, info, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$; or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
142. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
143. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.

WO 01/92282
144. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
145. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
146. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.

IPO DELHI 23-06-2015. 15:52
147. A use of a/compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
148. A use of a compound. of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
149. A use of a compound of the structure:

or $\downarrow$ pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
150. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
151. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
152. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
153. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
154. A use of a compound of Formula I:

(1)
or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid; including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluor, ido, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$; $\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and

IPO DELHI 23-06-2015 15:52

IPO DELHE 23-06-2015 15:52.
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
155. A use of a compound of Formula II:

(II)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are is independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluor, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloto, bromo, fluoro, jodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$R^{4}$ and $R^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
156. A use of a compound of Formula III:

(III)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); älkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ and $\mathrm{X}^{2}$ are independently selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
157. A use of a compound of Formula IV :

(IV)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionaliy substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{\prime}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
158. A use of a compound of Formula $V$ :

(V)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: $R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the defnition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{l}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, brọmo, chloro, fluoro, iodo, $O R^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $S R^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo; fluoro, iodo; $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NR}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
159. A use of a compound of Formula VI:

(VI)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid,
including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate; and
Y is hydrogen, bromo, chloro, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{R}^{5}$ or $\mathrm{SR}^{4}$;
$\mathrm{X}^{1}$ is selected from the group consisting of H , straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkóxyalkyl, chloro, brumu, fluoro, iodo, $\mathrm{OR}^{4}, \mathrm{NR}^{4} \mathrm{NK}^{5}$ or $\mathrm{SR}^{4}$; and
$\mathrm{R}^{4}$ and $\mathrm{R}^{5}$ are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).
160. A use of a compound selected from Formulas VII, VIII and IX:


(IX)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the trealment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently:H; phosphate (including monophosphate, diphosphate, triphosphaté, or a stabilized phosphate prodrug); acyl (including lower acyl);-alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$, and $\mathrm{R}^{3}$ are independently H or phosphate;
$R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, 2- Br -ethyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}(\mathrm{acyl}),-\mathrm{O}(\mathrm{low} e r ~ a c y l)$, -O(alkyl), -O(lower alkyl), -O(alkenyl), $\mathrm{CF}_{3}$, chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2}$, NH (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and
X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$, or $\mathrm{CH}_{2}$.
161. A use of a compound of Formulas $\mathrm{X}, \mathrm{XI}$ and XII :

(X)

(XI)

(XII)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivins, wherein: Base is a purine or pyrimidine base as defined herein; $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vito is capable of providing a compound wherein $\mathrm{R}^{1}, \mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are independently H or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alk l ) , $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alk $\dot{l} \mathrm{l})$, O (lower alkyl), -O (alkenyl), chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ is hydrogen, $\mathrm{OR}^{3}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, - $\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl $)$, - $\mathrm{O}($ lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2} ; \mathrm{NH}_{2}$, NH (lower alkyl), -NH (acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
162. A use of a compound selected from Formulas XIII, XIV and XV:

(XIII)

(XIV)

(XV)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of $\mathfrak{a}$ host infected with the flavivirus or pestivifus, wherein:

Base is a purine or pyrimidine base as defined herein;
$R^{1}, R^{2}$ and $R^{3}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given herein; a lipid, including a phospholipid; -an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in. vico is capable of providing a compound wherein $R^{1}, R^{2}$ and $R^{3}$ are independently $H$ or phosphate;
$\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}(a l k y l)$, O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, jodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
163. A use of a compound of Formula XVI:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein:

Base is a purine or pyrimidine base as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H ; phosphate (including munophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), O (lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$R^{7}$ and $R^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), - $\bigcirc$ (lower alkyl), -O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}($ lower alkyl $),-\mathrm{NH}($ acyl $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{8}$ and $\mathrm{R}^{10}$ are independeṇ́tly H , alkyl (including lower alkyl), chlorine, bromine or iodine;
alternatively, $R^{7}$ and $R^{9}, R^{7}$ and. $R^{10}, R^{8}$ and $R^{9}$, or $R^{8}$ and $R^{10}$ can come together to form a bond; and

X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
164. A use of a compound of Formula XVI:

(XVII)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: Base is a purine or pyrimidine bạse as defined herein;
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$. are independently H ; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester-including alkyl' or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents.aṣ described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceplable leaving group which when administered in vivo is capable of providing a compound wherein $R^{1}$ and $R^{2}$ are independently $H$ or phosphate; $\mathrm{R}^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl), $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ $\mathrm{O}\left(\right.$ lower alkyl), - O (alkenyl), chlorn, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}($ acyl) $),-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl; alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), - O (alkenyl), chlorine, bromine, iodine, $\mathrm{NO}_{2}$, $\mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $-\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{10}$ is H , alkyl (including lower alkyl), chlorine, bromine, or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{7}$ and $\mathrm{R}^{10}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
165. A use of a compound of Formula XVIII:

(XVIII)
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus, wherein: Base is a purine or pyrimidine base as defined herein;
$R^{1}$ and $R^{2}$ are independently $H$; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with
one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are independently H or phosphate; $R^{6}$ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br -vinyl, $-\mathrm{C}(\mathrm{O}) \mathrm{O}($ alkyl $),-\mathrm{C}(\mathrm{O}) \mathrm{O}($ lower alkyl), $-\mathrm{O}($ acyl), $-\mathrm{O}($ lower acyl), $-\mathrm{O}($ alkyl $),-$ O (lower alkyl), O (alkenyl), chloro, bromo, fluoro, iodo, $\mathrm{NO}_{2}, \mathrm{NH}_{2},-\mathrm{NH}$ (lower alkyl), $\mathrm{NH}\left(\right.$ acyl), $-\mathrm{N}(\text { lower alkyl })_{2},-\mathrm{N}(\text { acyl })_{2}$;
$\mathrm{R}^{7}$ and $\mathrm{R}^{9}$ are independently hydrogen, $\mathrm{OR}^{2}$, alkyl (including lower alkyl), alkenyl, alkynyl, Br -vinyl, O -alkenyl, chlorine, bromine, iodine, $\mathrm{NO}_{2}$, amino, loweralkylamino, or di(loweralkyl)amino;
$\mathrm{R}^{8}$ is H , alkyl (including lower alkyl), chlorine, bromine or iodine; alternatively, $\mathrm{R}^{7}$ and $\mathrm{R}^{9}$, or $\mathrm{R}^{8}$ and $\mathrm{R}^{9}$ can come together to form a bond; and X is $\mathrm{O}, \mathrm{S}, \mathrm{SO}_{2}$ or $\mathrm{CH}_{2}$.
166. A use of a compound of the structurc:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
167. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.

IPO DELHT $23-05-201515:{ }^{289} 2$

WO 01/92282
168. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a lust infected with the flavivirus or pestivirus.
169. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
170. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
171. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
172. $\Lambda$ use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
173. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.

IPO DELHI 23-06-2015 15:2\%2
174. $\Lambda$ use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
175. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host, infected with the flavivirus or pestivirus.
176. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected with the flavivirus or pestivirus.
177. A use of a compound of the structure:

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a host infected will the flavivirus or pestivirus.
178. Use of the compound as described in any of the preceding claims 130-177, wherein the said compound is in the form of a dosage unit.
179. Use of the compound of claim 101, wherein the dosage unit contains 178 to 1500 mg of said compound.
180. Use of the compound of claim 178 or 179 , wherein said dosage unit is a tablet or capsule.

Figure 1: Chemical Structures of Illustrative Nucleosides

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboG

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboA

$\beta$-D-2'- $\mathrm{CH}_{3}-$ riboC

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboI.

$\beta$-D-2'- $\mathrm{CH}_{3}$-riboU

$\beta$-D-2'- $\mathrm{CH}_{3}$-ribo $T$

$\beta$-D-I'- $\mathrm{CH}_{3}-$ riboA



FIAU .

$\beta-\mathrm{D}-1$ '- $\mathrm{CH}_{3}-$ riboG


Ribavirin

Figure 2: Screening Phamacokinetics of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG in Cynomolgus Monkeys


Figure 3: Phamacokinetics of $\beta$-D-2'- CH $_{3}$-riboG in Cynomolgus Monkeys


Figure 3a


Figure 3b

IPO DELHI 23-06-2015 15:3/92

Figure 4: BVDV Cell Protection Assay (CPA) Of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG


Cell Protection Assay


IPO DELHT $23-06-2015 \cdot 151 / 52$

Figure 5: BVDV Cell Protection Assay (CPA) of Ribavirin



Cell Protection Assay

i
IPO OELHI 23-06-2015.15:52

Figure 6: BVDV Cell Protection Assays


Figure 7: Plaque Purified BVDV


Figure 8:BVDV Plaque Assay of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboU


Figure 9: Yield Reduction Assay of $\beta$-D-2'- $\mathrm{CH}_{3}$-riboG


4-log virus reduction at $9 \mu \mathrm{M}$

Figure 10: BVDV. Yield Reduction Assay for $\beta$-D-2'- $\mathbf{C H}_{3}$-riboC


## BEFORE THE CONTROLLER OF PATENTS, TIIEPATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS AC"I, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND
IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND
IN THE MATTER OF:

INDIA CARES
PETITIONER/OPPONENT
VS.

Pharmasset, Inc.
RESPONDENTS/APPLICANTS

## PRE-GRANT OPPOSITION BY INDIA CARES

Volume-III of IV
(Page Nos. 679 to 957)

| S. No. | Particulars | Page No. |
| :--- | :--- | :--- |
|  | Annexure-5 <br> US Patent No. 6348587 | $679-722$ |
|  | $\frac{\text { Annexure-6 }}{\text { Copy of WO 2002/057425 }}$ | $723-957$ |

## BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND
IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND
IN THE MATTER OF:

INDIA CARES
... PETITIONER/OPPONENT
VS.

Pharmasset, Inc.
... RESPONDENTS/APPLICANTS

## PRE-GRANT OPPOSITION BY INDIA CARES

$\begin{gathered}\text { Volume-III of IV } \\ \text { (Page Nos. } 679 \text { to } 957 \text { ) }\end{gathered}$

| S. No. | Particulars | Page No. |
| :--- | :--- | :--- |
|  | $\frac{\text { Annexure-5 }}{\text { US Patent No. 6348587 }}$ | $679-722$ |
|  | Annexure-6 <br> Copy of WO 2002/057425 | $723-957$ |

Dated this $23^{\text {rd }}$ day of June, 2015.

# cheha awmoro <br> CHITRA ARVIND <br> FOR RAJESHWARI \& ASSOCIATES 

To,
The Controller of Patents The Patent Office, Delhi '
(12) United States Patent

Schinazi et al.
(10). Patent No.: US 6,348,587 B1
(45) Date of Patent:
(54) 2'-FIUURONUCIEOSIDES
(75) Inventors: Raymond F. Schinazi, Decatur; Dennis C. Lota, Mcl)onough; Chung K. Chur, Athens; J. Jeffrey McAtec, Atlanta; Junxing Sui, Decatur; Yongseok Chi, Athens; Kyeong Lee, Athens; Join H. Hong, Athens, all of GA (US) ${ }^{1}$
(73) Assignees: Emory University, Atlanta; University of Georgia Research Foundation, Inc., Athens, both of GA (US)
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
(21) Appl. No.: 09/257,130
(22) Filed: lib. 25, 1999

Related U.S. Application Data
(60) Provisional application No. 60/080,569, filed on Apr. 3, 1998, and provisional application No. 60,075.893. filed on Feb. 25, 1998.
(51) Int. $\mathrm{Cl}^{7}$ $\qquad$ C07H 21/02; CO்71- 21/04; CO7H 1/(0); A01N 61/00; AOIN 43/04
U.S. Cl. $\qquad$ 536/25.3; 435/6; 514/1; 514/44; 536/1.11: 536/4.1; 536/22.1; 536/23.1

Field of Search $\qquad$ 4:3/6; 514/1, 44; 536/1.11, 4.1, 22. L. 23.1, 25.3

## References Cited

USS. PATENT I DOCUMENTS


## FOREIGN PATENT DOCUMENTS

EP
EP
EP
$W O$
WO
WO
$W O$
WO
WO
WO


## OTHER PUBLICATIONS

Balakrishna, el al., "Inhibition of Hepatitis B Virus by a Novel L-Nucleoside, 2'-Fluoro-5-Methyl-L-arabinofuranosyl Uracil," Antimicrobial Agents and Chemotherapy, Feb. 1996, pp. 380-356.
Borthwick, er al., "Synthesis and Enzymatic Resolution of Carbocyclic 2'-Ara-fluoro-Guanosine: A Potent New Anti-Herpetic Agent," J. Chem. Soc., Chem. Common, 1988.
Ching, et al., Journal of Biological Chemistry, vol. 267(20), pp. 13938-13942 (1092).
(List continued on next page.)

## Primary Examiner-Jezia Riley

(74) Attorney, Agent, or Firm-Sherry M. Knowles, Esq.; Josephine Young; King \& Spalding

A class of 2 '-fluoro-nucleoside compounds are disclosed which are useful in the treatment of hepatitis B infection, hepatitis C infection, HIV and abnormal cellular proliferation, including tumors and cancer. The compounds have the general formulae:


$\mathrm{Y}=\mathrm{O} . \mathrm{S} . \mathrm{CH}_{2} . \mathrm{CHF}$


$\mathrm{N}=\mathrm{SCH}$
wherein
Base is a purine or pyrimidine base; $\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}$, $\mathrm{N}_{3}$, CN , halogen, including $\mathrm{F}_{3}$ or $\mathrm{CF}_{3}$, lower alkyl, amino; loweralkylamino, di(lower)alkylamino, or alkoxy, and base refers to a purine or pyrimidine base;
$\mathrm{R}^{2}$ is H , phosphate; including monophosphate, diphosphate, triphosphate, of a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or chelesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vino, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof.

## OTHER PUBL.ICATIONS

Chu, el al., "Use of 2'-Fluoro-5-methyl-L-arabinofura; nosyluracil as a Novel Antiviral Agent for Hepatitis B Virus and Epstein-Harr Virus" Antimicrobial Agents und Chemotherapy, Apr. 1995 pp. 979-981.
Furman, el al., "The Anti-Hepatitis B Virus. Activities, Cytotoxicilies, and Anatolic Profiles of the ( - ) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1, 3-oxathiolane-5-yl]-Cytosine" Antimicrobial Agents and Chemotherapy, Dec. 1992, pp. 2686-2692.
Martin, et al., "Synthesis and Antiviral Activity ol Monotluoro and Dilluoro Analogues of Pyrimidine Desxyritonucleosides against lluman Immunodeficiency Vinus (HIV-1),".I. Med, Chem. 1996, 3.3, 2137-2145.
Schinazi, et al, Mutations in retoviral genes associated with drug rusistance, Imternational Antiviral News, 1997
Schinazi, et al., "Selective Inhitition of Human Immunodeficiency vinuss by Racemates anod Lamtioners of cis-5-Fluero 1-[3-(Hydroxymu hyl)-1,
 Chemotherapy, Nov. 1902, plı. 2423-2431.
Sterzycki, et al., "Synthesis and Anti-lilV Nativity of Several 2'-Fluoro-Containing Pyrimidine Nucleusides,". J. Med. Chem. 1990.

Su, T.S., el al., "Synthesis and Antiviral Effects of Several 1-(2-Deuxy-2-fluóro-B-D-arábinofuranosyl)-5-. alkyluracils. Some Structure-Activity Relationships," J. Med. Chem., 1986, 29, 151-154.
Wantanabe, et al., "Synthesis and Anti-HIV Activity of 2'-"Up"-Fluoro Analogues of Active Anti-Aids Nucleosides 3'-Azido-3'-deoxythymidine (AZT) and 2'.3'-dideoxycytidine (DIDC)," J. Med. Chem. 1990, 33, 2145-2150.
Siddliqui MÁt al., Tetrahed. Letters, vol. 39 No. 13 Mar. 26, 1998.
'Gyota, A., et al., Tetrahedron vol. 51, No. 32, pp. 8783-8798, 1995:
Yoahimura, Y., el al., J. ()rg. Chem., 1999, 64, 7912-7920. Marquez, V.E., et al., Nucleosides \& Nucleotides, 14(3-5), 555-558 (1995).
Machida, H., et al., Antiviral Research, 39(1998) p. 129-137.
Wanlanabe, ct al., "Synthesis and Anti-HIV Activity of: 2'-"Up"-Fluoro Analogues of Active Anti-Aids Nucleosides . 3'-Azido-3'-deoxythymidine (AZT) and 2',3'-dideoxycytidine (DDC)," J. Med. Chem. 1990, 33, 2145-2150.

[^2]
## 2'FLUORONUCLEOSIDES

This application clams priority to U.S. provisional patent application No. $66,075,893$, filed on Feb. 25, 1998 and Ser. Nu . (r) $/ 1080,569$, tiled on Apr. 3, 1998.

The invention described herein was made with Government support under number Al32351 awarded by the National Institutes of Healith. The United Stales Government has certain right to this invention.

Tbis invention is in the area of pharmaceutical chemistry, and in particular, includes $2^{2}$-fluoronucleosides and methents for their preparation and use.

## BACKGROUND OF THE INVENTION

Synthetic nuclensides such ass 5 -indo-2'-donxyuridine and 5-fluoro-2'-deoxyuridine have been used for the treatment of cancer and herpes viruses for a number of years. Since the 1980's, synthetic nucleosides have also treen a focus of interest for the treatment of HIV, hepatitis, and Epstein-Barr viruses.
In 1981, acupired immune deficiency syndrome (AIDS) was idenified as a disease that severely compromises the human imnune system, and that almosi without exception leads to death. In 1983, the etiological cause of AIDS was determined to be the hunain immunode ficiency virus (HIV). In 1985, it was reported that the synthetic maclenside 3'-azidu-3'-denxymymidine (AZT) inhibits the replication ot human immunodeficiency virus. Since then, a number of other syinthetic nucleosides, including $2^{\prime}, 3^{\prime}$-dideoxyinosine (IDDI), $2^{\prime}, 3^{\prime}-$ dideoxycytidine (DDC), and $2^{\prime}, 3^{\prime}$-didcoxy- $2^{\prime}$, 3'-didehydrollymidine (1)4T), have been proven to be effective against HIV. After cellular phosphorylation to the 5'-triphosphate by cellular kinases, these synthetic nucleosides are incorporated into a growing strand of viral DNA, causing chain termination due to the absence of the 3'hydroxyl group. They can also inhibit the viral enzyme reverse transeriplase.
The success of various synthetic nucleosides in inhibiting the replication of HIV in vivo or in vitro has led a number, of researchers to design apd test nuckosides that substitute a heteroatum for the carbon atom at the 3 -pusition of the nucleoside. Europeañ. Patent Application Publication No. o 337713 and U.S. Pat. No. 5, 041,449 , asşigned to BioChem Pharma, Inc., disclose racemic 2 -subssituted-4-substituted-1,3-dioxolanes that exhibit antiviral activity. U.S. Pat. No. 5,047,407 and European Patent Application No. 0382 526, also assigned to BioChem Pharma, Inc., disclose that a number of racemic 2-subsitituted-5-substituted-1,3oxathiolane nucluosides have antiviral activity, and specifically report that the racemic mixture of 2 -hydroxymethyl5 -(cytosin-1-yl)-1,3-oxathiolume (referred to below as BCH189) has approximately the same activity against HIV as AZT, with linle toxicity. The ( - )-enantiomer of the racemate HCH-189, known as 3TC, which is covered by U.S: Pat. No. $5,539,116$ to Liota et al., is currently sold for the treatment of HIV in combination with AZT in humans in the U.S.

It has also been disclosed that cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane ("F"IC") has potent HIV activity. Schinazi, et al., "Selective Inhibition of Human Immunodeficiency virusis by Racemates and Enantiomers of cis-5-Fluoro-1-[2-(1lydroxymethyl)-1,3-Oxathiolane-5yl]Cytosine" Antimicrobial Agents and Chemotherapy, November 1992, pp. 2423-2431. Sce also U.S. Pat. No. $5,210,085$; WO 91/11186, and WO 92/14743.
Another virus that causes a serious human heallh problem is the hepatitis B virus (referred to below as "H13V"). H 13 V

A tumor is an unregulated, disorganized proliferation of cell growth. A tumor is malignant, or cancerous, it it has the

## 3

prepertics of invasiveness and metastasis. Invasiveness refers to the tendency of a tumor to enter surrounding tissue, breaking through the basal lamimas that detine the boundarics of the tissues, thereby often entering the bedy's circulatory system. Metistasis refers to the tendency of at tumor to migrate 16 other areas of the body and establish areas of proliferation away from the site of initial appearance.

Cancer is now the second leading cause of death in the United States. Uver $8,000,000$ persons in the United States have been diagnosed with cancer, with $1,208,0000$ new diagnoses expected in 1994. Over 500,000 people die annually from the disease in this country.

Cancer is now fully understood on the molecular level. It is known that exposure of a cell to a carcintogen such as ${ }^{\circ}$ certain viruses, certain chemúicals, or radiation, Icads to DNA alleration that inactivates a "suppressive" gene or activates an "oncogene". Suppressive genes are growith regulaiory genes, which upon mutation, can no longer control cell growth. Oncugenes are initially normal genes; (called prooncongene:) that by mutation or altered context of expression lxecome transforminy gencs. The products of transforming senes cause inappropriate cell growth. More than twenty different normal cellular genes can hecome oncogenes by genetic alteration. Transformed .eclls differ from normal cells in many ways, including ccll morphology, cell-to-cell interactions, membrane content, cyluskeletal structure, protein secretion, gene expression and moriality (transformed cells can grow indefinitely).
All of the various cell types of the body can be transformed into benign or inalignant tümor cells. The mosi frequent tumor site is lung, followed by colorectal, breast, prostate, bladder, pancreis, and then ovary. Other prevalent types of cancer include leukenia, central nervous system cancers, including brain cancer, melaroma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer.

Cancer is now primarily treated with one or a combination of three years of therapies: surgery, radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast. colon, and skin, it cannot be used in the treatment of tumors located in other areas, such as the backbone, nor in the treatment of disseminated necoplastic conditions such as leukemia.

Chemotherapy involves the disruption of cell replication or cell melabolism. It is used most often in the treatment of leukemia, as well as breast, lung, and testicular éancer.

There are five major elasses of chemotherapeutic agents currently in use for the treatment of cancer: natural products and their derivatives; anthacyclines; alkylating agents; antiprolifuratives (also called antimetabolites); and hormional agents. Clicmotherapeutic agcols are often reforred to as antineoplastic agents.

The alkylating agents are believed to act by alkytating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents includs: nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A disidvantage with these compounds is that they not only attach malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue.

Antimetabulites are typically reversible or itreversible enzyme inhibitors, or compounds that otherwise interfere of with the efpication, Itamslation or transcription of nuctere acids

Several synthetic nucleosides have been identified that exhibit anticancer activity. A well known nucleoside derivalive with strong anticancer activity is 5 -fluorouracil. 5-Pluorouracil has been used clinically in the treatment of malignant tumors, including, for example, carcinomas, sarcomas, skin cancer, cancer of the digestive organs, and breast cancer. 5-Fluorouracil, however, causes serious adverse reactions such as nausea, alopecia, diarrhea, stomatitis, leukocytic thrombocytopenia, anorexia, pigmentation, and edema. Derivatives of 5 -fluorouracil with anti-cancer activity have been described in U.S. Pat. No. $4,336,381$, and in Japanese patent publication Nos. $5(1-50383,50.50384,50-64281,51-146482$, and $53-84981$.
U.S: Pat. No. $4,000,137$ discloses that the peroxidate oxidation product of inosine, adenosine, or cytidine with methanol or cthanol has activity against lymphocytic leukemia.

Cytosine arabinoside (also referred to as Cytarabin, araC, and Cytosar) is a nucleoside analog of deoxycytidine that was first synthesized in 1950 and introduced into clinical medicine in 1963. It is currently an important drug it the treatment of acule myeloid leukemia. It is also active against acule lymphocytic leukemia, and to a lesser extent, is useful in chronic inyelocytic lcukemia and non-Hodgkin's lymphoma. The primary action of araC is inhibition of nuclear DNA synthesis. Handschumacher, R. and Cheng, Y., "Purine and Pytimidine Antimetabolites", Cancer Medicine, Chapter XV-1, 3rd Edition, Edited by J. Holland, el al., Lea and Febigol, publishers.

5-Azacytidine is a cytidine analog that is primarily used in the treatment of acute myelocytic leukemia and myelodysplastic syndrome.

2-Fluoroadenosine-5'-phosphate (Fludara, also referred to as FaraA)) is one of the most active agents in the treatment of chronic lymphocytic leukemia. The compound acts by inhibiting DNA synthesis. Treatment of cells with F-araA is associated with the accumulation of cells at the G1/S phase boundary and in $S$ phase; thus, $i l$ is a cell cycle $S$ phasespecific drug. Incorporation of the active metabolite, F-araATP, retards DNA chain elongation. F -araA is also a potent inhibitor of ribonucleotide reductase, the key enzyme responsible for the formation of DATP.

2-Chlorodeoxyadenosine is useful in the treatment of low grade B-cell neoplasms such às chronic lymphocytic leukemia, nọ-Hodgkins' lymphoma, and hairy-cell leukemia.

In designing new biologically active nucleosides, there have been a number of attempts to incorporate a fluoro substituent into the carbohydrate ring of the nucleoside. Fluorine has been suggested as a substituent because it might serve as an isopolar and isosteric mimic of a hydroxyl group as the C-F bond length ( $1.35 \AA$ ) is so similar to the $\mathrm{C}-\mathrm{O}$ bond length ( 1.43 A ) and because lluorine is a hydrogen bond acceptor. Fluorine is capable of producing significant electronic changes in a molecule with minimal sieric perturbation. The substitution of fluorine for another group in a molecule can cause changes in substrate metabolism because of the high strength of the C-F bond (116 $\mathrm{kcal} / \mathrm{mol}$ vs. $\mathrm{C}-\mathrm{H}=100 \mathrm{kcal} / \mathrm{mol}$ ).

A number of references have reported the synthesis and use of 2'-arabinofluoro-nucleosides (i.e., nucleosides in which a 2'-fluoro group is in the "up"-configuration). There have been several reports of 2-fluoro- 3 -D-arabinofuranosyl nucleosides that exhibil activity against hepatitis $B$ and herpes. Sce for example, U.S. Pat. No. $4,666,892$ to Fox, et al.; U.S. Pat. No. 4,211,773 to Lopel, ef al; Su, et al.,

Nucleosides. 136, "Synthesis and Antiviral Effects of Sewaral 1-(2-Deoxy-2-fluoro-(3-1)-arabinoluranosyl)-5alkyluracils." "Sone Structure-Activity Relationships," $J$. Med Chem., 1986, 29, 15̣1-154; Borthwick, et al., "Synthesis and Enzymatic Resolution of Carbocyclic 2'-Ara-fluoro-Guarosine: A Potent Now Anti-Herpcitic Agent," J. Chem. Soc., Chem. Common, 1988; Wantanabe, et al., "Synthesis and Anti-HIV Activity of 2'-"Up"-Fluoro Analoges of Active Anti-Aids Nucleosides 3'-Azido-3'deoxythymidine (AZT) and 2 '; 3 -dideoxycytidine (DDC)," J. Med. Chem. 1990, 33, 2145-2150; Martin, et al., "Syn" thesis and Antiviral Activity of Monofluoro and Difluoro Analogues of Pyrimidine Deoxyribonucleosides against Human Immunodeficiency Virus (HIV-1)," J. Med., Chem. 1990, 33, 2137-2145; Sterzycki, et al., "Synthesis and Anti-HIV Activity of Several 2'-Fluoro-Conlaining Pyrimidine Nucleosides," I Med Chem. 1990, as well as EleA 316 017 also filed by Sterzycki, et al.; and Montgomery, et al., "9-(2-Deoxy-2-fluoro- $\beta$-D-arahinofuranosyl)guanine: A Metabolically Stable Cytotoxic Analogue of 2'-Deoxyguanosine." U.S. Pal. No. 5,246,924 discloses a method for treating a hepatitis infection that includes the administration of 1-(2'-deoxy-2'-fuoru-B-D-arabinofuranosyl)-3-ethyluracil), also referred to as "FEAU." U.S. Pat. No. 5,034,518 discloses 2 -fluoro-9-(2-deoxy-2-fluoru- $\beta$-D-arabinofuranosyl)adeninc nucleosides which exhibit anticancer activity by altering the metabolism of adenine nucleosides by reducing the ability of the compound to serve c as a substrate for adenosine. EPA 11292023 discloses that certain $\beta$-1)-2'-Iluoroarabinonucleosides are active against viral infections
U.S. Pal. No. S,128,458 discloses $\beta$-D-2',3'-dideoxy 4 thioribonucleusides as antiviral agents. U.S. Pat. Nu. 5,446, 029 discloses that $2^{\prime}, 3^{\prime}$-dideoxy- $\mathbf{3}^{\prime}$-fluoronucheosides have antihepatitis activity.

European Patent Application No. 0109227 A2 discloses certain 3 'substituted $\beta$-( 1)-pyrimidine and purine nucleisides for the treatment of hepatitis $B$.

It hays alma, been disclosed that L-FMAU (2'- fluoro-5. methyl- $\beta$-I-atabinofuranosyluracil) is a potent anti-HBV and anti-LBV agent. See Chur. et al., "Use of 2'-liluorro-5. methyl- $\beta$-1-amabinofuranosylunacil as a Novel Antiviral Agent for Hepatitis' B Virus and Epsicin-Barr Virus" Antimicrobial Agents and Chemotherapy. April leys pages 979-98 1; Balakrishna, et al., "Inhibition of Ilepatitis 13 Virus by a Novel I.-Nucleoside, 2'-llunru-5-Mchyl- $\beta$ - I . arabinofuranosyl Uracil," Antimicrobial Agents and Chemotherapy, Feburary 1996, pages 380-356; U.S. Par Nos. 5,587,362; 5,567,688; and 5,565,438.
U.S. Pat. Nos. 5,426,183 and $5,424,416$ disclose procusses for preparing $2^{\prime}$-dcoxy-2', $2^{\prime}$-dilluoronucleosides and 2'-dcoxy-2'-ीuoro nucleosides. Sec also "Kinetic Studies of 2', 2'-difluorndeoxycytidine (Gemcitabine) with Purified Human Denxycytidine Kinase and Cytidioe Deaminase," BioChemical Pharmacology, Vol. 45 (No. 9) page, 4857-1861, 1993.
U.S. Pat. No. 5,446,(129 to Eriksson; et al., discloses that certain $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-huoronucleosides have hepatitis 13 activity. U.S. Pat. No. $5,128,458$ discloses certain 2', 3'-dideoxy-4'-thioribonucleosiles wherein the 3 '-substituent is H , azide or lluoro. WO $94 / 14831$ discloses certain 3'-fluoro-dihydropyrimidine nucleosides. WO 92/08727 discloses $\beta$-L-2'-deoxy-3'-fluoro-S-substituted uridine nuclcosides for the treatment of herpes simplex 1 and 2 .

EPA Publication No. 0352248 discloses a bronte genus oi

didehydro-2'-fluoro-I-glycero-pent-2-eno-furanosyl nucleosides.

## SUMMARY OF THE INVENTION

la one embodiment of the invention, a 2'- $\alpha$-fluornucleoside is provider of the structure:
herpes, and hepatitis. While certain $2^{\prime}$-fluorinate purine nucleosides fall within the broad genus, there is no information given in the specification on how to make these compounds in the specification, and they are not among specifically disclosed wi the preferred list of nucleosides in the -specification. The specification does disclose how to make 3'-ribofuranosyl fluorinate nucleosides. A similar specification is found in WO 88/09001, filed by Aktiebolaget Astra.

European Patent Application 0357571 discloses a broad group of $\beta-D$ and $a=D$ pyrimidine nucleosides for the treatment of AJDS which among the broad class generically includes nucleosides that can be substituted in the $2^{\prime}$ or 3'-position with a fluorine group. Among this broad class, however, there is no specific, disclosure of 2'-fluorinated nucleosides or a method for their production.

EPA 0463470 discloses a process for the preparation of (5S)-3-fluoro-tetrahydro-5-[(hydroxy) methyl ]-2-(3H)furanone, a known intermediate in the manufacture of 2'-fluoro-2', 3'-dideoxynucleosides such as 2'-Ruoro-2',3'dideoxycytidine.
U.S. Ser. No. 07/556,713 discloses $\beta$-D-2'fluoroarabinofuranosyl nucleosides, and a method for, their production, which are intermediates in the synthesis of 2',3'-dideoxy-2'-fluoroarabinosyl nucleosides.
U.S. Pat. No. 4,625,020 discloses a method of producing 1-halo-2-deoxy-2-fluoroarabinoluranosyl derivatives bearing protective ester groups from 1,3,5-tri-O-acylribofuranose.

There appears to be a lack of disclosure of $\beta$-L.-2'-fluororiboltiranosyl nucleosides for medicinal uses, including for IIIV, hepatitis ( B or C ), or proliferative conditions. At least with respect to 2'ribofuranosyl nucleosides, this may be because of the prior perceived difficulty in placing a fluor group in the $2^{\prime}$-ribofiuranosyl configuration. With, respect to L-2'-Auoro.2', 3'-unsaturated purine nucleosides, it may be because the purine nucleosides are unstable in acidic media, resulting in glycosyl bond cleavage.
In light of.the fact that HIV acquired immune deficiency syndrome, AIDS-related complex, and hepatitis B and C viruses have reached epidemic levels worldwide, and have tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat these diseases that have low toxicity to the host. Further, there is a need to provide new anliproliferative agents.

Therefore, it is an object of the present invention to provide a method and composition for the treatment of human patients infected with hepatitis B or C .

It is another object of the present invention to provide a method and composition for the treatment of human patients infected with HIV.

It is a further object of the present invention to provide new antiproliferative agents.

It is still another object of the present invention to provide a new process for the preparation of 2 '-fluoro-ribofuranosyl nucleosides.

It is yet another object of the present invention to provide a new process for the preparation of $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}, 3^{\prime}$ -

$\vdots$

Base is a purine or pyrimidine base as defined further herein:
$\mathrm{R}^{1}$ is $\mathrm{OH}, \| \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen; including F , or $\left(\%_{3}\right.$, lower alkyl, amine, loweralkylarnion, deflower) alkylamim, or alkoxy, dial base rules to a marine or pyrimidine base;
$R^{2}$ is 11 , phosphate, including monophosphate, ? diphosphate, triphowphate, or a stabilized phosphate prodrug; acyl, or other pharmacsutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{i}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally. substituted with one or more substituent as described in the definition of aryl given above, a:Tipid, including a phospholipid, an amino acid, peptide, or cholesterol; and
$\mathbf{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound.
In a second embodiment, a 2 -fluoronucleoside is proviced of the formula:

$\mathrm{Y}=\mathrm{O} . \mathrm{S}: \mathrm{CH}_{2}, \mathrm{CHF}$
wherein the substituent are as defined above.
In a third embodiment, a $2^{2}$-gluoronucleoside is provided of the formula:

wherein the substituent are as defined above.
In a fourth embodiment, a $2^{2}$ - Aluoronucleoside is provided (if the structure:
${ }^{0}$ wherein the substituent are as defined above
These 2'-fluoronucleosides can be either in the $\beta$-L or $\beta$-D configuration. The $\beta$-L configuration is preferred.
The 2 'fluoronucleosides are biologically active molecules which; are useful in the treatment of hepatitis B, hepatitis C or HIV. The compounds are also useful for the treatment of abnormal cellular proliferation, including tumors and cancer. One can easily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.
In another embodiment, for the treatment of hepatitis or HIV, the active compound or its derivative or salt can be administered in combination or alternation with another antiviral agent, such as an anti-HIV agent or anti-hepatitis agent, including those of the formula above. In general, in 25 combination therapy, an effective dosage of two or more agents are administered together, whereas during alternation therapy, an effective closing of each agent is administered serially. The dosages will depend on absorption, inactivation, and excretion rates of the drug as well as other 0 factors known to those of skill in the ant. It is to be noted that dosage values will also vary with the severity of the conditon to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedutes should be adjusted over time according to the individual 35 need and the professional judgment of the person adminsturing or supervising the administration of the compositions.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include 2-hydroxymethyl-5-(5-ltuorocytosin-1-yl)-1,3-oxathiolane 0 (FTC); the (-)-enantiomer of 2-hydroxymethyl-5(cytosin-1-yl)-1,3-oxathinlane ( 3TC); carbovir, acyclovir, interferon, famciclovir, penciclovir, AZT, DDI, DDC, D4T, abacavir, L.-(-)-FMAU, L-DDA phosphate prodrugs, and $\beta$-Ddioxolane nucleosides such as $\beta$-D-dioxolanyl-guanine 5 (DG), $\beta$-D-dioxolanyl-2,6-diaminopurine (DAPD), and ( -D-dioxolanyl-6-chloropurine (ACP), non-nucleoside RT inhibitors such as aevirapine, MKC-442, DMP-266 (sustiva) and also protease inhibitors such as indinavir, saquinavir, AZT, DMP-450 and others.
The compounds can also be used to treat equine infectious anemia virus (EIAV), feline immunodeficiency virus, and simian immunodeficiency virus. (Wang, S., Montelaro, R., Schinazi, K. 'F., Jagerski, B., and Mellors, J. W.: "Activity of nucleoside and non-nucleoside reverse transcriptase inhibi5 tors (NNRTI) against equine infectious anemia virus (EIAV) ." First National Conference on Human Retro viruses and Related Infections, Washington, D.C., Dec. 12-16, 1993; Salon D.C., "Equine Infectious Anemia," Vel. Chin. North Am. Equine Tract. United States, 9: 321-336, 1993; 0-Philpott, M. S., Ebner, J. P., Hoover, E. A., "Evaluation of 9 -(2-phosphonylimethoxyethyl) adenine therapy for feline immunodeficiency virus using a quantitative polymerase chain reaction," Vet. Immunol. Immunopathol. 35:155166, 1992.)

65
A new and completely diasterenselective method for the introduction of fluorine into a non-carbohydrate sugar ring precursor is also provided. The method includes reacting a
chiral, non-carbohydrate sugar ring precursor (4S)-5(protected oxy)-pentan-4-olide, which can be prepared from L-glutamic acid, with an electrophilic source of Iluorine, including but not limited to N -fluoro.(bis) benzenesulfonimide, to yield key intermedate fuorolacionc 6. The fluorolactone is reduced to the lactol and acetylated to give the anomeric acetate and then used for the synthesis of a number of novel $\beta-\mathrm{L}-\alpha-2^{2}$-tluoronucleosides. The corresponding D-enantiomer can.also be synthesized using D-glutamic acid as a starting material.

In an alternative cmbodiment, a fluorinated glycal is prepared which is dehydrogenated and then converted to a 2',3'-dideoxy-2',3'-didehydro-2'-fluoronucleoside or a $\beta$-L or $\beta$-D-arabinosyl-2'-lluoronucleoside, as discussed further beluw.

A method for the facile preparation of $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}, 3^{\prime}$ -didehydro-2'-lluoronucleosides is also presemted that includes the direct cundensation of silylated 6 -6hloropurine: with key immediate, which is prepared from 1.-2,3-0. isupropylidene glyceraldenhyde:

## DETMIED DESCRIPTION OF TIIE INVENTION

The inveution as disclused herein is a compounct, method and composition for the treatmell of HIV, hepatitis ( $B$ or $C$ ), or abnormal cellular proliferation, in humans or sther host animals, that moludes administering an edicelive amount of a 2'-huore-nuclenside, a pharmaceutically acceptable derivative, in luding a compound which has been alkylated or acylated al the $5^{\prime}$-position or on the purine or pyrimidine, or a pharnaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier The compounds of this invention either possess antiviral (i.e., anti-1HV-1, anti-HIV-2, or anti-hepatitis (13 or ()) activity, ur amtiproliferative activity, or are metalulized to a compoupd that exhibits such activity.
In summary, the present invention includes the following features:
(a) $\beta$-L aud $\beta$-1)-2'-fluoronucleosides, as described herein, and pharmaceutically acceptable derivatives and salts thereof;
(b) $\beta-L$ and $\beta$-D-2 - - fluuronucleosides as described herein, and pharmaceutically acceptable derivatives and salts thereof tor use in micdical therapy, for example for the treatunent or prophylaxis of an HIV or hepatitis ( B or C ) infection or for the treament of abnormal cellular prolileration;
(c) 2', 3'-1)ideoxy-2',3'-diduhydro-2'-fluory-I-glycero-pen-2-eno-furanosyl nucleosides, and pharmaceutically acceptable derivatives and salts thereot for use in .medical therapy, lor example for the treatment or prophylaxis of an fllv or liepatitis ( Br C ) infection or for the Ireatment of abnormal cellular prolifcration
(d) use of these 2 -fluoronuclcosides, and pharmaceutically acceptable derivatives and salts thereof in the manufacture of a medicament for treatment of an HIV or hepatitis infection or for the treatment of abnormal cellular proliferation,
(e) pharmaceutical formulations comprising the 2'-fluoronucleosides or a pharmaceutically acceptable derivative or salt thereof together with a pharmaceutically accepable carrier or diluent;
(f) processes for the preparation of $\beta-\mathrm{L}$ and $\beta-\mathrm{D}-2^{\prime}-\alpha$ fluoronucleosides, as described in more delail below, and
(g) processes for the preparation of $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}, 3^{\prime}$ - 65 didehydro-2'- fuoro-L-glycero-pent-2-eno-turanosyl nucteonides.
I. Active Compound, and Physiologically Acceptable Derivatives and Salts Thercof
A $2^{\prime}-\alpha$-fluoro-nucleoside is provided of the structure:

whercin $R^{1}$ is $\mathrm{H}, \mathrm{OH}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or C. F $_{3}$, lower alkyl, amino, loweralkylamino, di(lower) alkylamino, or alkoxy, and base refers to a purine or pyrimidinc base.
$R^{2}$ is $H$, phosphate, including monophosphate, cliphnsphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when admiristered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate, sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{*}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound.
In a second embodiment, a 2 -fluoronucleoside is provided of the formula:


In a third embodiment, a 2-fluoronucleoside is provided of the formula:
secondary, or tertiary hydrocarion of $C_{1}, C_{1}, C_{10}$ and specifically in includes methyl, ethyl, propyl, isopropyl, cyclopropyl, hutyl, isobutyl, i-butyl, pentyl, cyclopentyl, iscopentyl, ncopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpemyl,2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group can be optionally substituted with one or more moietics selected fiom the group consisting of hydroxyl, amino, alkylarnino, arylamino, alkoxy, aryloxy, nitro, cyato, sulionic acid, sulfate, phesphonic acid, phosphate, or phosphonate, either inprotected, or protected as necessary, as known to thosy skilled in the art, for example, as taught in Greene, el.al., Protectice Groups in Oryarric Synthesis, John Wilcy and Sons, Second Edition, 1991. hereby incorporated by reference.

The icrm lower alkyl, as used herein, and unless wherwise specified, refers to a $C_{1}$ to $C_{4}$ saturated straight, branched, or if appropriatc. a cyclic (for example, cyclopropyl) alkyl group.

The term alkylamino or arylamino refers to an amino group that has one or two alkyl or aryl substituents, respectively.
The tem "protected" as used herein and unluss otherwise defined relien to a group that is added to an uxygen, initrogen, or phosphorus alom to prevent its lurther reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known 10 those skilled in the art of organic synthesis. The term aryl, as uscd herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl, and preferably phenyl. The aryl group can be ciptionally substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, èither unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greenc, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The term alkaryl or alkylaryl refers to an alkyl group with an aryl substituent. The term aralkyl or arylalkyl refers to an aryl group with an alkyl substituent.

The term halo, as usedjhercin, includes chloro, bromo, indo, and fluoro.
The term purine or pyrimidine base includes, but is not limited to, adeniné, $N^{6}$-alkylpurines, $N^{\circ}$-acylpurines (wherein acyl is $\mathrm{C}(\mathrm{O})$ (alkyl, aryl, alkylaryl, or arylalkyl). $\mathrm{N}^{6}$-bencylpurine, $\mathrm{N}^{6}$-halopurine, $\mathrm{N}^{\text {i}}$-vinylputine, $\mathrm{N}^{6}$-acetylenic purine, $\mathrm{N}^{6}$-acyl purine, $\mathrm{N}^{6}$-hydroxyalkyl purine, $\mathrm{N}^{6}$-thioalkyl purine, $\mathrm{N}^{2}$-alkylpurines, $\mathrm{N}^{-}$-alkyl- 6 thiopurines, thyminc, cytosine, 5 -lluorocytosine 5-methylcytosine, $\quad$-azapyrimidinc, including 6-azacytosine, 2- and/or 4-mercaplopyrmifine, uracil, 5 -halouracil, including 5-huorouracil, $\mathrm{C}^{5}$-alkylpyrimidines. $C^{5}$-benzylpyrimidines, $\quad C^{s}$-halopyrimidines. $\left(^{5}\right.$-vinylpyrimidine, ( ${ }^{*}$-acetylenic pyrimidine, $C^{5}$-acy) pyrimidine, $C^{5}$-hydroxyalkyl purine, $C^{5}$-anidopyrimidine. $C^{s}$-cyanopyrimidine, $\quad C^{5}$-nitropyrimidinc. (: ${ }^{5}$-aminopyrimidine. $N^{2}$-alkylpurines, $N^{2}$-alkyl-6 thiopurines, S-azacytidinyl, 5 -azauracilyl, mazohpyridinyl. imidazolnpyridinyl, pyrrolopyrimidinyl, and pyrazolopyri midinyl. Purinc bases incluck, but are not lmited to, guanine, ads nike, hypoxanlhinc, $2 ;$ o-diaminopurime. and o-chloropurne. Functional osigen and nitrogen groups on the base can be protected as lececssary or desired Suitable protecting groups are well kimwn to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, I-butyldincoliylsilyl, and t-butyldiphenylsilyl, $\mid$ myl, alkyl groups, acyl groups such as acclyl and propionyl. methanesulfonyl, and p-tolucinesulfonyl.

The active compound can be administered as any derivative that upon administration to the recipient, is capable of providing directly or indirectly, the parent compound, or that exhibits activity itsell. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and a compound which has been alkylated or acylated at the 5 'position or on the purine or pyrimidine base (alternatively referred to as "pharmaccutically acceptable derivatives"). Further, the modifi. cations can afiect the biological aclivity of the compound, in some cases increasing the activity over the parent compound. This cam easily be assessed by preparing the derivative and testing its antiviral activity according to the methods described bercin, or olher method known to those skilled in the art.

The term acyl'refers to a carboxylic acid ester in which the non-carbonyl moiety of the cster group is selected from straight, branched, or cyclic alkyl or lower allkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, $C_{1}$ to $C_{4}$ alkyl or $C_{1}$ to $C_{4}$ alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group.
As used herein, the term "substantially free ol" or "substantially in the absence of" refers to a nuclenside composition that includes at least $9.5 \%$ to $98 \%$, or more preferably, $99 \%$ to $100 \%$, of the designated enantiomer of that nucleosicle.
Nucleotide Prodrug Formulations
Any of the nucleosides described herein can be administrated as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide procirug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research; 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

The active nucleoside can also be provided as a 5'-phosphoether lipid or a 5 '-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L. S., N. Iyer, E. Leake, A. Raben, Modest L: K., D. L.: W., and C. Piantadosi. 1990. "Novel membraneinteractive ether lipid analogs that inhibit infectious HIV-1 production and induce detective virus formation." AIDS Res. Ilum. Retro Viruses. 6:491-501; Piantadosi, C.., J. Mäasco C. J., S. L. Morris-Natschke, K. L. Meyer, F. Gumus, J. $\mathfrak{i}$. Surles, K.S. Ishaq, L. S. Kucera, N. lyer, C. A. Wallen, S. Piantadosi, and E. J. Modest. 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates tor anti-HIV activity." J. Med. Chem. 34:1408.1414; Hosteller, K. Y., D. D. Richmari, D. A. Carson, L. M. Stuhmitler, G. M. T. van Wijk, and H. van den Bosch. 1992. "Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 3'-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3,-deoxythymidine..: Antimicrob. Agents Chemother. 36:2025.2029; Hosetler. K. Y., L. M. Stuhmiller, H. B. l.coling, 11 . van den Busch, and D. 1). Richman, 1900 .
. US 6,348,587 B1
"Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." $J$. Biol. Chem. 265:61127.
Nonlimiting examples of U.S. patents that disciluse suitable lipophilic substituents that can be covalenily incorporated into the nucleoside, preferably at the $5^{\prime}-\mathrm{OH}$ position of the nucleoside or lipophilic preparations, include U.S. PaI. Nos. 5,149,794 (Sep. 22, 1992, Yatvin et al.); U.S. Pat. No. 5,194,654 (Mar. 16, 1993, Hostetler et al., U.S. Pat. No. 5,223,263 (Jun. 29, 1993, Hosteter et al.); U.S. Pat. No. $5,256,641$ (Oct. 26, 19y3, Yaivin el al.); U.S. Fat. No. 5,411,947 (Maty 2, 1995, Hostuler et al.); U.S. Pat. No. 5,463,092 (Oct. 31, 1995, Hostetler et al.); U.S. Pat. No. 5.543,389 (Allg. 6, 1996, Yatvin et al.); U.S. Pat. No. 5,543,390 (Aug. 6, 1996, Yatvin ei al.); U.S. '1at. Nu. 5,543,391 (Aug. 6, 1996, Yatvin et al.); and U.S. P'at. No. $5,551,728$ (Sep. 10, 1996; Basiva et al.), all of which are incorporated herein by reference. Forcign patent applications that disclose lipophilic sulstituents that can be attaithed to the nucleosides of the present invention, or lipophilic preparations, include WO 89/(12733, wO $90 / 00555$, wo 91/16920, W0) 91/1891.1, WO 93/00910, wo 9.4/26273. WO 96/15132, EP 03511287 , EP 939170544 , and WO 91/19721.

Nonlimiting examples' of nucleotide prodrugs are described in the following references: Ho, I). II. W. (1973) "Distribution of Kinase and deaminase of $(\beta-1)$. arabinoftiranosylcytosine in tissues of man and musc." Cancer Ress.3.3, 2816..282(); Holy, A. (1993) Isopolar phosphorous-modified nucleotide analngues," In: We Clercy (Ed.), Advunces in Antiviral Drug Design, Vol. I, JAl Press. pp. 179-231; Hong, C. 1., Nechacv, A., and West, C. R. (1 979a) "Syuthesis and anlitumun activity of $1-\beta-1$-arabino. furanosyleytwine conjugates of contisol and cortisome." Bicohe:m. Bieq/ys: Rs. Commun. n8, 1223-1225; Hong. ( $($ 1., Nechaev, A., Kirisits, A. J Huchheit, D. J. and West, (C' R. (1981) "Nuctcoside conjugates as potemial mitumon agents. 3. Synthesis and annlumor activity of 1-( $\beta-1$ ). arabinoturanosyl) eytosine conjugates of corticosictiods and sclected lipophilic alcohols." J. Med. Chem. 28, 171...777; Ilosteller, K. Y., Stuhmiller, I. M., Lenting, II. 13. M. van dien Bosch, H. and Richman J. Biol. Chem. 265, 6112-(6)17; Hosteller, K. Y., Carson, D. A. and Richman, 1). D. (1991); "Phosphatidylazidothymidine: mechanism of antirctroviral action in CEM cells." J. Biol. Chem. 266, 1171-1-11717; Hosteller, K. Y., Korba, B. Sriclhar, C., Gardener, M. (1.994a) "Antiviral activity of phosphatidyldideoxytytidine in hepatitis B-infected cells and enhanced hepatic uptake in mice." Antiviral Res. 24, 59-67; Hosteller, K. Y., Richman, D. D., Sridhar. C. N. Felgner, P. L. Felgner, J., Risci, J., Gardener, M. F. Selleseth, D. W. and Ellis, M, N. (1994b) "PIonsphatidylazidothymidine and phosphatidyl-ddC: Assessment of uptake in mouse lymphoid tissues and antiviral acivities in human immunodeficiency virus-infected cells and in rauscher leukemia virus-inlicted mice." Antimicrobial Agents Chemother. 38, 2792-2797; Hunston, R. N., Jones, A. A McGuigan, C., Walker, R. T., Balzarini, J., and DeClercq, E (1984) "Synthesis and biological properties of some cyclic phosphotriesters derived from 2'-deoxy-5-flourouridine." $J$ Med. Chem. 27, 440-444; Ji, Y. H., Moog, C., Schmitl, G. Bischoff, P. and Luu, B. (1990); "Monophosphoric acil esters of $7-\beta$-hydroxycholesterol and of pyrimidine nucleo side as potential antitumor agenis: synthesis and preliminary evaluation "f antitumor activity." J. Med. Chem. 3.3 2264-2270; Jones, A. S., McGuigan, C., Walker, R. T., Balzarimi. J. and DeClercq. E. (1984) "Synthesis, properties. and biokegical activity of some mescoside cyelic phosphe. Chem. Chemother. 1107-1113; McGuigan, C., O'Connor, T. J, Nicholls, S. R. Nickson, C. and Kinchington, D. (1990b) "Synthesis and anti-HIV activity of sorne novel substituted dialkyl phosphate derivatives of AZT and ddCyd." Antiviral Chem. Chemother. 1, 35:5-360; McGuigan, C., Nicholls, S. R., O'Connor, T. J., and Kinchington, D. (199(k) "Synthesis of some it novel dialkyl phosphate derivative of 3'-modified nucleosides as potential anti-AJDS drugs." Antivira/ Chem. Chemother. 1, 25-33; McGuigan, C., Devin, K. G., 5 O'Connor, T. J., and Kinchingion, D. (1991) "Synthesis and anti-HIV activity of some haloalkyl phosphoramidate derivatives of 3'-azido-3'-deoxythylmidine (AZT); potent activity of the trichlorocthyl methoxyalaninyl compound." - Amiviral Res. 15, 255-263; McGuigan, C., Pathirana, R. N., Balzarini, J. and DeClerca, E. (1993b) "Intracellular delivcry of bioactive AZT nucleotides by aryl phosphate derivatives of AZT.' J. Med. Chem. 36, 1048-1052.

Alkyl hydrogen phosphate derivatives of the anti-HIV agent AZT may be less toxic than the parent nucleoside 5 analogue. Andiviral Chem. Chemother. 5, 271-277; Meyer, R 13., Jr., Shuman, D. A. and Robins, R. K. (1973) "Synthesis of purine nucleoside 3 '5'cyclic phosphoramidates.

Tetrahedron Le'tl. 269-272; Nagyvary, J. Gohil. R. N., Kirchner, C. R. and Stevens, J. D. (1973)."Studies on neutral esters of cyclic AMP," Bicx'hem. Biophys: Res. Commun. 55, 1072-1077: Nanane, A. Gruyelle, C., Fillion, M. P., Fillion, G. and Huynh-1)inh, T. (1992) "Inproved brain delivery of AZT using a glycusyl phosphuriester prodrug." J. Med. Chem. 35, 3034-31144; Nargeot. J. Nerbonne, J. M. Engels, J. and Leser, II. A. (1983) Niml. Acud. Sci. U.SA. So, 2305-2399; Nu Ison, K. A., Benuude, W. G. Siscr, W. N. and Hutchinson. J. P. (1987) "The question of chair-fwist equilibria for the phosphate rings of nucleoside cyctic 3 ', 5 monophosphates. 'H NMR and $x$-ray crystallographic study of the diastercomers of thymidine phenyl eyclic $3^{\prime}, 55^{\prime}$ monophosphate." J. Am Chem. Soc. 1(1), 405s-4064; Nerbonne, J. M., Richard, S., Nargcot, J. and Lester, H. A. (1984) "New photoactivatable cyclic nucleotides produce intracellular jumps in cyclic AMP and eyclic GMP concentrations." Nature-301, 74-76; Neumann, J. M., Herve, M., Debouzy, J. C., Guerra, I: I., Gouyetle, C., Dupraz, B. and Huyny-Dinh, T. (1989) "Synthesis and transmembrane transport studics by NMR of a glucosyl phospholipid of thymidine." J. Am. Chem. Soc. 111, 427(1-4277; Ohno, R., Talsumi, N., Hirano, M., Imại, K. Mizoguchi, H., Nakamura, T., Kosaka, M., Takatuski, K., Yamaya, T., Toyama K., Yoshida, T., Masaoka, T., Hashịnoto; S.. Ohshima, T., Kimura, I., Yamadia, K. and Kimura, J. (1991) "Treatment of myelodysplașic syndromes with orally administered 1- $\beta$ -D-arabinouranosylcytosinc-5' stearylphosphate." Oncology 48, 451-455. Palomino, E., Kessle, D. and Honvit\%, J. P. (1989) "A dihydropyridine carricr system tor sustained delivery of 21.3 dideoxynucleosides to the brain:" I. Med. Chem. 32, 22-625; Perkins, R. M., Barney, S. Wiltrock, R., Clark, P. H., L.cvin, R. Lambert, D. M., Petteway, S. R., Serafinowska, H. T., Bailey, S. M., Jackson, S., Harnden, M. R. Ashion, R., Sutton, D., Harvey, J. J. and Brown, A. G. (1993) " Activity of BRL47923 and its oral prodrug, SB203657A against a rauscher murine leukemia virus infection in mice." Antiviral Res. 20 (Suppl. I). 84; Piantadosi, C., Marasco, C. J., Jr., Norris-Natschke, S. L., Meycr, K. L., Gumus, F., Surles. J. R., Ishaq, K. S., Kucera, I.. S. Iyer, N., Wallen, (C A., Piantadosi, S. and Modest, E. J. (1991) "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-FlV-1 sctivity." J. Med. Chem. 34, 1408-1414; Iompon, A., Lefcluver, I., Imbach, J. $1 .$. , Kalm, 'S and Farquhar, 1). (1994). "Decomposition pathways of the mono- and bis(pivatoyloxymethyl) esters of azidothymidine-5'-monophosphate in cell extract and in tissue culture medium; an application of the 'on-line ISRP. cleaning IIPI.C technique." Antiviral Chem (hemother. 5, $91-98$; Postemark, T. (1.974) "(yclic AMP and cyclic GMP"' Anrul Rev: Pharmacol. 14, 23-33; Prisbe, E. J., Martin, J. C. M., McGhee, D. P. C., Barker, M. F., Smee, D. F. Duke, A E., Mathews, T. R. and Vurheyden, J. P'. J. (i.i86) "Synthesis and antiherpes virus aclivity of phosphate an.phisphonate derivatives of $9-[(1,3$-dihydroxy-2-propoxy) nethyl $]$ guanine." J. Med Chem. 29, 671-675; Pucch,'I., Goisselin, G., L.efebvre, I., Pompon, a., Auberlin, A. M. Dim, and Imbach, J. L. (1993) "Intracellular delivery of nucleoside monophosphate through a reductase-mediated activation process." Antivral Res. 22, 155-174; Pugaeva, V. P., Klochkeva, S. I., Mashbis, F. I. and Eizengarl, R. S. (1969). "loxicological assessment and health standard ratings for ethylene sulficle in the industrial atmosphere." Gig. Trf. Pref. Zabol. 14, 47-48 (Chem. Abstr. 72, 212): Robius, R. K. (1984) "The potential of nucleotide analogs as inhibitors of Recro viruses. and tumors." Pharm. Re's. 11-18; Rosowsky, A., Kim. S. H., Ross and J. Wick, M. N. (1982) "I.ipophilic 5:
(alkylphospbate) esters of 1- $\beta$-D-arabinofiranosylcytosine and its $\mathrm{N}^{4}$-acyl and 2.2' anhydro-3'0-acyl derivatives as potental prodrugs." J. Med Chem. 25, 171-178; Róss, W. (1961)"Increatsed sensitivity of the walker turnoul towards aromatic nilrogen mustards carrying basic side chains following glucose pretrearment." Biochem. Pharm. 8, 235-240; Ryu, E. K., Ross, R. J. Matsushita, T., MacCoss, M., Hong, C'. I. and West, C. R. (1982). "Phospholipidnucleoside conjugates. 3. Synthesis and preliminary biologin cal evaluation of $1-\beta$-D-a rabinofiiranosylcytosine 5 ' diphosphate [-], 2-diacylglyccrols." J. Med. Chem. 25, 1.322-1.329; Satilill, R. and Hume, W. J. (1986) "The degradation of 5 -iododeoxyuridine and 5 -bromoethoxyuridine by serum from ditterent sources and its consequences for the use of these compounds for incorporation into DNA." Chem. Biol. Interuct. 57, 347-3.55; Saneyoshi, M., Morozumi, M., Kudlama, K.. Machida, J., Kuninaka, A. and Yoshino, H. (1980) "Syothetic nucleosides and nucleotides. XVI. Synlhesis and biological evaluations of a series of $1-\beta-\mathrm{D}$ 0 arabinofuranosylcytosine 5 '-alky or arylphosphates." Chem Pharm. Bull. 28, 2915-2923; Sastry, J. K., Nehetc, P. N., Khan, S., Nowak, B. J., Plunkett, W., Arlinghaus, R. B. and Farquhar, D. (1992) "Membrane-permeable dideoxyuridine S'-monophosphate analogue inhibits buman immunodefi5 ciency virus infection." Mol. Pharmacol. 41, 441-445; Shaw, J. P., Jones, R. J. Arimilli, M: N., Louie, M. S., Lee, W. A. and Cundy, K. C. (1994) "Oral bioavailability of PMEA from PMEA prodrugs in male Sprague-Dawley rats." 9th Annual AAPS Meeting. San Diego, Calif. (Ahstract). o Shuto, S., Ueda, S., Imamura, S., Fukukawa, K. Matsuda, A and Ueda, T. (1987) " $A$ facile one-step synthesis of 5 ' phosphatidylnucleosides by an enzymatic two-phase reaction." Tetrahedron I.ett. 28, 199-202; Shuto, S. Itoh, H., Ueda, S., Imamura, S., Kukukawa, K., Tsujino, M., :5 Malsuda, A. and Uedla, T: (1988) Pharm. Bull. 36, 209-217. An example of̣ a useful phosphate prodrug group is the S-acyl-2-thioethyl group, also referred to as "S $\wedge$ TE".

## II. Combination and Alternation Therapy

It has been recognized that drug-resistant variants of HIV and HBV gan ernerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by -mutation of a gene that encodes for an enzyme used in viral replication, and most typically in the case of HIV, reverse 5 transcriptasc, protease, or DNA polymerase, and in the case of HBV, DNA polymerase. Recently, it has been demonstrated that the efficacy of a drug against HIV infection can the prolonged, augmented, or restored by administering the compound in conbination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Neternativcly, the pharmacokinetics, biodistribution, or sither parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces mulliple simultaneous stresses on the virus.

The second antiviral agent for the treatment of HIV, in one embodiment, can be a reverse transcriptase inhibitor (a "RTI"), which can be either a synthetic nucleoside (a "NRTI") or a non-nucleoside compound (a "NNRTI"). In an alternative embodiment, in the case of HIV, the second (or third) antiviral agent can be a protease inhibitor. In other embodiments, the second (or third) compound can be a pyrophosphate analog, or a fusion binding inhibitor A list compiling resistance data collected in vitro and in vivo for a number of anliviral compounds is found in Schinazi, el al,

Mutations in retroviral genes associated with drug resistance, Intcrnational Antivinıl News, 1997.

Preferred compounds for combination or allernation therapy for the treatment of HBV include 3TC., FTC, L-FMAU, interferon, $\beta$-D-dioxolanyl-guanine ( 1 X(i), $\beta-1$ )-dioxolanyl-2,6-diaminopurine (DAPD), and $\beta-1$ ). dioxolanyl-6-chloropurine (ACP), famciclovir, penciclovir, BMS-200475, bis pom PMEA (adefovir, dipivoxil); lobucavir, ganciclovir, and ribavarin.

Preferred examples of antiviral agents that can be used in combination or alternation with the compounds disclosed herein for HIV therapy include cis-2-hydroxymelhyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3oxathiolane ( $3 \mathrm{I}^{\circ} \mathrm{C}$ ); carbovir, acyclovir, foscarnet, interferon, AZT, DDI, IIDC, D4T, CS-87 (3'-azido-2',3'-lideoxyuridine), and $\beta$-n.dinvolane nurlensides such is $\beta$ - $D$ -dioxolanyl-guanine (1)X(i), $\beta$-D-dioxolanyl-2,6diaminopurine (DAPD), and $\beta$-1)-dioxolanyl- 6 -chloropurine (ACP), MKC-442 (6-benzyl-1-(cthoxymethyl)-5-isopropyl uracil.

Preferred protease inhibitors include crixivan (Merck), nelfinavir (Agouron), ritonavir (Abbolt), sayuinavir (Roche), DMP-266 (Sustiva) and DMP-450 (DuPont Merck).

A more comprohensive list of compounds that can be administercd in combination or alternation with any of the disclosed nuclensides include ( $1 \mathrm{~S}, 4 \mathrm{R}$ )-4- $\mathbf{~ 2}$-amino-6-eyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1methanol succinate ("1592", ä carbovir analog; GlaxoWellcume); 3'TC: (-)- $\beta$-L-2', 3'-dideoxy-3'thiacytidine (GlaxoWelleome); a-APA R18893: a-nitro-anilino-phenylacetamide; A-77003; C2 symmerry-based protease inhilitor (Abboll); A-75925: C2 symmictry-based protease inhintor (Abbott); AAP-BHAP: hishelcroarylpiperazinc analog (Upjohn); AR'-538: C2 symmetry-based protease inhibitor ( $\wedge$ bboil); AzddU: $3^{\prime}$-azido- $2^{\prime}, 3^{\prime}$ dideoxyuridine: AZT: 3'-azido-3'-deoxythymidine (GlaxoWellcume); AZT-p-ddI: 3'-azido-3'-dcoxythymidilyl( $5^{\prime}, 5^{\prime}$ )-2', $3^{\prime}$-dideoxyinosinic acid (Ivax); BHAP: bisheteroarylpiperazine;: BIL $\dot{A}$ 1906: $\mathrm{N}-\{-1 \mathrm{~S}-[[[3-[2 S-\{(1,1$. dimethylcthyl)aminojcarbonyl\}-4R-j3-pyridinylmethy) thio)-1-piperidinyl]-2R-hydroxy-1S-(phenylmethyl)propyl] amino]carbonyl]-2-methylpropyl\}-2-quinolinecarboxamide (Bio Mega/Boehringer-Ingelheim); BILA 2185: N-(1,1-dimethylethyl)-1-[2S-[[2-2,6-dimethyphenoxy)-1-(xoethyl] amino]-2R-hydroxy-4-phenylbutyl]4R-pyridinylthio)-2piperidinecarboxamide (BioMegalBoehringer-Ingelheim); BM +51.0836 : thiazolo-isoindolinone derivative; BMS 186, 318: aminodiol derivative HIV-1 protcasc inhibitor (Bristol-Myers-Squibh); d4API: 9-[2,5-dihydro-5. (phosphonomethoxy)-2-furancl]adenine (Gile:l); d4C: 2',3'-didehydro-2',3'-didcoxycytidine; d4T: $2^{\prime}, 3^{\prime}$-didehydro-$3^{\prime}$-deoxythymidine (Bristol-Myers Squibb); ddC; 2', 3'didcoxycytidine (Roche); ddl: 2',3'-dideoxyinosine (Bristol-Myers-Squibb); DMP-206: a 1,4 -dihy $($ ro- $2 \mathrm{H}-3$, 1-benzoxazin-2-one; DMP-450: \{[4R-(4-a,5-a, (6-b,7-b)]-hexahydro-5,6-bis(bydroxy)-1,3-bis(3-a mino)phenyl] methyl)-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-oné\} bismesylate (Avid); DXG:(-)- $\beta$-D-dioxolane-guadposine (Triangle); EBU-dM:5-ethyl-1-ethoxymethyl-6-(3,5dimethyllenzyl)uracil; E-EBU: 5-ethyl-1-ethoxymethyl-6. benzyluracil; DS: dexiran sulfate; E.EPSeU

1-(ethoxymethyl)-(6-phenylselenyl)-5-ethyluracil; E-EPU; 1-(ethoxymethyl)-(6-phenyl-thio)-5-ethyluracil; FTC: $\beta 2^{\prime}, 3^{\prime}-$ dideoxy-5-fluoro-3-thiacylidine (Triangle); HBY097: S-4-iscopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxalin- $2(L H)-1$ hione; ' HEPT: $1-[(2-$ hydroxyethoxy)methyl]-6-(phenylthio)thymine; HIV. 1:human immunodeficiency virus type 1 ; JM2763: $1,1^{\prime}$-( 1 , 3-propanediyl)-bis-1,4,8,11-tetraazacyclotetradecane (Johnsón Matthey); JM3100:1, 1'-[1,4-phenylenebis-(methylene)]-bis-1,4,8,11-ktraazacyclotetradecane(Johnson Mathey); KNI-272: (2S,3S)-3-amino-2-hydroxy-4phenylbutyric acid-containing tripeptide; L-697,593;5-ethyl-6-methyl-3-(2-phthalimido-ethyl)pyridin-2(1 H)-one; L-735,524: hydroxy-aminopentane amide HIV-1 protease inhibitor (Merck); L-697,661: 3-\{[(-4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino \}-5-ethyl-6-methylpyridin-
 dideoxycytidine; L-FDOC:(-)- $\beta$-L-5-fluoro-dioxolane cytosine; MKC442:6-benzyl-1-ethoxymethyl-5isopropyluracil (1-EBU; Triangle/Mitsubishi); Nevirapine: 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyridol[3,2-b:2',3'-e]diazepin-6-one (Boehringer-Ingelheim); NSC648400:1-benzyloxymethyl-5-ethyl-6-(alphapyridylthio)uracil (E-BPTU); P9941: [2-pyridylacetyl-IlelheAla-y(CHQH)]2 (Dupont Merck); PFA: phosphonoformate (loscarnet; Astra); PMEA: 9-(2. phosphonylmethoxyethyl)adenine (Gilead); PMPA: (R)-9-(2-phosphonyl-methoxypropyl)adenine (Gilead); Ro 31-8959: hydroxyethylamine derivative HIV-1 protease inhibitor (Roche); RPI-312: peptidy] protease inhibitor, 1-[(3s)-3-(n-alpha-benzyloxycarbonyl)-1-asparginyl)-amino-2-hydroxy-4-phenylbutyryl]-n-tert-butyl-1-proline amide; 2720: 6-chloro-3,3-dimethyl-4-(isopropenyloxycarbonyl)-3,4-dihydro-quinoxalin-2(1. H)thione; SC-52151: hydroxyethylurea isostere protease inhibitor (Searle); SC-55389A: hydroxyethyl-urea isostere protease inhibitor (Searle); TIBO R82150: (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]-benzodiazepin-? (1H)-thione (Janssen); TIBO 82913: (+)-(5S)-4,5,6,7,-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1jk]-[1,4]benzo-diazepin$\underline{2}(1 \mathrm{H})$-thione (Janssen); TSAO-m3T: [2',5'-bis-O-(tert-butyldimethylsilyl)-3'-spiro-5'-(4'-amino-1', 2'-oxathiole-2', 2 '-dioxide)]-b-D-pentofuiranosyl-N3-methylthymine; U90152:1-[3-[(1-methylethyl)-a mino $]-2-$ pyridinyl $]-4-[[5-$ [(methylsulphonyl)-amino]-1H-indol-2yl]carbonyl]. piperazine; UC: thiocarboxanilide derivatives (Uniroyal); UC-781 $=\mathrm{N}$-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furancarbothioamide; UC-82-N-[4-chloro-3-(3-methyl:?-butenyloxy)pbenyl]-2-methyl-3. thiophenecarbothioamide; VB 11,328 : hydroxyethylsulphonamide proteasc inhibitor (Vcrtcx); VX-478:hydroxyethylsulphonamide protease inhibitor (Vertex); XM 323: cyclic urea protease inhibitor (Dupont Merck).
Combination Therapy for the Treatment of Proliferative Conditions

In another embodiment, the compounds, when used as an antiproliferative, can be administered in combination with another compound that increases the effectiveness of the therapy, inclucling but not limited to an antifolate, a 5-fluoropyrimidine (including 5 -huorouracil), a cytidinc
analogue such as $\beta$-L-1,3-dioxolanyl cytiditic or $\beta-\mathrm{L}-1,3^{\circ}$ dioxolanyl 5 -fluorocytidine, antimetabolites (including purine antimetabolites, cytarabine, fudarabine, Iloxuridine, 6-mercaptopurine, methotrexale, and (-Ibioguanine), hydroxyurca, mitotic inhibitors (including (1TTI, Etoposide (VP-2l), axol, and vinca alkaloids such as vincristine and vinblastine, an alkylating agent (including but not limited to busulfan, chlorambucil, cyclophosphamide, ifofamide, mechlorethamine, melphalan, and tholepa), nonclassical alkylating agents, platinum containing compounds, blcomycin, an anti-tumor antibiotic, an ántliracycline such as doxorubicin and dannumycin, an anthracenedione, topoisomerase II inhibitors, hormonal agents (including but not limited to corticosteroids (dexamethasune, prednisone, and m̈ethylprednisone), androgens such as fluoxymesterone and methyltestosterone, estrogens such as diethylstilbesterol, aptiestrngens such as tantioxifen, LHRH analogues such as léuprolide, antiandrogens such ay flamide, aminoglutethimide,. megestrol acetate, and medroxyprogesterone), asparaginase, carmustine, lomustine, hexamethyl-melamine, dacarbazine, mitotane, streptozocin, cisplatin, carboplatin, levamasole, and leucovorin. The compounds of the present invention can also be used in combination with enzyme therapy agents and immune system modulators such as an interferon, interleukin, tumor necrosis factor, macrophage colonystimulating factor and colony stimulating factor.

## III. Process for the Preparation of Active Compounds

In one emhodiment of the iuvention, a diastereoselective reaction for effecting the introduction of lluorine into the sugar portion of novel nucleoside analogs is provided. This synthesis can be used to make both purine and pyrimicline derivatives. The key step in the synthelic ruite is the fluorination of a chiral, non-carbohydrate sugar ring precursor (4S)-5-(protected-oxy)-pentan-4-olide, for examplic, (4S)-5-(t-butyldiphenylsiloxy)-pentan-4-olicle 4 using an electrophilic fluorine source, including, but nọ limited to. N -fluoro-(bis)benzenesultonimide 5. This. relatively new class of N -fluorosulfonimide reagents was originally devel. oped by Barnette in 1984 and since then has seen much refinement and use äs a convenient and highly reactive source of electrophilic tluorine (Barnette, W. E. J Am. Chem Soc. 1984, 106, 452.; Davis, I. A.; Ilan; W., Murphy, C. K J. Org. Chem. 1995, 61, 4730; Snieckus, V.; Bcaulieu, F., Mohri, K.; Han, W.; Murphy, C. K.; Davis, I. A. T'irahedron lett. 1994, $35(21), 346,5)$. Mus often, these reagents art used to deliver tluorine fo nucleophiles such as cin lates and metalated aromatics (Davis, r. A.; Han; W., Murphy, C. K J. Org. Chem. 1995, 60, 4730 ). Specifically, N -fluoro-(bis) henzëncsulfonimide ( $\mathrm{Nl} \mathrm{Fi}_{\mathrm{S}}$ ) in an air stable, casily handled solid with suthicient steric bult tostereoselcetively lluorinate the enolate of silyl-protecter! tactone 4. As a manlimiting example of lhis process, the symbesis of Hoorolathone 6 and its use as a common internediate in the synthesis of a number of novel $\alpha-2$ - Huorn nucleosides is dexcribed in detail below. Given this description, one ol urdinary skill can routinely mudify the pocess as desired to accumplisth. a desired objective and to prepare a compound of interest.

Any source of electrophilic fluorine can be used that Huorinates the precursor (4S)-5-(protected-oxy)-pentan-4. olide, for example, (4S)-5-(t-butyl-diphenylsiloxy)-pentan-4-olide. Nturnative sources of electrophilic fluorine include N-fluorosulfams (Differding, ei al, Ter. Letı. Vol. 29, No. 47 pp 6087-6090 (1988); Chemical Reviews,-1992, Vol 02. No. 4 (517)), N-Huoro-O-benzcuedisultonimick. (Lét. Leet. Vol.

35, pages 3456-3468 (1994), Tet. Lett. Vol 35. No. 20, pages 3263-3266 (1994)); J. Org. Chem. 1995, 60, 4730-4737), 1-fluoroethene and synthetic equivalents (Matthews, Tet. LetI. Vol. 35, No. 7, pages 1027-1030 (1994); Accufluor lluorinating agents sold by Alliert Signal, Inc., Buffalo Research I.aboralory, Buffalo, N.Y. (NFTh (1-fuoro-4-bydroxy-1,4-diazoa-bicyclo[2.2.2]octane bis (tetrafluoroborate)), NFPy (N-fluoropyridinium pyridine heptafuorodiborate), and NESi ( N -fluorobenzenesulfonimide); electrophilic fluorinating reagents sold by Aldrich Chemical Company, Inc., including N-Huoropyridinium salts ((1-Huoro-2,4, 6 trimethylpyridinium triflate, 3,5-dichloro-1fluoropyridinium triflate, 1 -fluoropyridinium triflate, l-fluoropyridinium tetrafluoroborate, and 1 -fluoropyridinium pyridine heptafluorodiborate) see also $J$. Am. Chem. Soc., Vol 112, No. 23 1990); N -fluorosulfonimides and-amides ( N -fluoro- N -methyl-ptoluenesulfonamide, $\quad N$-lluoro-N-propyl-pcoluenesulfonamide, and N -fluorobenzenesulfonimide) ; N -fluoro-quinuclidinium fluoride ( $J$. Chem. Soc. Perkin Trans I 1988, 2805-2811); perfluoro-2;3,4,5ctrahydropyridine and perfluoro-(I-methylpyrrolidine), Banks, Cheng, and Haszeldine, Heterocyclic PolyfluoroCompounds Part II (1964); 1-fluoro-2-pyridone, J. Org. Chem., 1983 48, 761-762; quaternary stereogenic centers possessing a Huorine alom (J. Chem. Soc. Perkin Trans. pages 221-227 (1992)); N-fluoro-2,4,6-pyridinium triflate, Shimizu, Tetrahedron Vol 50(2), pages 487-495 (1994); N -fluoropyridinium pyridine heptafluorodiborate, J. Org. Chem. 1991, 56, 5962-5964; Umemoto, et al., Bull. Chem. Soc. . Jpn., 64 1081-1092 (1991); N -fluoroperfluoroalkylsulfonimides, J. Am. Chem. Soc., 1987, 109, 7194-7196; Purrington, et al., Lewis Acid Mediated Fluorinations of Aromatic Substrates, J. Org. Chem. $1991,56,142-145$.
A significant advantage of this methodology is the ability to access separately either the "natural" (1a) D or the "unnatural" (1b) L enantiomer of the nucleosides by appro. priate choice of L- or D- glutamic acid starting material, respectively.



Lactone 4 was synthesized by the roule shown in Scheme I from L-glutamic acid as described by Ravid el al.

1 a
(Tetrahedron 1978, 34, 1449) and Taniguchi et al. (Tetrahedron 1974, 30, 3547).


The enolate of lactone 4, prepared at $-78^{\circ} \mathrm{C}$. with LiHMDS in THF, is known to be stable. Several syntheses s using this enolate have been performed, including addition of elecrophiles such as diphenyldistienide. diphenyldisultide, and alkyl halides in high yield (I.iolta, D. C.; Wilson, I. J. Tetrahedron I.ctl. 1990, 31(13), 1s1.5; Cha, C. K.; Batu, J. K.; Beach, J. W.; Ahn, S. K.; Hang, H.; Jeong. I.. S.. Lee, S. J. J. Org. Chem., 1990, 5 S. 1418 ; Kawakami, II ; Lbata, T;-Korchi, K.; Matsusliti, II.; Naomi. Y.; lIth, K. (hem. Lett. 1990, 1459). However, addition of a THF solution of 5 to the emplace of 4 gave poon yichers of the desired monofluorinaled product 0 . Numerous by-products were formed including what wats surmised taw hos a difluorinated lactone that is inseparable from oiler impureties. For this reason, the order of addition of the reagent. was altered such that lactone 4 and NFSi 5 were dissolved together in THF and cooled to $-78^{\circ} \mathrm{C}$. Slow audition of LiHMDS resulted in a reaction yielding 6 as the only product in addition to a small amount of untreated starting material (eq 1).
liquation 1
(1)


Fluorolactone 6 could be obtained in $50-70 \%$ yield after silica gel column chromatography and crystallization. This reaction yielded a single diasicreomer of 6 , presumably due to the interaction of the sterically bulky. TB1)IS group and

Coupling of 8 with silylated pyrimidine bases was performed by standard Vorbruggen methodology (Telraliedron lett. 1978, 15, 1339) using TMS triflate as the Lewis acid. Alternatively, any other Lewis acid known to be useful to condense a base with a carbohydrate to form a nucleoside can be used, including tin chloride, titanium chloride, and uther tin or titanium compounds. A number of bases were successfully coupled in high yields ranging from $72 \%-100 \%$ after column chromatography (eq 2, Table 1).

Equation 2 .
(2)

15


$\beta: \alpha=2: 1$
9, 10, 11, 12, 13

TABLE. 1


Proton NMR indicated that the ratio of $\beta$ to $\alpha$ nucleoside anomers was approximately $2: 1$ in all cases. The sibyl protected nucleosides could not be resolved by column chromatography into the separate anomers. However, alice deprotection of the 5 '-oxygen with $\mathrm{NH}_{4} \mathrm{~F}$ in methanol (eq 3), the $\alpha$ and $\beta$ anomers could be readily separated and the results are summarized in Table 2."

Equation?


14b, , 55b, 10b, 1/7b, 3 sk

TABLE 2


- The classification of the free nucleosides as $\alpha$ or $\beta$ was based on the chemical shift of the anomeric proton (Table 3) - and on the polarity of the nucleosides as observed by thin layer chromatography. A trend for all of the $\alpha / \beta$ pairs of free nucleosides was observed in that the less polar compound of the two had an anomeric proton chemical shift that was notably upfield from that of the more polar compound.

TABLE 3


The correlation between anomeric proton chemical shift and absolute structure was verified by comparison of 18a (Nihata, S.; Ebata, T; Kawakami, H; Matsushida, H. Bull. Chem. Soc. Jpn. 1995, 68, 1509) and 18 b (Aerschot, A. V.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. J. Med. Chem. 1989, 32, 1743) with previously published spectral data and through X-ray crystal structure determination of 146 and 15 b . This finding is the opposite of the 30 usual trend for nucleosides in which the a anomer is normalty the less polar of the two. Presumably, in the "down" 2'-Huorinated nucleosides, the strong dipole of the C--F bond opposes the $\mathrm{C}-\mathrm{N}$ anomeric bond dipole in the $\beta$ isomer and reduces the overall molecular dipole. 25 Conversely, the a anomer has a geometry that allows - reinforcement of the molecular dipole through the addition of the $\mathrm{C}-\mathrm{F}$ and $\mathrm{C}-\mathrm{N}$ bond dipoles. Thus, the a anomer is more polar than the $\beta$ anomer in the case of $\alpha$-2'fluorn nucleosides.
The $\alpha$ and $\beta$ anomers 17 a and 17 b could not be separated by column chromatography because the free amino group caused the nucleosides to streak on silica gel. Therefore, it was necessary to use $\mathrm{N}^{4}$-acetylcytosine to prepare 11 and then resolve 16a and 16b. The $\mathrm{N}^{4}$-acetyl group was removed as quantitatively with a saturated solution of ammonia in mellianol in order to obtain separated 17a and 17b. When 5 -fluorocytosine was used as the base (compound 10), the anomers 15 a and 15 b were easily separated and no streaking on silica gel was observed.
Of the ten nucleosides listed in Table 2, it appears that only 176 (Martin, J. A.; Bushnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrell, J. H.; Parks, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A.; Kincbington, D. J. Med. Chem. 1990, 33(8), 2137; 4: Zenchofi, G. 13.; Sun, R.; Okabe, M.J. Org. Chem. 1991, 56, 4392), 18a (Njihata, S.; Ebata, T.; Kawakami, H.; Matsushida, H. Bull. Chem. Soc. Jpn. 1995, 68, 1509), and 18b (Aerschot, A. V.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. J. Med. Chem. 1989, 32, 1743) have been 50 synthesized previously: They, like the numerous known 2'- $\beta$ or "up" fluor nucleoside analogs ${ }^{14}$ have been synthesized from natural precursors (ie., they are in the $\beta-D$ configuration). It appears that no $\beta$-L-2'-fluororibofuranosyl nucleosides have been identified in the litera55 lure prior to this invention.

Fluorine is usually introduced into these molecules through nucleophilic attack on an anhydro-nucleoside (Mengel, R.; Guschlbauer, W. Angew. Chem., Int. Ed. Angl. 1978, 17, 525) or through replacement and inversion of a 60 stereochemically fixed hydroxyl group with diethylarninosulfur trifluoride (DAST) (Herdewijn, P.; Äerschot, A. V.; Kerremans, L. Nucleosides Nucleotides 1989, 8(1), 65). One advantage of the present methodology is that no hydroxyl group is needed for fluorine introduction. Thus, the process 65 is not limited to natural nucleosides or sugars as starting materials, and provides an easy to access the unnatural enantiomers of the 2 'flue no nucleosides.

Accordingly, several unnatural nucleosides were synthesized using this synthetic route with D-glutamic acid 19 as the starling material (Scheme 3). The sugar ring precursor 20 was fluorinated in the manner described above and coupled with various silylated bases (Table 4).




Yields of Unnatural Nucleoside Analogs


Compounds 30 and 31 may be synthesized from a common intermediate 32 , which may be accessed through pelenylation of tluoroglycal 29 .

## Scheme $n$





31


30

35
Selenylated compound 32 may be transformed into the "up" fluoro analog 31 through reduction with Rancy nickel. Alternatively, oxidation of the selenide 32 with $\mathrm{NaIO}_{4}$ or hydrogen peroxide followed by thermal elimination of the selenoxide intermediate lead 1030 . Both of these transformations on the unfluorinated systems are well documented and have been reported (Wurster. J. A.; Ph. I). Thesis, Emory University, 1995: Wilson, I.. J.; Ph. D. Thesis, Emory University, 199?).

In addition, the synthesis of the enantiomers of nucleosides 30 and 31 is also possible since they arise from the conantiomer of 29 .

An alternative route for the preparation of compounds' of 40 the type represented by 30 , the $2^{\prime}, 3$ '-dideoxy 2 2, $3^{\prime}$. . didehydro-2'-flouro-nucleosides, is shown in Scheme 7. This route provides simple, direct access to this class of compounds utilizing a wide range of silylated bases and has been successfully completed.

Scheme 7


sitylated base, TMSOTf


15
Formation of silyl ketene acetal from 6 allows for the stereoselective addition of phenyl selenium bromide to generate compound 36 as a single isomer Redurion and acetylation of this compound proceeds smoothly and in high yid over lie two steps to 17 . The a orientation of the phenyl semen!! group allows hor sterenselection in the subsequent glyersylation slap, ant synthesis of tic $\beta$ ixmener of the nucleoside 38 is accomplished in good yod. (compound 38 may be oxidized with hydrogen peroxide in dichlo. romethane to yield the elimination product 39 , hut in out experience, it was merely necessary to adsorb 38 onto silica: gel and allow to stand for several hours, after which time 39 could be eluted from a plug column in nearly quantitative yield. Removal of the protected group from 39 to obtain the final compound 30 was performed as before and resulted in a good yield ( $81 \%$ ) of product nucleoside


The same series of chemical transformations that were used for the synthesis of 30 and 31 may also be used for the synthesis of 34 and 35.

## Experimental Section

General Procedures
N-Fluoro-(bis)benzencsulionimide 5 was (attained from Allied Signal, and was used without further purification. All
other reagents were obtained from Aldrich Chemical Company and were used without further purification. Melting points were determined on à Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were 2) obtained on a Nicolet Impact $400 \mathrm{FT}-1 \mathrm{R}$ spectrometer. ${ }^{1} \mathrm{H}$ NMR and ${ }^{13} \mathrm{C}$ NMR spectra were recorded on either NT-360 or Varian 400 MHz spectrometer. TLC plates were silica gel $60 \mathrm{l}_{254}(0.25 \mathrm{~mm}$ thickness) purchased from EM Science. Flash chromatography was carried out with silica gel 60 5 (230-400 mesh ASTM) from EM Science. All reactions were performed in flame-dried glassware under an ammosphere of dry argon. Solvents were removed by rotary evaporation. Elemental analyses were performed by Atlantic Microlab, Inc, Atlanta, Ga.
(2S,4R)-5-(t -butyldiphenylsiloxy)-2-fluoropentan-4slide (20). To a flask was added (4R)-5.(t-butyldiphenylsiloxy)-pentan-4-olide ( $20.0 \mathrm{~g}, 0.0564 \mathrm{~mol}$, 1.0 eq .) and N -fluoro-(bis)benzenesulfonimide (NFSi) 5 ( $17.80 \mathrm{~g}, 0.0564 \mathrm{~mol}, 1.0 \mathrm{eq}$.) in 250 mL of anhydrous THF. 35 The solution was cooled to $-78^{\circ} \mathrm{C}$. and $68.0 \mathrm{~mL}(0.0680$ mol, 1.2 eq .) of a 1.0 M solution of LiHMDS in THF was added dropwise over a period of 1 hr . This was allowed to stir at $-78^{\circ} \mathrm{C}$. for an additional 2 hrs . and was then warmed to room temperature to stir for one bour. After completion, 40 the reaction was quenched with $10, \mathrm{~mL}$ of saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution. The mixture was diluted with three volumes of diethyl ether and was poured onto an equal volume of saturated $\mathrm{NaHCO}_{3}$. The organic layer was washed a second time with saturated $\mathrm{NaHCO}_{3}$ and once with saturated NaCl .
$45^{\circ}$ 'The organic layer was dried over $\mathrm{MgSO}_{4}$, filtered, and concentrated to a light yellow oil. The oil was purified by silica gel column chromatograpy using a $30 \%$ diethyl ether/ $70 \%$ hexanes solvent system. The resultant white solid was then crystallized from hot hexanes to yield $13.04 \mathrm{~g}(62 \%$ 50 yield) of a transparent crystalline solid: $\mathrm{R}_{f}(30 \%$ diethyl ether $70 \%$ hexanes) $m 0.26$; mp 1.15--116 ${ }^{\circ} \mathrm{C}^{1}{ }^{1} \mathrm{H}$ NMR (360 $\mathrm{MlHz}, \mathrm{CDCl}_{3}$ ) d $7.63-7.60(\mathrm{~m}, 4 \mathrm{H}), 7.45-7.35(\mathrm{~m}, 6 \mathrm{H}), 5.49$ ( $\mathrm{dt}, \mathrm{J}=52.9$ and $7.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), $4.69(\mathrm{~d}, \mathrm{~J}=9.36 \mathrm{~Hz}, 1 \mathrm{H}), 3.91$. (d, J=11.5 Hz, 1H), $3.60(\mathrm{~d}, \mathrm{~J}=11.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.72 \cdots 2.40$ ( m , $552 \mathrm{H}), 1.05(\mathrm{~s}, 9 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $172.1(\mathrm{~d}$, $\mathrm{J}=20.5 \mathrm{~Hz}), 135.5,135.4,132.3,131.7,130.1,128.0,127.9$, $85.6(\mathrm{~d}, \mathrm{~J}=186.6 \mathrm{~Hz}), 77.3(\mathrm{~d}, \mathrm{~J}=5.3 \mathrm{~Hz}), 65.0,31.8(\mathrm{~d}$, $\mathrm{J}=20.5 \mathrm{~Hz}$ ) , 26.7, 19.1; IR (thin film) 2958, 1796, 1252, 1192, $1111,1016 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\mathrm{M}+\mathrm{Li}$ ] $60 \mathrm{C}_{2} \mathrm{H}_{25} \mathrm{O}_{3} \mathrm{FSiLi}$ : 379.1717. Found: 379.1713. Anal. Talc. CHAFFS: C., 67.71; H, 6.7.6. Found: C, 67.72; H, 6.78.

5-O-(t-butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-(L)-erythron-pentofuranose (21). To a flask was added lactone $20(12.12 \mathrm{~g}, 0.0325 \mathrm{~mol}, 1.0 \mathrm{eq}$.$) and 240 \mathrm{~mL}$ of anhydrous 65 THF. The solution was cooled to $-78^{\circ} \mathrm{C}$. and 65 mI , ( 0.065 $\mathrm{mol}, 2.0 \mathrm{eq}$.) of a 1.0 M solution of DIBALH in hexanes was added dropwise over a period of 30 min. This was allowed

10 stir at $-78^{\circ} \mathrm{C}$. for 3 hrs , after which time the reaction was quenched by the slow addition of $2.93 \mathrm{~mL}(0.16 .3 \mathrm{~mol}, 5.0$ eq.) of water. The reaction was allowed to warn to room temperature and stir for 1 hr ., after which lime a clear gelatinous solid formed throughout the entire Hask. The reaction mixture was diluted with two volumes of diethyl ether and was poured onto an equal volume of salurated aqueous sodium potassium tartrate solution in an Erlenmeyer flask. This was stirred for 20 min . until the emulsion had broken. The organic layer was separated and the aqueous layer was extracted three times-winh 250 uL ut diethyl ether. The combined organic layers were dried over $\mathrm{MgSO}_{4}$, filtered, and concentrated to a light yellow oil. The product was purificd by silica gel column chromatography using a 6:1 hexanes/ethyl acetate solvent system. The resulting cleạ oil was crystallized from boiling hexanes to give 11.98 g ( $98 \%$ yield) of a white crystalline solid: $\mathrm{R}_{\text {( }}(30 \%$ diethyl ether $70 \%$ hexanes) $=0.33$; $\mathrm{mp} 66-67^{\circ} \mathrm{C}$. H NMR ( 300 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 7.68-7.66(\mathrm{~m}, 4 \mathrm{H}), 7.55-7.38(\mathrm{~m},(1) \mathrm{l}), 5.39$ (t, J $7.6 \mathrm{~Hz} ., \mathrm{Ill}), 4.99(\mathrm{dl}, \mathrm{J}-52.2$ and $4.3 \mathrm{~Hz}, \mathrm{IH}) .4 .52(\mathrm{~m}$, $1 \mathrm{H}), 3.88(\mathrm{dcl}, \mathrm{J}=10.8$ and $2.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.65(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}$, 111), $3.49(\mathrm{dct}, \mathrm{J}=7.9$ and $1.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.44-2.07(\mathrm{~m}, 2 \mathrm{H})$, 1.07 (s, 91l); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHI}, \mathrm{Cl}^{2} \mathrm{Cl}_{3}$ ) d 135.7, 135.5, $132.2,132.1 .130 .2,130.0 ; 129.8,127.9,127.7,99.8(\mathrm{~d}$, $\mathrm{J}=31.1 \mathrm{~Hz}$ ), $9 \mathrm{~h} .6(\mathrm{~d}, \mathrm{~J}=17 \mathrm{~B} .3 \mathrm{~Hz}) .79 .4,64.8,29.9(\mathrm{~d}, \mathrm{~J}=21.2$ Hz), 26.8, 19 !; IR (thin film) 3423, 2932, 1474, 1362, 111.3 $\mathrm{cm}^{-1}$; 1 HRMS calculaled for $[\mathrm{M}+1 . \mathrm{i}] \mathrm{C}_{21} \mathrm{ll}_{2}, \mathrm{O}_{3}$ FSili: 381.1874. Found: 381.1877. Anal. Calc. $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{O}_{3} \mathrm{FSi}: \mathrm{C}$, 67.35; H, 7.27: Found: (?, 67.42; H, 7.31.

1-O-Acetyl-5-O-(t-butyldiphenylsilyl)-2,3-dideoxy-2. Hluoro-(1) ersthron-pentofuranose (22). To a llask was added laclul $21(8.50 \mathrm{~g}, 0.0227 \mathrm{~mol}, 1.0 \mathrm{eq}$ ) and 170 ml of anhydrous $\mathrm{CII}_{2} \mathrm{Cl}_{2}$. Then, DMAP $(0.277 \mathrm{~g}, 0.001277 \mathrm{~mol}, 0.1$ cq.$)$ and acetic anhydride ( $13.5 \mathrm{~mL}, 0.143 \mathrm{~mol}, 6.3 \mathrm{eq}$.) were added and stirred at room temperature overnight. Upon completion, the reaction was poured onto saturated $\mathrm{NaHCO}_{3}$ solution. The organic layer was separated, and the aqueous layer was extracted three times with chloroform. The conr bined organic layers were dricd over $\mathrm{MgSO}_{4}$, filicred, and the solvent removed to yield a light yellow oil: The oil was purified by silica gel column chromatography, using an $8: 1$ hexanes/ethyl acetate solvent system to.give $9.85 \mathrm{~g}(99 \%$ yield) of a clear colorless oil: $\mathrm{R}_{f}(30 \%$ diethyl cther $70 \%$ hexanes) $=\left(0.4-4 ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(360 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 7.69-7.67\right.$ ( $\mathrm{III}, 4 \mathrm{II}$ ) , 7.4. $\mathrm{I}-7.38(\mathrm{~m}, 6 \mathrm{H}), 6.30(\mathrm{~d}, \mathrm{~J}=10.4 \mathrm{IL}, \mathrm{IH}), 5.06$ $(\mathrm{d}, \mathrm{J}=54.9 \mathrm{H} \%, 1 \mathrm{H}), 4.53(\mathrm{~m}, 1 \mathrm{H}), 3.8 \mathrm{l}(\mathrm{ckl}, \mathrm{J}=1 .(1.8$ and 4.3 $\mathrm{Hz}, 1 \mathrm{H}$ ), 3.72 (dcl, $\mathrm{J}=10.8$ and $4.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.38-2.12$ ( m , $2 \mathrm{H}), 1.89$ (s, 3H), 1.07 (s, 9H); ${ }^{13} \mathrm{CNMR}\left(1\left(10 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)\right.$ d 169.4, 135.6, 135.5, 133.2, 133.1, 129.s, 129.7, 127.8. $127.7,99.3$ ( $\mathrm{d}, \mathrm{J}=34.1 \mathrm{~Hz}$ ), $95.5(\mathrm{~d}, \mathrm{~J}=178.2 \mathrm{~Hz}$ ), 81.4, 65.3, $31.6(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}$ ), 26.8, 21.1, 19.3; IK (thin film) 3074 , $2860,1750,1589,1229,1113 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\mathrm{M}-\mathrm{OCOCH}_{3}$ ] $\mathrm{C}_{21} \mathrm{H}_{26} \mathrm{O}_{2}$ FSi: 357.1686. Yound: 357.1695 . Anal. Calc. $\mathrm{C}_{23} \mathrm{H}_{29} \mathrm{O}_{4} \mathrm{FSi}: \mathrm{C}, 66.32 ; \mathrm{H}, 7.02$. Found: C . 66.30; H, 7.04.

Representative procedure for the coupling of a silylated base with 22: (L)-5'-O-(t-butyldiphenylsilyl)-2',3-dideoxy-2'-fluoro-5-fluorocytidine (25). 'Гo a flask equipped with a short-path distillation head was added 5-fluorocytosine (2.01 $\mathrm{g}, 15.6 \mathrm{mmol}, 5.0 \mathrm{eq}), 35 \cdot \mathrm{~mL}$ of $1,1,1,3,3,3-$ hexamethyldisilazane, and a catalytic amount ( -1 mg ) of $\left(\mathrm{NH}_{4}\right)_{2} \mathrm{SO}_{4}$. The white suspension was heated to boiling for 1 hr . until the base was silylated and reaction was a clear solution. The excess HMDS was distilled off and the oily residue that remained was placed under vacuum for 1 hr . In remove the last traces of HMDS . A white solid resultel which was dissolved, moder argon, in 5 ml of mhydrons

1,2 -dichloroethane. To this clear solution was added a solulion of actate 22 ( $1.30 \mathrm{~g}, 3.12 \mathrm{mmol}, 1.0 \mathrm{eq}$.) in 5 mL of anhydrous 1,2 -dichloroethane. To this was added, at room lemperature, trimethylsilyl trifiuoromethanesulfonate (3.32 $\mathrm{mL}, 17.2 \mathrm{mmol}, 5: 5 \mathrm{eq}$.). The reaction was monitored by TLC. ( $10 \%$ methanol/ $90 \% \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ) and was observed to be complete in 4 hrs . The reaction mixture was poured onto saturated $\mathrm{NaHCO}_{3}$. The organic layer was then separated, and the aqueous layer was extracted three times with chloroform. The combined organic layers were dried over $\mathrm{MgSO}_{4}$, filtered, and the solvent removed to yield a white foam. The compound was purified by silica gel column chromatography using a gradient solvent system from $100 \%$ $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to $10 \%$ methanol in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The compound was isolated as 1.51 g ( $99 \%$ yield) uf a white foam: mixture of anomers $\mathrm{R}_{f}(100 \% \mathrm{EtOAc})=0.36 ; \mathrm{mp} 74-80^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ d $8.84(\mathrm{bs}, 1 \mathrm{H}), 8.04(\mathrm{~d}, \mathrm{~J}=6.4 \mathrm{~Hz}$, (1.6/1-1), 7.67-7.63(m), 411), 7.51-7.39 (int, 6.331 l$), 6.11(\mathrm{~d}$, $\mathrm{J}=20 \mathrm{~Hz}, 0.33 \mathrm{H}), 5.98(\mathrm{~d}, \mathrm{~J}=16.4 \mathrm{~Hz}, 0.67 \mathrm{H}), 5.88(\mathrm{bs}, 1 \mathrm{H})$, $5.41(\mathrm{~d}, \mathrm{~J}=52.4 \mathrm{~Hz}, 0.33 \mathrm{H}), 5.23(\mathrm{dd}, \mathrm{J}=50.4$ and 4 Hz , $0.67 \mathrm{H}), 4.56(\mathrm{~m}, 0.33 \mathrm{H}), 4.45(\mathrm{~m}, 0.67 \mathrm{H}), 4.23(\mathrm{dd}, \mathrm{J}=12.0$ and $1.6 \mathrm{~Hz}, 0.67 \mathrm{H}), 3.89(\mathrm{dd}, \mathrm{J}=11.2$ and $3.2 \mathrm{~Hz}, 0.33 \mathrm{H})$, $3.74-3.66(\mathrm{~m}, 1 \mathrm{H}), 2.45-1.96(\mathrm{~m}, 2 \mathrm{H}), 1.09(\mathrm{~s}, 6 \mathrm{H}), 1.06(\mathrm{~s}$, 3 H ) ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $158.6(\mathrm{~d}, \mathrm{~J}=14.4 \mathrm{~Hz}$ ), $158.4(\mathrm{~d}, \mathrm{~J}=1.4 .4 \mathrm{~Hz}), 153.9,153.8,136.6(\mathrm{~d}, \mathrm{~J}=240.5 \mathrm{~Hz})$, $136.3(\mathrm{~d}, \mathrm{~J}=239.7 \mathrm{~Hz}), 135.6,135.56,135.5,135.4,133.1$, $132.9,132.5,132.4,130.1,130.0,129.9,127.9,127.8,125.8$ $(\mathrm{d}, \mathrm{J}=33.4 \mathrm{~Hz}), 124.6(\mathrm{~d}, \mathrm{~J}=32.6 \mathrm{~Hz}), 96.5(\mathrm{~d}, \mathrm{~J}=182.0 \mathrm{~Hz})$, $91.7(\mathrm{~d}, \mathrm{~J}=18.5 .1), 90.7(\mathrm{~d}, \mathrm{~J}=35.6 \mathrm{~Hz}), 87.7(\mathrm{~d}, \mathrm{~J}=1.5 .2 \mathrm{~Hz}$ ), $81.5,79.5,64.9,63.0,33.5(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 30.6(\mathrm{~d}, \mathrm{~J}=20.4$ Hz ) $26.9,26.8,19.22,19.18$; IR (thin film) 3300,2960, 1682, $1608,1513,1109 \mathrm{~cm}^{-1}$, HRMS calculated for [M+Li] $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2} \mathrm{Li}: 492.2106$. Found:492.2085. Anal. Calc. $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2} .1 / 2 . \mathrm{H}_{2} \mathrm{O}: \mathrm{C}, 60.71 ; \mathrm{H}, 6.11 ; \mathrm{N}, 8.50$. Found: (:, $60.67 ; \mathrm{H}, 6.03 ; \mathrm{N}, 8.44$.

Representative Procedure for the deprotection of silylprotected nuclecosides: $\alpha$ - and $\beta$-(L)- $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}$-fluoro5 -lluoro cytidine (28a and 28 b ): Nucleoside 25 ( 1.098 g , $2.26 \mathrm{mmol}, 1.0 \mathrm{eq}$.) was dissolved in 1.5 mL of methanol to which was added ammonium fluoride $(0.838 \mathrm{~g}, 22.6 \mathrm{mmol}$, 10.0 eq.). This was stirred vigorously for 24 hrs., after which lime FLC ( $15 \%$ ethanol $/ 85 \%$ ethyl acetate) revealed that the reaction was complete. The reaction mixture was diluted with three volumes of ethyl acetate and was filtered through a small ( 1 cm ) silica gel plug. The plug was rinsed with 200 $m \mathrm{~m}$ of $15 \%$ ethanol/ $85 \%$ ethyl acetate solution and the solvent was removed to yicld a white foam. The compound was purified by silica gel column chromatography using a $15 \%$ ethanol/ $85 \%$ ethyl acetate solvent system which also effected the separation of the $\alpha$ and $\beta$ anomers. The yield of a as a white fuan was $0.190 \mathrm{~g}(0.768 \mathrm{mmol}, 34 \%$ yield) and the yield of $\beta$ as a white foam was $0.290 \mathrm{~g}(1.17 \mathrm{mmol}, 52 \%$ yield): (28a) R ( $15 \% \mathrm{EtOH}, 85 \%$ EtOAc) 0.22 ; mp - 199-203 ${ }^{\circ}$ C. (dec.). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 7.78 (d, $5 \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.07(\mathrm{~d}, \mathrm{~J}=19.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.37(\mathrm{~d}, \mathrm{~J}=54.0 \mathrm{~Hz}$, $1 \mathrm{H}), 4.60(\mathrm{~m}, 1 \mathrm{H}), 3.80(\mathrm{dd} \mathrm{J}=12.0$ and $3.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.56$ (dd, J=12.4 and $4.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.40-2.00 (m, 2H); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}$ ) d 157.7 (d, J=13.6 Hz), $153.2,135.9$ (d, J=239.0 Hz), $126.2(\mathrm{~d}, \mathrm{~J}=31.1 \mathrm{~Hz}), 92.4(\mathrm{~d}, \mathrm{~J}=183.6 \mathrm{~Hz})$, 86.7 (d, J=15.2 Hz), $79.6,62.7,-33.3(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz})$; IR ( KBr ) $3343,3100,1683,1517,1104 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\mathrm{M}+\mathrm{Li}] \quad \mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \mathrm{Li}$ : 254.0929. Found: 254.091.9. Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2}, 1 / 2 \mathrm{H}_{2} \mathrm{O}: \mathrm{C}, 42.19$; H , 4.72; N, 16.40. Found: C, 42.44; H, $4.56 ; \mathrm{N}, 16.56$. (28b) R, ( $15 \% \mathrm{ElOH}, 85 \% \mathrm{ElOAc})=0.37 ; \mathrm{mp} 182-186^{\circ} \mathrm{C}$. (dec.). ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $\mathrm{d}_{6}$ ) d $8.32(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.79$ (bs, 1H), $7 . .53$ (bs, 1H), 5.85 (cl, J=16.8 Hz, $H \mathrm{H}$ ), 5.37 ( l ,

## 34

$\mathrm{J}=4.8 \mathrm{~Hz}$ ). 5.18 ( $\mathrm{ld}, \mathrm{J}=51.6 \mathrm{ancl} 3.2 \cdot \mathrm{H} /$, 1 H ), 4.32 ( $\mathrm{m}, \mathrm{H} \mathrm{H}$ ), 3.88 (dd, J=12.0 and $2.8 \mathrm{~Hz}, 1 \mathrm{II}), 3.5!$ (dd, $\mathrm{J}=12.4$ and 2.4 $\mathrm{Hz}, 1 \mathrm{H}), 22\left(1-1.99(\mathrm{~m}, 2 \mathrm{H})\right.$; ${ }^{12}$ (. NMR ( 100 MHz , DMSO$\mathrm{d}_{\mathrm{f}}$ ) $\mathrm{d} 157.7(\mathrm{I}, \mathrm{J}=13.7 \mathrm{IL}), 153.2,136.1(\mathrm{I}, \mathrm{I}=2.37 .4 \mathrm{liz})$, $125.3(\mathrm{~d}, \mathrm{~J}=31.4 \mathrm{~Hz}), 97.3(\mathrm{~d}, \mathrm{~J}=176.8 \mathrm{~Hz}), 89.9$ ( $\mathrm{d}, \mathrm{J}=35.7$ Hz ), $81.6,602,30.3(\mathrm{~d}, \mathrm{~J}=19.7 \mathrm{~Hz})$; IR (K13r) 3457,2948 , $1678,15\left(19,1122 \mathrm{~cm}^{-1}\right.$; HRMS calculated for [M+L.i] $\mathrm{C}_{0} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2}$ Li: 254.0929. Found: 254.0935. Amal. Cale. $\mathrm{C}_{0} \mathrm{H}_{1}, \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2}: \mathrm{C}, 43.73 ; \mathrm{H}, 4.49 ; \mathrm{N}, 17.00$. Found: C, 43.69; H 4.53; $\mathrm{N}, 16.92$.
(D)-5'-()-(1-butyldiphenylsilyl)-2', $3^{\prime} \cdot$ dideoxy-2'- 1 luoro-5fluorouridine (9). mixture of anomers $\mathrm{R}_{f}:$ ( $1: 1$ hexanes/ EIOAc) $=0.48 ; \mathrm{mp} 65-70^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{TI} \mathrm{NMR}$ ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $10.0(\mathrm{bm}, 1 \mathrm{H}), 7.99(\mathrm{~d}, \mathrm{~J}=5.6 \mathrm{~Hz}, 0.63 \mathrm{H}), 7.65(\mathrm{~m}, 4 \mathrm{H})$, 7.42 (m, 6.37 H ), 6.12 (dd, $\mathrm{J}=18.0$ and $1.6 \mathrm{~Hz}, 0.37 \mathrm{H}), 6.00$ $(\mathrm{l}, \mathrm{J}=16 \mathrm{Ilz}, 0.63 \mathrm{H}), 5.37(\mathrm{dd}, \mathrm{J}=54.6$ and $\cdot 2.4 \mathrm{~Hz}, 0.37 \mathrm{H})$, 5.22 (dd, J=501. 4 and $4 \mathrm{~Hz}, 0.631 \mathrm{C}), 4.57$ (m, 0.37 H ). 4.44 ( m , $0.63 \mathrm{H}), 4.22(\mathrm{dd}, \mathrm{J}=12.2$ and $2.0 \mathrm{~Hz}, 0.63 \mathrm{H}), 3.92(\mathrm{dd}$, $\mathrm{J}=11.2$ and $3.2 \mathrm{H} \%, 0.37 \mathrm{II}), 3.71(\mathrm{~m}, 1 \mathrm{II}), 2.22(\mathrm{~m}, 2 \mathrm{H}), 1.09$ ( $\mathrm{s}, 5.67 \mathrm{H}$ ), $1074(\mathrm{~s}, 3.33 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{Mfl} \mathrm{L}, \mathrm{CDCl}_{3}$ ) d 157.2 (d, J=31.7 Hz), 157.1 ( $\mathrm{d}, \mathrm{J}=25.8 \mathrm{~Hz}$ ), 149.1, 148.8. $140.4(\mathrm{~d}, \mathrm{~J}=2.36 .6 \mathrm{~Hz}), 140.1(\mathrm{~d}, \mathrm{~J}=235.2 \mathrm{~Hz}), 135.6,135.5$. $135.4,132.9,132.7,132.4,132.3,130.1,130.0,129.9$, 127.9, $127.8,125.1(\mathrm{~d}, \mathrm{~J}=34.9 \mathrm{~Hz}), 123.6(\mathrm{~d}, \mathrm{~J}=34.1 \mathrm{~Hz})$, $96.4(\mathrm{~d}, \mathrm{~J}=182.0 \mathrm{~Hz}), 92.0(\mathrm{~d}, \mathrm{~J}=185.9 \mathrm{~Hz}), 90.2(\mathrm{~d}, \mathrm{~J}=37.2$ $\cdot \mathrm{Hz}), 87.0(\mathrm{~d}, \mathrm{~J}=15.2 \mathrm{~Hz}), 81.7,79.8,64.8,63.0,33.3(\mathrm{~d}$, $\cdot \mathrm{J}=21.2 \mathrm{~Hz}$ ), $31.0(\mathrm{~d}, \mathrm{~J}=2 \mathrm{~L} .2 \mathrm{~Hz}$ ), 26.9, 26.8, 19.2; IR (hinin film) $3185,1722,1117 \mathrm{~cm}^{-1}$; IIRMS calculated for $[\mathrm{M}+1$ ] $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}_{3}: 487.1866$. Found:" $487: 1853$. Anal. Cala. $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O} .4 \mathrm{SiF}_{2}: \mathrm{C}, 61.71 ; \mathrm{H}, 5.80$; N, 5.76. Found: C, 61.72; H, 5.86; N, 5.72.
(D)-5'-O-(t-butyldiphenylsilyl)-2',3'-dideoxy-2'-fluoro-5fluorocytidine (10). mixture of anomers $\mathrm{R}_{f}(100 \%$ EtOAc) $=$ 0.36 ; mp $75-81^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d 8.50 (bm, 1H), 8.05 (d, J=6.0 Hz, 0.67 H ), $7.67-7.63$ (m, 4H), $7.51-7.39(\mathrm{ni}, 6.33 \mathrm{H}), 6.10(\mathrm{~d}, \mathrm{~J}=20 \mathrm{~Hz}, 0.33 \mathrm{H}), 5.98(\mathrm{~d}$, $\mathrm{J}=16.4 \mathrm{~Hz}, 0.67 \mathrm{H}), 5.62(\mathrm{bm}, 1 \mathrm{H}), 5.41(\mathrm{~d}, \mathrm{~J}-52.4 \mathrm{~Hz}$, $0.33 \mathrm{H}), 5.23(\mathrm{dd}, \mathrm{J}=51.6$ and $4 \mathrm{~Hz}, 0.67 \mathrm{H}), 4.57(\mathrm{~m}, 0.33 \mathrm{H})$, $4.48(\mathrm{~m}, 0.67 \mathrm{H}), 4.24(\mathrm{dd}, \mathrm{J}=12.4$ and $2.0 \mathrm{~Hz}, 0.07 \mathrm{H}), 3.89$ (dd, J=11.2 and $3.2 \mathrm{z} \mathrm{Iz}, 0.33 \mathrm{H}$ ), $3.74-3.60(\mathrm{~m}, 1 \mathrm{H})$, $2.39-1.95(\mathrm{~m}, 2 \mathrm{H}), 1.09(\mathrm{~s}, 6 \mathrm{H}), 1.06(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 100 $\left.\mathrm{MH} z, \mathrm{CDCl}_{3}\right) \mathrm{d} 158.4(\mathrm{~d}, \mathrm{~J}=14.4 \mathrm{~Hz}), 158.3(\mathrm{~d}, \mathrm{~J}=1.52 \mathrm{~Hz})$, 153.8, $153.7,136.5(\mathrm{~d}, \mathrm{~J}=240.5 \mathrm{~Hz}), 136.2$ (d, J=241.8 Hz), $135.59,135.56,135.4,133.0,132.9,132.5,132.4,130.1$, 130.0, 129.9, 127.9, 127.8, 124.8 (d, J=31.9 Hz), $96.5(\mathrm{~d}$, $\mathrm{J}=181.3 \mathrm{~Hz}), 91.8(\mathrm{~d}, \mathrm{~J}=175.2 \mathrm{~Hz}), 90.7(\mathrm{~d}, \mathrm{~J}=24.9 \mathrm{~Hz})_{;} 87.8$ ( $\mathrm{d}, \mathrm{J}=21.2 \mathrm{H} /$ ), 81.6, 79.6, 64.9, 63.033 .5 ( $\mathrm{d}, \mathrm{J}=19.7 \mathrm{~Hz}$ ), 30.6 (d, J. 21.3 Hz ), 26.9, 26.8, 19.2, 14.2; IR (thin film) 3304, 2959, 1680, 1621, 1508, $1105 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \quad{ }^{\prime}{ }_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2} \mathrm{Li}: 492.2106$ Found:492.2110. Anal. C.alc. $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2}:$ C. $61.84, \mathrm{H}, 5$ $6.02 ; \mathrm{N}, 8.65$. Found: C, $61.86 ; \mathrm{H}, 6.09 ; \mathrm{N}, 8.55$
(D) $-\mathrm{N}^{4}$-acctyl-5'-O-(1-butyldiphenylsilyl)-2', $3^{\prime}$-dideoxy2 -fluoro-cytidine (11). mixture of anomers $\mathrm{R}_{\text {, }}(15 \%$ EIOH. $85 \%$ EIOAc) $=0.75$; mp $81-16^{\circ} \mathrm{C}$. 'HI NMR ( $+10 \mathrm{MH} \%$. $\left.\mathrm{CDCl}_{3}\right) \mathrm{d} 10.58$ (bs, 1 H$), 8.40(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 0.61 \mathrm{ll}), 7.86$ ( c, $\mathrm{J}=7.6 \mathrm{IIz}, 0.38 \mathrm{II}), 7.67-7.41(\mathrm{ml}, 6 \mathrm{H}), 7.27(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{H} \mathrm{\%}$, $1 \mathrm{H}), 6.12(\mathrm{I}, \mathrm{J}=15.8 \mathrm{H}, 1 \mathrm{H}), 5.5 \mathrm{~L}(\mathrm{~d}, \mathrm{~J}=52.6 \mathrm{~Hz}, 0.38 \mathrm{H})$, $5.21(\mathrm{dd}, \mathrm{Ja} .40 .8$ and $2.9 \mathrm{~Hz},(1.61 \mathrm{H}), 4.62$ ( $\mathrm{m},(0.2 \mathrm{kH} \mathrm{H}), 4.54$ $(\mathrm{m}, 0.61 \mathrm{H}), 4.28(\mathrm{~d}, \mathrm{~J}=11.5 \mathrm{~Hz} .0 .61 \mathrm{H}), 3.95(\mathrm{dd}, \mathrm{J}=11.9$ and $3.2 \mathrm{~Hz}, 0.3811), 179-3.70(\mathrm{nr}: 111), 2.46-2 .(\mathrm{H}(\mathrm{II}, 5 \mathrm{HI}) 1.12$

171.5, 171:3, 163.4, 154.9, 144.9, 144.1, 135.5, 135.4, 133.0, 132.8, 132.5, 132.2, 130.2, 130.1, 129.9, 128.0, $127.8,96.8(\mathrm{~d}, \mathrm{~J}=91.1 \mathrm{~Hz}), 96.2(\mathrm{~d}, \mathrm{~J}=147.9 \mathrm{~Hz}), 92.3,91.2$ (d, J=35.7 Hz), $90.5,88.5(\mathrm{~d}, \mathrm{~J}=15.9 \mathrm{~Hz}), 81.9,80.1,63.7$, $562.9,33.5(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 30.5(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 26.9,26.8$, $24.9,24.8,19.3,19.2$ IR (thin film) 3237, 2932, 1722, 1671, 1559, 1493, $1107 \mathrm{~cm}^{-1}$; HRMS calculated for [M+Li] $\mathrm{C}_{27} \mathrm{H}_{32} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{FSiLi}$ : 516.2306. Found: 516.2310. Anal. Calc. 63.45 ; H, 6.42 ; N, 8.09 .
(D) $-5^{\prime}$-O-(I-butyldiphenylsilyl)-2', $3^{\prime}$-dideoxy-2'-fluorocylidine (12). mixture ol anomers
$\mathrm{R}_{f}(15 \% \mathrm{EtOH}, 85 \% \mathrm{ElOAc})=\left(1.50 ; \mathrm{mp} 98-104^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}\right.$ $15 \mathrm{NMR}\left(360 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 7.97(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 0.64 \mathrm{H}, \mathrm{H}-6)$, $7.65(\mathrm{~m}, 4 \mathrm{H}) ; 7.47-7.38(\mathrm{~m}, 6.36 \mathrm{H}), 6.15(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}$, $0.30 \mathrm{H}), 6.05(\mathrm{~d}, \mathrm{~J}=16.6 \mathrm{Ilz}, 0.64 \mathrm{II}), 5.83(\mathrm{~d}, \mathrm{~J}-7.9 \mathrm{~Hz}$, $(0.36 \mathrm{H}), 5.46(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 0.64 \mathrm{H}), 5.30-5.10(\mathrm{~m}, 1 \mathrm{H}), 4.55$ $(\mathrm{m}, 0.36 \mathrm{H}), 4.44(\mathrm{~m}, 0.64 \mathrm{H}), 4.22(\mathrm{~d}, \mathrm{~J}=9.7 \mathrm{~Hz}, 0.64 \mathrm{H})$, 3.88-3.63 (m, 1.36H), 2.38-1.95 (m, 2H), $1.09(\mathrm{~s}, 5.76 \mathrm{H})$, $1.06(\mathrm{~s}, 3.24 \mathrm{H}) ;{ }^{23} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl} \mathrm{l}_{3}$ ) d $166 . \mathrm{s}$, $155.8,141.5,140.5,135.6,135.4,133.1,132.9,132.8$, $132.4,130.1,130.0,129.8,128.0,127.9,127.8,96.7$ (d, $\mathrm{J}=181.3 \mathrm{~Hz}), 93.4(\mathrm{~d}, \mathrm{~J}=140.3 \mathrm{~Hz}), 94.5,90.8(\mathrm{~d}, \mathrm{~J}=35.6 \mathrm{~Hz})$, $90.8,87.8(\mathrm{~d}, \mathrm{~J}=15.9 \mathrm{~Hz}), 81.2,79.4,65.0,63.2,33.7(\mathrm{~d}$, $\mathrm{J}=21.2 \mathrm{~Hz}), 30.8(\mathrm{~d}, \mathrm{~J}=20.4 \mathrm{~Hz}), 26.9,26.8,19.3,19.2$ IR (thin film) $3470,3339,1644,1487,11.13 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{25} \mathrm{H}_{30} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{FSiLi}: 474.2201$. Found: 474.2198. Anal. Calc. $\mathrm{C}_{25} \mathrm{H}_{30} \mathrm{~N}_{3} \mathrm{O}_{3}$ FSi: C, 64.21; H, 6.47; N, 8.99. Found: C, $64.04, \mathrm{H}, 6.58 ; \mathrm{N}, 8.76$.
$\alpha$-(D)-2',3'-Didenxy-2'-Huoro-5-fluorouridine (14a). R ( $100 \% \mathrm{EtOAc}$ ) $=0.38$; mp $153-155^{\circ} \mathrm{C} .{ }^{2} \mathrm{H}$ NMR ( 360 $\left.\mathrm{Ml} \mathrm{Iz}, \mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 7.80(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.11(\mathrm{~d}, \mathrm{~J}=18.7 \mathrm{~Hz}$, $1 \mathrm{H}), 5.35(\mathrm{~d}, \mathrm{~J}=52.9,1 \mathrm{H}), 4.59(\mathrm{~m}, 1 \mathrm{H}), 3.81(\mathrm{~d}, \mathrm{~J}=11.9 \mathrm{~Hz}$, 1 H ), 3.57 ( $\mathrm{dd}, \mathrm{J}=12.6$ and $3.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.36-2.15(\mathrm{~m}, 2 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $159.6(\mathrm{~d}, \mathrm{~J}=25.8 \mathrm{~Hz}$ ), 150.7, 141.5 ( $\mathrm{d}, \mathrm{J}=230.6 \mathrm{~Hz}$ ), 127.0 (d, J=34.9 Hz), 93.9 (d, $\mathrm{J}=185.1 \mathrm{~Hz}), 88.5(\mathrm{~d}, \mathrm{~J}=15.1 \mathrm{~Hz}), 81.8,64.3,34.3(\mathrm{~d}, \mathrm{~J}=20.5$ Hz ); IR ( KBr ) $3421,3081,1685,1478,1111 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{5} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}: 255.0769$. Found: 255.0778. Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{10 \mathrm{~N}}^{2} \mathrm{O}_{4} \mathrm{~F}_{2}: \mathrm{C}, 43.56 ; \mathrm{H}, 4,06 ; \mathrm{N}$, 11.29. Found: C, 43.59; H, 4.11; N, 11.17.
$\beta$-(D)-2', 3'-Dideoxy-2'-fluoro-5-fluorouridine (14b). $\mathrm{R}_{f}$ ( $100 \%$ EtOA ${ }^{\circ}$ ) $=0.54$; mp 152 154 (C. ${ }^{1} \mathrm{H}$ NMR ( 360 MHz , $\left.\mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 8.41(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.89(\mathrm{~d}, \mathrm{~J}=16.6 \mathrm{~Hz}, 1 \mathrm{H})$, $5.21(\mathrm{dd}, \mathrm{J}=51.5$ and $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{~m}, 1 \mathrm{H}), 4.00(\mathrm{~d}$, $\mathrm{J}=12.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.67(\mathrm{~d}, \mathrm{~J}=12.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.25-2.09(\mathrm{~m}, 2 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 159.7 (d, Ja 25.8 Hz ), $1.50 .7,141.8(\mathrm{~d}, \mathrm{~J}=229.8 \mathrm{~Hz}), 126.3(\mathrm{~d}, \mathrm{~J}=36.4 \mathrm{~Hz}), 98.3(\mathrm{~d}$, $J=179 \mathrm{~Hz}$ ), $91.9(\mathrm{~d}, \mathrm{~J}=37.1 \mathrm{~Hz}), 83.6,61.9,31.9(\mathrm{~d}, \mathrm{~J}=20.5$ IIz); IR (KBr) $3417,3056,1684,1474,1105 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}: 255.0769$. Found: 255.0764. Anal. Calc. $\mathrm{C}^{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{~F}_{2}$ : $\mathrm{C}, 43.56 ; \mathrm{H}, 4.06 ; \mathrm{N}$, 11.29. Found: C, 43.37; H, 3.98; N, 11.22.
a-(D)-2',3'-Didenxy-2'-fluoro-5-fluorocytidine (15a). $\mathrm{R}_{\text {; }}$ ( $15 \% \mathrm{EtOH}, 85 \% \mathrm{ElOAc})=0.22 ; \mathrm{mp} 198-203^{\circ} \mathrm{C}^{\prime}$ ( (dec.). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\mathrm{d} 7.78(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.07(\mathrm{~d}$, $\mathrm{J}=18.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.37(\mathrm{~d}, \mathrm{~J}=54.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.59(\mathrm{~m}, 1 \mathrm{H}), 3.80$ (dd, J=12.0 and $3.2 \mathrm{~Hz}, \mathrm{H}$ ), 3.57 (dd, J=12.4 and 4.4 Hz , $1 \mathrm{H}), 2.38-2.14(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $159.9(\mathrm{~s}, \mathrm{~J}=13.6 \mathrm{~Hz}), 156.5,138.3(\mathrm{~d}, \mathrm{~J}=240.4 \mathrm{~Hz}), 127.5(\mathrm{~d}$, $\mathrm{J}=33.4 \mathrm{~Hz}), 93.6(\mathrm{cl}, \mathrm{J}=184.3 \mathrm{~Hz}), 89.5(\mathrm{~d}, \mathrm{~J}=15.9 \mathrm{~Hz}), 81.8$,
.64.4, 34.5 (d, J=20.5 Hz); 1 R ( KBr ) 3486, 3098, $10 \times 1,1519$, $!108 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\left.\mathrm{M}+\mathrm{Li}\right] \mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \mathrm{Li}$ : 2.54:0929. Found: :254.09.29. Anal. Calc $\mathrm{C}_{9} \mathrm{H}_{111} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} .1 / 2 \mathrm{H}_{2} \mathrm{O}: \mathrm{C}, 42.19 ; \mathrm{H}, 4.72 ; \mathrm{N}, 16.40$. Found: C, 41.86; H, 4.75; N, 16.36 .
$\beta$-(D)-2',3'-Dideoxy-2'-fuoro-5-fluorocytidine (15b). R $(15 \% \mathrm{EtOH}, 85 \% \mathrm{EtOAc})=0.37 ; \mathrm{mp} 181-183^{\circ} \mathrm{C}$. (dec.). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 8.45 (d, J=7.2 Hz, 1 H ), 5.92 (dd, J=16.2 and $1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 5.18 (dd, J=50.8 and 4.0 Hz , 1 H ), $4.46(\mathrm{~m}, 1 \mathrm{H}), 4.05(\mathrm{dd}, \mathrm{J}=12.4 \mathrm{and} 2.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.72 (dd, J=12.8 and $2.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.27-2.05 (m, 2H); 13C NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 159.9 (d, J=13.6 Hz), $156.5,138.5$ (d), $\mathrm{J}=240.5 \mathrm{~Hz}$ ), 126.9 (d, J=33.4 Hz), $98.4(\mathrm{~d}, \mathrm{~J}=179.0 \mathrm{~Hz}$ ), 92.5 (d, Je36.4 Hz), $83.6,61.9,31.6(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}$ ); IR ( KBr ) $3494,2944,1689,1522,1106 \mathrm{~cm}^{-1}$; HIRMS calculated for [ $\mathrm{M}+\mathrm{Li}$ ] $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \mathrm{Li}$ : 254.0929 . Found: 254.0936. Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2}: \mathrm{C}, 43.73 ; 11,4.49 ; \mathrm{N}$, '17.00. Funmu: C, 49.84; H, 4.47; N, 19.05 .
$\alpha$-(D)- $\mathrm{N}^{-1}$-acetyl-2', $3^{\prime}$-dideoxy- $2^{\prime}$-fluoro-cytidine (16a). $\mathrm{R}_{f}$ ( $15 \% \mathrm{EIOH}, 85 \% \mathrm{EtOAc}$ ) $=0.40$ ) $\mathrm{mp} 208-212^{\circ} \mathrm{C}^{\prime}{ }^{1} \mathrm{H}$ NMR $\left(360 \mathrm{MHz}\right.$, DMSO- $\mathrm{d}_{6}$ ) d ( 10.91 , bs, 1 H ), 8.05 ( $\mathrm{d}, \mathrm{J}=7.2 \mathrm{~Hz}$, $1 \mathrm{H}), 7.25(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 0.08(\mathrm{dd}, \mathrm{J}=19.1 \mathrm{and} 2.9 \mathrm{~Hz}$, $1 \mathrm{H}), 5.42(\mathrm{~d}, \mathrm{~J}=52.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.97(\mathrm{bs}, 1 \mathrm{H}), 4.54$ (m; 1 Hi$)$, $3.63(\mathrm{~d}, \mathrm{~J}=13.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.47(\mathrm{~d}, \mathrm{~J}=13.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.35-2.15$ ( $\mathrm{m}, 2 \mathrm{H}$ ), $2.11(\mathrm{~s}, 3 \mathrm{H})$; 13 C NMR ( 10 O 1 MIIz , DMSO- $\mathrm{d}_{\mathrm{i}}$ ) d. 171.0, 162.6, 154.3, 14.5.7, 94.9, 92.0 (d, J. 183.6 Hz ), 87.5 (d, Jo15.9 Hz), 80.2, 62.6, 33.3 (d, J=19.7 Hiz), 24.4; IR ( KBr ) 3436, 3227, 1702, 1661, 1442, 11()2 $\mathrm{cml}^{\prime}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{11} \mathrm{H}_{1.4} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{Fl}$.i: 278.112 s . Found 278.1136. Anal. Calc. $\mathrm{C}_{11} \mathrm{H}_{1+4} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~F}: \mathrm{C}, 48.71 ;$ II, 5.20: N . 15.49. Found: $\mathrm{C}, 48.73 ; \mathrm{H}, 5.23 ; \mathrm{N}, 15.52$
(3-(D)- $\mathrm{N}^{4}$-acetyl-2', $3^{\prime}$-didenxy-2'-fluoro-cytidinc (16b). R, ( $15 \% \mathrm{EIOH}, 85 \%$ EIOAC) $=0.50$; mp $174-178^{\circ}$ ( $^{1} \mathrm{H}$ NMIK ( $\left.360 \mathrm{MHz}, \mathrm{DMS}()-\mathrm{d}_{6}\right) \mathrm{d}(10.9 \mathrm{~m}, \mathrm{hs}, 1 \mathrm{HI}), x+6(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}$, JH ), $7.18(\mathrm{~d} . \mathrm{J}=7.2 \mathrm{~Hz}, \mathrm{III}), 5.90(\mathrm{~d}, \mathrm{~J}=16.9 \mathrm{Iz}, 11 \mathrm{I}), 5.27(\mathrm{~d}$. J.52.9 H2, 111 I$), 5.27(\mathrm{bs}, 1 \mathrm{H}), 4.39(\mathrm{~m}, 1 \mathrm{H}), 3.88(\mathrm{~d}, \mathrm{~J}=13.9$ $\mathrm{Hz}, 1 \mathrm{H}), 3.01(\mathrm{~d}, \mathrm{~J}=13.0 \mathrm{~Hz} .1 \mathrm{II}), 2 \mathrm{il}(\mathrm{s}, 3 \mathrm{ll}), 2.2(\mathrm{O}-1.85$ (m, 2H); ${ }^{13}$ ( NAR ( $100 \mathrm{MI}!$. DMSO-d $\mathrm{d}_{\mathrm{i}}$ ) d $171.0,162.6$, 154.4, 144.7, 97.0 (d, J=177.5 Hz), 95.0. 90.7 ( $\mathrm{d}, \mathrm{J}=36.6$ $\mathrm{Hz}), 82.2,611.3,30.3(\mathrm{~d}, \mathrm{~J}=147 \mathrm{~Hz}), 24.3$; $\mathrm{IR}(\mathrm{Kilir}) 3447$, 3245, 17013, 1656, 1497, 1122 $\mathrm{cm}^{-1}$, HRMS calculated for [ $\mathrm{M}+\mathrm{Li} \mathrm{i}] \mathrm{C}_{11} \mathrm{II}_{14} \mathrm{~N}_{3} \mathrm{O}_{4}$ FLi: 278.1128 . Fuund: 278.11.33. Anal Calc. $\mathrm{C}_{11} \mathrm{H} \mathrm{H}_{1 .} \mathrm{N}_{3} \mathrm{O}_{4} \mathrm{~F}: \mathrm{C}, 48.71 ; \mathrm{H}, 5.2(1) \mathrm{N}, 15.49$. Found: C , 48.65H, 5.22; N, 15.46.
$\alpha$-(D)-2', 3'-Dideoxy-2'-fluoro-cytidine (17a). $\mathrm{R}_{f}$ ( $1.5 \%$ $\mathrm{EtOH}, 85 \% \mathrm{EtOAC}$ ) $=0 .\left(\mathrm{R} ; \mathrm{mp} 234-237^{\circ} \mathrm{C}\right.$. (dec.). 'I.I NMR ( $400 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}$ ) d $7.52(\mathrm{U}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{If}), 7.21$ (bm, 2 H ), 0.05 (dd, J=20.4 and $3.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.73$ (d, J. 7.2 ILz , $1 \mathrm{H}), 5.28(\mathrm{~d}, \mathrm{~J}=52.4 \mathrm{H} / \mathrm{l}, 1 \mathrm{H}), 4.93(\mathrm{I}, \mathrm{J}=56 \mathrm{~Hz}, \mathrm{H}), 4.45$ $(\mathrm{m}, 1 \mathrm{H}), 3.58(\mathrm{~m}, 1 \mathrm{H}), 3.43(\mathrm{~m}, 1 \mathrm{H}), 2.26-2.13(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ : NMR ( 100 MHz , DMSO-d $\mathrm{d}_{6}$ ) d $165.8,155.0,141.6,93.3$, $92.2(\mathrm{~d}, \mathrm{~J}=182.8 \mathrm{~Hz}), 86.6(\mathrm{~d}, \mathrm{~J}=15.1 \mathrm{~Hz}), 79.4,62.8,33.3$ (d, J=19.7 Hz); IR (KBr) 3366, 3199, ${ }^{1059,1399,1122 ~}$ $\mathrm{cm}^{-1}$; HRMS calculated for [M+Li] $\mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{FLi}$ : 236.1023. Fsund: 236.1014. Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}: \mathrm{C}$, 47.16; H, 5.28; N, 18.33. Found: C. 47.40; H, 5.34; N, 18.51.
$\beta$-(D)-2',3'-Dideoxy-2'-fluoro-cytidine. (17b). Nucleosidc $25(0.160 \mathrm{~g}, 0.59 \mathrm{mmol})$ was dissolved in 10 mL of saturated methanolic ammonia. After stirring for 5 min ., the reaction was 14 -complete. The methanolic ammonia was removerl and the resultant white solid was placed under vacuum and heated gently in a $60^{\circ} \mathrm{C}$. water hath for 2 hrs. to remove the acetamide hy-product ihrough sullimation The white solid
was crystallized from $5 \%$ methanol $/ 95 \%$ methylene chloride to give a quantitative yield of a white crystalline solid. $\mathrm{R}_{f}$ ( $15 \% \mathrm{EtOH}, 85 \% \mathrm{EtOAc}$ ) $=0.18$; mp $191-195^{\circ} \mathrm{C}$. (dec.). ${ }^{1} \mathrm{H}$ NMR $\left(360 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 8.10(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.92(\mathrm{~d}$, $J=17.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.82(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.13(\mathrm{~d}, \mathrm{~J}=50.0 \mathrm{~Hz}$, $1 \mathrm{H}), 4.39(\mathrm{~m}, 1 \mathrm{H}), 3.9(\mathrm{~d}, \mathrm{~J}=12.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.68$ (dd, J=13.0 and $2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.21-2.00(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 100 MHz , $\mathrm{CD}_{3} \mathrm{OD}$ ) d $165.9,155.0,140.8,97.3$ (d, J=176.8 Hz), 93.6, 90.3 (d, Ja35.6 Hz), 81.3, 60.7 , 31.0 (d, J=20.5 Hz); IR (KBr) $3397,3112,1680,1400,1178,1070 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\mathrm{M}+\mathrm{Li}$ ] $\mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{FLi}$ : 236.1024 . Found: 236.1028. Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3}$ F: C, $47.16 ; \mathrm{H}, 5.28 ; \mathrm{N}$, 18.33. Found: C, 47.01; H, 5.21; N, 18.29. (L)-5'-O-(t-butyldiphenylsilyl)-2', $3^{\prime}$-dideoxy-2'-Auoro-thymidine (23). mixture of anomers $\mathrm{R}_{f}\left(10 \% \mathrm{MeOH} / 90 \% \mathrm{CH}_{2} \mathrm{Cl}_{2}\right)=0.56$; mp G1-65 $5^{\circ} \mathrm{C} .{ }^{1}$ II NMR ( $360, \mathrm{MIII}, \mathrm{CDCl}_{3}$ ) d 9.48 ( $\mathrm{b} 3,1 \mathrm{III}$ ), $7.67(\mathrm{~m}, 4 \mathrm{H}), 7.45-7.37(\mathrm{~m}, 7 \mathrm{H}), 6.15(\mathrm{dd}, \mathrm{J}=20.2$ and 3.2 $\mathrm{Hz}, 0.36 \mathrm{H}), 5.99(\mathrm{~d}, \mathrm{~J}=18.4 \mathrm{~Hz}, 0.64 \mathrm{H}), 5.34(\mathrm{~d}, \mathrm{~J}=51.8 \mathrm{~Hz}$, $0.36 \mathrm{H}), 5.24(\mathrm{dd}, \mathrm{J}=52.2$ and $4.3 \mathrm{~Hz}, 0.64), 4.59(\mathrm{~m}, 0.36 \mathrm{H})$, $4.45(\mathrm{~m}, 0.64 \mathrm{H}), 4.17(\mathrm{dd}, \mathrm{J}=12.2$ and $2.5 \mathrm{~Hz}, 0.64 \mathrm{H}), 3.91$ (dd, $J=11.9$ and $2.9 \mathrm{~Hz}, 0.36 \mathrm{H}$ ), 3.81 (dd, J=11.5 and 2.9 Hz , 0.64 H ), $3.68(\mathrm{dd}, \mathrm{J}=10.8$ and $3.6 \mathrm{~Hz}, 0.36 \mathrm{H}$ ), 2.40-2.12 (m, $2 \mathrm{H}), 1.94(\mathrm{~s}, 1.08 \mathrm{H}), 1.61(\mathrm{~s}, 1.92 \mathrm{H}), 1.10(\mathrm{~s}, 5.76 \mathrm{H}), 1.07$ (s, 3.24 H ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $164.1,164.0$, $150.4,150.2,136.4,135.6,135.5,135.4,135.3,135.2$, $133.0,132.8,132.6,130.1,130.0,129.9,127.94,127.90$, $127.8,110.8,109.8,96.4(\mathrm{~d}, \mathrm{~J}=181.3 \mathrm{~Hz}), 92.1(\mathrm{~d}, \mathrm{~J}=185.8$ $1 \mathrm{lz}), 90.7$ (d, J=36.4 Hz), 86.6 (d, J=15.2 Hz), 89.9, 79.4, (4.9, 63.6, $33.4(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 32.0(\mathrm{~d}, \mathrm{~J}=21.2 \mathrm{~Hz}), 27.0$, $26.8,19.4,19.2,12.6,12.2$; IR (thin film) 318.3, 3050, 1696 , 1506, $1188 \mathrm{~cm}^{-1}$; IIRMS calculated for [M+Li] $\mathrm{C}_{20} \mathrm{H}_{3}, \mathrm{~N}_{2} \mathrm{O}, 4 \mathrm{SiF}: 489.2197$. Found: 489.2175 . Anal. Calc. $\mathrm{C}_{20} \mathrm{H}_{3} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}: \mathrm{C}, 64.71 ; \mathrm{H}, 6.47$; $\mathrm{N}, 5.80$. Found: C . 64.88; H, 6.56; N, 5.76.
(L)-5'-O-(i-butyldiphenylsilyl)-2', $3^{\prime}$-dideoxy-2' fluoro-5fluorouridine (24). mixture of anomers $\mathrm{R}_{f}$ (1:1 hexanes/ $\mathrm{ElOAc})=0.48 ; \mathrm{mp} 65-71^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $9.08(\mathrm{bs}, 0.4 \mathrm{H}), 9.00(\mathrm{bs}, 0.6 \mathrm{H}) 8.01(\mathrm{~d}, \mathrm{~J}=5.4 \mathrm{~Hz}, 0.6 \mathrm{H})$, $7.65(\mathrm{~m}, 4 \mathrm{H}), 7.42(\mathrm{~m}, 6.4 \mathrm{H}), 6.10(\mathrm{dd}, \mathrm{J}=20.2$ and 1.4 Hz , $(0.4 \mathrm{H}), 6.00(\mathrm{~d}, \mathrm{~J}=16.0 \mathrm{Itz}, 0.6 \mathrm{H}), 5.35(\mathrm{dd}, \mathrm{J}=52.4$ and 1.6 $\mathrm{II} \mathrm{c}, 0.4 \mathrm{H})$, ( $5.22, \mathrm{dd}, \mathrm{J}=51.2$ and $4 \mathrm{~Hz}, 0.6 \mathrm{H}$ ), 4.57. (m, $0.4 \mathrm{H}), 4.44(\mathrm{~m}, 0.6 \mathrm{H}), 4.22(\mathrm{dd}, \mathrm{J}=12.4$ and $2.0 \mathrm{~Hz}, 0.6 \mathrm{H})$, 3.91 (dd, J=11.2 and $2.9 \mathrm{~Hz}, 0.4 \mathrm{H}), 3.70(\mathrm{~m}, 1 \mathrm{H}), 2.45-2.00$ $(\mathrm{m}, 2 \mathrm{H}), 1.09(\mathrm{~s}, 5.4 \mathrm{H}), 1.07(\mathrm{~s}, 3.6 \mathrm{H}) ; 13 \mathrm{C}$ NMR ( 100 O $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 156.9(\mathrm{~d}, \mathrm{~J}=26.5 \mathrm{~Hz}), 148.8,148.8,140.3(\mathrm{~d}$, $\mathrm{J}=236.7 \mathrm{~Hz}$ ), 140.1 (dं, J=235.1 Hz), 135.6, 135.5, 135.4 , $132.9,132.7,132.4,132.3,130.2,130.1,129.9,127.9$, $127.8,125.1$ (d, J=34:9 Hz), 123.6 (d, J=34.2 Hz), 96.4 (d, $\mathrm{J}=182.9 \mathrm{~Hz}) 92.0(\mathrm{~d}, \mathrm{~J}=186.6 \mathrm{~Hz}), 90.2(\mathrm{~d}, \mathrm{~J}=36.0 \mathrm{~Hz})$ ), 86.9 (d, J=15.1. Hz), 81.7, 79.8, 64.8, 63.0, 33.2 ( $\mathrm{d}, \mathrm{J}=20.5 \mathrm{~Hz}$ ), 30.9 (d, J=20.4 Hz), 26.9, 26.8, 19.2; IR (thin film) 3191, 1719, $1113 \mathrm{~cm}^{-1}$; HRMS calculated for [M+Li] $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}_{2} \mathrm{Li}: 493.1946$. Found: 493.1952. Anal. Calc. $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}_{2}$ : C, $61.71 ; \mathrm{H}, 5.80 ; \mathrm{N}, 5.76$. Found: C, $61.73 ; \mathrm{H}, 5.83 ; \mathrm{N}, 5.77$.
$\alpha$-(L)-2', $3^{\prime}$-Dideoxy- $2^{\prime}$-fluoro-thymidine (26a). $\mathrm{R}_{f}(100 \%$ $\mathrm{E}(\mathrm{OAc})=0.25$; mp $147.149^{\circ} \mathrm{C} .{ }^{1} \mathrm{H} \operatorname{NMR}(360 \mathrm{MHz}$, $\left.\mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 7.45(\mathrm{~s}, 1 \mathrm{H}), 6.11(\mathrm{dd}, \mathrm{J}=19.4$ and $2.9 \mathrm{~Hz},(\mathrm{H})$, $5.30(\mathrm{~d}, \mathrm{~J}=53.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.58(\mathrm{mi}, 1 \mathrm{H}), 3.79(\mathrm{dd}, \mathrm{J}=12.2$ and $2.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.55(\mathrm{dd}, \mathrm{J}=12.2$ and $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.40-2.15(\mathrm{~m}$, $2 H 1), 1.87(\mathrm{~s}, 3 \mathrm{H}):{ }^{13} \mathrm{C}$ NMR (101 MH2, (D2.OD) d 166.6 ,
152.3, 138.6, $110.5,93.9$ ( $\mathrm{d}, \mathrm{J}=185.1 \mathrm{~Hz}$ ), 88.3 ( $\mathrm{d}, \mathrm{J}=15.1$ Hz ), 81.7, $64.4,34.5(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 12.6$; $\mathrm{IR}(\mathrm{Kl3r}) 3436$, 3166, 1727, 1667, 1362, $1186 \mathrm{~cm}^{-1}$; HRMS calculated for $\lceil\mathrm{M}+\mathrm{Li}\rceil \mathrm{C}_{10} \mathrm{H}_{1}, \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{FLi}: 251.1019$. Found: 251.11114. Anal Calc. $\mathrm{C}_{10} \mathrm{H}_{13} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}$ C, 49.18; $\mathrm{H}, 5.37$; $\mathrm{N}, 11.47$. Found: C , 49.32; H, 5.40; N, 11.29.
$\beta$-(L)-2', 3'-lideoxy-2'-hluoro-hymidine (26b). $R_{j}$ (106)\% $\mathrm{ElOAc})=0.38 \mathrm{mp} 186-188^{\circ} \mathrm{C} .{ }^{\mathrm{I}} \mathrm{H}$ NMR ( 300 MHz , $\mathrm{CD}_{3} \mathrm{OD}$ ) d $7.94(\mathrm{~s}, 1 \mathrm{H}), 5.93(\mathrm{~d}, \mathrm{~J}=17.6 \mathrm{H} \%, 1 \mathrm{II}), 5.20(\mathrm{~d}$, $\mathrm{J}=51.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.40(\mathrm{~m}, \mathrm{H}), 3.98(\mathrm{~d}, \mathrm{~J}=11.9 \mathrm{~Hz}, \mathrm{HI}), 3.18$ ( $\mathrm{d}, \mathrm{J}=13.0 \mathrm{H} \mathrm{\%}, 1 \mathrm{II}$ ), 2.37-2.10 (m, 2H), $1.83(\mathrm{~s}, .3 \mathrm{H}) ;{ }^{13} \mathrm{C}^{\circ}$ NMR ( $100 \mathrm{MII} \%,\left(\mathrm{D}_{3} \mathrm{OI}\right)$ d $16(6.7,152.3,1.88 .2,111.0,98.4$ ( $\mathrm{d}, \mathrm{J}=178.3 \mathrm{~Hz}$ ), $92.1(\mathrm{~d}, \mathrm{~J}=3 \mathrm{ll} .+\mathrm{Hz}), 83.1,62.4,32.5(\mathrm{~d}$, $\mathrm{J}=20.5 \mathrm{~Hz}), 12.6 ; \mathrm{IR}(\mathrm{KIJr}) 3478,3052,16 \mathrm{K4}, 1.313,1192$, $1105 \mathrm{~cm}^{-1}$ : Anal. Calc. $\mathrm{C}_{10} \mathrm{H}_{43} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}: \mathrm{C}, 49.18 ; 11,5.37 ; \mathrm{N}$, 11.47. Found: C, 49.29; 11, 5.44; N, 11.36.
$\alpha$-(L)-2',3'-dideoxy-2'-fluoro-5-fluorouridine (27a). Rf ( $100 \% \mathrm{EIOAC}$ ) $=\left(0.38\right.$; mp $15.5-157^{\circ} \mathrm{C}$.). ${ }^{1} \mathrm{H}$ NMR ( 40 ( $\left.\mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right)$ d $7.80(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.13(\mathrm{~d}, \mathrm{~J}=20.0 \mathrm{~Hz}$, $1 \mathrm{H}), 5.35(\mathrm{~d}, \mathrm{~J}=54.4 \mathrm{~Hz}, \mathrm{lH}), 4.63(\mathrm{~m}, 1 \mathrm{H}), 3.81(\mathrm{dd}, \mathrm{J}=11.9$ and $3.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.58 (dd, J=1.2.4 and $2.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.41-2.15(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 159.6 (d, J=150.7, 141.5 (d, J=230.6 Hz), $127.0(\mathrm{~d}, \mathrm{~J}=34.9 \mathrm{I} \%$ ), 93.9 ( $\mathrm{d}, \mathrm{J}=184.3 \mathrm{~Hz}$ ), 88.5 ( $\mathrm{d}, \mathrm{J}=15.1 \mathrm{~Hz}$ ), 81.9, 64.3, 34.3 (d, J=20.5 Hz); IR (K13r) 3401, 3098, 1651, 1458,1018
. $\mathrm{cm}^{-1}$; HRMS calculated for [M+Li] $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}$ : 2550769 . Found: 255.0771 . Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2}: \mathrm{C}$, 43.56; H, 4.06; N, 11.29. Found: C, 43.70; H, 4.17; N, 11.15 . B-(I)-2', 3'-dirdenxy-2'-lluoro-5-fluorouridine (27b). $\mathrm{R}_{f}$ ( $100 \%$ ElOAc) $=0.54 ; 153-156^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , $C D 30 D)$ d $8.46(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.94(\mathrm{~d}, \mathrm{~J}=1.62 \mathrm{~Hz}, 1 \mathrm{H})$, 5.25 (dd, J=51.6 and $4.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{~m}, 1 \mathrm{H}), 4.05$ (dd, $\mathrm{J}=12.8$ and $.2 .4 \mathrm{~Hz}, 1 \mathrm{H}), 3.72(\mathrm{dd}, \mathrm{J}=12.4$ and $2.4 \mathrm{~Hz}, 1 \mathrm{H})$, 2.34-2.09 (m, 2H); ${ }^{13}$ C NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 159.7 (d, J=25.8 Hz), 150.7, 141.8 (d, J $=230.6 \mathrm{~Hz}$ ), 126.3 (d, $\mathrm{J}=35.7 \mathrm{~Hz}$ ), 98.3 (d, $\mathrm{J}=184.6 \mathrm{~Hz}$ ), $91.9(\mathrm{~d} \mathrm{~J}=36.4 \mathrm{~Hz}$ ), 83.6 , 61.9, 31.9 ( $\mathrm{d} ; \mathfrak{j}=20.5 \mathrm{~Hz}$ ); IR (KBr) 3482, 3037, 1702, 1654, 1402, $1103 \mathrm{~cm}^{-1}$; HRMS calculated for [M+Li] $\mathrm{C}_{4} \mathrm{H}_{\mathrm{JU}} \mathrm{N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}$. 255.0769 . Found: 255.0764. Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}, \mathrm{F}_{2}: \mathrm{C}, 43.56 ; \mathrm{H}, 4.06 ; \mathrm{N}, 11.29$. Found: $\mathrm{C}, 43.59$; $\mathrm{H}, 4.06$; N, 11. 17.

Preparation of L-2'-Fluoro-2',3'-Unsaturated Nucloosides
$\wedge$ second facile synthesis of unsaturated 2'-lluoronucleosides has also now been accomplished and is described below. The synthesis involves reacting a prolected pyrimidine or purine base with key intermediate 309 in the presence of a Lewis acid, as described generally in Scheme 9 below. Representative compounds made according to this syumesis are described in Tables 5-6.

Scheme 9




60
Reagents; (i) .2-methoxypropene, DMF, p-tsoH (ii) $\mathrm{NalO}_{4}$, $\mathrm{H}_{2} \mathrm{O}$ (iii) ( EtO$)_{2} \mathrm{P}(\mathrm{O}) \mathrm{CHFCO}_{2} \mathrm{Et}, \mathrm{NaHMDS}, \mathrm{THF},-78^{\circ} \mathrm{C}$. (iv) $\mathrm{c}-\mathrm{HCl}, \mathrm{EtOH}$ (v) TBDMCl , imidazole, $\mathrm{CH} 2 \mathrm{Cl}_{2}$ (vi) DIBAI.-H Ch $\mathrm{Cl}_{2} \mathrm{Cl}_{2},-78^{\circ} \mathrm{C}$.(vii) $\mathrm{Ac}_{2} \mathrm{O}$, pyridine, $\mathrm{CH}_{2} \mathrm{Cl}_{2}$.

Scheme 9


301


$310 ; \mathrm{X}=\mathrm{OH}, \mathrm{Y}=\mathrm{H}$ 311: $\mathrm{X}=\mathrm{OH}, \mathrm{Y}=\mathrm{CH}_{3}$





317; $X=O 11, Y=11$
312; $\mathrm{X}=\mathrm{OH}, \mathrm{Y}=\mathrm{C}_{3} \mathrm{H}_{3}$


316: $X=$ Oll. $Y=H$ 318: $\mathrm{X}=$ Oil. $\mathrm{Y}=\mathrm{CH}_{3}$

$312: X=N H B z, Y=H$
$34_{i} X=\mathrm{NH}_{2}: Y=F$


313: $\mathrm{X}=\mathrm{NHBZ}, \mathrm{Y}=\mathrm{H}$
315; $X=\mathrm{NH}_{2}, Y=F$

$j$

so: $\mathrm{X}=\mathrm{NHBz}_{2}, \mathrm{Y}_{\boldsymbol{y}} \mathrm{H}$
322. $\mathrm{X}=\mathrm{NH}_{2}, \mathrm{Y}=\mathrm{H}$

324: $X=\mathrm{NH}_{3}, Y=F$

vi 3 3: $\mathrm{X}=$ NHBz, $\mathrm{Y}=\mathrm{H}$
233; $\mathrm{X}=\mathrm{NH}_{2}, \mathrm{Y}=\mathrm{H}$
325; $\mathrm{X}=\mathrm{NH}_{2}, \mathrm{Y}=\mathrm{F}$

Reagents; (i) siylated uracil, TMSOTf, DCE (ii) silylated thymine, IMSOTf, DCE (iii) silylated $\mathrm{N}^{+}-\mathrm{Bz}$-cytosinc, 45 $\cdot$ TMSOTf, $\mathrm{CH}_{3} \mathrm{Cn}$ (iv) 5 -F-cytosine, TMSOTf, $\mathrm{CH}_{3} \mathrm{CN}$ (v) - JBAF, $\mathrm{CH}_{3} \mathrm{CN}$ (vi) $\mathrm{NH}_{3} / \mathrm{MeOH}$

Scheme 9


309


1




340: $X=\mathrm{NHI}_{2}, \mathrm{Y}=\mathrm{F}$
342; $\mathrm{X}=\mathrm{Cl}, \mathrm{Y}=\mathrm{NH}_{2}$
344: $\mathrm{X}=\mathrm{OH}, \mathrm{Y}=\mathrm{NH}_{2}$

Reagents; (i) silylated 6-(l-purine, TMSOTI, I)CI: (ii) sily. lated 6-Cl-2-f-purine TMSOTf, DCE (iii) TISAF: $\mathrm{CH}_{3} \mathrm{C} \cdot \mathrm{N}$ 50 (iv) $\mathrm{NH}_{3} / \mathrm{I} \mathrm{ME}$ (v) $\mathrm{NH}_{3} / \mathrm{MeOH}, 90^{\circ} \mathrm{C}$. (vi) $\mathrm{HSCH}, \mathrm{CH}_{2} \mathrm{OH}$, $\mathrm{NaOMe}, \mathrm{McoH}$, reflux.

TABLE 2


US 6,348,587 B1

TABLE 2-continued

| No. | H-1*. | H-3' | H-4 | 11.5' | others |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $10^{6}$ | 6.77 (s) | 6.01 (s) | 4.81 (s) | 3.58 (s) | $\begin{aligned} & 11,5(\mathrm{~s},-\mathrm{NH}), 7.99(\mathrm{~d}, \mathrm{H}-6, \mathrm{~J}=\mathrm{S} \mathrm{~Hz}), 5.71(\mathrm{~d}, \mathrm{H}-5, \mathrm{~J}=\mathrm{SHL}), 5.13(\mathrm{t}, \mathrm{~J}=5.2 \\ & \mathrm{Hz}, \mathrm{OH}) \end{aligned}$ |
| $17^{\circ}$ | $\begin{aligned} & 6.77(1, \mathrm{~J}= \\ & 4.4 \mathrm{~Hz}) \end{aligned}$ | $\begin{aligned} & 6.02(\mathrm{~d}, \mathrm{~J}= \\ & 1.2 \mathrm{~Hz}) \end{aligned}$ | $\begin{aligned} & 5.02(\mathrm{pst}, \mathrm{~J}= \\ & 4,4.4 \mathrm{~Hz}) \end{aligned}$ | $3.50(\mathrm{~m})$ | $\begin{aligned} & 11,5(\mathrm{~s},-\mathrm{NH}), 7.56(\mathrm{~d}, \mathrm{H}-6, \mathrm{~J}=8 \mathrm{~Hz}), 5.70(\mathrm{~d}, \mathrm{H}-5, \mathrm{~J}=8 \mathrm{~Hz}): 4.94(\mathrm{t}, \mathrm{OH}, \mathrm{~J}= \\ & \dot{(H z}) \end{aligned}$ |
| $18^{\circ}$ | 6.77 (s) | 6.00 (s) | 4.80 (s) | 3.00 (s) | 1] $, 5(\mathrm{~s},-\mathrm{NH}), 7.89(\mathrm{~s}, \mathrm{H}-\mathrm{G}), 5.17(\mathrm{t}, \mathrm{J}=5.2 \mathrm{~Hz}, \mathrm{OH}), 1.76\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}-6\right)$ |
| $19^{\text {b }}$ | $\begin{aligned} & 6.78 \text { (ps t, } \mathrm{J}= \\ & 4,4.4 \mathrm{~Hz} \text { ) } \end{aligned}$ | 6.01 (s) | $5.05(t, J=4 \mathrm{~Hz})$ | 3.51 (m) | 11, $5(\mathrm{~s},-\mathrm{NH}), 7.37(\mathrm{~s}, \mathrm{H}-6), 4.94(\mathrm{t}, \mathrm{J} .06 \mathrm{~Hz}, \mathrm{OH}), 1.81$ (s, $\left.3 \mathrm{H}, \mathrm{CH}_{3}-6\right)$ |
| $20^{\circ}$ | 701 (s) | 5.71 (s) | 4,99 (s) | 3.88 (m) | 8.21 (d, J $=3 \mathrm{~Hz}, \mathrm{H} \cdot 6$ ), 7.71 (m, H-5, Ph-H) |
| $21^{\circ}$ | $\begin{aligned} & 7.16 \text { (ps t. J }= \\ & 3.6,4.4 \mathrm{~Hz}) \end{aligned}$ | 5.74 ( s ) , | $\begin{aligned} & 5.13(\mathrm{ps} 1, \mathrm{~J}= \\ & 3.2,4.8 \mathrm{~Hz}) \end{aligned}$ | 3.79 (m) | 7.92 ( $\mathrm{d}, \mathrm{J}=7.2 \mathrm{~Hz}, \mathrm{H}-6)^{\prime}, 7.57(\mathrm{~m}, \mathrm{H}-5, \mathrm{Pl}-\mathrm{H})$. |
| 220 | 685 (s) | $\begin{aligned} & 5.94(\mathrm{~d}, \mathrm{~J}= \\ & 1.2 \mathrm{Ha}) \end{aligned}$ | 4.76 (s) | 1.560 (s) | $\begin{aligned} & 7.86(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, \mathrm{H}-6), 7.36,7.32\left(2 \mathrm{~s}, \mathrm{NH}_{2}\right), 5.77(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, \mathrm{H}-5), 5.07 \\ & (\mathrm{t}, \mathrm{~J}=5.2 \mathrm{~Hz}, \mathrm{OH}) \end{aligned}$ |
| $23^{6}$ | $\begin{aligned} & 0.30(\mu \mathrm{si} . \mathrm{J}= \\ & 4.4,4.8 \mathrm{IL}) \end{aligned}$ | $\begin{aligned} & 5.94(\mathrm{~d}, \mathrm{~J}= \\ & 1.6 \mathrm{Hr})) \end{aligned}$ | 4.94 (m) | 319 (m) | $\begin{aligned} & 7.47(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, \mathrm{H}-6), 7.35,7.32\left(2 \mathrm{~s}, \mathrm{NH}_{3}\right) .5 .80(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz} \text { : } \\ & \mathrm{H} .5) \end{aligned}$ |

${ }^{2} \mathrm{CDCl}_{3}$.
${ }^{6}$ DMSO- ${ }^{6}$

TABLE 3.

| No. | H.1' | H-3' | H-4' | 11.5 | others |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $24^{2}$ |  |  |  |  |  |
| 25 |  |  |  |  |  |
| $20^{\circ}$ | $\begin{aligned} & 7.01(\mathrm{~s}), 0.93 \\ & (\mathrm{t}, \mathrm{~J}=4.4 \mathrm{H} 2) \end{aligned}$ | $\begin{aligned} & 5.85(1) \\ & 5.78(3) \end{aligned}$ | $\begin{aligned} & 5.18(p s 1, \mathrm{~s}=4 . \\ & 4.4121 .5 .0 .9(\mathrm{~s}) \end{aligned}$ | $\therefore \times 5$ ( 11 ) | $\begin{aligned} & \& .79 .8 .78(2 \mathrm{~s}, \mathrm{H}-8), 8.00,8.21(2 \mathrm{~s}, \mathrm{H}-2), 1.94\left(\mathrm{~s}, 5-\mathrm{CH}_{3}\right), 0.92,0.91 \\ & (2 \mathrm{~s}, \mathrm{Bu}), 0.111,0.105,0.097,0.095\left(4 \mathrm{~s}, 4 \times\left(\mathrm{H}_{3}\right)\right. \end{aligned}$ |
| $27^{2}$ | .6.8* (s) | 5.77 (i) | $5.12{ }^{51}$ | 3.85 (iII) | \$.00 (s, H. S $^{\prime}$, $0.91\left(\mathrm{~s},{ }^{\dagger} \mathrm{Bu}\right), 0.112,0.105\left(2 \mathrm{~s}, 2 \times \mathrm{CH}_{3}\right)$ |
| $23^{2}$ | 6.81 (111) | 5.84 (3) | $519(\mathrm{ml})$ | 3.31 (ii1) | 3.17 (s, H. 9 ), $\left.0.92\left(\mathrm{~s},{ }^{\top} \mathrm{Bu}\right), 0.11\right) 3,0.089\left(2 \mathrm{~s}, 2 \times \mathrm{CH}_{3}\right)$ |
| $29{ }^{2}$ |  |  |  |  |  |
| $30^{2}$ | 7.00 (n) | 5.86 (s) | 5.29 (m) | 3.87 (i1) | 8.78 (s, H-8), 8.22 ( $\mathrm{s}, \mathrm{H}-2)$ |
| $31^{2}$ | 6.81 (m) | $5.73(\mathrm{~J}, \mathrm{~J}=1.61 \mathrm{E})$ | 4.90 (d. $1=2.81 \mathrm{tr})$ | 3.55 (i11) | 3.19 (s, H +8 ), 0.91 (s, $\left.{ }^{\top} \mathrm{Bu}\right), 0.09,0.084\left(2 \mathrm{~s}, 2 \times \mathrm{CH}_{3}\right)$ |
| $32^{2}$ | 6.78 (m) | 5.75 (s) | 495 (mi) | $3 . \times 1$ (III) |  |
| $33^{2}$ | 6.76 (m) | $5.80 \text { ( } 1$ | $\begin{aligned} & 513(p \times 1.1= \\ & 44: 4.8 \mathrm{tze} \end{aligned}$ | 3. \% (in) | 7.84 (s, H-8), 0.91 (s, $\left.{ }^{\top} \mathrm{Bu}\right), 0.393,0.08\left(2 \mathrm{~s}, 2 \times \mathrm{CH}_{3}\right.$ |
| $34^{4}$ | $\begin{aligned} & 6.73 \text { (ps i. J }= \\ & 4.4: 4 . S \\|(z) \end{aligned}$ | 5.30 (s) | 5.09 (m) | $\therefore$ 代(13) | 7.84 (s, H-8), $5.12\left(\mathrm{~s}, \mathrm{NH}_{2}\right), 0.91$ (s, $\left.{ }^{\top} \mathrm{Bu}\right), 0.096,0.082\left(\mathrm{~s}, \mathrm{CH}_{3}\right)$ |
| $35^{\circ}$ | 6.90 (s) | 6.08 ins | 4.91 (s) | $3.1536)$ | 8.40 (s, H-8), 8.17 (s, H-2), 7.40 ( $\left.\mathrm{s}, \mathrm{NH}_{2}\right), 5.22(\mathrm{t}, \mathrm{J}=5.6 \mathrm{~Hz}, \mathrm{OH})$ |
| $30^{\circ}$ | $\begin{aligned} & 6.89(t, J= \\ & +H z) \end{aligned}$ | 6.06 (b) | $\begin{aligned} & 5.14(\mathrm{ps} t, \mathrm{~J}= \\ & 3.6,4 \mathrm{ll.}) \end{aligned}$ | 3.57 (III) | S.31 (s, H-8), $8.17(\mathrm{~s}, \mathrm{H}-2), 7.30\left(\mathrm{~s}, \mathrm{NH}_{2}\right), 4.97(\mathrm{t}, \mathrm{J}=6 \mathrm{~Hz}, \mathrm{OH})$ |
| $37^{6}$ | 6.94 (nt) | 6.15 (1, J = 1.6 ( Hz ) | 4.98 (s) | 3.6710 | 12.57 (br s, NH), 8.4 .3 ( $5, \mathrm{H}-8$ ), 8.17 (s, H-2), 5.17 (s, OH) |
| 38 | $\begin{aligned} & 6.87(\mathrm{ps} 1, \mathrm{~J}= \\ & 3.6,4.4 \mathrm{liz}) \end{aligned}$ | 6.06 (s) | $512(t, J=3,6 H \%)$ | 3.50 (111) | 8.26 (s, H-8), 8. 09 (s, H-2) |

${ }^{2} \mathrm{CDCl}_{3}$ :
${ }^{6}$ DMSO-d ${ }^{6}$

TABLE 4

| No. | H-1 | H. $3^{\prime}$ | H-4' | H. $5 \cdot$ | oithers |
| :---: | :---: | :---: | :---: | :---: | :---: |
| .39 ${ }^{\text {b }}$ | 6.30 (s) | $\begin{aligned} & 6.09(\mathrm{pst}, \mathrm{~J}= \\ & 1.2,1.6 \mathrm{~Hz}) \end{aligned}$ | $4.90(\mathrm{~s})$ | 3.62 (nt) | 8.3 $\mathrm{S}^{(\mathrm{s}, \mathrm{H}-8)}$, 7.99, $7.92\left(2 \mathrm{br} \mathrm{s}, \mathrm{NH}_{2}\right), 5.09(\mathrm{t}, \mathrm{J}=5.6 \mathrm{~Hz}, \mathrm{OH})$ |
| $40^{\circ}$ | 6.52 (m) | 6.07 ( $\mathrm{d}, \mathrm{J}=1.2 \mathrm{~Hz}$ ) | 5.12 (m) ${ }^{\circ}$ | 3.50 (mi) | $8.30(\mathrm{~s}, \mathrm{H} \cdot \mathrm{S}), 7.90\left(2 \mathrm{~s}, \mathrm{NH}_{3} \mathrm{j}\right.$ |
| $41^{\text {b }}$ | 6.76 (s) | 6.09 (s) | 4.91 (s) | 3.00 (s) | $8.38{ }^{(\mathrm{s}, \mathrm{H}-\mathrm{S})}$, $7.07\left(\mathrm{~s}, \mathrm{NH}_{2}\right), 5.10$ (s; OH) ${ }^{\circ} \cdots$ |
| $42^{6}$ | $6.72(t, j=4(12)$ | $6.06(\mathrm{t}, 1=1.2 \mathrm{~Hz})$ | $\begin{aligned} & 5.16 \text { (ps } 1 . J= \\ & 3.6,4+1 z) \end{aligned}$ | 3.60 (m) | 8.30 (s, H-8), $7.04\left(\mathrm{~s}, \mathrm{NH}_{2}\right), 4.98(\mathrm{i}, \mathrm{J}=6 \mathrm{~Hz}, \mathrm{OH})$ |
| $43^{\text {b }}$ | 6.60 (s) | 6.03 ( $\mathrm{d}, \mathrm{J}-1.2 \mathrm{~Hz}$ ) | 4.86 (s) | 3.59 (s) | 10.74 (brs, NH), 8.96 (s, H-8), 6.57 (s, $\mathrm{NH}_{2}$ ), $5.08(\mathrm{t}, \mathrm{J}=5.2 \mathrm{~Hz}, \mathrm{OH})$ |
| $44^{\text {b }}$ | 6.62 (m) | 6.01 (d, $\mathrm{J}=1.6 \mathrm{~Hz})$ | 5.08 (m) | 3.56 (m) | $7.82(\mathrm{~s}, \mathrm{H}-8), 6.57\left(\mathrm{~s}, \mathrm{NH}_{2}\right), 4.95(\mathrm{t}, \mathrm{J}=5.6 \mathrm{~Hz}, \mathrm{OH}) \quad$. |

${ }^{5}$ DMSO- ${ }^{\circ}$

TABLE 5

| no. | mp ${ }^{\text {c }}$ (. (solv) ${ }^{\text {a }}$ | $[\alpha]_{\mathrm{D}}, \mathrm{deg}$ | formula | anal. |
| :---: | :---: | :---: | :---: | :---: |
| 10 | syrup |  | $\mathrm{C}_{3} \mathrm{H}_{3} \mathrm{FN}_{3} \mathrm{O}_{1} \mathrm{Si}$ | $\bigcirc \cdot \mathrm{H}, \mathrm{N}$ |
| 11 | syrup |  | $\mathrm{Cin}_{3} \mathrm{H}_{3} \mathrm{FNO} \mathrm{F}_{4} \mathrm{Si}$ | $C, H, N$ |
| 12 | 144-1+6 ( A ) | -20.47 (c 0.30. $\mathrm{CHCl}_{3}$ ) | $\left.\mathrm{C}_{2 .} . \mathrm{H}_{28} \mathrm{FN}_{3}\right)_{4} \mathrm{Si}$ | C, H, N |
| 13 | 1.39-1+1 ( () | +157.68 (c.0.31, $\mathrm{CHCl}_{3}$ ) | $\mathrm{C}_{3} \mathrm{H}_{2} \mathrm{FN}_{3}(1) \mathrm{Si}$ | $\mathrm{C}, \mathrm{H}, \mathrm{N}$ |
| 14 | syrup |  |  | $\mathrm{C}, \mathrm{H}, \mathrm{N}$ |
| 15 | syrup |  |  | $\mathrm{C}, \mathrm{H}, \mathrm{N}$ |
| 16 | 101-162 (1) |  | $\mathrm{CuH}_{49} \mathrm{FN}_{2} \mathrm{O}, 0.3 \mathrm{H}_{2} \mathrm{O}$ | C. H, N |
| 17 | 1:6-1:7 1\%) | +1.36.55 (c0.14. MeOHi) |  | C. H , N |

TABI.E 5 -continued

| $n \mathrm{nc}$. | mp*' C.isoll ${ }^{\text {a }}$ | $[\alpha]_{\mathrm{D}:} \mathrm{Jcg}$ | formula | amal. |
| :---: | :---: | :---: | :---: | :---: |
| 14 | 149-15] (0) | -30.44 (c 0.81 MrOH ) |  | C. $\mathrm{H}, \mathrm{N}$ |
| 19 | 116-11s (E) | +132.43 (c $0 \cdot \square . \mathrm{McOH})$ |  | C. $\mathrm{H}, \mathrm{N}$ |
| 20 | 200-202-de. (C) | -54.3 (c) $0.3 \mathrm{di}\left(\mathrm{ClOCl}_{3}\right)$ | $\mathrm{C}_{\text {In }} \mathrm{IH}_{1}+\mathrm{FNa} \mathrm{N}_{4}$ | C. $\mathrm{H}, \mathrm{N}$ |
| 21 | 170-17? (C, |  | $\mathrm{C}_{1}, 1 \mathrm{IL}_{2}+\mathrm{NN}_{4}, 0.3110$ | C. H, N |
| 22 | 198-200 dei (B) | -21.31 (c $02 \mathrm{~S}, \mathrm{MeOH}$ ) | $\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{IN}^{\mathrm{N}, \mathrm{O},+\mathrm{H}_{2} \mathrm{O}}$ | C. $\mathrm{H}, \mathrm{N}$ |
| 2.3 | 120-121 (E) | +159.15 (c 0 $01 . \mathrm{McOH}$ ) | $\mathrm{Co}_{8} \mathrm{H}_{10} \mathrm{FN}, \mathrm{CO}_{1}$ | C, H, N |
| 24 | syrup |  |  | C. $\mathrm{H}, \mathrm{N}$ |
| 25 | syrup |  |  | C, $\mathrm{H}, \mathrm{N}$ |
| 26 | syrup |  | $\mathrm{C}_{1 n} \mathrm{H}_{2} \mathrm{FCO} \mathrm{Cl}_{4} \mathrm{O}_{2} \mathrm{Si}$ | C. H. N |
| 27 | foam | +9.80 ( $\left.0.30, \mathrm{CHCl}_{3}\right)$ |  | C. $\mathrm{H}, \mathrm{N}$ |
| 28 | syrup | +139.07 (c 0.18, $\mathrm{CHCl}_{3}$ ) | $\mathrm{C}_{10} \mathrm{H}_{5} \mathrm{~F}, \mathrm{ClN}, \mathrm{O}, \mathrm{Si}$ | C. $\mathrm{H}, \mathrm{N}$ |
| 29 |  |  |  | C.H.N |
| 30 | foam |  |  | C. H.N |
| 31 | 180-182 ( $A$ ) | +13.3.3 (c 0.54, $\mathrm{CHCl}_{3}$ ) | $\mathrm{C}_{15} \mathrm{HI}_{23} \mathrm{~F}_{2} \mathrm{~N}, \mathrm{O}$ ) Si 0 2acroon | C. H N |
| 32 | 129-130 (A) | +90.22 (c 0.23, $\mathrm{CHCl}_{3}$ ) | $\mathrm{C}_{15} \mathrm{H}_{3} \mathrm{HCON}_{5} \mathrm{O}_{5} \mathrm{Si}$ | C,H.N |
| 34 | 184-180 (A) | +110.53 (c0.13, $\mathrm{CHCl}_{3} \mathrm{l}$ |  | C.11. N |
| 34 | 128-130)(A) | +89.87 (c 0.15, $\mathrm{CHCl}_{3}$ ) | $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{FCON}_{5} \mathrm{O}, \mathrm{Si}$ | C. H.N |
| 35 | 188-189 (C) | -54.91 (c 0.17, MeOH) | $\mathrm{C}_{50} 11_{11}+\mathrm{N}_{5} \mathrm{O}, 10.3 \mathrm{H}, \mathrm{O}$ | c. $11, \mathrm{~N}$ |
| 311 | 169-171 (C) | +160.62 (c 0.19, MeOH) |  | C. H. N |
| 37 | 128-130 (E) | -50.21 (c 0.20, McOH) | $\mathrm{C}_{1}, 1 \mathrm{H}_{9} \mathrm{FN}, \mathrm{O}, 0.2 \mathrm{H}$ (0) | C. $\mathrm{H}, \mathrm{N}$ |
| 3 N | >200 dee (C) | +169.60) (c 0.20, MeOH | $\mathrm{C}_{14 \mathrm{H}} \mathrm{FN}, \mathrm{O}, \mathrm{OH} \mathrm{H}$ | C. H, N |
| 31 | 185-18s dec (B) | -56.15 (c 0.16. MeOH) | - | C. H, N |
| 4) | 180 dec ( $\mathrm{B}^{\text {( }}$ | +178.22 (c 0.10, MċOH) |  | $\mathrm{C}, \mathrm{H}, \mathrm{N}$ |
| 41 | 155-156 dec (B) | +10.64 ( c (1.17. McOH ) |  | $\mathrm{C}, \mathrm{H}, \mathrm{N}$ |
| 42 | 150-152 (131 | +142.49 ( $\mathrm{cos} 17 . \mathrm{MeOH}$ ) |  | C. $\mathrm{H}, \mathrm{N}$ |
| 4.3 | >200 dec (13) | +24.42 (c. $0.10 . \mathrm{DMF}$ ) |  | C. H, N |
| 4.1 | >210.dec ( ${ }^{\text {( }}$ ) | +58.68 ( c 0.10 , DMF) |  | C. $\mathrm{H}, \mathrm{N}$ |

"Solvents;
A: ElOActhexanes.
$\mathrm{B}: \mathrm{CH}_{2} \mathrm{Cl}_{2}-\mathrm{MeOH}$,
C: CHCl - McOll ,
D: THF-cyclohexine
E: lyophilyzed

Previously, the synthesis of 2 ', 3 '-unsaturated 1.)-nucleosides has been aceomplished via climination reaction starting from readily avaitable nucleoside amalug, which involved a lengthy moditication for individual moleosides Several groups reported D-2'-fluoro-2', 3'-unsaturated pyrimidine uucleosides by the elimination of suitable 2'-fluorinated nucleoside analogs (Martin, J. A., et al., J Med. Chem. 1990, 33, 2137-2145; Stezycki, R. Z., ct al., I. Med. Chi'm. 1990, 33, 2150-2157). This strategy for the synthesis of I.Fd4N, however, is accompanied by additional difficulties in the preparation of l.-nucleosides as the starting material. There are few examples of the synthesis of $2^{\prime}, 3^{\prime}$. unsaturated purine nucleosides by direct condensation due to the lability of the 2,3-unsaturated sugar numiety under the coupling comblitions in the presence of Lewis acid, excepr one case of the pyrimidine analog using a thiophenyl intermediate (Aldel-Medied, A. W.-S., el al., Symintesis 1991 , 313-317; Sujino, K., cl al., Tetrahedron, Lev1. 1996, 37, 6133-6136). In contrast to the 2,3-unsaturated sugar moicty, the 2-Huoro-2,3-unsaturated sugar, which bears enhaneed stability of glycosyl bond during the condensation with a heterocycle, was expected to lecome more suitable for the direct coupling reaction. Thus, (R)-2-Huorobutcoulide 506 , as a precusor for the key incermediate 508, wats chosen, which was prepared from L-glyceraldehyde acctonide 501

Starting from L-glyceraldeliyde acetonide, a mixture of (E) $-502 /(\mathrm{Z})-2$ (9:1 by ${ }^{1} \mathrm{H}$ NMR) was oblained via the

Homer-Emmons reaction in the presence of triethy I (x-fluorophosphonoacetate and sodium bis (trimethylsilyl) amide in THF (Thenappan, A., et al., J. Org. Chem., 1990, 55, 4639-4642; Morikawa, T., et al., Chem. Pharm. Bull. 1992, 40, 3189-3193; Patrick, T. B., et al., J. Org. Chem. $1994,59,1210-1212)$. Due to the difticulties in separating (L) $-502 /(Z)-502$ isomers, the mixtures were used in the following cyclization reaction under acidic condition to give the desired lactone 503 and uncyclized diol 504. The resulting mixture was converted to the silyl lactone 506 was subjected to reduction with DIBAL-H in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ at $78^{\circ} \mathrm{C}$. 10 give the lactol 507. The lactol 507 was treated with acetic anhydride to yield key intermediate 508 , which was condensed with silylated 6-chloropurine under Vorburggen conditions to aftord anomeric mixtures 509. Treatment of 509 with TBAF: in THF gave free nucleosides 510 and 511 , which was readily separated by silica gel column chromalography. Adenine analogs 512 and 513 were obtained by the treatement of compound 510 and 511 with mercaptoethanol and NaOMe a steel bomb at $90^{\circ} \mathrm{C}$., respectively. Ireatment of compounds' 510 and 511 with mercaptoethanol and NaOMe aftiorded the inosine analogs 514 and 515 , respectively. The sterochemical assignment of these compounds was based on th NOESY spectroscopy (cross peak between H-1' and H-4' in B-isomer 512).


Reagents: (i) ( EtO$)_{2} \mathrm{P}(\mathrm{O}) \mathrm{CHFCO}_{2} \mathrm{Et},\left[\left(\mathrm{CH}_{3}\right)_{3} \mathrm{Si}\right]_{2} \mathrm{NNa}$, $\mathrm{THF},-78^{\circ} \mathrm{C}$. (ii) $\mathrm{HCl} / \mathrm{EtOH}$ (iii) TBDMS Cl , imidazole, $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (iv) I M DIBAL.-H in $\mathrm{C}_{2} \mathrm{H}_{2} \mathrm{Cl}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2},-78^{\circ} \mathrm{C}$. (v) $\mathrm{Ac}_{2} \mathrm{O}$, pyr., $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (vi) silylated $6-\mathrm{Cl}$-purine, TMSOTf , DCE (vii) TBAF, $\mathrm{CH}_{3} \mathrm{CN}$ (viii) $\mathrm{NH}_{3} / \mathrm{MeOH}, 90^{\circ}: \mathrm{C}$. (ix) $\mathrm{HS}\left(\mathrm{CH}_{2} \mathrm{OH}, \mathrm{Na}(\mathrm{Md} / \mathrm{MeOH}\right.$, reflux


TABIE 7 -continued •

|  Fluor-diddenine and llspoxamhine against HIV-1 in PBM |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  | Cyoloxicit |  |  |
| Compound No. |  | $\begin{gathered} \mathrm{EC}_{\mathrm{Cim}_{\mu}}(1 \mathrm{IIM}) \\ \left(I^{\prime} B M M\right. \\ \text { Cells) } \end{gathered} .$ | PMC. <br> Cells <br> $10_{50}$ (11M) | $\begin{gathered} \text { Vero } \\ \text { Cells } \\ \mathrm{IC}_{510}(\mathrm{M} / \mathrm{M}) \end{gathered}$ | $\begin{gathered} \text { CEM } \\ \text { Cells } \\ \Gamma_{50}(\text { (11) }) \end{gathered}$ |
| 336 (a) | 47.0 | 313 | - 100 | \$100. | 2100 |
| 337 ( $\beta$ ) | $>100$ | $>100$ | >100 | $>100^{\circ}$ | >100 |
| 338 (a) | $>100$ | $>100$ | $>100$ |  | $\cdot>100$ |
| AZT | 0.004 | 1).04 | >100 | 39.0 | 14.3 |

Experimental section
Melting points were deternined on a Mel-teinp II laboratory device and are uncorrected. Nuclear magnetic res̃onance spectra were recorded on a Bruker 250 and AMX400 400 MHz spectrometers with tetramethylsilane as the internal reference; chemical shifts ( $\delta$ ) are reported in parts per million (ppm), and the signals are described as s (singlet), d (doublet), t (triplet), q (yuartet), br s (broad singlet), chd (doublet of doublet), and $m$ (multiplet). UV spectra were obtained on a beckman IUU 650 spectrophoroncter. Optical rotations were nleasured on a Jasco DIP-370 Digital Pola rimeter. Mass spectra were measured on a Micromass Inc. Autospec High Resolution double focussing secior (EBE) MS spectrometers. Infrared spectra were recorded on Nicolet 510 FF -IR spectrometer. Elemental analyses were performed by Atlantic Microlab; Inc., Norcross, Ga. All reactions were monitored using thin layer chromatography on Analtech, 200 mm silica $\mathrm{gel}^{\mathrm{Gl}} \mathrm{Gl}$ plates. Dry $1,2-$ dichloroethane, dichloromethane, and acetonitrile were obtained by distillation from ('aH2 prior to use. Dry THF was obtained by distillation from Na and ben\%ophẹnone when the solution became purple.

L -(S)-Glyceraldehyde acermide (302). A solution of L-gulonic- - -lactone ( 17.5 g , 0.98 mol ) in IJMF ( 1 L ) was. cooled to $0^{\circ} \mathrm{C}$. and p-oluenesulfonic acid ( $1.1 \mathrm{~g}, 5.65$ mmol ) was added portionwise with stirring. To the resulting solution, 2 -methoxypropene ( $87.7 \mathrm{~g}, 0.92 \mathrm{~mol}$ ) was added dropwise through a dropping funnel at $0^{\circ} \mathrm{C}$. Tlk reaction mixture was warmed up to room temperature and furthe stirred for 24 h . Alter the completion of the reaction, sodium carbonate ( 124 g ) was added ind the resulting suspension was vigorously stirred for 3 hours. It is then liltered ove glass filter and the filtrate is evaporated under vacuum. Ti, the yellow residue, toluene ( 170 mL ) is added whereupon crystatization occurred. The whid was fillerad by suction, washed with hexanes, ethanol ( $\%: 1 ; 1 \mathrm{~L}$ ), and dried to give yellowish sold 301 J ( $99.1 \mathrm{~g}, 19 \%$ ).

To a stirted suspension in $5,6-0$-is npropylidenc-1-gulono- 1,4 - actone ( $70.11 \mathrm{~g}, 11.12 \mathrm{~mol}$ ) in waler ( 270 ml. ), sodium mectiperisclate ( $123 \mathrm{~g}, 0.58$ mol) was anded portion wise at $0^{\circ} \mathrm{C}$. over 30 mom mainataning pF1 5.5 (atjusted by addition of 2 N NaOH ). The suspension was stirred at ronom lemperature for 2 hours, then salurated with sodiun chloride and filtered. The pH of the filtrate was adjusted to 6.5-7.11 and extracted with dichloromethane ( 5 tinies 200 ml. .) and ethyl acetate ( 5 times $3(6) \mathrm{mL}$ ). The combined organic layer were dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure ( $<20^{\circ} \mathrm{C}$.). And then the resulting residue was distilled to give $302 .(23.2 \mathrm{~g}, 69 \%$ ) as a colorless oil; b.p. $49-51^{\circ}$ C./16 Torr. $[\alpha]_{n} 25-66.4$ (c 6.3, benzenc).
(E)/(Z)-Ethyl-3-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2. Huoroacrylate (E. 303 and Z-303). A. sollution if triethy

2-fluorophosphonoacetate ( $39.2 \mathrm{~g}, 162 \mathrm{mmol}$ ) in THF ( 70 mL ) was cooled to $-78^{\circ} \mathrm{C}$ and a solution of sodium bis(trimethylsilyl)amide ( 1.0 M solution in THF, 162 mL , 162 mmol) was added dropwise. The mixture was kept for 30 min ai $-78^{\circ}(.2$, then a solution of $303(19.14 \mathrm{~g}, 147$ mamol) in THF ( 70 mL ) was added. After being stirred for 1 h at $-78^{\circ} \mathrm{C}$., the reaction mixture was treated with aqueous $\mathrm{NII}_{4} \mathrm{Cl}$ and extracted with ether. The ether phase was washed with saturated NaCl , dried over $\mathrm{MgSO}_{4}$, filtered and evaporated. The residue was chromatographed on silica gel to give E-303 and Z-303 ( $9: 1$ by ${ }^{1} \mathrm{H}$ NMR) as a pale yellowish oil ( $34.6 \mathrm{~g}, 97.9 \%$ ). ${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right) \delta 1.34,1.36$ $\left(2 \mathrm{t}, \mathrm{J}=8 \mathrm{~Hz},-\mathrm{CH}_{2} \mathrm{Cl}_{3}\right), 1.40,1.45\left(2 \mathrm{~s},-\mathrm{CH}_{3}\right), 3.69(\mathrm{~m}$, $\left.\mathrm{H}_{n}-5\right), 4.28\left(\mathrm{~m}, \mathrm{H}_{6}-5,-\mathrm{CH}_{2} \mathrm{CH}_{3}\right), 5.02(\mathrm{~m}, \mathrm{H}-4), 5.40(\mathrm{~m}$, $5 \mathrm{H}-4), 6.02$ (dd, $\mathrm{J}=8,20 \mathrm{~Hz}, \mathrm{H}-3$ ), 6.18 (dd, $\mathrm{J}=8,32 \mathrm{~Hz}, \mathrm{H}-3$ ).
(R)-(+)-4-[(tert-Butyldimethylsilyloxy)methyl]-2-fluoro-2-buten-4-olide (307). A solution of E-303 and Z-303 (19.62 $\mathrm{g}, 89.89 \mathrm{mmol}$ ) in 110 mL of anhydrous $\mathrm{EIOH}^{2}$ was trealed with 30 mL of conc. HCl and stirred at room temperature for 2 hr . The solvent was renoved in vacuo and the residue was coevaporated with Toluene ( $3^{*} 300 \mathrm{~mL}$ ) to give the lactone 304 and uncyclized ester 305. The resulting yellowish syrup was used for next reaction without further purification. - Butyldimethylsilyl chloride ( $27.1 \mathrm{~g}, 180 \mathrm{mmol}$ ) was added 5 to a mixture of 304,305 and Imidazole $(12.3 \mathrm{~g}, 180 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 250 mL ) and the reaction mixture was stirred for 4 h at room temperature. The resulting mixture was washed with water, dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentra!ed to dryness. The residue was isolated by silica gel column chromatography using $4 \%$ EtOAc-hexanes as an eluent to give 307 ( $28.0 \mathrm{~g}, 70.2 \%$ from compound 302 ) as a while crystalline solid. $\mathrm{mp} 48-50^{\circ} \mathrm{C}$.; $[\alpha]^{-8}{ }_{\mathrm{D}}+105.3$ (c 1.60 , $\left.\mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right) 80.07,0.08\left(2 \mathrm{~s}, 2 \times \mathrm{CH}_{3}\right), 0.88(\mathrm{~s}$, ${ }^{\prime} \mathrm{Bu}$ ), 3.88 (m, 2H, H-5), 5.01 (m, 1H, H-4), 6.73 (ps I, LH, $5 \mathrm{~J}=4 \mathrm{~Hz}$ ); Anal. Calcd for $\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{FO}_{3} \mathrm{Si}$ : C., 53.63; H, 7.77. Found: C, 53.70; H, 7.75.

1-Acelyl-4-[(teri-butyldimethylsilyloxy)methyl]-2. Huoro-2-buten-4-olide (309). Lactone 307 ( $20.58 \mathrm{~g}, 83.54$ mimol) was dissolved in 200 mL of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ under nitrogen amosphere, then the mixture was cooled $10^{-}-78^{\circ} \mathrm{C}$. and 1.0 M solution. of DIBAL-II in $\mathrm{Cl}_{2} \mathrm{Cl}_{2}$ ( 125 mL ) was added. The resulting mixiure was stirred for 2 hours at $-78^{\circ} \mathrm{C}$. The cold mixture was treated with dilute nitric acid, washed with water, and dried ( $\mathrm{Na}_{2} \mathrm{SO}_{4}$ ). Evaporation of the solvent gave 45 anomers of 308 as a pale yellow oil ( 16.6 g , crude yield $80 \%$ ), which was used for the next step without further purification.
$\mathrm{Ac}_{2} \mathrm{O}(25 \mathrm{~mL}, 0.27 \mathrm{~mol})$ was added to a solution of 308 and pyridine ( $22 \mathrm{~mL}, 0.27 \mathrm{~mol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(200 \mathrm{~mL}\right.$ ) al $0^{\circ}$ © C. and the resulting mixture was stirred for 16 hours. The raction mixture was washed with dilute HCl , saturater NaHCO 3 solution, and brine. The combined organic layer was dried, filtered, and concentrated to dryness. The residue was column chromatographed ( $6.5 \%$ EiOAc/hexanes) to 5 give $309(12.6 \mathrm{~g}, 65 \%)$ ats a colorless oil.
General Procedure for Condensation of Acctate 309 with Pyrimidine Bases.

A mixture of uracil ( $420 \mathrm{mg}, 3.75 \mathrm{mmol}$ ), hexamethyldisilazane ( 15 mL ) and ammonium sulfate ( 20 mg ) was 60 refluxed for 3 hours under nitrogen. 'lhe clear solution ,blained ivas concentrated to dryness in vacuo. TMSOTf $(0.7 \mathrm{~mL}, 3.14 \mathrm{mmol})$ were added to the solution of sugar 309 ( $728 \mathrm{mg}, 2.50 \mathrm{mmol}$ ) and the silylated base in dry DCE ( 20 mL ) at $0^{\circ} \mathrm{C}$. The reaction mixture was stirred for 2 hours 65 under nitrogen, poured into a cooled sat. $\mathrm{NaHCO}_{3}$ solution ( 30 mL ) aid stirred for 15 min . The resulting mixture was washed, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, fillured, and concentrated in vacuo.

The crude product was purifiel by column chromarography ( $3 \% \mathrm{McOH} / \mathrm{CHCl}_{3}$ ) to give $310(0.960 \mathrm{~g}, 2.73 \mathrm{mmol}, 73 \%$ ) as an inseparable anomeric mixture, which was used in the next slep without separation.

1-[5-O-(tert-Butyidimethylsilyl)-2,3-didenxy-2-1luoro-L: gyccro-pent-2-cnofuranosyl Juracil (310).

UV $\left(\mathrm{CHICl}_{3}\right) \lambda_{\text {max }} 257.5 \mathrm{nmı}$ : Anal. $\left(\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{FN}_{2} \mathrm{O}_{4} \mathrm{Si}\right) \mathrm{C}$, H, N.

1-[5-O-(tert-Butyidimethylsilyl)-2,3-dideoxy-2-fluoro-L-gycero-pent-2-enofuranosyl] thymine (311). Silylated thymine ( $242 \mathrm{mg}, 1.92 \mathrm{mmol}$ ), 307 ( $500 \mathrm{mg}, 1.72 \mathrm{mmol}$ ), aul TMSOTf ( 0.5 ml ., 2.25 mmol ) were reacted tor 2 h to give a mixture of 311 , which was purified by silica gel column
 meric mixture ( $0.392 \mathrm{~g}, 1.10 \mathrm{mmol}, 64 \%$ ) UV $\left.\left(\mathrm{CHICl}_{3}\right)\right\rangle_{\text {.,.mi }}$ 262.0 nm . Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{2}, \mathrm{l}: \mathrm{N}_{2} \mathrm{O}_{4} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$
$\mathrm{N}^{6}$ - Benzoyl-1-[5-()-(ieri-butyllimenthtsilyl)-? 3. 3 . dideoxy-2-lluoru-(a,b)-L-glyacro-pent-2-enotioranosyl] cytosine ( 312 and 313 ). Silylated $N^{6}$-benzayl cylusine ( 790 mg, 3.67 mmol ), 307 ( $470 \mathrm{mg}, 1.62 \mathrm{mmol}$ ), and $\mathrm{TMSO}^{\prime} \mathrm{Tl}$ ( $0.5 \mathrm{~mL}, 2.25 \mathrm{monol}$ ) were reacted for 2 h ougive mixtures of 312 and 313 , which were puritied by silica be! column (. $30 \%$ EIOAc hexane) to alloril $\beta$ anomer 31 ? ( $0.3 .4 \mathrm{y}, 0.76$ . nimọl, $47.1 \%$ ) as a while solys ind $\alpha$ anomer 31.3 chroma. lugraphy ( $0.2 .3 \mathrm{~g}, 0.52$ mol, $41.8 \%$ ) as a white wilid. 312
 N.; 513 : UV $\left.\left(\mathrm{CH}^{\prime} 1_{3}\right)\right\rangle_{\text {max }} 260.5$ nm. Allal $\left(\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{FN}_{3}()_{4} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

5-Fluoro-1-[5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-j Auoro-(asb-1-glycero-pent-2-cnoturanosyl]cylosile (314 and 31.5). Silylated 5 -fluoro-cylosine ( $300 \mathrm{mg}, 2.32 \mathrm{mmol}$ ), 309 ( $360 \mathrm{mg}, 1.24 \mathrm{mmol}$ ), and TMSOTl ( $0.4 \mathrm{~mL}, 1.86$ mmol) were reacted for 2 h to give a mixture of $31+$ and 315 , which was purified by silica gel column chrontatugraphy ( $3 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ) to atford $\beta$ anomer 314 as a white solid $(168 \mathrm{mg}, 37.8 \%)$ and a anomer $315(121 \mathrm{mg}, 27.1 \%)$ as a white solid. 314: UV. (MeOH) $\lambda_{\text {max }} 281.5 \mathrm{~nm} ; 315:$ UV (MeOH) $\lambda_{\text {max }} 281.5 \mathrm{~nm}$.
 furanosyl)uracil (316 and 317). Telra-n-butylammoniunn fluoride ( $0.6 \mathrm{~mL}, 0.6 \mathrm{mmol}$ ) was added to a mixture of 310 ( $177 \mathrm{mg}, 0.52 \mathrm{mmol}$ ) in Till: $(15 \mathrm{~mL}$ ) and the reaction mixture was stirred at room temperalure for 15 min . The solvent was removed and the residue was purified by silic: gel column chromatography ( $2 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ ) to give $\beta$ anomer $316(52.8 \mathrm{mg},(1.23 \mathrm{mmol}, 44.5 \%)$ and $\alpha$ anomer 317
 nm ( $\mu \mathrm{H} 7$ ); Anal. ( $\left.\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{FN}_{2} \mathrm{O}_{4}, 0.3 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N} .317$ : UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 261.0 \mathrm{~nm}(\mathrm{pH} 7)$; Anal. $\left(\mathrm{C}_{9} \mathrm{H}_{6} \mathrm{I} \mathrm{N}_{2} \mathrm{O}_{1} .0 .2 \mathrm{H}_{2} \mathrm{O}\right)$ ( $, ~ H, N$.

1-(2,3-Dideoxy-2-1luoro-( $\alpha, \beta$ )-1.-gycero-pent-2-enofuranosyl)thymine ( 318 and 319 ). Tetra-n-butylammonium thuoride ( $0.8 \mathrm{~mL}, 0.8 \mathrm{mmol}$ ) was added to a mixture of 311 ( $240 \mathrm{mg}, 0.67 \mathrm{mmol}$ ) in TIII $(10 \mathrm{~mL})$ at $1^{\circ}(\therefore$ and the reaction mixure was stitred at room temperature at ri tor 1.5 min. The solvent was removed and the residuc was purified by silica sel column chomatography ( $40 \% \mathrm{THF}$ cyclohexane) to give $\beta$ anomer $318(66.5 \mathrm{mg}, 0.28 \mathrm{minol}$, $41 \%$ ) and a anomer $319(52.8 \mathrm{mg}, 0.23 \mathrm{mmol}, 26 \%)$.

318: UV ( $\mathrm{H}_{2} \mathrm{O}$ ) ) Max 265.5 nm ( pH 7 ); Anal. $\left(\dot{C}_{10} \mathrm{IH}_{1}, \mathrm{JN},()_{4},\left(1,4 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}, 319 . \mathrm{UV}\left(\mathrm{H}_{2}(1)\right)_{\text {, min }} 266.0\right.$

$N^{6}$-Benzoyl-1-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2enoturanosyl)cytosine (320). Tetra-n-butylammonium fluoride ( 1 M in THF ) ( $1 \mathrm{~mL}, 1 \mathrm{mmol}$ ) was added to a solution of the $\beta$ anomer 312 ( $280 \mathrm{mg}, 0.63 \mathrm{mmol}$ ) in THF ( 10 mL ) and the reaction was allowed to stir at room temperature for I h. The reaction mixture was concentrated under the reduced pressure and the residue was purified by fiash silica gel column using $2.5 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ to give 320 ( 218 mg ,

## $0.66 \mathrm{mmol}, 75 \%$ ) as a white solid.

UV (MenH) $\lambda_{\text {max }} 260.5 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{1 \downarrow} \mathrm{FN}_{3} \mathrm{O}_{4}\right) \mathrm{C}, \mathrm{H}$, N.
$\mathrm{N}^{\text {o }}$-Benzoyl-1-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-pent-2enofuranosyl)cylosine (325). Tetra-n-butylammonium fluo- ride ( 1 M in THF) was added to a solution of the $\beta$ anomer 315 in acelonitrile and the reaction was allowed io stir at

US 6,348,587 B1
rewom temperature for 1 ll . Thi reaction muxture was concontrated under the reduced plessure and the resulue was purified by fiash silica gel column using $12 \%$ Mcoll/(II( 1 , to give 325

General procedure for condensation of acetalc 309 with purine bases. A mixture of 6 -chloropurine ( $1.20 \mathrm{~g}, 7.75$ monol), hexamethyldisilazane ( $\mathbf{2 5} \mathrm{mL}$ ) and ammonium sulfate (catalytic amount) was refluxed for 4 h under nitrogen. The clear solution was obtained was concentrated in vacuo and the residue was dissolved in dry $D C E(10 \mathrm{~mL})$ and reactecl will a Isolution of $307(1.50 \mathrm{~g}, 5.17 \mathrm{mmol})$ in DCE ( 40 mL ) and trimethylsilyl triflate ( $1.5 \mathrm{~mL} ., 7.75 \mathrm{mmol}$ ) al room lemperalure. After stirring the mixture for 1 h al room temperature under nitrogen, the reaction. solution was then poured into an ice cold saturated $\mathrm{NaHCO}_{3}$ solution ( 20 mL ) and stirred for 15 min . The organic layer was washed with water and brine, and dried ovar $\mathrm{MgSO}_{4}$. The solvents were removed under reduced pressure and the residue was separated by silica gel column chromatography using $12.5 \%$. ElOAc/hexanes to give anomeric mixture 326 ( 1.25 g . $62.9 \%$ ) as a syrup.

6-Chloru-9-[5-O-(tert-butyidimethylsilyi)-2,3-dideoxy-2. fluoro-1-gyecro-pent-2-cinofuranosyl]purine (326)

326: UV (McOll) $\lambda_{\text {tha. }} 265.0 \mathrm{~nm}$, Anal $\left(\mathrm{C}_{16} \mathrm{H}_{2} \mathrm{CIF} \mathrm{N}_{1} \mathrm{O}_{2} \mathrm{Si}\right) \mathrm{C}, \mathrm{II}, \mathrm{N}$.

6-Chloro-2-fluoro-9-5-0-(lerr-butyldimelliylsilyl)-2,3. dideoxy-2-Huoro-( $\alpha, \beta$ )-L Leyecro-pent-2-enofiluranosyl] purine ( 327 and 328 ). A mixture of silylated 2 -fluoro-6chloropurine [prepared from $1.170 \mathrm{~g}(6.78 \mathrm{mmol})$ of 2 -fluoro-6-chloropurine and dry DCE( +0 ml .) was stirred for 16 h at room temperature. After work-up similar to that of 326 , purificaton ly silica gel column chromatography ( $12 \%$ EiOAc/hexancs) gave 0 anonicr 327 ( $685 \mathrm{mg}, 1.70$ minol. $30.0 \%$ ) as a while foam and a anomer $328(502 \mathrm{mg}, 1.25$ nımol, $22.1 \%$ as an yellowish syrup. 327 : $\mathrm{UV}(\mathrm{McOH})$ ).,.,mas 268.5 nm . Anal. ( $\mathrm{C}_{16} \mathrm{H}_{2}, \mathrm{~F}_{2} \mathrm{Cl} \mathrm{N}_{4} \mathrm{O}_{2} \mathrm{Si}$ ) C, $\mathrm{H}, \mathrm{N} ., 328$ : UV ( MeOH ) $)_{\text {ma }}, 269.0 \mathrm{mn}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{-1} \mathrm{~F}_{2}\left(\mathrm{Cl} \mathrm{N}_{4} \mathrm{O}, \mathrm{Si}\right) \mathrm{C}, \mathrm{H}\right.$, N.

6-Chloro-9-(2,3-dideoxy-2-fluoro-( $\alpha, \beta$ )-L-gycero-pent. 2 -enofuranosyl)purine ( 329 and 330). A solution of 326 (1.2 $\mathrm{g}, 3.12$ nunol) in diry $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL})$ yas treated with TBAF ( 1 M solution in T1YF) ( $3.2 \mathrm{~mL}, 3.2$ minol) and stirred for 1 h . Aller evaporation of solvent, the diryness was purified by column chromatography ( $3 \% \mathrm{Me}\left(\mathrm{OH} / \mathrm{CHCl}_{3}\right.$ ) to obtain $\beta$ anomer 329 ( $296 \mathrm{mg}, 35 \%$ ) as a white solid and as anomer $3.30(380 \mathrm{mg}, 45 \%)$ as a foan.

329: UV (MeOH) $\lambda_{\text {ma.. }} 265.1 \mathrm{~nm}$.; 330: UV (McOH) $\lambda_{\text {man }}$ 265.0 nm ( 322 ).

6-Amino-2-fluoro-9-[5-O-(tert-butyidinethyilsilyl)-2,3. dideoxy-2-fluoro- $\beta$-l-gycero-pent-2-enofuranosyl]purine (331) and 6-Chloro-2-amino-9-[-5-6)-(心ゃ!. butyidimethylsilyl)-2,3-didedny-2-fluoro- 3 -L-gycero-pent2 -enofuranosyl]purine (332) Dry ammonia was bubbled into a stirred solution of $327(420 \mathrm{mg}, 1.04 \mathrm{mmol})$ in dry DME: ( 35 mL ) at room temperature overnight. The salts were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by silica' gel column chromatography ( $25 \%$ EIOAc/hexanes) to give two compounds, 331 ( $114 \mathrm{ng}, 0.30 \mathrm{mmol}$ ) as a white solid and 332 ( $164 \mathrm{mg}, 0.41 \mathrm{mmul}$ ) as a white solid.

331:UV (MeOH) $\lambda_{m a .4} 268.5 \mathrm{~nm}$. Anal. 6 ( $\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~F}_{2} \mathrm{~N}_{5} \mathrm{O}_{2} \mathrm{Si0}$.2Acetone) $\mathrm{C}, \mathrm{H}, \mathrm{N}, 332: \mathrm{UV}$ (MeOH) $\lambda_{\text {max }} 307.5$ nm. Anal. (C) $\left.C_{10} \mathrm{H}_{23} \mathrm{FN}_{5} \mathrm{O}_{2} \mathrm{CliSi}\right) \mathrm{C}, \mathrm{II}, \mathrm{N}, \mathrm{Cl}$.

## 54

6-Amino-2-fluoro-9-[5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fuoro-a-L-gycero-pent-2-enofuranosyl]purine (333) and 6-Chloro-2-amino-9-[-5-0-(tert-butyldimethylsilyl)-2,3-dideoxy-2-lluoro- $\alpha$-L-gycero-pent-2-cinofuranosyl]purine (334). Dry ammonia was bubbled into a stirred solution of $333(420 \mathrm{mg}, 1.04 \mathrm{mmol})$ in dry DME ( 35 mL ) at room temperature overnight. The salts were remowed by filtration and the filtrate was evaporated 10 under reduced pressure. The residue was purified by silica gcl column chromatography ( $25 \%$ EIOAc/hexanes) to give iwo compounds, $332(150 \mathrm{mg}, 0.38 \mathrm{mmol})$ as a white solid and $333(69.3 \mathrm{mg}, 0.18 \mathrm{mmol})$ as a white solid.
333: UV (MeOH) $\lambda_{\text {max }} 269.0 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~F}_{2} \mathrm{~N}_{5} \mathrm{O}_{2}\right.$ SiO.3Acclonc) C, H, N, 334: UV (MeOH) $\lambda_{\text {ma. }} 309.5 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~F} \mathrm{ClN} \mathrm{O}_{2} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
'9-(2,3-dideoxy-2-Huoro- $\beta$-L-gycero-pent-2enofuranosyl)adenine (335). A solution of 329 ( 100 mg , $0.369 \mathrm{mmol})$ and saturated $\mathrm{NH}_{3} / \mathrm{MeOH}(50 \mathrm{~mL})$ was heated 20 al $90^{\circ} \mathrm{C}$. in a steel bomb for 24 h . After cooling to room iemperature, the solvent was removed under reduced pressure and the residual syrup was purified by column chro. matography using $6 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ as an eluent to give $335(70 \mathrm{mg}, 75 \%)$ as a white solid. 335 : UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 258$ $25 \mathrm{~mm}(\epsilon 18,800)(\rho \mathrm{H} 2), 25 \times .5 \mathrm{~nm}(\epsilon 18,800)(\mathrm{pHI} 7), 258.5 \mathrm{~nm}$ (E 19,100$)$ (pH.11). Anal. ( $\mathrm{C}_{10} \mathrm{H}_{10} \mathrm{lN}_{5} \mathrm{O}_{2} .0 .2 \mathrm{H}_{2} \mathrm{O}$ ), $\mathrm{C}, \mathrm{H}, \mathrm{N}$.
9-(2,3-dideoxy-2-lluoro-a-L-gycero-pent-2enoluranosyl)adenine (3.36). A solution of 330 ( $99 \mathrm{mg}, 0.366$ mmol) and saturated $\mathrm{NH}_{3} / \mathrm{MeOH}(50 \mathrm{~mL})$ was heated at $90^{\circ}$ ( $\therefore$ in a steel bomb for 24 h . After cooling to room temperature, the solvent was removed under reduced pres-- sure and the residual syrup was purified by column chromatography using $6 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ as an eluent to give $35.336(72 \mathrm{mg}, 78 \%)$ as a white solid.

336: UV ( $\left.\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 258 \mathrm{~nm}(\epsilon 21,100)(\mathrm{pH} 2), 259 \mathrm{~nm}$ $(\epsilon 21,500)(\mathrm{pH} 7), 259 \mathrm{~nm}(\epsilon 22,600)(\mathrm{pH} 11)$. Anal. $\left(\mathrm{C}_{10} \mathrm{H}_{10} \mathrm{FN}_{5} \mathrm{O}_{2}, 0.3 \mathrm{MeOH}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
2-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2. enofuranosyl)hypoxanthine (337). A mixture of 329 (100 $\mathrm{mg}, 0.369 \mathrm{nmhol}), \mathrm{NaOMe}(0.5 \mathrm{M}$ solution in MeOH$)(2.94$ $\mathrm{mL}, 1.46 \mathrm{mmol}$ ) and $\mathrm{HSCH}_{2} \mathrm{CH}_{2} \mathrm{OH}(0.1 \mathrm{~mL}$, 1.46 mmol$)$ in $\mathrm{MeOH}(20 \mathrm{~mL}$ ) was refluxed for 4 h under nitrogen. The 45 reaction mixture was cooled, neutralized wilh glacial AcOH and evaporated to dryness under vacuum. The residue was purified by sitica gel column chromatography ( $10 \% \mathrm{MeOH} /$ $\left(\mathrm{HCl}_{3}\right)$ to alford $337(74 \mathrm{mg}, 80 \%)$ as a white solid. 37 : UV $\left(\mathrm{II}_{2} \mathrm{O}\right) \lambda_{\text {max }} 247 \mathrm{~nm}(\epsilon 12,400)(\mathrm{pH.2}), 247.5 \mathrm{~nm}(\epsilon 613,000)$ ${ }^{0}(\mathrm{pH} 7), 253 \mathrm{~nm}(\epsilon 13,100)(\mathrm{pH}$ 11). Anal. $\left(\mathrm{C}_{1} 0 \mathrm{H}_{9} \mathrm{FN}_{4} \mathrm{O}_{3} \cdot 0.2 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

9-(2,3-dideoxy-2-fluoro-a-l-gycero-pent-2enofuranosyl)hypoxanthine (338). A mixture of 330 (100 $5 \mathrm{mg}, 0.369$ ), $\mathrm{NaOMe}(0.5 \mathrm{M}$ solution in MeOH$)(2.94 \mathrm{~mL}$, 1.46 mmol ) and $\mathrm{HSCH}_{2} \mathrm{CH}_{2} \mathrm{OH}(0.1 \mathrm{~mL}, 1.46 \mathrm{mmol})$ in $\mathrm{MeOH}(20 \mathrm{~mL})$ was relluxed for 4 h under nitrogen. The reaction mixture was cooled, neutralized with glacial AcOH and evaporated to dryness under vacuum. The residue was ${ }^{50}$ purified by silica gel column chromatography ( $10 \% \mathrm{MeOH} /$ ( $\mathrm{HCl}_{3}$ ) to atford 338 ( $70 \mathrm{mg}, 80 \%$ ) as a white solid. 338 : $\mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\max } 247.5 \mathrm{~nm}(612,700)(\mathrm{pH} 2), 247.5 \mathrm{~nm}$ $(\epsilon 13,700)(\mathrm{pH} 7), 252.5 \mathrm{~nm}(\epsilon 13,100)(\mathrm{pH} 11)$. Anal. $\left(\mathrm{C}_{10} \mathrm{H}_{9} \mathrm{FN}_{4} \mathrm{O}_{3} .0 .3 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

2-Fluoro-6-amino-9-(2,3-dideoxy-2-fluoro- $\beta$-L-gycern-pent-2-enoturanosyl)purine (339). A solution of 31 (10.1 mg,
0.26 mmoll) in dry acetonitrile ( 15 ml .) was treated with TBAF ( 1 M volution in THF) ( 0.35 mL , $(0.35 \mathrm{mmol}$ ) and stirred for 30 inin. After evaporation of solvent, the drymess was puritied by columu chromatography ( $9 \%$ CH, $\mathrm{Cl}, \mathrm{F}$ MeOH ) to ohtain 339 ( $64.7 \mathrm{mg}, 0.24$ mnoul, $92.3 \%$ ) ats a white crystalline solid. UV ( $\left.\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 269.0 \mathrm{~nm}(\mathrm{pH} 7)$.

2-Fluort-(1-amino-9-(2,3-didicoxy-2-fluoro- $\alpha-1$--gycuro-pent-2-enofur anosyl)purine (3.10). A solution of 333 (73.4 $\mathrm{mg}, 0.19 \mathrm{n}$ mull) in dry acetonitrile ( 10 mL ) was treated with TBAF ( 1 M solution in T11F) ( 0.25 mL , 0.25 mmol ) and stirred for 30 min . After evaporation of solvent, the dryness was purified by columu chromatography $\left(9 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} /\right.$ MeOH ) to. ohtain 340 ( $46.2 \mathrm{mg}, 0.17 \mathrm{mmol}, 90.3 \%$ ) as a white crystalline solid. UV ( $\left.\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 269.0 \mathrm{~nm}(\mathrm{pH} 7)$.

2-Amino-(6-chloro-9-(2,3-dideoxy-2-fluoro- 3 -1.-gycero. pent-i-enofuranosyl)jurine (341). A soluticio of 3.32 (143.5 $\mathrm{nig}, 0.40 \mathrm{mmol}$ ) in dry acctonitrile ( 15 mL ) was treated with TBAF ( 1 M solution in THII) ( $0.6 \mathrm{~mL}, 0.60$ mmol) and stirred for 30 min . After evaporation of solyent, the dryacss was puriliced by colunn chrematography ( $5 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} /$ MeOII) to (wlain 341 ( $109 \mathrm{mgn}, 0.382 \mathrm{mmol}, 95.5 \%$ ) as a white crymalline solid. UV ( $1 \mathrm{I}_{2} \mathrm{O}$ ) $\lambda_{\text {max }} 308.5 \mathrm{~nm}(\mathrm{pH} 7)$

2-Amilu-(0-chloro-9-(2,3-dideoxy-2-fluoro- $($-1-gyecro-pent-2-enoluranosyl)purine (342). A solution of 334 ( 145 $\mathrm{mg}, 0.36 \mathrm{mmol}$ ) in dry acetonitrile ( 10 mL ) was treated with. T'BAF ( 1 M solution in THE) ( $0.5 \mathrm{~mL}, 0.50 \mathrm{mmol}$ ) and stirred for 30 min . After evaporation of solvent, the dryness was purilied by column chromatography $(9) \% \quad \mathrm{CH}_{2} \mathrm{Cl}_{2} /$ MeOH ) to obtain 342 ( $99.9 \mathrm{mg}, 0.35 \mathrm{mmol}, 904 \%$ ) as a white crystalline solid. UV ( $\left.\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 309.0 \mathrm{~nm}(\mathrm{pH} 7)$.

9:(2,3-dideoxy-2:fuoro- $\beta$-t-gycero-pent.2. .cnofuranosyl)guanine (343). A mixture of $\cdot 3 \dot{4} 1(63.6 \mathrm{mg}$. ( 0.223 mmol ), 2-mercaptocthanol ( $0.06 \mathrm{~mL}, 0.89 \mathrm{mmol}$ ) and $1 \mathrm{~N} \mathrm{NaOMe}(0.89 \mathrm{~mL}, 0.89 \mathrm{mmol})$ in $\mathrm{MeOH}(10 \mathrm{~mL})$ was refluxed for 5 h under nitrogen. The mixture was cooled,
neutralized with glacial $\wedge \mathrm{COH}$ and concentrated to dryness under reduced pressure. The residue was purified by column chromatography ( $12 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ ) to obtain 343 ( 30.1 mg, 0.113 mrnol, $50.7 \%$ ) as a white solid. UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }}$ $253.5 \mathrm{nin}(\mathrm{pH} 7)$.
9-(2,3-dideoxy-2-nuoro-a-1-gycero-pent-2-- enofuranosyl)guanine (344). A mixture of 342 ( 59.3 mg , $0.208 \mathrm{mmol}), 2$-mercaptothanol ( $0.07 \mathrm{~mL}, 1.04 \mathrm{mmol}$ ) and 1 N NaOMe ( $1.04 \mathrm{~mL}, 1.04 \mathrm{mmol}$ ) in $\mathrm{MeOH}(10 \mathrm{~mL})$ was retluxed for 5 h under nitrogen. The mixture was cooled, neutralizcd with glacial AcOH and concentrated to dryness under vacuum. The residue was purified by column chromatography ( $12.5 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{McOH}$ ) to obtain 344 ( 28.0 mg , $0.105 \mathrm{mmol}, 50.5 \%)$ as a white solid. UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\max } 253.0$ $\mathrm{nm}(\mathrm{pH} 7)$.

Synthesis of cis-( $\pm$ )-Carbocyclic d4 Cytosine Nucleosides and their 5 '-Triphosphates Referring to Scheme 11, starting from diethyl diallylmalonate (701), the 4-carbethoxy-1,6heptadiene (702) was synthesized in $78 \%$ yield (W. A. Nugent, J. Am. Chem. Soc., 1995, 117, 8992-8998). Compound 703 was synthesized from compound 702 in $71 \%$ yield (L. E. Martinez., J. Org. Chem., 1996, 61, 7963-7966), and compound 705 was synthesized from compound 704 in 43\% yield (D. M. Hodgson, J. Chem. Soc. Perkin. Trans. I, 1994, 3373-3378). The key intermediate cis-(土)-3-acetoxy-5-(acetoxymethyl)cyclopentene (708) can be alternatively synthesized from cyclopentadiene and formaldehyde in acetic acid using a Prins reaction (E. A. Saville-Stones, J. Chem. Soc. Perkin Trans. I, 1991, 2603-2604) albeit it suffers low yield and inseparable problems; or from a bicyclic lactone which was synthesized by multiple steps through 4 steps ( $F$. Burlina, Bioorg. Med. Chem. Lett., 1997, 7, 247-250). The latter methodology gave a chiral 708 [( - -)-enantiomer], aluhough it nceded to synthesized a chiral bicyclic lactone. $\mathrm{N}^{4}$-Acetyl-5-fluorocytosine was synthesized from 5 -lluorocytosine and p-nitrophenyl acetate (A. S: Steinfelkl, J. Chem. Research (M), 1979, 1437-1450).

Schenie 11



- -continued


$709 \mathrm{X}=\mathrm{F}, \mathrm{R}=\mathrm{H}$ $710 \mathrm{X}=\mathrm{F}, \mathrm{R}=\mathrm{Ac}$ $711 X=H, R=A c$
$\mathrm{NaOMc} /$
$\mathrm{MeOH} \cdot$

$714 X=F$
$715 X=H$
i) 2-chloro-4H-

1,3,?-benzodioxa-phosphorin-4-onel dioxane/DMF/Py
ii) pyrophosphoric acid/ Bu $\mathrm{N}_{2} / \mathrm{DMF}$ iii) $\mathrm{I}_{2} / \mathrm{H}_{2} \mathrm{O} / \mathrm{Py} \mathrm{TH} \mathrm{H}$

Experimental Part
General. All reagents were used as received unluss stated otherwise. Avhydrous solvents were purchased from Aldrich Chemical Co. Melting points (M.p.) were determined on an Electrothermal digit melling point apparatus and ire uncorrected. ${ }^{1}$ II and ${ }^{1} 3 \mathrm{C}$ NMR spectra were taken on a Varian Unity Plus 400 spectrometer at room lemperature and reported in popm downlield from internal letramethylsilane
4-Carbelhoxy-1,6-heptadiene (702) A mixture of diethyl diallymalonate ( $701 ; 50 \mathrm{~g}, 208$ mmol ), sodium cyanide ( 20.7 s, 422 monol) and DMS() ( 16 ki mL ) was heated at $160^{\circ} \mathrm{C}$ : lor 6 l . After being cooled tw 1 ., the mixture was added 11 400 mL . of water and ithe prodici was extratied into hexame: $(4 \times 100 \mathrm{nal}$ ) Alter evaporatinn of the solvent at reclueed pressure, the essidue was distilind (42-43 $1 \cdot /$ I ling) to give 27.34 g ( $78 . i$ ) if 702 as a collorless liquid. 'II NMIR (:IM) $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) 85.80-5.70\left(\mathrm{IIT}, 2 \mathrm{H}, 2\left(\mathrm{H}=\mathrm{CH}_{2}\right), 5.1(1-5.112\right.$ $\left(\mathrm{m}, 4 \mathrm{H}, 2\left(\mathrm{H}=\mathrm{CH}_{2}\right), 4.14\left(4,2 \mathrm{H}, \mathrm{J}=7.2 \mathrm{~Hz}, \mathrm{OCH}_{2}\right)\right.$, $2.54-2.48$ ( $\mathrm{m}, 11 \mathrm{I}, \mathrm{CH}$ ), $2.41-2.34,2.29-2.23(2 \mathrm{~m}, 411 . .2$ $\left(\mathrm{CH}_{2}\right), 1.25\left(1, \mathrm{~J}=7.2 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{Cl}_{3}\right)$.
( $\pm$ )-3-Cyclopentenecarboxylic Acid, Elhyl Ester (703): A flame-dried 500 ml llask was charged with 2,6. dibromophenol ( $1.20 \mathrm{~g}, 4.76 \mathrm{mmol}$ ), tungsten oxychloride $\left(0.813 \mathrm{~g}, 2.3 \mathrm{~s}_{\mathrm{mmol}}\right.$ ), and anhydrous toluene ( 25 mL .). The resulting suspension was heated at reflux under nitrogen for 1 h , and then the solvent was evaporated in vacuo. The solit residue was broken up with a spatula and dried in vacuo lor 30 min . To the residue were added toluene ( 160 mL ), E1., P P), ( $1.54 \mathrm{~g}, 4.76 \mathrm{~mL}$ ) , and $702(22 \mathrm{~g}, 131.0 \mathrm{mmol})$. The mixture was heated at $90^{\circ} \mathrm{C}$. under uitrogen for, 1.5 h . Alter being cooled to r.t., the mixture was filticed through a celite, and the celite was rinsed wilh $t-\mathrm{BuOMe}$. The combined fillrates were washed with $1 \% \mathrm{NaO}$ ! ! soln, water, and brine, and concentrated by evaporation al reduced pressure. The residue was distilled ( $37-38^{\circ}$ C./1 Torr) 10 give $13.06 \mathrm{~g}(71 \%)$ of 703 as a colorless liquid. 'H NMR ( $400 \mathrm{MHz}, \mathrm{CDC} \mathrm{I}_{3}$ ) $65.67(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CII}=\mathrm{CH}) .4 .14\left(4,2 \mathrm{H}, \mathrm{I}=7.2 \mathrm{~Hz}, \mathrm{O}\left(\mathrm{H}_{2}\right), 3.11\right.$
(pentuplet, $\mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}), 2.65(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 4 \mathrm{H}, 2$ ( $\mathrm{H}_{2}$ ), $1.27\left(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$.
( $\pm$ )-1-(Hydroxymethyl)-3-cyclopentene (704). To a cold $\left(-78^{\circ} \mathrm{C}\right.$.) solution of $703(7 \mathrm{~g}, 50 \mathrm{mmol})$ in dry THF ( 150 mL.) was added $\mathrm{LiAlH}_{4}$ ( 1 M soln in $\mathrm{THF}, 25 \mathrm{~mL}, 25 \mathrm{mmol}$ ), and the reaction solution was stirred at $-78^{\circ} \mathrm{C}$. under ardon for 4 h . Then the reactinn solution was allowed to warm to $11^{\circ} \mathrm{C}$., and 2.5 mL of water, 2.5 mL of $15 \% \mathrm{NaOH}$, and 7.5 - ml. of water were added sequentially. After warming to ri.t,

65
$\left.\mathrm{H}_{2} \mathrm{OH}\right), 36.5(\mathrm{~d}, \mathrm{CH}), 31.4\left(\mathrm{t}, 2 \mathrm{CH}_{2}\right)$. cis-( $\pm$ )-3-Acetoxy-5-(aceloxymathyl)cyclopentene (708).
To a solution of diphenyl disclenctide: $(2.70 \mathrm{~g}, 8.65 \mathrm{mmol})$ the precipitates were fillered through a celite, and the celite was washed with hol ElOAc. The combined filtrates were washed with 0:1 N NaOH , and brine, dried ( $\mathrm{MgSO}_{4}$ ), filtered, coricentrated and dried in vacuo to give 4.294 g ( $84 \%$ ) of 704 as a pale yellow liquid. ${ }^{1} \mathrm{H} \operatorname{NMR}(400 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 5.68(\mathrm{~s}, 2 \mathrm{H}, 2 \mathrm{CH}=\mathrm{CH}), 3.57(\mathrm{~d}, \mathrm{~J}=6.0 \mathrm{H} \angle, 2 \mathrm{H}$, $\left.\mathrm{CH}_{2} \mathrm{OH}\right), 2.54-2.48\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{CH}+\mathrm{CH}_{2}\right), 2.15-2.10(\mathrm{~m}, 2 \mathrm{H}$, $\mathrm{CH}_{2}$ ).
cis-( $\pm$ )-4-(Hydroxymethyl)-1,2-epoxycyclopentane (705). To a solution of 704 ( $930 \mathrm{mg}, 9.1 \mathrm{mmol}$ ), and vanady! actylacetonate ( 10 mg ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL}$ ) was added $1-\mathrm{BuO}_{2} \mathrm{H}\left[3 \mathrm{M}\right.$ soln in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, prepared from a mixture of $1-\mathrm{BuO}_{2} \mathrm{H}(70 \%$ by weight in water, $41 \mathrm{~mL}, 0.3$ mol) and $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}(59 \mathrm{~mL})\right.$ by drying ( $2 \times \mathrm{MgSO}_{4}$ ) and storage over $4 \AA$ molceular sieve, $10 \mathrm{~mL}, ~-30 \mathrm{mmol}]$ dropwise. After stirring at r.t. for 24 h , aqueous $\mathrm{Na}_{2} \mathrm{SO}_{3}$ ( $15 \%$ soln, 60 mL ) was added, and the mixture was stirred al r.I. for 6 h . The organic layer was separated, washed with sal. $\mathrm{NaHCO}_{3}$, and brine, and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexane/EtOAc ( $2: 1$ ) to give 460 mg ( $43 \%$ ) of 705 as a colorless liquid. ${ }^{1}{ }^{1} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.54(\mathrm{~s}, 2 \mathrm{H}$, $\left.(\mathrm{CH})_{2} \mathrm{O}\right), 3.49\left(1, \mathrm{~J}=4.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{OH}\right), 2.95(\mathrm{bs}, 1 \mathrm{H}, \mathrm{OH})$, $2.44-2.40(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}), 2.05-2.02\left(\mathrm{~m}, 4 \mathrm{H}, 2 \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl} \mathrm{l}_{3}$ ) $\delta 66.9\left(\mathrm{~d},(\mathrm{CH})_{2} \mathrm{O}\right), 59.2(\mathrm{t}$,
in anhydrous $\mathrm{EtOH}\left(100 \mathrm{~mL}\right.$ ) wals added $\mathrm{NaBH}_{4}$ in portions The solution was stirred until the yellow color turned to colorless, and then a solution of $705(1.70 \mathrm{~g}, 14.4 \mathrm{mmol})$ in anhydrous TIIF ( 10 mL ) was added. The reaction solution was heated at rellux for 1 h under nutrogen, and then the solvent was evaporated in vacuo. To the residue was adkled EiOAc ( 80 mL ) and water ( 30 mL ). The organic phase was separated, washed with brine, dried. $\left(\mathrm{MgSO}_{4}\right)$, fillered, concentrated and dried in vacuo. The obtained ( $\pm$ )-1 hydroxy-4-(hydroxymethyl)-2-(phenylselenenyl)-cyclopentane (706; light yellow sil) was uied for the uext teaction dirce:ly without further purification. Tilite crude product 706 were aclded anhydrous $\mathrm{CH}_{2}\left(\mathrm{C}_{2}(60 \mathrm{~mL}), \mathrm{El}_{3} \mathrm{~N}(30 \mathrm{~mL}, 216\right.$ mmol), and IDMAP ( 50 mg ). The resulting solution was coroled to $0^{\circ}$ (., and Ac: 0 ( $14.7 \mathrm{~g}, 1.14$ monol) was added dropwise. Alier being stirred al r.t. under argon wernight. evaporation of the solvent provided ( $x$ )- 1-iscioxy-4. (acetoxymethyl).2-(phenylsclencolyl)-cychopentanc (707, light ycllow uil). To a colld ( $0^{\circ} \mathrm{i} \cdot$ ) solution of $707 \mathrm{in} \mathrm{Cll}_{2}\left(\mathrm{I}_{2}\right.$ ( 50 mL ) comaimug 3 drops if pyridine was athed $30 \%$ $\mathrm{H}_{2} \mathrm{O}_{2}$ soln (20 mLL over a perisk of 5 min. Alter being stirred at $1^{\circ}\left({ }^{\circ}\right.$. for 30 mun and al r.t. Lor another 301 min, the reaction mixture was diluted by addition of $\left(\mathrm{H}_{2}\left(\mathrm{Cl}_{2}(5) \mathrm{ml}.\right)\right.$ The organic phase was separated, washed with water, sat $\mathrm{NaHCO}_{3}$, and brine, dried. $\left(\mathrm{M}_{3} \mathrm{SO}_{4}\right)$, filtered, and concentrated by evaporation in vacuo. The residuc was purified by Hash chromatography on silica gel eluting will $0-1(1 \%$ EiOAc in hexane to give 2.254 g ( $70 \%$, for the three sleps) of 708 as a pale brown liguid. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $6.01-6.00,5.92-5.90(2 \mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}=\mathrm{CH}), 5.66-5.64(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{H}-3), 4.04\left(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{H} \mathrm{Iz}, 2 \mathrm{II}, \mathrm{CH}_{2}(\mathrm{O}), 2.98-2.92(\mathrm{~m}, \mathrm{III}\right.$, $\mathrm{H}-5), 2.53-2.46(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4 \mathrm{a}), 2.08,2.04\left(2 \mathrm{~s}, 6 \mathrm{H}, 2 \mathrm{Cll}_{3}\right)$. 1.60-1.54 (m, 211, H-41). ${ }^{13}$ ( NMR ( $\left.100 \mathrm{Mlly}, \mathrm{CDCl}_{j}\right)^{\text {) }}$ ) 171.1, $17(1.9(2 \mathrm{~s}, 2 \mathrm{C}=0), 137.0,131.4 \cdot(2 \mathrm{~d}, \mathrm{Cll}=(\mathrm{Cl}), 79.2$ (d, C-3), $67.4\left(\mathrm{t}, \mathrm{CH}_{2} \mathrm{O}\right), 43.7$ (d, C-5), 33.4 ( $1, \mathrm{C}-4$ ), 21.3 $20.9\left(2 \mathrm{q}, 2\left(\mathrm{H}_{3}\right)\right.$.
cis-( $\pm$ )-Carbocyclic $5^{\prime}$-(0):acelyl-2', $3^{\prime}$-didehydro-2', $3^{\prime}$. dideoxy-5-lluorocytidine (709). A suspension of 5 -fluorocytosine ( $258 \mathrm{mg}, 2 \mathrm{mmol}$ ) and $\mathrm{Nall}(58 \mathrm{mg}, 2.4$ nımol) in anhydrous IDMSO ( 15 mL ) was heated in a pre-warmed sil bath at $70^{\circ}$. C . for 30 min . Then the resulting. solution was cooled to r.t., and $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right) .4\left(73 \mathrm{mg}, 0.06 \mathbf{B}^{3}\right.$ mmol) and a solution of 708 ( $298 \mathrm{mg}, 1.5 \mathrm{mmol}$ ) it anhydrous TIIF ( 2 mL ) were added respectively. The reaction mixture was stirred al $70^{\circ} \mathrm{C}$. under argon fir 3 diays After removal of the solvent by evaporation in vacuo, the residue was treated with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$. The precipitaten were tiltered through a celite, and the celite was washed with ( $: \mathrm{H}_{2} \mathrm{Cl}_{2}$. The combined filtrates were concentrated, and the residue was puritied by tlash chromatography on silica gel eluting with $11-5 \%$ MeOH in $\left(\mathrm{IH}_{2} \mathrm{Cl}_{2}\right.$ to give 40 mg ( $10 \%$ ) of 709 as a light hrown solid. Recrystallization from $\mathrm{MeOH}^{\prime}$ ( $\mathrm{H}_{2} \mathrm{C}_{2}$ /hexance provided pure product as white powelers. M.p. $182-184^{\circ}\left(\therefore{ }^{1} \mathrm{H}\right.$ NMR ( $140 \mathrm{MHLz},(1) \mathrm{Cl}_{3}$ ) त 7.43 (d, $\mathrm{J}=6.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-6$ ), 6.18-6.10 (111, 1H, H-3'), 5.83-5.81 (m, $\left.1 \mathrm{H}, \mathrm{H}-2^{\prime}\right), 573-5.71\left(\mathrm{~m}, \mathrm{IH}, \mathrm{II}^{\prime} 1^{\prime}\right), 4.23-4.21,4.08-4.04$ ( $2 \mathrm{~m}, 2 \mathrm{II}, \mathrm{Cl}_{2} \mathrm{O}$ ), 3.14-3.12 ( $\mathrm{m}, \mathrm{HH}, \mathrm{H}-\mathrm{4}^{\prime}$ ), 2.92-2.84 ( m, $\left.1 \mathrm{H}, \mathrm{H}-6^{\prime} \mathrm{a}\right), 2.08\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.41-1.35\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{II}-6^{\prime} \mathrm{b}\right)$.
cis-(土)-Carbocyclic $\mathrm{N}^{4},{ }^{3}$ '-()-diacetyl-2', $\mathbf{3}^{3}$-didehycro-2', 3'-dideoxy-5-fluorocytidine (710). In an analogy manner to the procedure for 709 , the title compound 710 was prepareal from $708(560 \mathrm{mg}, 2.828 \mathrm{mmol})$ and $\mathrm{N}^{i}$-atectyl-.5. Iluorocytusine ( $726 \mathrm{mg}, 4.24 \mathrm{mmol}$ ): 560 mg ( $04 \%$, brown (ril). This crude product was used directly lor the next reaction without further purification. cis-(f)-('arbocyclic $\mathrm{N}^{4}, 5^{\prime}$-()-diacelyl-2', 3'-didehydro-2', $\mathbf{3}^{\prime}$-dideoxycytioline (711). In all analogy manner to the procelure lier $7(0)$, the
title compound 711 was prepared from 708 ( $272 \mathrm{mg}, 1.37$ mmol) and $\mathrm{N}^{4}$-acetylcytosine ( $316 \mathrm{mg}, 2.06 \mathrm{mmol}$ ): 108 mg $(27 \%)$ of white powders. M.p. $169.5-171.5^{\circ}$ C. ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.80(\mathrm{bs}, 1 \mathrm{H}, \mathrm{NH}), 7.72(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}$, 1H, H-6), 7.39 (d, J=6.8 IIz, III, II-5), 6.19-6.17 (m, IH, (11-3'), 5.86-5.81 (m, 1H, H-2'), 5.77-5.75 (m, 1H, H-1'), 4.17-4.13, 4.07-4.02 ( $2 \mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{O}$ ), 3.18-3.10 (m, 1H1, II-4'), 2.96-2.88 (m, 1H, II-6'a), 2.27, 2.06 ( $2 \mathrm{~s}, 6 \mathrm{H}, 2 \mathrm{CH}_{3}$ ), $1.43-1.37(\mathrm{~m}, 1 \mathrm{H}, 11-6 \mathrm{~b}) .{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ $170.8(\mathrm{~s}, 2 \mathrm{C}=0$ ), $162.0(\mathrm{~s}, \mathrm{C}-4), 155.6(\mathrm{~s}, \mathrm{C}-2), 145.3$ (d, ( -6 ), $139.2(\mathrm{~d}, \mathrm{C} 3$ '), 130.0 (d, C2'), $96.8(\mathrm{~d}, \mathrm{C}-5), 66.3(\mathrm{I}$, (C-5'), 62.8 (d, C-1'), 44.2 (d, C-4'), 34.7 (, C- $\left.-6^{\prime}\right), 25.0,20.9$ (2q. $2 \mathrm{Ch}_{3}$ ).
cis-( $\pm$ )-Carbocyclic $2^{\prime}, 3^{\prime}$-didehydro- $2^{\prime}, 3^{\prime}$-dideoxy-5lluorocytidine (712). To a flask contaiuiug 709 ( $33 \mathrm{mg}, 0.12$ mmol ) was added NaOMc ( 0.5 M soln in $\mathrm{MeOH}, 0.5 \mathrm{~mL}$ ). The reaction solution was stirred at r.t. for 1 h , and then the solvent was evaporated in vacuo. The residue was puritied by llash chromatography on silica gel eluting with $5-10 \%$ MeOH in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $17 \mathrm{mg}(61 \%)$ of 712 as a light brown solid. Recrystallization from $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ /hexane provided pure product as white powders. M.p. 205.5-206. $0^{\circ}$ (. ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}\right) \delta 7.66(\mathrm{~d}, \mathrm{~J}=6.0 \mathrm{~Hz}, \mathrm{IH}$, $1 \mathrm{I}-6), 7.60,7.40\left(2 \mathrm{bs}, 2 \mathrm{II}, \mathrm{NH}_{2}\right), 6.06-6.05\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-3^{\prime}\right)$, $5.6 \mathrm{~S}-5.65\left(\mathrm{~m}, 1 \mathrm{H}, 1 \mathrm{H}-2^{\prime}\right), 5.53-5.50\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 4.77-4.75$ ( $\mathrm{m}, \mathrm{IH}, \mathrm{H}-4^{\prime}$ ), $3.50-3.48,3.41-3.37$ ( $2 \mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5^{\prime}$ ), 2.79-2.77. (m, 1H, H-6'a), 1.34-1.27 (m, 1H, H-6'b). ${ }^{13} \mathrm{C}$ NMR ( $\left.100 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{c}_{0}\right) \delta 157.0\left(\mathrm{~d}, \mathrm{~J}_{C-F}=11.9 \mathrm{~Hz}, \mathrm{C}-4\right)$, $154.0(\mathrm{~s}, \mathrm{C}-2), 139.2\left(\mathrm{~d}, \mathrm{C}-3^{\prime}\right), 135.8\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{c}} . \mathrm{F}=241.3 \mathrm{~Hz}\right.$, ('-5), 130.2 (d, C-2'), 126.8 (d, J $\mathrm{J}_{\text {. F }}=11.8 \mathrm{~Hz}, \mathrm{C}-6$ ), 63.5 ( t , (C. 5 '), 61.3 (d, C-1'), 47.2 (d, C-4'), 33.3 (I, C-6'). MS (FAB) $\mathrm{m} / \mathrm{e} 226\left(\mathrm{MH}^{+}\right)$. Anal. ( $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{FN}_{3} \mathrm{O}_{2}$ ) caled C $53.33, \mathrm{H}$ $5.37, \mathrm{~N}$ 18.66; found C 53.10 , H 5.40 , N 18.44 . In an analogy manner to the above procedure, the title compound 712 was also prepared from $710(750 \mathrm{mg}, 2.42 \mathrm{mmol}): 320$ ing ( $59 \%$, white powders). cis-( $\pm$ )-Carbocyclic $2^{\prime}, 3^{\prime}-$ didehydro-2',3'-dideoxycytidine (713). In an analogy manner to the procedure for 712, the title compound 713 was prepared from 711 ( $75 \mathrm{mg}, 0.257 \mathrm{mmol}$ ): $48 \mathrm{mg}(90 \%$, white solid). M.p. $200-201^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO-d6) $\delta$ $7.40(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{IIz}, \mathrm{III}, \mathrm{II}-6), 7.03,6.95$ ( $2 \mathrm{bs}, 2 \mathrm{II}, \mathrm{NII}_{2}$ ), (i.07-6.05 (m, 1H. H-3'), $5.67(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5)$, 5.65-5.64 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}-2^{\prime}$ ), $5.55-5.52\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 4.71-4.68$ ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}-4^{\prime}$ ), $3.43-3.36\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5^{\prime}\right), 2.78-2.76$ (m, 1H, $\left.11-6^{\prime} \mathrm{a}\right), 1.24-1.18$ (m, HI, H-6'b). ${ }^{13} \mathrm{C}$ NMR ( 100 MHL , DMSO-d6) $\delta 165.5$ (s, ( -4 ), 155.8 ( $\mathrm{s}, \mathrm{C}-2$ ), 142.2 (d, C-6), 138.6 (d, C-3'), $130.5\left(\mathrm{~d}, \mathrm{C}-2^{\prime}\right), 93.7$ (d, C-5), 63.9 (t, C-5'), 60.8 (d, C-1'), 47.3 (d, C-4'), 34.0 (t, C-6'). MS (FAB) m/e $208\left(\mathrm{MHI}^{+}\right)$. Anal. ( $\mathrm{C}_{10} \mathrm{HH}_{13} \mathrm{~N}_{13} \mathrm{O}_{2}$ ) calcd D 57.96, H 6.32, N 20.28; found C 57.35, H 6:27, N 20.02. HRMS (FAB) caled for $\left(\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{~N}_{3} \mathrm{O}_{2}\right)$ : 208.1086; found 208.1088.
cis-( $\pm$ )-Carbocyclic $2^{\prime}, 3^{\prime}$-didehydro- $2^{\prime}, 3^{\prime}$-dideoxy-5tluorocytidine $5^{\prime}$-triphosphate, triethylhydrogenammonium sall (714). To a solution of $712(10 \mathrm{mg})$ in anhydrous DMF $(0.3 \mathrm{~mL})$ and pyridine ( 0.1 ml ) was added a $1 . \mathrm{M}$ solution of 2 -chloro-4H-1,3,2-benzodioxaphosphorin-4-one in anhydrous 1,4 -dioxane ( 0.05 mL ). The reaction solution was stifred at r.t. for 15 min . Then, a solution of 1 M pyrophosphoric acid- $\mathrm{Bu}_{3} \mathrm{~N}$ in anhydrous DMF ( 0.12 mL ), and $\mathrm{Bu}_{3} \mathrm{~N}$ ( 0.05 mL ) was added sequentially. After stirring at r.t. for another $15^{\circ} \mathrm{min}$, a solution of $\mathrm{I}_{2} / \mathrm{H}_{2} \mathrm{O} /$ pyridine $/ \mathrm{THF}$ was added to the above solution dropuvise until the iodine color persisted (about 0.5 mL ), and then the mixture was concentrated by evaporation in vacuo. The residue was dissolved in water ( 2 mL ), washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 1 \mathrm{~mL})$, filtered, and purified by FPLC (column: HiLoad 26/10 Q Sepharose Fast How; bullicr A: $0.01 \mathrm{M} \mathrm{Et}_{3} \mathrm{NIICO}_{3}$; buffer B: 0.7 M
$\mathrm{Et}_{3} \mathrm{NHCO}_{3}$; thow rate: 10 mL min; gradient: illereasing butfer $B$ from $0 \%$ at beginning $1010 \%$ at 4 min, then io $1.00 \%$ at 64 min ). Collection and lyophilization of the appropriate fractions allorded 714, as a enforless syrup. HPLC [column: $10(0 \times 4.6 \mathrm{~mm}$ Rainin Hydropore SAX ionic exchange; bufticr $\mathrm{A}: 10 \mathrm{mM} \mathrm{NH}_{4} \mathrm{H}_{2} \mathrm{PO}_{4}$ in $10 \% \mathrm{McOH} / \mathrm{H}_{2} \mathrm{O}$ (plI 5.5); butfer B: $125 \mathrm{mM} \mathrm{NH} 4_{4} \mathrm{H}_{2} \mathrm{PO}_{4}$ in $10 \% \mathrm{McOH} / \mathrm{H}_{2} \mathrm{O}$ (ply 5.5 ); flow rate: $1.0 \mathrm{~mL} / \mathrm{min}$; gradient: increasing B from $0 \%$ at beginning to $100 \%$ at 25 mín] retention time: 11.9 min. MS (FAB) m/e 464 ([M-H] ${ }^{+}$).
cis-(土)-Carbucycilic 2',3'-diduhydro-2',3'-dideoxycylidiue 5 -phosphate (715). In an analogy manner to the procedure for 714 , the title compound 715 was prepared from 713. HPLC (same conditions as above) retention time:. 12.1 min. MS (FAB) m/c 446 ([M-1I] ${ }^{+}$).

Inhibitory effect of ( $\pm$ )-Carboxy-D4FC-triphosphate against HIV-1 reverse transcriplase.

Extension assays were performed using a $\left.r(1)_{, ~ .(d C . ~}^{(1)}\right)_{12} 18$ homopolymer template-primer (Pharmacii, Piscataway, N.J.) and the HIV- 1 heterodimer p $66 / 51$ reverse transcriptase (RT, Biolechnology (icteral, Rehovat, Isracl). The standard reactoon mixture ( $(00,11)$ contained 100 mM Tris hydrochloride ( pH 8.0 ), $50 \mathrm{mM} \mathrm{KCl}, 2 \mathrm{mM} \mathrm{Mg}\left(\mathrm{I}_{2}, 0.05\right.$ units $/ \mathrm{ml} \mathrm{r}(\mathrm{I})_{n}(\mathrm{dC})_{12} .18,5 \mathrm{mM}$ DTT, $100, \mu \mathrm{~g} / \mathrm{ml}$ Bovine Scrum Albumm, and $1 \mu \mathrm{M}^{3} \mathrm{H}-\mathrm{dClP}$ ( $23 \mathrm{Ci} / \mathrm{mmol}$ ). 3 TCTP ( $0.001-50$, M M was the positice control. Compounds were incubated I br at $37^{\circ} \mathrm{C}$. in the seaction mixture with t unit HIV-1 RTS The reaction was stopped with the addition of an equal volune of cold $10 \%$ TCA $0.05 \%$ sodium pyrophosphate and incubated 30 minutes at $4^{\circ}$ C. The precipitated nucleic acids were harvested onto fiberglass filter paper using a Packard manual harvester (Meriden, Comn.). The radiolabel uptake in counts per minute (epm) was determined using a Packard 9000 Direct Beta counter.

## IV. Anli-HIV Activily

In one embodiment, the disclosed compounds, or their pharmaceutically acceptable clerivatives or salts or pharmaceutically acceptalle formulations containing these comporunds are urefull in the prevention andelreatinent of IIIV infections and other related conditions such as AIDS-related complex (ARC), persisient generalized lymphadenopathy ( ${ }^{\circ} G L$ ), All $S$-related neurological conditions, anti-IllV antibody positive and HIV-posilive condilions, Kaposi's sarcoma, thrombocylopenia purpurea and opportunistic intections. In addition, these compounds or formulations can be-used prophylactically to prevent or retard the progression of clinical illncss in individuals who are anti-IIIV antibody or HIV-antiger positive or who have been It exposed to HIV.

The ability of nucleosides to inhibit HIV can be measured by various experimental techniques. One technique, described in detail below, measures the inhibition of viral replication in phylohemagglutinin (PHA) stimulated human peripheral blood mononuclear (PBM) cells infected with HIV-1 (strain LAV). The amount of virus produced is determined by measuring the virus-coded reverse transcriptase enzyme. 'The amount of enzyme produced is proportional to the amount of virus produced.

Antiviral and cytotoxicity assays: Anti-HIV-1 activity of the compounds is determined in human peripheral blood mononuclear (PBM) cells as described previously (Schinazi, R. F.; McMillan, A.; Cannon, D.; Mathis, R.; Lloyd, R. M. Jr.; Peck, A.; Sommadossi, J.-P.; St. Clair, M.; Wilson, J.; Furman, P. A.; Painter, G.; Choi, W.-B.; Lioll, D. C. Antimicroh. Agent: Chemoiher. 1992, 36, 2423; Scfina7i, R. F.: Sommadossi, J.-P.; Saalmann, V.; Canmon, D.; Xic. M. Y.; ILart, C.; Smith, G.; Hahn, E. Armimicroh. Agemts

Chemoher. 1990 , 34, 1061). Stock solutions (20-40 mM) of the compounds were prepared in sterile DMSO and then diluled to the desired concentration in complete medium. 3'-axidu-3'-dcoxythymidine (AZT) stock solutions are made in water. Cells are infected with the prototype HIV-1 $1_{\text {LA } / \text { al a }}$ nultiplicity of infection of 0.01 . Virus obtained from the cell supernatant are quantitated on day 6 after infection by a reverse transcriptase assay using poly(rA $)_{n}$.oligo(dT) $)_{12-18}$ as template-primer. The DMSO present in the diluted solution ( $<0.1 \%$ ) should have no effect on the virus yield. The toxicity of the compounds can be assessed in human PBM, CEM, and Vero cells. The antiviral EC. So $^{\text {a }}$ and cytotoxicity $\mathrm{IC}_{50}$ is obtained from the concentration-response curve using the median effective method described by Chou and Talalay (Adv: Enzyme Regul. 1984, 22, 27).

Three-day-old phytohemagglutinin-stimulated PBM cells $10^{\circ}$ cells/ml) from hepatitis B and HIV-1 seronegative healithy donors are infected with HIV-1 (strain LAV) at a concentration of about 100 times the $50 \%$ tissue culture infectious dose (TIC.D SO) per ml and cultured in the presence and absence of various concentrations of antiviral compounds.

Approximately one hour after infection, the medium, with the compound to be tested ( 2 times the final concentration in medium) or without compound, is added to the flasks ( 5 ml ; final volume 10 ml ). AZT is used as a positive control.

The cells are exposed to the virus (about $2 \times 10^{5} \mathrm{dpm} / \mathrm{ml}$, as cletermined by reverse transcriptase assay) and then placed in a $\mathrm{CO}_{2}$ incubator. HIV-1 (strain LAV) is obtained from the Center for Disease Control, Atlanta, Ga. The methods used for culturing the PBM cells, harvesting the virus and determining the reverse transcriptase aclivity are Hose described by McDongal et al. (J. Immunn. Meth. 76, 171-183, 1985) and Spiral el al. (J. Clin. Meth. 25, 97-99, 1987), except that llngizone was not included in the medium (see Schinazi, et, al., Antimicrob. Agents Chemother. 32, 1784-1787 (1988); ld., 34:1061-1.067 (1990)).

On day 6, the cells and supernatant are transterred to a 15 mil tube and centrifuged at about 900 g for 10 minutes. Five ml of supernatant are removed and the virus concentrated by centritugation at 40,000 rpm for 30 minutes (Beckman 70:1 'li rotor). The solubilized virus pellet is processed for determination of the levels of reverse transcriptase. Results are expressed in dpm/ml of sampled supernatant. Virus from smaller volumes of supernatant ( 1 ml ) can also be concentratcd by centrifugation prior to solubilization and determination of reverse transcriptase levels.

The median effective ( $E C_{s 0}$ ) concentration is determined by the median effect-method (Antimicrob. Agents Chemother. 30, 491-498 (1986). Brictly, the percent inhibition of virus, as determined from measurements of reverse transcriptase; is plotted versus the micromolar concentration of compound. The EC so $_{0}$ is the concentration of compoind al which there is a $50 \%$ inhibition of viral growth.

Mitogen stimulated uninfected human PBM cells ( $3.8 \times$ $10^{5}$ cells $/ \mathrm{ml}$ ) can be cultured in the presence and absence of drug under similar conditions as those used for the antiviral assay described above. The cells are counted after 6 days using a hemacytometer and the trypan blue exclusion method, as described by Schinazi et al., Antimicrobial Agents and Chemotherapy, 22(3), 499 (1982). The $1 \mathrm{C}_{50}$ is the concentration of compound which inhibits $50 \%$ of normal cell growth.

Table 7 provides data on the anti-HIV activity of selected compounds. Using this assay, it was determined that ( $\pm$ )-carbocyclic-D4FC.-TP (2', 3'-unsaturated-5-fluorocylidine)
exhibited an L.C $C_{50}^{i}$ of $0.4(1,4 \mathrm{M}$, and ( $\pm$ )-carbocyclic-D4C.TP ( $2^{\prime}, 3^{\prime}$-unsalurated cytidince) exhibits an $\mathrm{EC}_{50}$ of $0.38 \mu \mathrm{M}$.

## V. Anti-Ilcpatils B Activity

The ability of the active compounds to inhibit the growth of hepatitin virus in 2.2.15 cell cullures (HepGi2 cells transformed with hepatitis virion) can be evaluated as described in detail below.

A sumnary and description of the assiay for antivirad effects in this culture system and the analysis of HBV DNA has been described (Korba and Milman, 19yl, Antiviral Res., 15:217). The antiviral evaluations are optimally performed on wor separate passages of cells. Nil wells, in all plates, are secded at the same density and at the same time.

Due to the inherent variations in the levels of both intracellular and extracellular IIBV DNA, only depressions greater than $\mathbf{3 . 5 - l o l d}$ (for 1 IBV virion DNA) or 3 . (o-fiold (for HBV DNA replication intermediates) from the average levels for these HBV INA forms in untreated cells are considered to be statistically significant ( $\mathrm{P}<(1,05$ ). The levels of integraled HBV DNA in carla cellular 1DNA preparation (which remain constant on a per cell basis in these experiments) are used to calculate the levels of intracellular .HBV DNA forms, thereby ensuring that equal amounts of cellular DNA are compated between separate samples.

Typical values for extracellular. HBV virion DNA in untreated cells ranged from $5010150 \mathrm{pg} / \mathrm{ml}$ culture medium (average of approximately $76 \mathrm{pg} / \mathrm{ml}$ ). Intraccllular HBV DNA replication internediates in untreated cells ranged from 50 to $100 \mu \mathrm{~g} / \mathrm{pg}$ cell DNA (average approximately 74 $\mathrm{pg} / \mathrm{tg}$ cell DNA). In general, depressions in the levels of intracellular HBV DNA due to treatment with antiviral compounds are less pronounced, and occur more slowly, than depressions in the livels of HBV virion DN $\wedge$ (Korb: and Milman, 1991, Antiviral Res., 15:217).

The manner in which the hybridization analyses can be performed for these experiments resulted in an equivalence of approximately 1.0 pg of intracellular HBV DNA to $2-3$ genomic copies per cell and $1.0 \mathrm{pg} / \mathrm{ml}$ of extracellular HBV DNA to $3 \times 10^{5}$ viral particles $/ \mathrm{ml}$.

Toxicity aualyses were performed to assess whether any observed antiviral effects are due to a general elliet on cell viability. The method used berein are the measurement of the uptake of neutral red dye, a standard and widely used assay for cell viability in a variety of virus-host systems, including IISV and IIIV. Toxicity analyses are performed in 96 -well tlat bottomed tissuc culture plates. Cells for the toxicity analyses are cultured and treated with test compounds with the same schedule as described for the antiviral evaluations below. Each compound are tested at 4 concentrations, each in triplicate cultures (wells " $\Lambda$ ", " $B$ ". and "C"). Uptake of neural red dye are used to determine the relative level of toxicity. The absorbance of imernalized dye at 510 nm ( $\wedge_{\text {siu }}$ ) are used for the quantiative analysis. Values are presented as a percentage of the average $\mathrm{A}_{s, \ldots}$ in values in リseparate cultures of tuntreated colls maintained on the same 96 -well plate as the lesi compounds.

## VI. Anti-I lepaliis C Activity

Compcounds can exhihit anti-hepatilis $C$ activily by inhib. iting HCV prlymerase, hy inhilhiting wher enzyomes needed in the replia ation cycle, or toy wher knoww methods. A number of assays have beesi published to asesess these activitics

W() 47/13033. filed ori Sup. 27, 1990, low Emory Universily, listing (C Hagedorn and A. Remoddus as
inventors, and which claims priority to U.S. Ser. No. 60/004, 383, filed on Seplember 1995, describes an HCV polymerase assay that can be used to evaluate the activity of the compounds described hercin. This application and invention is exclusively licensed to Triangle Pharmaceuticals, Inc., Durlam, N.C. Another HCV polymerase assays has been reported by Bartholomeusz, el al., Hepatitis C virus (HCV) RNA polymerase assay using cloned HCV non-structural proteins; Antiviral Therapy 1996:1(Supp 4) 18-24.

## VI. Treatment of Abnormal Cellular Proliferation

In an alternative embodiment, the compounds are used to Ireal abnormal cellular proliferation. The compound can be cevaluated for activity by testing in a routine screen, such as that performed cost by the National Cancer Institute, or by using any other known screen, for example as described in WO 96/07413.

The extent of anticancer activity can be easily asscsscd by assaying the compound according to the procedure below in a C.EM cell or other tumor cell line assay. CEM cells are human lymphoma cells (a T-lymphoblastoid cell line that can be obtained from ATCC., Rockville, Md.). The toxicity of a compound to CEM cells provides useful information regarding the activity of the compound against tumors. The 2s toxicity is measured as $1 C_{50}$ micromolar). The $1 C_{50}$ refers to that concentration of test compound that inhibits the growth of. $50 \%$ of the tumor cells in the culture. The lower the $I C_{50}$, the mere active the compound is as an antitumor agent. In general, $2^{\prime}$-fluoro-nucleoside exhibits antitumor activity and can be used in the treatment of abnormal proliferation of cells if it exhibits a toxicity in CEM or other immortalized tumor cell line of less than 50 micromolar, more preferably, less than approximately 10 micromolar, and mosi preferably, less than 1 micromolar. Drug solutions, including cyclohex35 imide as a positive conrrol, are plated in triplicate in $50 \mu 1$ growth medium at 2 times the final concentration and allowed to equilibrate at $37^{\circ} \mathrm{C}$. in a $5 \% \mathrm{CO}_{2}$ incubator. Log phase cells are added in $50 \mu$ growth medium to a tinal concentration of $2.5 \times 10^{3}$ (CEM and SK-MEL-28), $5 \times 10^{3}$ (MMAN, MDA-MB-435s, SKMES-1, DU-145, LNCap), or $1 \times 10^{4}$ (PC-3, MCF-7) cells/well and incubated for 3 (DU145, PC-3, MMAN), 4 (MC.F-7, SK-MEL-28, CEM), or 5 (SK-MES-1, MDA-MB-435s, LNCaP) days at $37^{\circ} \mathrm{C}$. under a $5 \% \mathrm{CO}_{2}$ air atmosphere. Control wells include media alone 45 (blank) and cells plus media without drug. After growth. period, $15 \mu$ of Cell Titer 96 : kit assay dye solution (Promega, Madison, Wis.) are added to each well and the plates are incubated 8 hr at $37^{\circ} \mathrm{C}$ in a $5 \% \mathrm{CO}_{2}$ incubator. Promega Cell Titer 96 kit assay stop solution is added io each well and incubated $4-8 \mathrm{hr}$ in the incubator. Absorbance is read at 570 nm , blanking on the medium-only wells using a Biotek Biokinetics plate reader (Biotek, Winooski, $\mathrm{V}_{\mathrm{t}}$.). Average percent inhibition of growth compared to the untreated control is calculated. $1 \mathrm{C}_{50}, I \mathrm{IC}_{90}$, slope and r value 55 are calculated by the method of Chou and Talalay. Chou T-C, Talalay P. Quantitative amalysis of dose-effect relationships: The combined effects of multiple drugs or enzyme inhibilors. Adv Enzyme Regul 1984, 22:27-55.

The active compound can be administered specifically to 60 treat abnormal cell proliferation, and in particular, cell hyperproliferation. Examples of abnormal cell proliferation include, burare not limited to: benign tumors, including, but not limited to papilloma, adenoma, firoma, chondroma, osteoma, lipoma, hemangioma, lymphangioma, leiomyoma, 65 rhabdomyoma, meningioma, neuroma, ganglioneuroma, nevus, pheochromocyloma, neurilemona, fibroadenoma, teratoma, hydatidiform nole, granuosa-theca, Brenner
tamor, arrhenoblastoma; hilar cell tumor, scx cord mescnchyme, interstitial cell tumor, and thyoma as well as proliferation of smooth muscle cells in the course of development of plaques in vascular tissuc; malignant tumors (cancer), including but not limited to carcinoma, inclucling renal cell carcinoma, prostatic adcnocarcinoma, bladder carcinoma, and adenocarcinoma, fibrosarcoma, chondrosarcoma, osteosarcoma, liposarcuma, hemangiosarcoma, lymphangiosarcoma, leiomyosarcoma, rhabdomyosarcoma, myclocylic leukemia, erythroleukemia, multiple myeloma, glioma, meniogeal saticoma, thyoma, cystosarcoma phyllodes, nephroblastoma, teratoma choriocarcinoma, cutancous T-cell lymphoma (Cl(it), cutaneous tumors primary to the skin (for example, basal cell carcinoma, squamous cell carcinoma, mclanoma, and Bowen's discase), breast and other tumors infiltrating the skin, Kaposi's sarcoma, and premalignant and malignant diseases of inucosal tissues, including oral, bladter, and rectal diseascs; preneoplastic lesions, mycosis tlngoides, psoriasis, dermatomyositis, rheumatoid arthritis, viruses (for example, warts, herpes simplex, and condyloma acuminaia), molluscuin contagiosun, promalignant and malignant diseases of the female genital traci (cervix, vagina, and valva) The compounds can alsa be used to induce abortion.

In this embodiment, the active compound, or its pharma ceutically acceptable sall, is administered in an chlective: treatment anount to decrease the hyperprotiteration of the target cells. The active compound can be modifiedsoinclude a targeting moiety that concentrates the compoind at the active sitc. 'largeting noieties can include an antibody or antibody fragment that hinds io a protein on the surface of the target cell, including but not limited to cpidermal growth factor receplor (EGFR), c-Est-2 family of seceptors and vascular colhothelial growth lictor (VEGF).

## V'll. Pharmaceutical Compositons

Humans solfering from any of the dismeders described herein can the treated by athmistering to the pationt an dfective amount of the active componad or a pharmacea. lically acceptable derivalive or sall thereof in the presence of a pharmaceulically acceptable carrier or dilucilt. The aclive inaterials con be administered by any appropriate roule, lur example, orally, parenterally, inıravenously, intradermally, subcutancously, or topically, in liquid or sulid lorm.

A preferred dose of the compound for all at the aboveinentioned conditions will be in the range from aboul 11050 $\mathrm{mg} / \mathrm{kg}$, prelerably 1 to $20 \mathrm{mg} / \mathrm{kg}$, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The elfective dosage range of the pharmaceutically acceptable derivalives can be calculated based on the weight of the parent nucleoside to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as aboye using the weight of the derivative, or by other meatis known to those skilled in the art.

The compound is convenicntly administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg , preferably 70 to 1400 mg of active ingredient per unit dosuge form. A oral dosage of 50-1000 mg is usually convenient.

Ideally the active ingredient should be administered (1) achieve peak plasma concentrations ol the active compound of from about 0.2 to 70 pM , preferably about 1.0 to $10 \mu \mathrm{M}$ This may be achieved, for example, by the intravenous injection of a 0.1 to $5 \%$ solution of the active ingredient, optionally ios saline, or administered as a bilus of the active ingredicul.
.The concentration of active compound in the drug composition will depend on absorplion, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration range's set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a nutmber of smaller doses to is be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally inclucle an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or acljuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds ol a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or laclose, a disintegrating agent such as alginic acid, Primogel, ur corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange tlavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and tlavors.

The compound or a pharmaceutically acceptable derivalive or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatorics, or othe: antivirals, including other nucleoside compounds. Solutions or suspetsions used for parenteral, intradermal, subcutancous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylenc glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or melhyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate butfered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against
rapid elimination from the body, such as a controlled release formulation, including implants and microcncapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyamhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Method, for preparation of such formulations will be apparent to those skilled in the art. The materials cat also be obtained commercially from Ala Corporation.

Liposomal suspensions (including liposumes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmanutically acceptable caprices. These may ire prepared according to methods how to those skilled in the art, for example, as described in U.S. Pat No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipids) (such an slearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline: arachadoyl phosphatidyl choline, and chuleskrol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the combiner. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or miphosphak derivalives is then introduced into the container." "he container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

This invention has been described with refercone to its preferred embodiments. Variations and modifications of the invention, will be obvious to those skilled in the arm from the foregoing detailed description of the invention.

We claim:

1. A method for the treatment of hepatitis $B$ infection in humans, comprising administering to a patient in need thereof an effective treatment amount of a 2 -lltoro- $\beta$-1) nucleoside of the formula:


## wherein

Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy, and base relies to a purine or pyrimidine base;
$\mathrm{R}^{2}$ is H , monophosphate, diphosphate, Iriphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally substitufted with one or more subsituents selected from the
4. group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutidally acceptable carrier.
3. A method for the treatment of abnormal cell proliferalinn in humans, comprising administering to a patient in need thereof an effective treatment amount of a 2 'fluorsalL nucleoside of the formula:

$45^{\circ}$
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl. amino, loweralkylamino, di(lower)alkylamino;
$R^{2}$ is $H$, monophosphate, diphosphate, Iriphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally substitoted with one or more substituent selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, an amino acid, pepticle, or cholesterol; and
$\mathrm{R}^{3}$ is acyl; alkyl, phosphate; or other pharmaceutically acceptable leaving group which when administered in vino, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceulaically acceptable carrier.

US 6,348,587 B1
4. A 2 -Aluorn-( $(\beta-\mathrm{D}$ or $\beta-1)$-nucleoside of the formula:


Y゙ $\# \mathrm{~S}, \mathrm{CH}$ or $\mathrm{CHF}^{\circ}$
wherein
Base is a purine base;
$\mathrm{R}^{1}$ is $\mathrm{H} . \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, C.F, lower alkyl, amino. loweralk ylamino or di(lower)-alkylanino;
$R^{2}$ is $I I$, monophosphate, diphosphate, iriphusphate, it stabilized phosphate prodnug, acyl, or other pharmaceutically acceptable leaving group which when admintistered in viva, is capable of providing a compound wherein $R^{2}$ is H or phosphate; sulfonate ester, benzel, wherein the phenyl group is optionally sulssittuted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acicl. sulfate, phosphonic acid, phosphate, or plosphonate; a lipid, an amino acid, pepide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other paarmaceutically acceprable leaving group which when administered in vivo, is capable of being cleaved tit the parent compound, or a pharmaccutically aceeptable salt thereof, optionally in combination with a pharmaceutically asceptable carricr.
5. The compound of claim 4, wherein the base is a purinc base, $R^{2}$ is H . monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt therenf.
6. The compound of claim $t$, wherein the purine base is selected from the group consisting of guanine, adenine. hypoxanthine, 2,6-diaminopurine and 6 -chloropurine, or a pharmaceutically acceptable solt thercof.
7. A pharnaccutical composition comprising an effective treatment amount of a $\cdot 2^{2}$-fluorn-( $(\beta$-D or $\beta$ - L )-nucleoside of the formula:


$$
\mathrm{Y}=\mathrm{S}, \mathrm{CH}_{2} \text { or } \mathrm{CHF}
$$

## wherein

Base is a purine base;
$\mathrm{R}^{1}$ is $\mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alk y , amino, loweralkylamino or di(lower)-alkylamino;
$\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable laving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate cster, benzyl, wherein the phenyl group is optionally substituted with one or more substituents selected frdm the group consisting of hydroxyl, amioco, alkylamino,
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino, loweralk ylamino or di(lower)-alkylamiio;
$R^{2}$ is H. monophosphate, diphosphate, iriphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally substituted with one or more substituents selected from the group cunsisting of hydroxyl, amino, alkylamino, arylaminu, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, plosphate, or pheisphonate; a lipid, an amino acid. pephite, or chulesuend; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaccutically acceplable leaving grnup which when administered in . vivo, is capable of being cleaved to the parent compound, or a pharmaticeutically acceptable salt thereof, uptionally in combination with a pharmaceutically acceptable carrier.
11. A method for iohibiting the replication of HIV comprising administering to a host in need thereof an effective treatment amount of a $2^{\prime}$-lluoro-( $\beta$-D or $\beta$-L.)-nucluoside of' 2 the formula:

$\mathrm{Y}=\mathrm{S}, \mathrm{CH}_{2}$ or CIIF
wherein
Base is a purine base;
$\mathrm{R}^{1}$ is $\mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino. loweralkylanino or di(lower)-alkylanino;
$R^{2}$ is II, monophosphate, diphosphate, triphusphate, it ${ }^{5}$ stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group whill when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester. benzyl, wherein the phenyl groupi is optionally substituted with one or more substituents selected from the group consisting of hydruxyl, amino, alkylamino. arylamino, alkoxy, aryloxy, nitro, cyann, sullimic acid, sulfate, phowphonic acid, plosphate, of phesphonate: : s lipid, an amino acis, peptide, or cholesterol; and
$\mathrm{R}^{\frac{1}{3}}$ is acyl. alkyl, phisphati, or other pharmaccultically acceptable leaving group, which when adminnslered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceplable sall thereof, oplionally in combination wilh a pharmacii. tically acceptable carrier.
12. A method for the treatment of abnormal cell prolif. cration in humans comprising administering to a hos in need thereof an effective treatment amoun of a ${ }^{2}$-fluoronucleoside of the formula:

## Base is a purine base;

$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino;
$R^{2}$ is $H$, monophosphate, diphosphate, triphosphate, it slabilized phọsphate prodrug, acyl, or other pharmaceutically acceptatile leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally substituled with one or noore substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
14. Thę compound of claim 13, wherein the base is a purine base, $\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable sall thereol.
15. The compound of claim 14 , wherein the purine base is selceted from the group consisting of guaninc, adeninc, hypoxanthine, 2,6-diaminopurine and 6-chloropurine, or a pharmaccutically acceptable salt thereof.
16. A pharmaceutical composition comprising ant:lifective 5 treatment amount of a 2 -fluoro- $\beta$-L-nucleoside of The formula:


## wherein

Base is a purine base;
$\mathrm{R}^{1}$ is OH, $\mathrm{H},\left(\mathrm{OR}^{3}, \mathrm{~N}_{3}\right.$, CN , halogen, $\left(\mathrm{F}_{3}\right.$, lower alkyl, 20 amins, loweralkylamino, di(lower)alkylamins.
$R^{2}$ is $H$, monophosphate, diphosphate, triphorphate, a stabilized phosphate prodrug acyl, or other pharmaceulically acceptable leaving group which when administered in vivo, is capable of providing a compomal ?s whercin $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl. whercin the phenyl group is uptionally substituted with one or nore substituents $x$ elected from the group consisting of bydroxyl, ammo, alkylanino, arylamino, alkoxy, aryluxy, nitro, on me, sulfond acid. sulfate, so phosphenic acid, plasphate. or phosphe nate; a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, allyyl, phesphaice, or other pharmancutically acceptatle leaving group which when adminsisered in vivo, is capable of being cleaved to the parem compound, or a pharmaceutically acceptalle sall thereof, optionally in combination with a pharmaceutically acceptable carrier.
17. The composition of claim 16, wherein the base is: purine basc selected from the group consisting of guaninc, adenine, hypoxanthine, 2,6-diaminopurine and 6 -chloropurine, or a pharmaceutically acceplable sall thereof.
18. A method for the treatment of hepatitus $B$ infection comprising administering to a patient in weed thereof an 4
 the formula:

wherein
Base is a purime base:
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}_{\text {; }}$ halogen, $\mathrm{CF}_{3}$, lower alkyl, 60 amino, loweralkylanino, di(lower)alk ylaminu;
$R^{2}$ is II, monuphosphate, diphosphate, triphesphate, a stabilized phosphate prodrue acyl, or other pharmaceutically acceptahle laving group which when admenisered in vivo, is capable of providing a com- os pound whercin $R^{2}$ is $H$ or phesphate, sultomite ester. benzyl, wherein the phengl group is uphineally sulsti-

55

[^3]74
tuted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphatc, or phosphonatc; a lipid, an amino acicl, peptide, or cholestcrol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptablc carrier. .
19. A meihod for the treatment of hepatitis C infection comprising administering to a host in need thereof an elfective treatment amount of a 2 -lluoro-( $\beta-\mathrm{D}$ or $\beta$-L.)nucleoside of the formula:

wherein
Base is a purine or pyrimidine basc;
$\mathrm{R}^{1}$ is $\mathrm{OH} ;^{3} \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylanino or di(lower)alkylamino;
$\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylaplino, alkoxy, aryloxy, nitro, cyano, sultonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, an ámino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable ol being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
20. A method for the inhibition of HIV comprising administering to a host in need thereof an effective treatment. 50 amount of a 2 -fluoro- $\beta$-L-nucleoside of the formula:

wherein
Base is a purine base;
$R^{1}$ is $O H, H, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, or di(lower)alkylamino;
$\mathrm{R}^{2}$ is H , monophosphate, diphosphate iriphosphate, a stabilized phosphate prodrug, acyl, or oher pharma-
ceutically acceptable leaving group which when adminishred in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H "p phosphate; sulfonate ester. benzyl, wherein the phem! group is optiwally substi. luted with one or nore silstituents selected from the group consisting of hydroxyl, amine, alk ylamino, arylamins, alkoxy, arylosy, nitro, cyann, sulfunic acid, sulfatc, phosphonic acid, phosphate, or phosplonate, a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which whei administerel it vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptahle sall the reof, optionally in combination with a pharmaceutically acceptable carrier.
21. A method for the treatment of abnormal cellular proliferation in humans comprising administering to a host in need thereof an effiective treatment amount of a 2 '-fluoronucleoside of the formula:

wherein
Base is a purine or pyrimidine basc;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}{ }^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, aminu, loweralkylaniino or di(lower)alkylamino;
$R^{2}$ is II, monophosphate, diphosphate, Iriphosphate, a stabilizal phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administured in vivo, is capable of providius a compound wherein $R^{2}$ is H. or phosphate; sulfonate ester, benzyl, wherein the phenyl group is opstionally substituted with one or more substituents sclected from the group wosisting of hydroxyl, amino, alkylamino. arylamino, alkoxy, aryloxy, nitro, cyano, sulfinic acid, sulfate, phosphonic acid, phosphate, or plosphonate; a lipid, an amino acid, peplide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceprable leaving group which when administered ip vivo, is capable of being cleaved: io the parent compound, or a pharmaceutically acceptable sall therenf, optionally in combination with a pharmaceutically acceptable carrier.
22. A 2'-lluoro-nuclewidel 2'-lluoro- $\beta$ An-nuckenside of the formula:


- $R^{\prime}$ is $H$, monophosphate, diphosphate, triphosphate, a stabilized phosphate prodru\& acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound whectin $R^{2}$ is 11 or phosphate; sulfonate esier, benzyl, wherein the phenyl group is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, an amino acid, peptide, or cholesterol; and
$R^{k}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of bcing cleaved to the parent compound, or a pharmaceutically acceptable salt, thereof, optionally in combination with a phannaceu-' tically acceptable carner.

23. The compound ol claim 22, wherein the base is a purine base; $\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt thereof.
24. The compound of claim 23, wherein the purine base is selected from the group consisting of guanine, adenine, hypoxanthine, 2,6-cliaminopurine and 6 -chloropurine, or a pharmaceutically acceptable salt thereof.
25. A pharmaceutical composition comprising an effective tratment amount of a $2^{\prime}$-fluoro- $\beta$-L.-nucleoside of the fornula:
wherein
Base is a purine base;
$\mathrm{R}^{1}$ is $\mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\dot{\mathrm{C}} \mathrm{F}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino;
$R^{2}$ is $H$, monophosphate, diphosphate, triphosphate, a stabilized phosphate prodrug, acyl, or other pharma- ? ceutically accoptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, an-amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
26. The composition of claim 25 , wherein the base is a purine base selected from the group consisting of guanine, adenine, hypoxanthine, 2,6-diaminopurine and 6 -chloropurine, or a pharmaceutically acceptable salt thereof.
27. A method for the treatment of hepatitis $B$ infection comprising administering to a host in need thereof an effective treatment amount of a 2'- $\beta$-fluoro- $\beta$-L-nuclenside of the formula:

wherein
Base is a purine base;
$\mathrm{R}^{1}$ is OII, $\mathrm{II},\left(\mathrm{R}^{3}, \mathrm{~N}_{3}, \mathrm{CN}\right.$, halogen, $\mathrm{Cl}_{3}$, lower alkyl, amins, luweratkylamino ar di(lower)alkylaminu;
$R^{2}$ is $H$, monuphosphate, diphosphate, iriphosphate, a stabilized phosphate prodrus, acyl, or other pharmaecutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate cster, benzyl, wherein the phenyl group is oprionally substituted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylainino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sullate, phosphonic acid, phosphate, of phosphonate; a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is asiyl, alkyl, phosphate, or other pharmaceutically asceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceplable sall thereof, uptionally in combination with a pharmaciutically anceptable carrier.
28. A nethod for the treatment of hepatitis $(:$ infection comprising administering to a patient in need thereof ant effective treatment amount of a 2-fluoro- $\beta$-I. uncheoside of the formula:

wherein
Base is a purinc or pyrimidine base;
$\mathrm{R}^{1}$ is OII, II, $\mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{Cl}_{3}$, lower alkyl. amino, loweralkylamino, di(lower)alkylamin $\langle; \quad$,
$\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfomate ester, benzyl, wherein the phenyl group is optionally substiluted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylaminh, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic, acid, sulfate, phosphonic acid, phosphate, or phosphonate; a 60 lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the paren compound, or a pharmaceutically acceptable sali 65 thereof, optionally in combination with a pharmacenlically asceptable carrier.

0
29. A method for the inhibition of HIV comprising administering to a host in need thereof an effective treatment amount of a 2 '-liuoro- $\beta$-l.-nucleoside of the lormula:
wherein
Base is a purine base; $\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino or di(lower) alkylamino;
$R^{2}$ is II, monophosphate, diphosphate, triphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
30. A method for the treatment of abnormal cellular proliferation in humans comprising administering to a host in need thereof an effective treatment amount of a $2^{\prime}$-fluoro-$\beta$-L-nucleoside of the formula:

## wherein

Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is II, $\mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, $\mathrm{CF}_{3}$, lower alkyl, amino, lowerakylamino or di(lower)alkylamino;
$\mathrm{R}^{2}$ is H , monophosphate, diphosphate, Itiphosphate, a slabilized phosphate prodrug, acyl, or other pharmaceuticálly acceptable leaving group which, when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester, benzyl, wherein the phenyl grioup is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, - sulfate, phosphonic acid, phosphate, or phosphonate; a lipid, atl amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phusphate, or other pharmaceutically acceptable leaving group which when administered in
vivo, is capable of betng cleaved to the parent compound, or a pharmaceutically acceplable salt theresf, optionally in combination with a pharmaceutically acceptable ciarrier.
31. A 2 - -luoro- 3 -L-nucleoside of the formula:

wherein
Base is a purine base;
$\mathrm{R}^{1}$ is $\mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}, \mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, or di(lower)alkylamino;
$R^{2}$ is $H$, monophosphatc, diphosphatc, triphosphate, a stabilized phosphate prodrug, acyl, or other pharma. ceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester. benzyl, wherein the phenyl group is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, amino, atkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sultionic acid, sulfare, phosphonic acid, phosphate, or phosphnnate; a lipid, an amino acid, pepride, or cholesternl; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharniaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharnacueutically acceplable' salt thereof.
32. The 2'- fluoronucleoside of claim 31, wherein the bast is a purine base, $R^{2}$ is hydrogen, monophosphate, diphosphate, triphosphate or acyl, or a pharuateutically acceptable salt thereof
33. The 2'-fluoronucleoside of claim 31, wherein the purine base is selected lirom the group consisting if guanine adenine, hypoxanthine, 2, o-diaminopurinc and 6-chloropurine, or a pharnaceutically accepable sall thereof.
34. A pharmaceutical composition comprosing an effective Ireatment anmum of a ${ }^{2}$-flurno-h'L-nuclenside of the for mula:-

wherein
Base is a purine base;
$\mathrm{R}^{1}$ is $O R^{3}, \mathrm{~N}_{3},\left(\mathrm{~N}, \mathrm{CF}_{3}\right.$, lower alkyl, amino, loweralkylamino, or di(lower)alkylamino;
$\mathrm{R}^{2}$ is H , monophosphate, diphosphata triphosphate, a stabilized phosphate prodrug, acyl, or other pharnaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is $H$ or phosphate; sulfonate este, benzyl, wherein the phenyl group is optionally substituted with one or more sulssituents selecied from the

Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}, \mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower) alkylamino, or alkoxy, and base refers to a purine or pyrimidine base;
$R^{2}$ is H , monophosphate, diphosphate, triphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providinits a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulloutaice ester, benzyl, wherein the phenyl group is optionally substi. toted with one or more substituent selected from the group, consisting of hydroxyl, amino, alkylandino, arylanino, alkoxy, aryloxy, nitro, cyano, sullionic acid, sulfate, phosphoric acid, phosphate, or phosplionate; a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharquaceutically acceptable leaving group which when administered in vino, is capable of being cleaved to the parent compound, or a pharmacoutically acompanhe sill thereof.
38. A method for inhibiting the replication of IIIV comprising administering to a patient in need thereof and elective treatment amount of a 2 -fluors- $\beta$-L-nuclenside of the formola:


## wherein

Base is a purine base: .
$\mathrm{R}^{1}$ is $O \mathbb{R}^{3}, \mathrm{~N}_{3},\left(\mathrm{~N}, \mathrm{CF}_{3}\right.$, lower alkyl, ammo, loweralkylamino, or di(lower)alkylanino;
$R^{2}$ is II, monophosphate, diphosphate, triphosphate, a stabilized phosphate prodrug, acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $R^{2}$ is $H$ or phosphate; sulfonate ester, benzyl, wherein the phenyl group is optionally sulbsiitufted with one or more substituent selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfuric acid, sulfate, phosphoric acid, phosphate, or phosphonate; a lipid, an amino acid, peptide, or cholesterol; and - L -arabinonucleoside is OH or $\mathrm{OR}^{3}$.
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof.
39. The 2 -fluoro- $\beta$-D or $\beta$-L-nucleoside of claim 13, (wherein $R^{1}$ and $R^{2}$ are hydrogen.
40. The pharmaceutical composition of claim 16, wherein $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ of the $2^{2}$-fluoro- $\beta$ - L -nucleoside are hydrogen.
41. The method of claim 18 , wherein $R^{1}$ and $R^{2}$ of the 2'-fluoro- $\beta$ - L-nucleoside arc hydrogen.
42. The method of claim 20 , wherein $R^{1}$ and $R^{2}$ of the 2'-Huoro- 3 -L-nucleoside are hydrogen.
43. The method of claim 21, wherein $X$ of the 2'-fluoronucleoside is S .
44. The 2'-fuoro- $\beta$-L-nucleoside of claim 22, wherein $\mathrm{R}^{1}$ and $R^{2}$ are hydrogen.
45. The pharmaceutical composition of claim 25, where in $\mathrm{R}^{2}$ and $\mathrm{R}^{2}$ of the $2^{2}$-fluor- $\beta$ - L -nucleoside are hydrogen.
46. The method of claim 29 , wherein $R^{1}$ and $R^{2}$ of the

2 -fluoro- $\beta$-L-arabinonucleosicle are hydrogen.
47. The method of claim 27 , wherein $R^{1}$ and $R^{2}$ of the

2 '-huoro- $\beta$-L-arabinonuclcoside are hydrogen.
48. The method of claim 30, wherein X of the 2'-fluoro-$\beta$-L-arabinonucleoside is $\mathrm{CH}_{2}$.
49. The ${ }^{2}$-fluor- $\beta$-D or $\beta$-L-nucleoside of claim 13, wherein $\mathrm{R}^{1}$ is OH or $\mathrm{OR}^{3}$.
50. The pharmaceutical composition of claim 16, wherein $\mathrm{R}^{\prime}$ of the $2^{\prime}$-fluor- $\beta$-L-nucleoside is OII or $\mathrm{OR}^{3}$.
51 . The method of claim 18, wherein $\mathrm{R}^{1}$ of the $2^{\prime}$-fluors-13-1 .-nucleoside is OH or $\mathrm{OR}^{3}$.
52. The -method of claim 20; wherein $R^{1}$ of the 2'-fluoro$\beta$ - L -nucleoside is OH or $\mathrm{OR}^{3}$.
53. The 2'-Hiuoro- $\beta$-L-nuclenside of claim 22 , wherein $\mathrm{R}^{1}$ is OH or $\mathrm{OR}^{3}$.
54. The $p$ harmaceutical composition of claim 25 , wherein $\mathrm{R}^{\prime}$ of the 2 -hetero- $\beta$ - L -nucleoside is OH or $\mathrm{OR}^{3}$.
55. The method of claim 27, wherein $R^{1}$ of the $2^{\prime}$ 'flucro-3-L-arabinonucleoside is OH or $\mathrm{OR}^{3}$.

*     *         *             *                 * 


## UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 6,348,587 Bl

Page 1 of 1
APPLICATION NO. : 09/257130
DATED
: February 19, 2002
INVENTOR (S) : Raymond F. Schinazi et al.

It is certified that error appears in the above-Idenified patent and that said Lettore Patent is hereby corrected as shown below:

Column 1, line 7, "number Al32351" should read --grant numbers A132351 and Al 28731--

Signed and Sealed this
Second Day of June, 2009


JOHN DOLL.
Arcing Dircefin of the United States Paten and Trademark Office


PCT
(10) International Publication Number WO 02/057425 A2
(51) International Patent Classification':

CI IN
(21) International Application Number: PCT/US02/01531
(22) International Filing Date: 18 January $2012(18.01 .200$ )

| (25) Filing language: | . . | Eng̣lislı |
| :--- | :--- | :--- |
| (26) Publication Language: | English |  |

(30) Priority Data: 60263.313 60/282,069 60/299, 120

22 January 2001 (22.0i. 2001 )
ISS (4) 2001 (19.0 6.2001 ) ISS 60/344,528

25 a-tober 2001 ( 25.102001 )
is
25 C-tober 20Q1 (25.10.2001) US
(71) Applicants for all designated States except US): MERCK \& CO., INC. [US/US];. 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). ISIS PHARMACEUTICALS, INC. [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).
(72). Inventors; and
(75) Inventors/Applicauts (for US only): CARROLL, Steven, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). LAFEMINA, Robert, L. [US/JJS]; [26 East Lincoln Avenue, Kahway, NJ 07065-()907 (US). HALL, Dawn, L. [US/US|; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (idS). HIMMEL.BERGF.R, Amy, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). KUO, Lawrence, E. [US/US]; 126 East Lincoln Avenue. Rahway, NJ 07065-0907 (US). MACCOSS, Malcolm [(iB/US]; 126 East I lincoln Av: ene, Rahway, NJ 07065-0907 (US). OLSEN, David, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). RUTKOWSKI, Carrie, A. [US/US]; 126 East Lincoln Avenue. Rahway, NJ 07065-0907 (US). TOMASSINL, Joanne, E. [US/US]; 126 East! Lincoln Avenue, Rahway, NJ 07065-0907 (US). AN, Haoyun
[US/US]; 2292 Faraday Avenue: Carlsbad, CA 92008 (US). BHAT, Balkrishen [IN/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). BHAT, Neelima [IN/US]; 2292 Faraday Avenue, Carlsbad, C^ 92008 (US). COOK, Phillip, Dan [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). ELDRUP, Anne, B. [DK/US]; 2292 Faraday avenue, Carlsbad, CA 92008 (US). GUINOSSO, Charles; J. [US/US]; ??92 Faraday Avenue, Carlsbad, CA 92008 (US). PRHAVC, Marija [SI/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). PRAKASH, Thazha, P. [IN/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).
(74) Common Representative: MERCK \& CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
(81) Designated States (national): $\mathrm{AE}, \mathrm{AG}, \mathrm{AL}, \mathrm{AM}, \mathrm{AT}, \mathrm{AU}$, $A Z, B A, B B, B G, B R, B Y, B Z, C A, C H, C N, C O, C R, C U$, CZ, DE, DK, DM, DZ, EC., FE, ES, Fl, GB, GD, GE, GM, GM, HR, MU, ID, IL, IN, IS, JP, KL, KG, KR, KL, LC, DK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MK, MR, NO, NZ, OM, MI, PL, Pr, RD, RU, SD, SE, SG, SI, SK, Sh, TU, TM, TN, TR, TR, TR, VA, VG, US, UK, VA, YO, ZN, RM, LW.
(84) Designated States (regional): ARIPO patent. (GH, GM, KB, LS, MW, MR, SD, SL, SK, TR, JG, RM, ZN), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, Fl, FR, GB, GR, IE, IT, LU, MC, NJ., PT, SE, TR), OAPI patent (BF, BI, CF; CG, CI, CM, GA, GS, GQ, GU, ML, MR, NE, $S N, T D, T G)$.

## Published:

- without international search report and to be republished upon receipt of that report

For two-letier codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginming of each regular issue of the PCT Gazelle.
(54) Title: NUCLEOSIDE DIERIVATIVES AS INIIBITIOR:S OH: RNA-DEPENDEN'T RNA VIRAL POLYMERASE
(57) Abstract: 'lIthe present invention provides nucleoside delivatives which are inhibitors of RNA -dependent RNA viral polymerase. These compounds are inhibitors of RNA-dejendent RNA vital replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replycation, and/ur for the treatment of hepatitis 1 : infection. The invention also describes pharmaceutical compositions containing such nucleoside derivatives alone we in combination with sher agents active against RNA -dependent RNA viral infection, in particular HCV infection. Neo disclose: are methods of inhibiting RN $\wedge$-dependent RNA polymerase, inhibiting RNA dependent RNA viral replication, under treating RNA-dependent RNA , viral infection with the nucleoside derivatives of the present invention.

## TITLE OF THE INVENTION <br> NUCLEOSIDE DERIVATIVES AS INHBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE

FIELD OF THE INVENTION
The present invention provides nucleoside derivatives which are inhibitors of RNA-dependent RNA viral polymerase. These compounds are inhibitors of RNA-dependent RNA viral teplication and are useful for the treatment of RNAdependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and for the treatment of hepatitis C infection.

## BACKGROUND OF THE NVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be $2-15 \%$ of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about $20 \%$ of people clear the virus, but the rest harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their off-spring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon- $\alpha$ alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection. The 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); H. Rosen, et al., "Hepatitis C virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5: 393399 (1999); D. Moradpour, et al., "Current and evolving therapies for hepatitis C,"

## 725

European J. Gastroenterol. Hepatol., 11: 1189-1202 (1999); R. Bartenschlager, "Candidate Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40: 378-393 (1997); G.M. Laucr and B.D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345: 41-52 (2001); B.W. Dymock, "Emerging therapies for hepatitis C virus infection," Emerging Drugs, 6: 13-42 (2001); and C. Grab, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001); the contents of all of which are incorporated by reference herein in their entirety.
i) ifferent 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.

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 $\mathrm{C}, \mathrm{E} 1$, and E 2 , and the nonstructural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS 5B, 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. NS5B polymerase is therefore considered to be an essential component in the HCV replication complex [see K. Ishi, et al., "Expression of Hepatitis C Virus NS5B Protein: Characterization of Its RNA: Polymerase Activity and RNA Binding," Hepatology, 29: 1227-1235 (1999) and V. Lohmann, et al., "Biochemical and Kinetic Analyses of NS5B RNA-Dependent RNA Polymerase of the Hepatitis C Virus," Virology, 249: 108-1 18 (1998)]. Inhibition of HंCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of HCV -specific antiviral therapies.

It has now been found that nucleoside compounds of the present invention and certain derivatives thereof are potent inhibitors of RNA-dependent RNA viral replication and in particular HCV replication. The 5'-triphosphate derivatives of the nucleoside compounds are inhibitors of RNA-dependent RNA viral polymerase and in particular HCV NS5B polymerase. The instant nucleoside compounds and derivatives thereof are useful to treat RNA -dependent RNA viral infection and in particular HCV infection.

It is therefore an object of the present invention to provide nucleoside compounds and certain derivatives thereof which are useful as inhibitors of RNAdependent RNA viral polymerase and in particular as inhibitors of HCV NS5B polymerase.

It is another object of the present invention to provide nucleoside derivatives which are useful as inhibitors of the replication of an RNA-dependent RNA virus and in particular as inhibitors of the replication of hepatitis $C$ virus.

It is another object of the present invention to provide nucleoside compounds and certain derivatives which are useful in the treatment of RNAdependent RNA viral infection and in particular in the treatment of HCV 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 nucleoside compounds and derivatives thereof for use as inhibitors of RNA-dependent RNA viral polymerase and ie particular as inhibitors of HCV NS5B polymerase.
, It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside compounds and derivatives thereof for use as inhibitors of RNA-dependent RNA viral replication and in particular as inhibitors of HCV replication:

It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside compounds and derivatives thereof for use in the treatment of RNA-dependent RNA viral infection and in particular in the treatment of HCV infection:

It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside compounds and derivatives thereof in combination with other agents active against an RNA-dependent RNA virus and in particular against HCV.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral polymerase and in particular for the inhibition of HCV NS5B polymerase.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral replication and in particular for the inhibition of HCV replication.

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

It is another object of the present invention to provide nucleoside compounds and certain derivatives thereof 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 and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

It is another object of the present invention to provide for the use of the nucleoside compounds and certain derivatives thereof 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 RNAdependent RNA viral infection and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

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

## SUMMARY OF THE INVENTION

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

(I)
or a pharmaceutically acceptable salt thereof; wherein B is selected from the group consisting of

$\mathrm{A}, \mathrm{G}$, and L are each independently CH or N ;

D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2},{ }^{\text {C }} \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} 11 \mathrm{R} 11$, C-CSNR11R11, C-COOR11, C-C $=\mathrm{NH}) \mathrm{NH}_{2}$, C-hydroxy, C-C1-3 alkoxy, C-amino,
C.C1-4 alkylamino, C-di(C1-4 alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and $\mathrm{C}_{1-3}$ alkoxy;
$E$ is $N$ or $\mathrm{CR}^{5}$;
W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{9} \mathrm{R}^{10}$;
R1 is hydrogen, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{2}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy, halogen, $\mathrm{C}_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms, $\mathrm{C}_{1-10}$ alkoxy, optionally substituted with $\mathrm{C}_{1-3}$ alkoxy or 1 to 3 fluorine atoms, C2-6 alkenyloxy,

C1-4 alkylthio, $\mathrm{C}_{1-8}$ alkylcarbonyloxy, aryloxycarbonyl, azido,
amino, C1-4 alkylamino, and di( $\mathrm{C}_{1-4}$ alkyl) amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{1}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $\mathrm{R}^{1}$ and $\mathrm{R}^{3}$ is selected from the group consisting of hydrogen, hydroxy, halogen, C1-4 alkyl, optionally substituted with 1 to 3 fluorine atoms, $\mathrm{C}_{1-10}$ alkoxy, optionally substituted with hydroxy, $\mathrm{C}_{1-3}$ alkoxy, carboy, or 1 to 3 fluorine atoms,
C2-6 alkenyloxy, $\mathrm{C}_{1-4}$ alkylthio, C1-8 alkylcarbonyloxy, aryloxycarbonyl, azide, amino, C 1-4 alkylamino, and di( $\mathrm{C}_{1-4}$ alkyl) amino; or
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC}(0-4$ alkyl;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di $\left(\mathrm{C}_{1-4}\right.$ alkyl) amino, $\mathrm{C}_{3}-6$ cycloarkylamino, halogen, $\mathrm{C}_{1-4}$ alkyd, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$;
$\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2}-6$ alkenyl, $\mathrm{C}_{2}-6$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen; $\mathrm{R}^{14}$ is $\mathrm{H}, \mathrm{CF}_{3}, \mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl) amino;
$\mathrm{R}^{7}$ is hydrogen, amino, $\mathrm{C}_{1-4}$.alkylamino, $\mathrm{C}_{3-6}$ cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl) amino;
each R11 is independently H or $\mathrm{C}_{1-6}$ alkyl;
R8 is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or (C1-4 alkyl)0-2 aminomethyl;
5 R12 and R13 are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl; and
$\mathrm{R}^{9}$ and R 10 are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=0) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCIIMeCO} 2 \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl $) \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,


with the provisos that (a) when $R 1$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is fluoro, then the other of $\mathrm{R}^{3}$ and $\mathrm{R}^{4}$ is not hydrogen, halogen, azido, trifluoromethyl, $\mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, or $\mathrm{C}_{1-10}$ alkoxy; (b) when $R^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is halogen, hydroxy, $C_{1-6}$ alkoxy, or $C_{2-6}$ alkenyloxy, then the other of $R^{3}$ and $R^{4}$ is not hydrogen, fluoro, or azido; and (c) when $R^{1}$ and $R^{3}$ are hydrogen and $R^{2}$ is hydroxy, then $R^{4}$ is not hydroxy.

The present invention also provides novel compounds of structural formula IV of the indicated stereochemical configuration which are useful as inhibitors of RNA-dependent RNंA viral polymerase. The compounds of formula IV are also inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection:

(iv)
wherein B is selected from the group consisting of





$\mathrm{A}, \mathrm{G}$, and L are each independently CH or N ;
D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, C-NHCONH2, C-CONR11R11,
C-CSNR11R11, C-COOR11, C-C $=\mathrm{NH}) \mathrm{NH}_{2}$, C-hydroxy, C-C1-3 alkoxy, C-amino,
5 C-C1-4 alkylamino, C-di(C1-4 alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and $\mathrm{C}_{1-3}$ alkoxy;
E is N or CR ${ }^{5}$;
10 W is O or S ;
R 1 is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{2}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydrox $\dot{y}$,
halogen,
C1-4 alkyl, optionally substituted with 1 to 3 fluorine atoms,
$\mathrm{C}_{1-10}$ alkoxy, optionally substituted with $\mathrm{C}_{1-3}$ alkoxy or 1 to 3 fluorine atoms,
20
C2-6 alkenyloxy,
C1-4 alkylthio,
$\mathrm{C}_{1-8}$ alkylcarbonyloxy, aryloxycarbonyl,
azide,
amino,
$\mathrm{C}_{1-4}$ alkylamino, and
di( $\mathrm{C}_{1-4}$ alkyl)amino; or

R 2 is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2} ; 4$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{1}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of

> hydrogen,
hydroxy,
halogen,
$C_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms, $C_{1-10}$ alkoxy, optionally substituted with hydroxy, $C_{1-3}$ alkoxy, carboy, or 1 to 3 fluorine atoms,
C2-6 alkenyloxy, $\mathrm{C}_{1-4}$ alkylthio, C1-8 alkylcarbonyloxy, aryloxycarbonyl, azide, amino,
C1-4 alkylamino, and di( $\mathrm{C}_{1-4}$ alkyl) amino; or
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC}_{0}-4$ alkyl;
each $\mathrm{R}^{4}$ is independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \dot{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; R 5 is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2-6}$ alkenyl, $\mathrm{C}_{2}-6$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen; $\mathrm{R}^{14}$ is $\mathrm{H}, \mathrm{CF}_{3}, \mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, C3-6 cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl) amino;
$\mathrm{R}^{7}$ is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or
di( $\mathrm{C}_{1-4}$ alkyl) amino;
each R11 is independently H or $\mathrm{C}_{1-6}$ alkyl;
$\mathrm{R}^{8}$ is H , halogen, CN , carboy, $\mathrm{Cl}_{1-4}$ alkyloxycarbonyl, N 3 , amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl) $0-2$ aminomethyl;
R12 and R13 are each independently hydrogen, methyl, hydroxymethyl, or
fluoromethyl; and
$\mathrm{R}^{9}$ and R 10 are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO} 2 \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl )O(C=O)C1-4 alkyl;

provided that at least one of R 9 and R 10 is not hydroxy.
The present invention further provides novel compounds of structural formula XII of the indicated stereochemical configuration which are useful as inhibitors of RNA-dependent RNA viral polymerase and in particular of HCV NS 5B polymerase:

wherein $\mathrm{R}^{\mathrm{a}}$ and $\mathrm{R}^{\mathrm{h}}$ are each h independently selected from the group consisting of hydrogen, cyano, azido, halogen, hydroxy, mercapto, amino, $\mathrm{C}_{1}-4$ alkoxy, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, and $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-4}$ alkoxy; $\mathrm{C}_{1-4}$ alkylthio, or one to three fluorine atoms; $\mathrm{Rb}^{\mathrm{b}}$ is $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $C_{1-4}$ alkoxy, $C_{1-4}$ alkylthio, or one to three fluorine atoms;
$\mathrm{Rc}^{\mathrm{c}}$ is hydrogen, fluorine, hydroxy, mercapto, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{Cl}_{\mathrm{j}}-4$ alkyl; or $\mathrm{R}^{\mathrm{b}}$ and $\mathrm{RC}^{\mathrm{C}}$ together with the carbon atom to which they are attached form a 3- to 6-membered
saturated monocyclic ring system optionally containing a heteroatom selected from O , S , and $\mathrm{NC}_{0}-4 \mathrm{alkyl}$;
$\mathrm{Rd}^{\mathrm{d}}$ is hydrogen, cyano, nitro, $\mathrm{C}_{1-3}$ alkyl, $\mathrm{NHCONH}_{2}$, CONRjRj, CSNRjRj, COORj, $\mathrm{C}(=\mathrm{NH}) \mathrm{NH}_{2}$, hydroxy, $\mathrm{C}_{1-3}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ 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, carboy, and $\mathrm{C}_{1-3}$ alkoxy; $\mathrm{Re}^{\mathrm{e}}$ and Rf are each independently hydrogen, hydroxy, halogen, $\mathrm{C}_{1-4}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, $\mathrm{C}_{3}-6$ cycloalkylamino, di (C3-6 cycloalkyl)amino, or C4-6 cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, $\mathrm{C}_{1-4}$ alkyl, and $\mathrm{C}_{1-4}$ alkoxy;
RE is hydrogen, ${ }^{\text {C }}{ }_{1-4}$ alkyl, $\mathrm{C}_{2-4}$ alkynyl, halogen, cyano, carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, azide, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{\text {li }}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, ( $\mathrm{C}_{1-4}$ alkyl )0-2 aminomethyl, or C4-6 cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from'halogen, hydroxy, amino, $\mathrm{C}_{1-4}$ alkyl, and $\mathrm{C}_{1-4}$ alkoxy; $\mathrm{R}^{\mathrm{i}}$ is hydrogen, $\mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{RmRn}^{n}$; each Rj is independently hydrogen or $\mathrm{C}_{1-6}$ alkyl;
$\mathrm{R}^{\mathrm{k}}$ and $\mathrm{Rl}^{\mathrm{l}}$ are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl; and
Rm and Rn are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=0) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl) $\mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,

with the proviso that when $R^{a}$ and $R^{c}$ are $\alpha$-hydroxy, $\mathrm{Re}^{\mathrm{e}}$ is amino, $\mathrm{R}^{\mathrm{b}}$ is $\beta$-methyl and $\mathrm{Rh}^{h}$ is hydrogen or $\mathrm{Rh}^{h}$ is $\beta$-methyl and $\mathrm{Rb}^{\mathrm{b}}$ is hydrogen, and $\mathrm{Rf}^{\mathrm{f}}, \mathrm{Rg}, \mathrm{Ri}^{\mathrm{i}}, \mathrm{Rk}$, and $\mathrm{Rl}^{\mathrm{l}}$ are hydrogen, then $\mathrm{Rd}^{\mathrm{d}}$ is not cyano or $\mathrm{CONH}_{2}$.

The compounds of formula XII are also inhibitors of RNA-dependent RNA viral replication and in particular of HCV replication and are useful for the treatment of RNA-dependent RNA viral infection and in particular for the treatment of HCV infection.

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 and in particular against HCV.


(I)
or a pharmaceutically acceptable salt thereof;
wherein B is selected from the group consisting of




and

$\mathrm{A}, \mathrm{G}$, and L are each independently CH or N ;
D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{Cl}_{1-3}$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} 11 \mathrm{R} 11$,

C-CSNR 11R11, C-COOR 11, C-C $\left(=\mathrm{NH}^{2}\right) \mathrm{NH}_{2}$, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C-di(Cl-4 alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and $\mathrm{C}_{1-3}$ alkoxy;
$E$ is $N$ or CR 5;
W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{9}{ }^{\mathrm{R}} 10$;
$\mathrm{R}^{1}$ is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{2}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
halogen,
$\mathrm{C}_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms, $\mathrm{C}_{1-10}$ alkox $\dot{y}$, optionally substituted with $\dot{\mathrm{C}}_{1-3}$ alkoxy or 1 to 3 fluorine atoms,
C2-6 alkenyloxy,
$\mathrm{C}_{1-4}$ alkylthio,
$\mathrm{C}_{1-8}$ alkylcarbonyloxy, aryloxýyarbonyl, azido, ámino, $\mathrm{C}_{1-4}$ alkylamino, and di( $\mathrm{C}_{1-4}$ alkyl) amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy; or 1 to 3 fluorine atoms and one of $R^{1}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
halogen,
$\mathrm{C}_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms; $\mathrm{C}_{1-10}$ alkoxy, optionally substituted with hydroxy, $\mathrm{C}_{1}-3$ alkoxy, carboxy, or 1 to 3 fluorine atoms,

> C $2-6 ~ a l k e n y l o x y, ~^{2}$ C $1-4 ~ a l k y l t h i o, ~^{\text {C }}$-8 alkylcarbonyloxy, aryloxycarbonyl, azido, amino, $\mathrm{C}_{1-4}$ alkylamino, and di(C1-4 alkyl) amino; or
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ together with the carbon atom to which they are attached form a 3- to 6di( $\mathrm{C}_{1-4}$ alkyl) amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or (C1-4 alkyl)0-2 aminomethyl;
R12 and R13 are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl; and
$\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl $) \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,


with the provisos that (a) when $R^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is fluors, then the other of $R^{3}$ and $R^{4}$ is not hydrogen, halogen, azido, trifluoromethyl, $\mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, or $\mathrm{C}_{1-10}$ alkoxy; (b) when $R^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is halogen, hydroxy, $C_{1-6}$
alkoxy, or C2-6 alkenyloxy, then the other of $\mathrm{R}^{3}$ and $\mathrm{R}^{4}$ is not hydrogen, fluoro, or azido; and (c) when $R^{1}$ and $R^{3}$ are hydrogen and $R^{2}$ is hydroxy, then $R^{4}$ is not hydroxy.

In one embodiment of the present invention is the method of inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent viral replication, and/or treating RNA-dependent RNA viral infection with a compound of structural formula II which is of the, stereochemical configuration:

(II)
wherein $B$ is

or


D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} 11 \mathrm{R} 11$, C-CSNR 11R11, C-COOR11, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C-di(Cle $C_{1-4}$ alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-
yl ), or C-(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;
$E$ is $N$ or $C-R^{5}$;
W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R} 9 \mathrm{R} \cdot 10$;
$20 \mathrm{R}^{1}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is selected from the group consisting of.
hydrogen,
hydroxy,

> halogen,
$\mathrm{C}_{1-3}$ alkyl, trifluoromethyl, C 1 -4 alkoxy, C1-4 alkylthio, $\mathrm{C}_{1}-8$ alkylcarbonyloxy, aryloxycarbonyl,
azido,
amino,
C1-4 alkylamino, and di( $\mathrm{C}_{1}-4$ alkyl)amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{1}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $\mathrm{R}^{1}$ and $\mathrm{R}^{3}$ is selected from the group consisting of
hydrogen,
hydroxy,
fluoro,
$\mathrm{C}_{1-4}$ alkyl, trifluoromethyl, C1-4 alkoxy,
$\mathrm{C}_{1-4}$ alkylthio,
$\mathrm{C}_{1}-8$ alkylcarbonyloxy,
azido,
amino,
$\mathrm{C}_{1-4}$ alkylamino, and di(C1-4 alkyl)amino; or
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3 - to 6 membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC}_{0-4}$ alkyl;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C} 1-4$ alkylamino, di( $\mathrm{C}_{1-4}$
30 alkyl)amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1}-4$ alkyl, $\mathrm{C}_{1}-4$ alkoxy, or $\mathrm{CF}_{3}$; $\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2}-6$ alkenyl, $\mathrm{C}_{2}-6$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen; R 7 is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di( $C_{1-4 ~ a l k y l) a m i n o ; ~}$
each $\mathrm{R}^{11}$ is independently H or $\mathrm{C}_{1-6}$ alkyl;

R 8 is H , halogen, CN , carboxy, $\mathrm{C}_{1}-4$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl; and $\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{C}_{1-4}$ alkyl, or

or


## D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, C-NHCONH2, C-CONR 11 R 11 ,

 alkylamino, ${ }^{\prime}$-di( $\mathrm{C}_{1}-4$ alkyl)amino, C-halogen, C -(1,3-oxazol-2-yl), C -(1,3-thiazol-2yl ), or C-(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;

W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R} 9 \mathrm{R}{ }^{10}$;
$\mathrm{R}^{1}$ is hydrogen, $\mathrm{CF}_{3}$, ur $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and
the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
fluoro,
C1-3 alkyl,
trifluoromethyl,
C1-8 alkylcarbonyloxy;
Cl-3 alkoxy, and
amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{1}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and
the other of $R 1$ and $R^{3}$ is selected from the group consisting of
hydrogen,
hydtoxy,
fluoro,
C1-3 alkyl,
trifluoromethyl,
C1-8 alkylcarbonyloxy,
Cl-3 alkoxy, and
ámino; or
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC} 0-4 \mathrm{alkyl}$;
$\mathrm{R}^{6}$ is $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino,
$\mathrm{C}_{3-6}$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$;
$\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2-6}$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen;
$\mathrm{R}^{7}$ is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di(Cl-4 alkyl)amino;
each $\mathrm{R}^{11}$ is independently H or $\mathrm{C}_{1-6}$ alkyl;
$R 8$ is $H$, halogen, $C N$, carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl; and $\mathrm{R}^{9}$ and $\mathrm{R10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{t}$-butyl, or $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=0) \mathrm{iPr}$; with the provisos that (a) when $R^{1}$ is liydrogen and $R^{2}$ is fluors, then $R^{3}$ is not hydrogen, trifluoromethyl, fluoro, $\mathrm{C}_{1-3}$ alkyl, amino, or $\mathrm{C}_{1-3}$ alkoxy; (b) when $\mathrm{R}^{1}$ is hydrogen and $R^{2}$ is fluor, hydroxy, or $C_{1-3}$ alkoxy, then $R^{3}$ is in ul hydrogen or fluors; and (c) when $R^{1}$ is hydrogen and $R^{2}$ is hydroxy, then $R^{3}$ is not $\beta$-hydroxy. In a class of this embodiment is the method of inhibiting RNAdependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with a compound of structural formula III wherein B is

and $\mathrm{W}, \mathrm{Y}$, and the R substituent are as defined under this second embodiment.
In a second class of this embodiment is the method of inhibiting RNAdependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with a compound of structural formula III wherein B is

and $\mathrm{Y}, \mathrm{D}$, and the R substituent are as defined under this second embodiment.
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 Picomaviridae viral polymerase. In a subclass of this class, the Picomaviridae viral polymerase is rhinovirus polymerase, poliovirus 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 polymerasc, West Nile virus polymerase, Japanese encephalitis virus polymerase, Banzii virus polymerase, and bovine viral diarrhea virus (BVDV) polymerase. In a subclasis 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 RNAdependent RNA viral replication is Flaviviridae viral replication or Picornaviridae viral replication. In a subclass of this class, the Picomaviridae viral replication is rhinovirus replication, poliovirus 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, Banzi 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 RNAdependent RNA viral infection is Flaviviridae viral infection or Picomaviridae viral infection. In a subclass of this class, the Picomaviridae viral infection is rhinovirus infection, poliovirus infection, or 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, Banzi virus infection, and bovine viral diarrhea virus infection. In a subclass of this subclass, the Flaviviridae viral infection is 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-dcpendent RNA viral infection wherein the compound is selected from:


3'-deoxycytidine,
2-amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl-ß-D-ribofuranosyl)-7H-pyrrolo- [2,3- $d$ ]pyrimidin-5-carbonitrile,
2-aminu-5-methyl-7.(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidin-4( 3 H )-one,
8 -azidoguanosine,
8 -aminoguanosine,
8 -bromoadenosine,
8 -aminoadenosine,
8-bromoguanosine;
3'-deooxy-3'-fluorocytidine, 3'-deoxy-3'-fluoroguanosine,
4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide,
2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidin-5-carbonitrile,
2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,
2-amino-4-chloro-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3- $d$ ]pyrimidine, .
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-thione,
2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3$d$ ]pyrimidine,
2-amino-7-( $\beta$-D-ribofuranosyl)-7 7 -pyrrolo $[2,3-\tau]$ pyrimidine, 2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
1-( $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d$ ]pyrimidin-4(3H)-one,
4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -pyrazolo [3,4- $d$ ]pyrimidine,
2-amino-6-chloro-9-( $\beta$-D-ribofuranosyl)-9H-purine,
2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-5carbonitrile,

6 -methyl-9-( $\beta$-D-ribofuranosyl)-9H1-purine,
2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-4(3H)-one, 2-amino-4-chloro-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,
2-amino-7-( $\beta$-D-arabinafuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one,
2-amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-
d]pyrimidin-5-carbonitrile,
2-amino-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d] pyrimidin-
4(3H)-one,
9-( $\beta$-D-arabinofuranosyl)-9 H -purin- $6\left(1 \frac{1}{H}\right.$ )-one,
1-( $\beta$-D-arabinofuranosyl)-1 $H$-cytosine,
2-amino-4-chloro-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,
3'-deoxy-3'-(fluoromethyl)-guanosine,
2'-amino-2'-deoxycytidine,
4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7 7 -pyrrolo[2,3- $d$ ]pyrimidin-5carbonitrile, 2'-O-methyladenosine,
4-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2;3- $d$ ]pyrimidine, 3'-amino-3'-deoxy-2'-O-methyl-adenosine, 3'-deoxy-3'-methyl-uridine, 6-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 $\dot{H}$-imidazo[4,5-c]pyridin-4(5H)-one, 6 -amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(3H)-oine,
3'-deox y-3'-fluorouridine,
3'-deoxy-3'-fluoroadenosine,
2-amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3$d]$ - pyrïnidin-5-carbonitrile,
3'-deoxy-5-methyl-uridine,
3'-deoxy-2'-O-(2-methox yethyl)-3'-methyl-5-methyluridine,
2'-amino-2'-deoxy-uridine,
2-amino-9-( $\beta$-D-arabinofuranosyl)-9H-purin-6(1H)-one,
3'-deoxy-3'-methylguanosine,

2'- $O_{-}^{-}$[4-(imidazolyl-1)butyl]guanosine, 2'-deoxy-2'-fluoroguanosine, 2'-deoxyguanosine, 2-amino-7-(2-deoxy-2-fluogro- $\beta$-D-ribofuranosyl)-7 $H$-pyrrolo[2,3-d]pyrimidin- 4(3H)-one, 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7 H -pyrrolo[2,3-d]pyrimidin-5-carbonitrile,
2-amino-5-iodo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrulu[2,3-d]pyrimidin-4(3H)one,
2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile,
2-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 2-amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3d] pyrimidin-4(3H)-one, 2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 6-amino-1-(2-O-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)one,
6-amino-1-(2-deoxy- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5F)-one, 6 -amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one,
6-amino-1-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 6-amino-1-( $\beta$-D-arabinofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5H)-one, 2'-O-[2-(N,N-diethylaminooxy)ethyl]-5-methyluridine, 5-ethynyl-2'-O-(2-methoxyethyl)-cytidine, 1-(2-C-methyl- $\beta$-D-arabinofuranosyl)uracil, 5-methyl-3'-deoxycytidine, 2-amino-2'-O-methyladenosine, 2'-deox y-2'-fluoroadenosine, 3'-deoxy-3'-fluoroadenosine, 3'-deoxy-3'-methyladenosine, 2-amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,

4-amino-7-(3-deoxy-3-fluoro-13-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-5carboxamide,
4-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-( $\beta$-D-arabinofuranosyl)-7 H -pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine; 4-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidiné (tubcridiin), 4,6-diamino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3d] pyrimidin-5-carboxamide, 4-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine, 4-amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)- 1 H -imidazo[4,5-c]pyridine, 4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -imidazo[4;5-c]pyridine,
4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo $[3,4-d]$ pyrimidine, 4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine; and the corresponding $5^{\prime}$-triphosphates, $5^{\prime}$ -
[bis(isopropyloxycarbonyloxymethyl)]monophosphates, $5^{\prime}$-mono-(S-C1-4 alkanoyl-2-thioethyl)monophosphates, and 5'-bis-(S-C1-4 alkanoyl-2thioethyl)monophosphates thereof; or a pharmaceutically acceptable salt thereof.

Further illustrative of the invention is a method for inhibiting RNAdependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection wherein the compound is selected from:

2'-O-methyl-cytidine,
2'-C-methyl-cytidinc,
3',5'-di-O-octanoyl-2'-O-methyl-cytidine,
3'-O-octanoyl-2'-O-methyl-cytidine,
4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -pyrazolo[3,4- $d$ ]pyrimidine,
4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine-5carbọnitrile,

4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d$ ]pyrimidine-5carboxamide, 2'-C-methyladenosine, 8-amino-2'-C-methyladenosine,

3'-deoxy-3'-methyl-cytidine, 4-aminu-7-(3-deoxy-3-methyl- $\beta$-D-ribofurannsyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 3'-deoxyadenosiné, 4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyirolo[2,3-d]pyrimidine, 4-amino-7-(3-deaxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carboxamide, 3'-amino-3'-deox yadenosine, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 4-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidin-5-carbonitrile, 2-amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
6-amino-1-( $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4( 5 H )-one, $3^{\prime}$-deoxyguanosine, 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)óne, 2'-O-methylguanosine,
2-amino-7-(2-O-methyt- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-5H-pyrrolo[3,2-d]pyrimidin-4( $3 H$ )-one,
7-(2-O-methyl- $\beta$-D-ribofuraṇosyl)-7H-pyrrolo[2,3-d]pyrimidine, 3'-deoxy-cytidine,
2-amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidin-4(3H)one,
2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidine-5-càrbonitrile;

2-amino-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, .
8 -azidoguanosine,
8-aminoguanosine,

5

8 -bromoadenosine, 8 -aminoadenosine, 8 -bromoguanosine, $3^{3}-\mathrm{deox} y=3^{2}=$ fluorocytidine; 3'-deoxy-3'-fluoroguanosine, 4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]-pyrimidin-5-carboxamide, 2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile, 2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d] pyrimidine, d] pyrimidine,
2-amino-4-chloro-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidine,
2-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7 $\dot{H}$-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-cl]pyrimidin-4(3H)-one,
4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-i $H$-pyrazolo[3,4- $d$ ]pyrimidine, 2-amini-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, and
2-amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3$d$ ]pyrimidin-5-carbonitrile; and the corresponding 5'-triphosphates, 5'-
[bis(isopropyloxycarbonyloxymethyl)]monophosphates, $5^{\prime}$-mono-(S-pivaloyl-2-thioethyl)monophosphates, and 5'-bis-(S-pivaloyl-2thioethyl)monophosphates therenf; or a pharmaceutically acceptable salt thereof.

Even further illustrative of the present 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 wherein the compound is selected from

2'-O-methyl-cytidine,
2'-C-methyl-cytidine, 3',5'-di-O-octanoyl-2'-O-methyl-cytidine, 3'-O-octanoyl-2'-O-methyl-cytidine, 4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -pyrazolo[3,4- $d$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine-5carbonịtrile,
4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine-5carboxamide, $2^{\prime}$ - $C$-methyladenosine,
8-amino-2'-C-methyladenosine, 8 -bromoguanosine,
8 -aminoguanosine,
8 -aminoadenosine,
4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3d] pyrimidine,
2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidin-5-carboxamide, 4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1H-pyrazolo[3,4- $d$ ]pyrimidine, 2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile; and the corresponding $5^{\prime}$-triphosphates thereof;

2'-O-methylcytidine-5'-[bis-(S'pivaloyl-2-thioethyl)phosphate],
2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7 H -pyrrolo[2,3-
‘ $d$ ]pyrimidine-5’-[bis-(S-pivaloyl-2-thioethyl)phosphate],
3'-deoxyguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], and
3'-deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate];
or a pharmaceutically acceptable salt thereof.
Yet further illustrative of the invention is a method for inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral - 28 -

## 752

replication, and/or treating RNA-dependent RNA viral infection wherein the compound is selected from:

2'-O-methylcytidine,
2'-C-methylcytidine,
$3^{\prime}, 5^{\prime}$-di-O-octanoyl-2'-O-methyl-cytidine,
3'-O-vctanoyl-2'-O-methyl-cytidine,
4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine-5carbonitrile,
4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine-5-
carboxamide,
2'-C-methyladenosine,
8-amino-2'-C-methyladenosinc,
2'-O-methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate],
2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-
d] pyrimidine-5'-[bis-( $S_{i}$ pivaloyl-2-thioethyl)phosphate], and
3'-deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]; or a pharmaceutically acceptable salt thereof.

The present invention also provides novel compounds of structural formula IV of the indicated stereochemical configuration which are useful as inhibitors of RNA-dependent RNA viral polymerase:

(IV)
wherein $B$ is selected from the group consisting of


A, G , and L are each independently CH or N ;
D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1}-3$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} 1_{\mathrm{R}} 11$, C-CSNR 11R11, C-COOR11, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4
5 alkylamino, C-di(C1-4 alkyl) amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2yl ), or C-(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;
$E$ is $N$ or $\mathrm{CR}^{5}$;
10 W is O or S ;
$\mathrm{R}^{1}$ is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is hydroxy or $\mathrm{C}_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from. the group consisting of hydrogen,
hydroxy,
halogen,
$\mathrm{C}_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms, $\mathrm{C}_{1}-10$ alkoxy, optionally substituted with $\mathrm{C}_{1}-3$ alkoxy or 1 to 3 fluorine atoms,
C2-6 alkenyloxy, $\mathrm{C}_{1}-4$ alkylthio, $\mathrm{C}_{1-8}$ alkylcarbonyloxy, aryloxycarbonyl,
azido,
amino,
$\mathrm{C}_{1-4}$ alkylamino, and di(C1-4 alkyl)amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy; or 1 to 3 fluorine atoms and one of $\mathrm{R}^{1}$ and $\mathrm{R}^{3}$ is hydroxy or $\mathrm{C}_{1-4}$ alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy, halogen, C1-4 alkyl, optionally substituted with 1 to 3 fluorine atoms; $\mathrm{C}_{1-10}$ alkoxy, optionally substituted with hydroxy, $\mathrm{C}_{1-3}$ alkoxy, carboxy, or 1 to 3 fluorine atoms, C2-6 alkenyloxy, $\mathrm{C}_{1-4}$ alkylthio, C1-8 alkylcarbonyloxyy, aryloxycarbonyl, azido, amino, $\mathrm{C}_{1-4}$ alkylamino, and di( $\mathrm{C}_{1-4}$ alkyl)amino; or
R1 and R2 together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC} 0-4$ alkyl;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH} ; \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; $\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2-6}$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino; $\mathrm{CF}_{3}$, or halogen; R 14 is $\mathrm{H}, \mathrm{CF}_{3}, \mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3-6}$ cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl)amino;
$\mathrm{R}^{7}$ is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl)amino; each R11 is independently H or $\mathrm{C}_{1-6}$ alkyl; $\mathrm{R}^{8}$ is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, N 3 , amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or (C1-4 alkyl)0-2 aminomethyl;

R12 and R13 are each independently hydrogen or methyl; and
$R 9$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=0) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl $) \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,


5 provided that at least one of $R^{9}$ and $\dot{R}^{10}$ is not hydroxy.
The compounds of formula IV are also inhibitors of RNA-dependent
RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection.

In one embodiment, there are provided novel compounds of structural formula $V$ which are of the stereochemical configuration:

(V)
wherein $B$ is.

or


D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{Cl}_{1}-3$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} 11 \mathrm{R} 11$, alkylamino, ${ }^{\prime}$ C-di( $\mathrm{C}_{1-4}$ alkyl)amino, C -halogen, C -(1,3-oxazol-2-yl), C -(1,3-thiazol-2yl ), or C -(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and Cl-3 alkoxy; W is O or S ;

E is N or $\mathrm{C}-\mathrm{R}^{5}$;
R 1 is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{2}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of
hydrogen,
hydroxy,
halogen,
C1-3 alkyl,
trifluoromethyl,
C1-4 alkoxy,
$\mathrm{C}_{\text {l-4 }}$ alkylthio,
$\mathrm{C}_{1-8}$ alkylcarbonyloxy,
aryloxycarbonyl,
azide,
amino,
$\mathrm{C}_{1-4}$ alkylamino, and
di( $\mathrm{C}_{1-4}$ alkyl) amino? or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, or $\mathrm{C}_{1-4}$-alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{1}$ and $R^{3}$ is hydroxy or $C_{1-4}$
alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of
hydrogen',
hydroxy,
fluors,
Ci-4 alkyl,
trifluoromethyl,
C1-4 alkoxy,
C1-4 alkylthio,
C1-8 alkylcarbonyloxy,
azide,
amino,
$\mathrm{C}_{1-4}$ alkylamino, and
di( $C_{1-4}$ alkyl) amino; ot
$R^{1}$ and $R^{2}$ together with the.carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC} 0-4$ alkyl;
$\mathrm{R}^{4}$ and R 6 are eách independently H , $\mathrm{OH}, \mathrm{SHI}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$
5. alkyl)amino, $\mathrm{C}_{3-6}$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; $\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2-6}$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen;
R 7 is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di(C1-4 alkyl)amino;
each $\mathrm{R}^{11}$ is independently H or $\mathrm{C}_{1-6}$ alkyl;
$\mathrm{R}^{8}$ is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl; and
$\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl, or $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl, provided that at least one of $\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ is not hydroxy. In a second embodiment, there are provided novel compounds of structural formula VI:

(VI)
wherein $B$ is

or


20 D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\left(\mathrm{N}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{Cl}_{1-3}\right.$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR}$ IIRII, C-CSNR11R11, C-COOR11, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C -di( $\mathrm{C}_{1-4}$ alkyl)amino, C -halogen, C -(1,3-oxazol-2-yl), C -(1,3-thiazol-2-
hl), or C-(imidazol-2-yl); wherein alkyl is unṣubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboy, and $\mathrm{C}_{1-3}$ alkoxy; W is O or S ;

R 1 is hydrogen, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{2}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is selected from the group consisting of hydrogen, hydroxy,
fluors,
C1-3 alkyl, trifluoromethyl, C1-3 alkoxy, C1-8 alkylcarbonyloxy, and amino; or
$\mathrm{R}^{2}$ is hydrogen! $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R 1$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy, fluors, C1-3 alkyl, trifluoromethyl; C1-3 alkoxy, $\mathrm{C}_{1}-8$ alkylcarbonyloxy, and amino; or
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3 to 6 membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC}_{0}-4$ alkyl;
R 6 is $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; R5 is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2}-6$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$; or halogen; R 7 is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di(Cl-4 alkyl) amino;
each Rll is independently H or $\mathrm{C}_{1-6}$ alkyl;
$\mathrm{R}^{K}$ is H , halogẹn, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl; and R9 and $\mathrm{K}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0)$ t-hutyl, or $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{iPr}$, provided that at least one of $\mathrm{R}^{9}$ and R 10 is not hydroxy. Illustrative of the novel compoundẹ of structural formula VI of the present invention are the following:

2'-O-methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate],
2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-
$d]$ pyrimidine-5'r[bis-( $S$-pivaloyl-2-thioethyl)phosphate],
3'-deox yguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate],
2'-O-methylguanosine-5'-[bis-( $S$-äcetyl-2-thioethyl)phosphate],
2'-O-methylguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate],
8-bromo-2'-O-methylguanosine-5'-[bis-( $S$-pivaloyl-2-thioethyl)phosphate],
2-amino-3,4-dihydro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-4-oxo-7H-pyrrolo[2,3- $d$ ]pyrimidine-5’-[bis-( $S$-pivaloyl-2-thioethyl)phosphate], 2-amino-5-bromo-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7Hpyrrodo $[2,3-d]$ pyrimidine-5'-[bis-( $S$-pivaloyl-2-thioethyl)phosphate], 5-bromo-2'-O-methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], 3'-deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], and 2'-O-methylcytidine-5’-[bis(isopropyloxycarbonyloxymethyl)]phosphate.

The present invention further provides novel compounds of structural formula XII of the indicated stereochemical configuration or a pharmaceutically acceptable salt thereof which are useful as inhibitors of RNA-dependent RNA viral polymerase:

(XII)
wherein $\mathrm{R}^{\mathrm{a}}$ and $\mathrm{R}^{\mathrm{h}}$ arc each independently selected from the group consisting of hydrogen, cyano, azido, halogen, hydroxy, mercapto, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, and $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{1-4}$ alkylthio, or one to three fluorine atoms; $\mathrm{Rb}^{\mathrm{b}}$ is $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C1-4 alkoxy, $\mathrm{C}_{1-4}$ alkylthio, or one to three fluorine atoms;
$R^{c}$ is hydrogen, fluorine, hydroxy, mercapto, C1-4 alkoxy, or $C_{1-4}$ alkyl; or $R^{b}$ and RC together with the carbon atom to which they are attached form a 3- to 6-membered saturated monocyclic ring system optionally containing a heteroatom selected from O , S , and $\mathrm{NC} 0-4$ alkyl;
$\mathrm{R}^{\mathrm{d}}$ is hydrogen, cyano, nitro, $\mathrm{C}_{1-3}$ alkyl, $\mathrm{NHCONH}_{2}$, CONRjRj, CSNRjRj, COORj, $\mathrm{C}(=\mathrm{NH}) \mathrm{NH}_{2}$, hydroxy, $\mathrm{C}_{1-3}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ 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, caңboxy, and $\mathrm{C}_{1-3}$ alkoxy; :
Re and Rf are each independently hydrogen, hydroxy, halogen, $\mathrm{C}_{1-4}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylaminu, di (C1-4 alkyl) amino, $\mathrm{C}_{3}-6$ cycloalkylamino, di (C3-6 cycloalkyl)amino, or $\mathrm{C} 4-6$ cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, C1-4 alkyl, and $C_{1-4}$ alkoxy;
Ry is hydrogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{2-4}$ alkynyl, halogen, cyano, carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, azido; amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl; ( $\mathrm{C}_{1-4}$ alkyl )0-2 aminomethyl, or $\mathrm{C}_{4}-6$ cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, $\mathrm{C}_{1-4}$ alkyl, and $\mathrm{C}_{1-4}$ alkoxy; $\mathrm{R}^{\mathrm{j}}$ is hydrogen, $\mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4} ; \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(0) \mathrm{RmRn}^{2}$; each Rj is independently hydrogen or $\mathrm{C}_{1-6}$ alkyl;
$\mathrm{Rk}^{\mathrm{k}}$ and $\mathrm{R}^{\mathrm{l}}$ are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl; and
$\mathrm{Rm}^{\mathrm{m}}$ and $\mathrm{Rn}^{\mathrm{n}}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1}-4$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO} 2 \mathrm{Mc}, \mathrm{OCH}(\mathrm{C} 1-4$ alkyl $) \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,

PCT/US02/01531

 $\mathrm{Rh}^{\mathrm{h}}$ is hydragen or Rh is $\beta$-methyl and Rb is hydrogen, and $\mathrm{Rf}, \mathrm{Rg}, \mathrm{Ri}, \mathrm{Rk}$, and Rl are hydrogen, then Rd is not cyano or $\mathrm{CONH}_{2}$.

The compounds of formula XI are also inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection.

In one embodiment of the novel compounds of structural formula XII are the compounds of structural formula XII:


XIII
wherein $\mathrm{R}^{\mathrm{a}}$ is hydrogen, halogen, hydroxy, amino, or $\mathrm{C}_{1-3}$ alkoxy;
$\mathrm{Rb}^{\mathrm{b}}$ is $\mathrm{C}_{1-3}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino,
$\mathrm{C}_{1-3}$ alkoxy, $\mathrm{C}_{1-3}$ alkylthio, or one to three fluorine atoms;
$\mathrm{RC}^{\mathrm{C}}$ is hydroxy, fluoro, or $\mathrm{C}_{1-4}$ alkoxy;
Rd is hydrogen, cyano, methyl, halogen, or $\mathrm{CONH}_{2}$;
RS's is hydrogen, amino, or $\mathrm{C}_{1-4}$ alkylamino;
$\mathrm{Ri}^{\mathrm{i}}$ is hydrogen, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{PO}_{3} \mathrm{H}_{2}$; and
$\mathrm{Rc}^{\mathrm{c}}$ and $\mathrm{R}^{\mathrm{f}}$ are cach independently hydrogen, hydroxy, halogen, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, or $\mathrm{C}_{3-6}$ cycloalkylamino;
with the proviso that when $\mathrm{R}^{\mathrm{a}}$ and $\mathrm{R}^{\mathrm{c}}$ are $\alpha$-hydroxy, $\mathrm{Re}^{\mathrm{e}}$ is amino, $\mathrm{R}^{\mathrm{b}}$ is methyl, and $\mathrm{Rf}^{\mathrm{f}}, \mathrm{Rg}$, and $\mathrm{R}^{\mathrm{i}}$ are hydrogen, then $\mathrm{R}^{\mathrm{d}}$ is not cyano or $\mathrm{CONH}_{2}$.

In a second embodiment of the compounds of structural formula XII are the compounds of structural formula XII wherein:
$\mathrm{Rb}^{\mathrm{b}}$ is methyl, fluoromethyl, hydroxymethyl, difluoromethyl, trifluoromethyl, or aminomethyl;
$R^{C}$ is hydroxy, fluors, or methoxy;'
$R \mathrm{Ra}$ is hydrogen, fluor, hydroxy, amino, or methoxy;
$\mathrm{Ri}^{\mathrm{i}}$ is hydrogen or $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}$;
Kg is hydrogen or amino;
$\mathrm{Rd}^{\mathrm{d}}$ is hydrogen, cyano, methyl; halogen, or $\mathrm{CONH}_{2}$; and
Re and $\mathrm{Rf}^{\mathrm{f}}$ are each independently hydrogen, fluoro, hydroxy, or amino; with the proviso that when $R^{b}$ is $\beta$-methyl, $\mathrm{R}^{\mathrm{a}}$ and. $\mathrm{Rc}^{\mathrm{c}}$ are $\alpha$-hydroxy, $\mathrm{Re}^{\mathrm{e}}$ is amino, and $\mathrm{Rf}^{\mathrm{f}} \mathrm{Rg}$, and $\mathrm{R}^{\mathrm{i}}$ are hydrogen, then $\mathrm{Rd}^{\mathrm{d}}$ is not cyan or $\mathrm{CONH}_{2}$.

Illustrative of the novel compounds of the present invention of structural formula XIII which are useful as inhibitors of RNA-dependent RNA viral polymerase are the following:
4-amino-7-(2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-methylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-dimethylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2;3- $d$ ]pyrimidine, 4-cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-vinyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine,
4-amino-7-(2-C-hydroxymethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d]$ pyrimidine-5carboxylic acid,
4-amino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2,4-diamino-7-(2-C-methyl- $\beta$-D-ribofuranosyi)-7H-pyirrolo[2,3- $d$ ]pyrimidine, 2-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
30 2-amino-4-cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine,
2-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 4-amino-7-(2-C-ethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
4-amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,

7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 $H$-pyrsolo[2,3- $d$ ]pyrimidin-4(3H)-one, 2-amino-5-methyl-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, 4-amino-7-(3-deoxy-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d] pyrimidine, 4-amino-7-(3-deoxy-2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine,
4-amino-2-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(3-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3- $c]$ ]pyrimidine, 4-amino-7-(3-C-methyl- $\beta$-D-xylofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-7-(2,4-di-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, and 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3d] pyrimidine;
and the corresponding 5'-triphosphates;
or a pharmaceutically acceptable salt thereof.
Further illustrative of the novel compounds of the present invention of structural formula XIII which are useful as inhibitors of RNA-dependent RNA viral polymerase are the following:
4-amino-7-(2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d]$ pyrimidine, 4-amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-imino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino=5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 $\dot{H}$-pyrrolo $[2,3-d]$ pyrimidine, 4-amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, and
4-amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, and the corresponding 5 '-triphosphates;
or a pharmaceutically acceptable salt thereof.
further structurally novel nucleoside derivatives of the present invention which are useful as inhibitors of RNA-dependent RNA viral polymerase are the following:
3'-deoxy-3'-methyl-cytidine;
3',5'-di-O-octanoyl-2'-O-methyl-cytidine, 3'-O-octanoyl-2'-O-methyl-cytidine,

4-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrroló[2,3- $d$ ]pyrimidin-5carboxamide,
2-amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidin-4(3H)-one,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 2-amino-7-(2- $O$-methyl- $\beta$-D-ribofuranosyl)-5H-pyrrolo[3,2- $d$ ]pyrimidin-4(3H)-one, 7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine, 2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidin-5-carbonitrile,
10 2-amino-5-methyl-7-(2- $\dot{O}$-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin$4(3 H)$-one,
2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carbonitrile,
2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d] pyrimidine,
2-amino-4-chloro-5-methyli 7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3d]pyrimidine, 2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidin-4(3H)thione,
20 2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuraniosyl)-7 H -pyrrolo[2,3-d]pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-orie, 2-amino-4-chloro-7-(2-deoxy-z-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
2-amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3- $d$ ]pyrimidin-5-. carbonitrile,
9-( $\beta$-D-arabinofuranosyl)-9H-purin- $6(1 \mathrm{H})$-one, 3'-amino-3'-deoxy-2'-O-methyl-adenosine,
30 8-amino-2'-C-methyladenosine,
6-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 6-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(3H)one,
3'-deoxy-2'-O-(2-methoxyethyl)-3'-methyl-5-methyluridine,

2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile;
2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carbonitrile,

2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
6-amino-1-(2-O-methyl- $\beta$-D-ribufuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 6-amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)one, 6-amino-1-(2-dcoxy-2-fluoro- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5H)-, one,
1-(2-C-methyl- $\beta$-D-arabinofuranosyl)uracil,
4-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine, 2-amino-7-(-3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7 H -pyrrolo-[2,3- $d$ ]pyrimidin-5-carboxamide,
4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1 H -pyrazolo[3,4- $d$ ]pyrimidine, 4-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 $1 /$-imidazo[4,5-c]pyridine, and 4-amino-1-(3-dcoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine; and the corresponding 5 '-triphosphates; or a pharmaceutically acceptable salt thereof.

In a further embodiment the novel compounds of the present invention arc 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 Flaviviridue virus or a Picomaviridae virus. In a subclass of this class, the Picomaviridae virus is a rhinovirus, a poliovirus, 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, Banzi virus, and bovine viral diarrhea virus (BVDV). In a subclass of this subclass, the Flaviviridae virus is hepatitis $C$ wirus.

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, isohexyl, 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 (ie., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl).

The term "cyçloheteroalkyl" is intended to include non-aromatic heterocycles containing one or two heteroatoms selected from nitrogen, oxygen and sulfur. Examples of 4-6-membered cycloheteroalkyl include azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl, imidazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, piperazinyl, and the like.

The term "alkoxy" refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., $\mathrm{C}_{1-4}$ alkoxy), or any number within this range [i.e.,; methoxy (NeO-), ethoxy, isopropoxy, etc.].

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

The term "alkylamino" refers to straight or branched alkylamines' of the number of carbon atoms specified (e.g., $\mathrm{C}_{1-4}$ alkylamino), or any number within this range [i.e., methylamino, ethylamino, isopropylàmino, $t$-butylamino, etc.].

The term "alkylsulfonyl" refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e.g., $\mathrm{C}_{1-6}$ alkylsulfonyl), or any number within this range [ie., methylsulfonyl ( $\mathrm{MeSO}_{2}-$ ), 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., $\mathrm{C}_{1-4}$ alkyloxycarbonyl), or any number within this range [ie., methyloxycarbonyl (MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl].

The term "aryl" includes both phenyl, naphthyl, and pyridyl. The aryl group is optionally substituted with one to three groups independently selected from $\mathrm{C}_{1-4}$ alkyl, halogen, cyano, nitro, trifluoromethyl, $\mathrm{C}_{1-4}$ alkoxy, and $\mathrm{C}_{1-4}$ alkylthio.

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 plurally.

The term " 5 '-triphosphate" refers to a triphosphoric acid ester derivative of the 5 '-hydroxyl group of a nucleoside compound of the present invention having the following general structural formula VII:
wherein $B, Z, R^{l}-R^{4}, R^{12}$, and $R^{13}$ are as defined above. The compounds of the present invention are also intended to include pharmaceutically acceptable salts of the triphosphatc ester as well as pharmaceutically acceptable salts of 5'-monophosphate and 5 '-diphosphate ester derivatives of the structural formulae VIII and DX, respectively,


VIII


IX

The term " 5 '-(S-acyl-2-thioethyl)phosphate" or "SATE" refers to a mono- or di-ester derivative of a 5 '-monophosphate nucleoside of the present invention of structural formulae X and XI, respectively, as well as pharmaceutically acceptable s'alls of the mono-ester,



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- $\alpha$, pegylated interferon- $\alpha$ (peginterferon- $\alpha$ ), a combination of interferon- $\alpha$ and ribavirin, a combination of peginterferon- $\alpha$ and ribavirim, a combination of interferon- $\alpha$ and levovirin, and a combination ofpeginterferon $\alpha$ and levovirin. Interferon- $\alpha$ includes, but is not limited to, recombinant interferon- $\alpha 2 a$ (such as Roferon interferon available from Hoffmànn-LaRoche, Nuṭley, NJ), pegylated interferon- $\alpha 2 \mathrm{a}$ (Pegasys ${ }^{\mathrm{TM}}$ ), interferon- $\alpha 2 b$ (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ ), pegylated interferoṇ- $\alpha 2 \mathrm{~b}$ (PegIntron ${ }^{\mathrm{TM}}$ ), a recombinant consensus interferon (such as interferon alphacon-1), and a purified interferon- $\alpha$ 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 is an amidino 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, such as LY570310 (VX-950). HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent targetfor inhibition of HCV replication, Both substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in WO 98/17679, 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, WO 01/74768, WO 01/81325, and GB2337262. 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 LMPDH. 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 admiņistered in combination with the antiviral agent amantadine ( 1 -aminoadamantitane) [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); and U.S. Patent No. 3,480,613 (Nov. 25, 1969), the contents 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-adenosine, $2^{\prime}$-C-methyl-guanosine, and 9 -(2-C-methyl- $\beta$-D-ribofuranosyl)-2,6-diaminopurine.

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 novel nucleoside compouinds and derivatives thereof 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 this invention and a pharniaceutically 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 treating 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, levovirin, viramidine, thymosin alpha-1, an inhibitor of HCV NS3 serine protease, interferon- $\alpha$, pegylated interferon- $\alpha$ (peginterferon- $\alpha$ ), a combination of interferon- $\alpha$ and ribavirin, a combination of peginterferon- $\alpha$ and ribavirin, a combination of interferon- $\alpha$ and levovirin, and a combination of peginterferon- $\alpha$ and levovirin. Interferon- $\alpha$ includes, but is not limited to, recombinant interferon- $\alpha 2$ (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), interferon-a2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), a consensus interferon, and a purified interferon- $\alpha$ 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 nucleoside compounds and derivatives thereof and their pharmaceutical compositions for the manufacture of a medicament for the inhibition of RNA-dependent RNA viral replication, in particular HCV replication, and/or the treatment of RNA-dependent RNA viral infection, in particular HCV infection. Yet a further aspect of the present invention provides for nucleoside compounds and derivatives thereof and their pharmaceutical compositions for use as a medicament for the inhibition of RNAdependent RNA viral replication, in particular HCV replication, and/or for the, treatment of RNA -dependent RNA viral infection, in particular HCV infection.

$$
\text { Y - } 48 \text { - }
$$

The pharmaceutical compositions of the present invention comprise a compound of structural formula I, IV, or XII 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 formulae I, IV, and XII 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 maybe 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; excipient such as dicalcium phosphate; a disintegrating agent such as corm 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 formulae I, IV, and XI 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 cay 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 formulae I, IV, and XII are administered orally.

For oral administration to humans, the dosage range is 0.01 to- 1000 $\mathrm{mg} / \mathrm{kg}$ body weight in divided doses. In one embodiment the dosage range is 0.1 to $100 \mathrm{mg} / \mathrm{kg}$ body weight in divided doses. In another embodiment the dosage range is
0.5 to $20 \mathrm{mg} / \mathrm{kg}$ 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 and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend nucleoside derivatives having the $\beta-D$ stereochemical configuration for the five-membered furanose ring as depicted in the structural formula below, that is, nucleoside compounds in which the substituents at $\mathrm{C}-1$ and $\mathrm{C}-4$ of the five-membered furanose ring have the $\beta$-stereochemical configuration ("up" orientation as denoted by a bold line).

$\beta$-D-
The stereochemistry of the substituents at the $\mathrm{C}-2$ and $\mathrm{C}-3$ positions of the furanose ring of the compounds of the present invention is denoted either by a dashed line which signifies that the substituent, for example R 2 in structural formula VI, has the $\alpha$ (substituent "down") configuration or a squiggly line which signifies that the substituent, for example $R^{3}$ in structural formula VI, can have either the $\alpha$ (substituent "down") or $\beta$ (substituent "up") configuration.

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 tautomer such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formulae I, IV, and XII. An example of keto-enol tautomers which are intended to be encompassed within the compounds of the present invention is illustrated below:


Compounds of structural formulae I, IV, and XII 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 chromatography using an optically active stationary phase.

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

The stereochemistry of the substituent at the $\mathrm{C}-2$ and $\mathrm{C}-3$ positions of the furanose ring of the novel compounds of the present invention of structural formula XII is denoted by squiggly lines which signifies that substituent $R^{a}, R^{b}, R^{c}$ and Rh can have either the $\alpha$ (substituent "down") or $\beta$ (substituent "up") configuration independently of one another.

(XII)

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, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, csylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabbamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate; mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N -methylglucamine ammonium salt, oleate, oxalate, pamoate (embunate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacietate, succinate, tannate, tartrate, teoclate, tosylale, 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, manganous, 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, $\mathrm{N}, \mathrm{N}$-dibenzylethylenediamine, diethylamine, 2-
diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine rcsins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Also, in the casc 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 aćyl derivatives of alcohols, such as acetate or maleate, can be employed. Included are those esters and acyl groups known in the art for mødifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

## Preparation of the Nucleoside Compounds and Derivatives of the

## Invention

 invention can be prepared following synthetic methodologies well-established in the practice of nucleoside and nucleotide chemistry. Reference is made to the following text for a description of synthetic methods used in the preparation of the compounds of the present invention: "Chemistry of Nucleosides and Nucleotides," L.B. Townsend, ed., Vols. 1:3, Plenum Press, 1988, which is incorporated by reference herein in its entirety.A representative general method for the preparation of compounds of the present invention is outlined in Scheme 1 below. This scheme illustrates the synthesis of compounds of the present invention of structural formula $1-7$ wherein the
treatment of the furanoside of formula $1-3$ with a hydrogen halide in a suitable organic solvent, such as hydrogen bromide in acetic acid, to afford the intermediate furanosyl halide 1-4. A C-1 sulfonate, such methanesulfonate ( $\mathrm{MeSO}_{2} \mathrm{O}-$ ), trifluoromethanesulfonate ( $\mathrm{Cr}_{3} \mathrm{SO}_{2} \mathrm{O}$-), or p-toluenẹcuilfonate (-OTs), may also serve as a useful leaving group in the subsequent reaction to generate the glycosidic (nucleosidic) linkage. The nucleosidic linkage is constructed by treatment of the intermediate of structural formula $\underline{1-4}$ with the metal salt (such as lithium, sodium, or potassium) of an appropriately substituted $1 H$-pyrrolo[2,3-d]pyrimidine $1-5$, such as an appropriately substituted 4 -halo-1 H -pyrrolo[2,3-d]pyrimidine, which can be generated in situ by treatment with an alkali hydride (such as sodium hydride), an alkali hydroxide (such as potassium hydroxide), an alkali carbonate (such as potassium carbonate), or an alkali hexamethyldisilazide (such as NaHMDS) in a suitable anhydrous organic solvent, such as acetonitrile, tetrahydrofuran, 1 -methyl-2pyrrolidinone, or $\mathrm{N}, \mathrm{N}$-dimethylformamide (DMF). The displacement reaction can be catalyzed by using a phase-transfer catalyst, such as TDA-1 or triethylbenzylammonium chloride, in a two-phase system (solid-liquid or liquidliquid). The optional protecting groups in the protected nucleoside of structural formula 1-6 are then cleaved following established deprotection methodologies, such as those described in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," $3^{\text {rd }}$ ed., John Wiley \& Sons, 1999. Optipnal introduction of an amino group at the 4 -position of the pyrrolof $2,3-\mathrm{d}]$ pyrimidine nucleus is effected by treatment of the 4 -halo intermediate $1-6$ with the appropriate amine, such as alcoholic ammonia or liquid ammonia, to generate a primary amine at the $\mathrm{C}-4$ position $\left(-\mathrm{NH}_{2}\right)$, an alkylamine to generate a secondary amine ( -NHR ), or a dialkylamine to generate a tertiary amine (-NRR'). A 7H-pyrrolo[2,3-d]pyrimidin-4(3H)one compound may be derived by hydrolysis of 1-6 with aqueous base, such às aqueous sodium hydroxide. Alcoholysis (such as methanolysis) of 1-6 affords a C-4 alkoxide (-OR), whereas treatment with an alkyl. mercaptide affords a C-4 alkylthio (-SR) derivative. Subsequent chemical manipulations well-known to practitioners of ordinary skill in .the art of organic/medicinal chemistry may be required to attain the desired compounds of the present invention.

## TPO DELHI 23-OE-2015 15:55

Scheme 1




The examples below provide citations to literature publications, which contain details for the preparation of final compounds or intermediates employed in the preparation of final compounds of the present invention. The nucleoside compounds of the present invention were prepared according to procedures detailed in the following examples. The examples 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 appreciate that -56. :
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

## 3'-Deoxyguanosine




This compound was prepared following the procedures described in Nucleosides Nucleotides, 13: 1049 (1994).

## EXAMPLE 2:

15 3'-Deoxy-3'-fluoroguanosine


This compound was prepared following the procedures described in $J$. Med. Chem. 34: 2195 (1991).

EXAMPLE 3

## 8-Azidoguanosine



This compound was prepared following the procedures described in 5 Chem. Charm. Bull.16: 1616 (1968).

## EXAMPLE 4

## 8-Bromoguanosine



This compound was obtained from commercial sources.
EXAMPLE 5
15
2'-O-Methylguanosine


This compound was obtained from commercial sources.

## EXAMPLE 6

## 3'-Deoxy-3'-(fluoromethyl)guanosine



To a solution of 1,2-O-diacetyl-5-O-(p-toluoyl)-3-deoxy-3-
(fluoromethyl)-D.-ribofuranose ( $257 \mathrm{mg}, 0.7 \mathrm{mmol}$ ) [prepared by a similar method as that described for the corresponding 5-O-benzyl derivative in J Med. Chem. 36: 353 (1993)] and $N^{2}$-acetyl- $O^{6}$-(diphenylcarbamoyl)guanine ( $554 \mathrm{mg}, 1.43 \mathrm{mmol}$ ) in anhydrous acetonitrile ( 6.3 mL ) was added bis(trimethylsilyl)acetamide (BSA) ( 1.03 g, 5 mmol ). The reaction mixture was stirred at reflux for 30 minutes, and the bath was removed. The reaction mixture was cooled in an ice bath and TMS-triflate ( 288 $\mathrm{mg}, 1.3 \mathrm{mmol}$ ) was added with'stirring. After addition was complete, the reaction was heated at reflux for 2 hr ., the reaction mixture was poured onto ice and extracted with chloroform ( $5 \times 10 \mathrm{~mL}$ ). The combined organic layers were washed with aqueous saturated sodium bicarbonate, brine and dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The solvent was removed under reduced pressure and the residue chromatographed over silica gel using $5 \%$ acetone/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ as the eluant to furnish the fully protected corresponding nucleoside derivative. This was dissolved in 1,4-dioxane ( 1.5 mL ) to which was added $40 \% \mathrm{MeNH}_{2} / \mathrm{H}_{2} \mathrm{O}(1.3 \mathrm{~g}, 17 \mathrm{mmol})$. The reaction mixture was stirred for 1
day, evaporated and the residue crystallized with ether/ MeOH to provide the title compound ( 58 mg ). ${ }^{1} \mathrm{H}$ NM. MR (DMSO- $d_{6}$ ): $\delta 2.7 \dot{6}-2.67(\mathrm{~m}, 1 \mathrm{H}) ; 3.55-3.50(\mathrm{~m}, 1 \mathrm{H})$, 2.76-2.67 (m, 1H); 3.71-3.66(m, 1H), 4.08-4.04 (m, 1H), 4.77-4.50 (m, 3H), $5.06(\mathrm{t}$, $1 \mathrm{H}, J=5.3 \mathrm{~Hz}), 5.69(\mathrm{~d}, 1 \mathrm{H}, J=3.4 \mathrm{~Hz}), 5.86(\mathrm{~d}, 1 \mathrm{H}, J=5.1 \mathrm{~Hz}), 6.45(\mathrm{bs}, 2 \mathrm{H}), 7.97$
5 ( $\mathrm{s}, 1 \mathrm{H}$ ) , $10.59(\mathrm{~s}, 1 \mathrm{H}) .{ }^{19} \mathrm{~F}$ NMR (DMSO- $d_{6}$ ): $\delta-221.46(\mathrm{~m}, \mathrm{~F})$.

## EXAMPLE 7

10 2-Amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-5carboxamide


This compound was prepared following the procedures described in 15 Tetrahedron. Lett. 25: 4793 (1983).

## EXAMPLE 8

2-Amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-

## carbonitrile



- 60 -

This compound was prepared following the procedures described in J. Am. Chem. Soc. 98: 7870 (1976).

## EXAMPLE 9

2-Amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one


Step A: 2-Amino-7-(5-0-tert-hutyldimethylsilyl-2,3-O-isopropylidene- $\beta$-D. ribofuranosyl)-4-chloro-5-ethyl-7H-pyrrolo [2,3-d] pyrimidine
To a stirred suspension of 2-amino-4-chloro-5-ethyl-1 H -pyrrolo[2,3d] pyrimidine |described in EP 866070 (1998)] ( $1.57 \mathrm{~g}, 8 \mathrm{mmol}$ ) in dry MeCN (48 mL ) was added $\mathrm{NaH}(60 \%$ in mineral oil; $0.32 \mathrm{~g}, 8 \mathrm{mmol}$ ), and the mixture was stirred at room temperature for 1 h . A solution of 5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene- $\alpha$-D-ribofuranosyl chloride. [generated in situ from the corresponding. lactol ( $1.95 \mathrm{~g}, 6.4 \mathrm{mmol}$ ) according to Wilcox et al., Tetrahedron Lett., 27: 1011 (1986)] in dry THF ( 9.6 mL ) was added at room tẹmperature, and the mixture was stirred overnight, then evaporated to dryness. The residue was suspended in water ( 100 mL ) and extracted with EtOAc. $(200+150 \mathrm{~mL})$. The combined extracts were washed with brine, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated. The residue was purified on a silica gel column using .a solvent system of hexanes/EtOAc: 7/1. Appropriate fractions were collected and evaporated to dryness to give the title compound ( 1.4 g ) as a colorless foam:

Step B: 2-Amino-4-chloro-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine
A mixture of the compound from Step A ( $1.19 \mathrm{~g}, 2.5 \mathrm{mmol}$ ) in MeOH ( 100 mL ) and water ( 50 mL ) was stirred with DOWEX H ${ }^{+}$(to adjust pH of the mixture to 5) at room temperature for 2.5 h . The mixture was filtered and the resin
thoroughly washed with MeOH . The combined filtrate and washings were evaporated and the residue coevaporated several times with water to yield the title compound $(0.53 \mathrm{~g})$ as a white solid.

Step C: 2-Amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one
A mixture of the compound from Step B ( $104 \mathrm{mg}, 0.32 \mathrm{mmol}$ ) in 2 N aqueous NaOH ( 10 mL ) was stirred at reflux temperature for 15 min . The solution was cooled in ice bath, neutralized with 2 N aqueous HCl , and evaporated to dryness. The residue was suspended in MeOH , mixed with silica gel, and evaporated. The solid residue was placed onto a silica gel column (packed in a solvent mixture of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 10 / 1$ ) which was eluted with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 10 / 1$ and $5 / 1$. The fractions containing the product were collected and evaporated to dryness to yield the title compound ( 48 mg ) as a white solid.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CD}_{3} \mathrm{OD}\right): \delta 1.22(\mathrm{t}, 3 \mathrm{H}), 2.69(\mathrm{q}, 2 \mathrm{H}), 3.69,3.80(2 \mathrm{~m}, 2 \mathrm{H}), 4.00(\mathrm{~m}, 1 \mathrm{H})$, $4.22(\mathrm{~m}, 1 \mathrm{H}), 4.45(\mathrm{t}, 1 \mathrm{H}), 5 ; 86(\mathrm{~d}, 1 \mathrm{H}, J=6.0 \mathrm{~Hz}), 6.60(\mathrm{~d}, 1 \mathrm{H}, J=1.2 \mathrm{~Hz})$.

## EXAMPLE 10

2-Amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrolo[2,3-d]pyrimidin-4(3H)-one


Step A: 2-Amino-7-(2,3-anhydro- $\beta$-D-ribofuranosyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidine
To a mixture of 2 -amino-7-( $\beta$-D-ribofuranosyl)-4-chloro-7H-pyrrolo[2,3- $d$ ]pyrimidine ( $1.8 \mathrm{~g}, 6.0 \mathrm{mmol}$ ) in acetonitrile ( 80 mL ) were added a solution of $\mathrm{H}_{2} \mathrm{O} / \mathrm{CH}_{3} \mathrm{CN}(1: 9,1.08 \mathrm{~mL})$ and then $\alpha$-acetoxyisobutyryl bromide ( 3.5 $\mathrm{mL}, 24 \mathrm{mmol})$ : After 2 h stirring at room temperature, saturated aqueous $\mathrm{NaHCO}_{3}$
( 170 mL ) was added and the mixture was extracted with EtOAc $(300+200 \mathrm{~mL})$. The combined organic phase was washed with brine ( 100 mL ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated to a pale yellow foamy residue. This was suspended in anhydrous MeOH ( 80 mL ) and stirred overnight with 25 mL of DOWEX OH with anhydrous MeOH ). The resin was filtered, washed thoroughly with MeOH and the combined filtrate evaporated to give a pale yellow foam (1.92 g).
Step B: 2-Amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-4-methoxy-7H-pyrrolo[2,3dlpyrimidine
A solution of $\mathrm{LiEt}_{3} \mathrm{BH} / \mathrm{THF}(1 \mathrm{M}, 75 \mathrm{~mL}, 75 \mathrm{mmol})$ was added dropwise to a cold (ice bath) dcoxygenated (Ar, 15 min ) solution of the compound from Step A ( 1.92 g ) under Ar. Stirring at $0^{\circ} \mathrm{C}$ was continued for 4 h . At this point the reaction mixture was acidified with $5 \%$ aqueous acetic acid ( 110 mL ), then purged with Ar for 1 h and and finally evaporated to a solid residue. Purification on a silica gel column úsing $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ as eluent yielded target compound as a colourless foam ( 1.01 g ).

Step C: 2-Amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine$4(3 H)$-one
A mixture of compound from Step B ( $0.4 \mathrm{~g}, 1.4 \mathrm{mmol}$ ) in 2 N aqueous $\mathrm{NaOH}(40 \mathrm{~mL})$. was stirred at reflux temperature for 3 h . The solution was cooled in ice bath, neutralized with 2 N aqueous HCl and evaporated to dryness. The residue was suspended in MeOH , mixed with silica and evaporated. The residue was placed onto a silica gel column which was eluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 10 / 1$ and $5 / 1$ to give the title compound as white solid ( 0.3 g ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.85,2.12(2 \mathrm{~m}, 2 \mathrm{H}), 3.55,3.46$ ( $2 \mathrm{dd}, 2 \mathrm{H}$ ), $4.18(\mathrm{~m}, 1 \mathrm{H}) ; 4.29$ $(\mathrm{m}, 1 \mathrm{H}), 4.85(7,1 \mathrm{H}), 5.42(\mathrm{~d}, 1 \mathrm{H}) 5.82(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}=2.4 \mathrm{~Hz}), 6.19(\mathrm{~s}, 2 \mathrm{H}), 6.23(\mathrm{~d}, 1 \mathrm{H}$, $J=3.6 \mathrm{~Hz}), 6.87(\mathrm{~d}, 1 \mathrm{H}), 10.31(\mathrm{~s}, 1 \mathrm{H})$.

## EXAMPLE 11

- 

2-Amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one


Step A: 2-Amino-4-chloro-7-(5-t-butyldimethylsilyl-2,3-O-isopropylidene- $\beta$ -
D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine
HMPT ( $10.65 \mathrm{ml}, 55 \mathrm{mmol}$ ) was added portionwise over 30 min . to a
solution of 5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-D-ribofuranose ( 13.3 g , $44 \mathrm{mmol})$, dry THF ( 135 mL ), $\mathrm{CCl}_{4}(5.62 \mathrm{~mL}, 58 \mathrm{mmol})$ under $\mathrm{N}_{2}$ at $-76^{\circ} \mathrm{C}$. After 30 min., the temp. was raised to $-20^{\circ} \mathrm{C}$. In a separate flask, a suspension of 2-amino-4-chloro-1 $H$-pyrrolo-[2,3-d]-pyrimidine ( $15 \mathrm{~g}, 89 \mathrm{mmol}$ ) in $\mathrm{CH}_{3} \mathrm{CN}(900 \mathrm{~mL}$ ) was treated at $15^{\circ} \mathrm{C}$ with $60 \% \mathrm{NaH}(3.60 \mathrm{~g} ., 90 \mathrm{mmol}$.). The reaction was stirred 30 min. whereupon the previous reaction mixture was cannulated with vigorous stirring. The reaction was stirred 16 hrs. and then concentrated in vacuo. The resulting semisolid was added to ice/water/EtOAc and extracted with EtOAc ( $3 \times 200 \mathrm{~mL}$ ), dried $\mathrm{NaSO}_{4}$, filtered and evaporated. The resulting oil was chromatographed on silica gel (EtOAc/ Hexane 1/1) to afford the product as an oil (9.0 g).

Step B:
2-Amino-4-chloro-7-(B-D-ribofuranosyl)-7H-pyrrolo 2,3 -d]pyrimidine A solution of the compound from Step A ( $5.76 \mathrm{~g}, 13 \mathrm{mmol}$ ) in $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(1200 \mathrm{~mL} / 600 \mathrm{~mL})$ and Dowex WX8-400 (4.8 g) was stirred 16 hrs . at room temperature. The resin was filtered off and the filtrate evaporated to afford the title compound as a white solid; yield 3.47 g .
${ }^{1}$ II NMR (DMSO- $d_{6}$ ): $\delta 3.56(\mathrm{~m}, 2 \mathrm{H}), 3.86(\mathrm{~m}, 1 \mathrm{H})_{r} 4.07(\mathrm{~m}, \mathrm{lH}), 4.32(\mathrm{~m}, 1 \mathrm{H}), 4.99$ $(\mathrm{t}, 1 \mathrm{H}), 5.10(\mathrm{~d}, 1 \mathrm{H}) ; 5.30(\mathrm{~d}, 1 \mathrm{H}), 6.00(\mathrm{~d}, 1 \mathrm{H}), 6.38(\mathrm{~d}, 1 \mathrm{H}), 6.71(\mathrm{~s} \mathrm{br}, 2 \mathrm{H}), 7.39(\mathrm{~d}$, lH).

Step C: 2-Amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine
A solution of the compound from Step B ( $1.0 \mathrm{~g}, 3.3 \mathrm{mmol}$ ) in dry
IMF ( 100 mL ) at $15^{\circ} \mathrm{C}$ was treated with $60 \% \mathrm{NaH}(0.14 \mathrm{~g}, 3.5 \mathrm{mmol})$. After 30
-64-

IPO DELHI 23-06-2015 15:55
min., iodomethane ( $47 \mathrm{~g}, 3.3 \mathrm{mmol}$ ) was added portionwise to the stirred solution. The reaction! was stirred at room temperature for 16 hrs . and then evaporated at a temperature below $40^{\circ} \mathrm{C}$. Thé resulting solid was chromatographed on silica gel to , afford the product as a white solid; yield 0.81 g .
$5{ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 3.25(\mathrm{~s}, 3 \mathrm{H}), 3.54(\mathrm{~m}, 2 \mathrm{H}), 3.87(\mathrm{~m}, 1 \mathrm{H}), 4.07(\mathrm{~m}, 1 \mathrm{H}), 4.22$ $(\mathrm{m}, 1 \mathrm{H}), 5.01(\mathrm{~m}, 1 \mathrm{H}), 5.16(\mathrm{~d}, 1 \mathrm{H}), 6.07(\mathrm{~d}, 1 \mathrm{H}), 6.37(\mathrm{~d}, 1 \mathrm{H}), 6.70(\mathrm{~s} \mathrm{br}, 2 \mathrm{H}), 7.40$ (s, 1H). Mass spectrum: $\mathrm{m} / \mathrm{z} 316(\mathrm{M}+1)^{+}$.

Step D: 2-Amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d lpyrimidin-4 ( 3 H )-one
A solution of the compound from Step C ( $80 \mathrm{mg}, 0.25 \mathrm{mmol}$ ) in $\mathrm{NaOH} / \mathrm{H}_{2} \mathrm{O}(1.6 \mathrm{~g} / 20 \mathrm{ml})$ was heated at reflux for 7 hrs ., whereupon the solution was adjusted with dilute HCl to a pH of 7 and then evaporated. Chromatography of the resulting solid on silica gel with EtOAc/MeOH $8 / 2$ afforded the product as a white
${ }^{1} \mathrm{H}$ NMR (DMSO-d $\mathrm{d}_{6}$ : $8.3 .2 \underset{1}{2}(\mathrm{~s}, 3 \mathrm{H}), 3.52(\mathrm{~m}, 2 \mathrm{H}) 3.81(\mathrm{~m}, 1 \mathrm{H}), 4.00(\mathrm{~m}, \mathrm{IH}), 4.19$ $(\mathrm{m}, 1 \mathrm{H}), 5.10(\mathrm{~s} \mathrm{br}, 2 \mathrm{H}), 5.95(\mathrm{~d}, \mathrm{H}), 6.27(\mathrm{~d}, 1 \mathrm{H}), 6.33(\mathrm{sbr}, 2 \mathrm{H}), 6.95(\mathrm{~d}, 1 \mathrm{H})$, 10.55 (s br, 1H).

2-Amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3$ - $d$ ]pyrimidin-4(3H)-one


This compound is described in Biochemistry, 33: 2703 (1994) and was synthesized by the following procedure:

Step A: 2-Amino-7-(5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene- $\beta$-D-ribofuranosyl)-4-chloro-5-methyl-7 H -pyrrolo[2,3-d]pyrimidine -65-

To a stirred suspension of 2-amino-4-chloro-5-methyl-1 H -pyrrolo[2,3d]pyrimidine (Liebigs Ann. Chem. 1984, 4, 708) ( $0.91 \mathrm{~g}, 5 \mathrm{mmol}$ ) in dry MeCN (30 ml ) was added NaH ( $60 \%$ in mineral oil; $0.2 \mathrm{~g}, 5 \mathrm{mmol}$ ) and the mixture was stirred at room temperature for 0.5 h . A solution of $5-\mathrm{O}$ text butyldimethylsilyl-2,3-O- isopropylidene- $\alpha$-D-ribofuranosyl chloride [generated in situ from the corresponding lactol ( $1.22 \mathrm{~g}, 4 \mathrm{mmol}$ ) according to Tetrahedron Lett. 27: 1011 (1986)] in dry THF (6 mL ) was added at room temperature, and the mixture was stirred overnight, then evaporated to dryness. The residue was suspended in water ( 100 mL ) and extracted with EtOAc ( $2 \times 100 \mathrm{~mL}$ ). The combined organic extracts were washed with brine, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated. The residue was purified on a silica gel column using a solvent system of hexanes/EtOAc: 7/1 and 5/1. Appropriate fractions were collected and evaporated to dryness to give the title compound $(0.7 \mathrm{~g})$ as a colorless foam.

Step B: 2-Amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3dlpyrimidine
A mixture of the intermediate from Step A ( $0.67 \mathrm{~g}, 1.4 \mathrm{mmol}$ ) in $\mathrm{MeOH}(70 \mathrm{ml})$ and water ( $3^{3} \mathrm{ml}$ ) was stirred with.DOWEX $\mathrm{H}^{+}$(to adjust pH of the mixture to 5 ) at room temperature for 4 h . The mixture was filtered and the resin thoroughly washed with MeOH . The combined filtrate and washings were evaporated and the residue coevaporated several times with water to yield the title compound $(0.37 \mathrm{~g})$ as a white solid.

Step C:-: 2-Amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one:
A mixture of intermediate from Step B ( $100 \mathrm{mg}, 0.32 \mathrm{mmol}$ ) in 2 N aqueous $\mathrm{NaOH}(20 \mathrm{~mL})$ was stirred at reflux temperature for 1.5 h . The solution was cooled in ice bath, neutralized with 2 N aqueous HCl and evaporated to dryness. The residue was suspended in MeOH , mixed with silica gel and evaporated. The solid residue was placed onto a silica gel column (packed in a solvent mixture of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 10 / 1$ ) which was eluted with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 10 / 1$ and $5 / 1$. The fractions containing the product were collected and evaporated to dryness to yield the title compound ( 90 mg ) as a white solid.
${ }^{1} \mathrm{H}$ NMR (DMSO- $\mathrm{d}_{6}$ ): $\delta 2.15(\mathrm{~d}, 3 \mathrm{H}), 3.47,3.50(2 \mathrm{~m}, 2 \mathrm{H}), 3.75(\mathrm{~m}, 1 \mathrm{H}), 3.97$ (m, $1 \mathrm{H}), 4.17(\mathrm{~m}, 1 \mathrm{H}), 4.89(\mathrm{t} ; \mathrm{H}), 4.96(\mathrm{~d}, 1 \mathrm{H}), 5.14(\mathrm{~d}, 1 \mathrm{H}), 5.80(\mathrm{~d}, 1 \mathrm{H}, J=6.4 \mathrm{~Hz})$, $6.14(\mathrm{~s}, 2 \mathrm{H}), 6.60(\mathrm{q}, 1 \mathrm{H}, J=1.2 \mathrm{~Hz}), 10.23(\mathrm{~s}, 1 \mathrm{H})$.

## EXAMPLE 13

## 2-Amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-

## Step A:

2-Amino-4-chloro-7- $\beta$-D-ribofuranosyl-7H-pyrrolo $2,3-d]$ pyrimidine-5-carbonitrile.
This intermediate was prepared according to J. Chem. Soc. Perkin
d]pyrimidine-5-carbonitrile
 Trans. 1.2375 (1989).

Step B: , 2-Amino-4-chloro-7-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)- $\beta$-D-ribofuranosyll-7H-pyrrolo[2,3- $d$ ]pyrimidine-5-carbonitrile To a solution of the compound from Step A ( $1.64 \mathrm{~g}, 5.00 \mathrm{mmol}$ ) in DMF ( 30 mL ) was added imidazole ( $0.681 \mathrm{~g}, 10.0 \mathrm{mmol}$ ). The solution was cooled to $0^{\circ} \mathrm{C}$ and 1,3 -dichloro-1,1,3,3-tetraisopropyldisiloxane ( $1.58 \mathrm{~g}, 5.00 \mathrm{mmol}$ ) was added dropwise: The bath was removed and the solution stirred at room temperature for 30 minutes, evaporated in vacuo to an oil, taken up in ethyl acetate ( 150 mL ) and washed with saturated aqueous sodiumbicarbonate ( 50 mL ) and with water ( 50 mL ). The organic phase was dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was purified on silica gel using ethyl acetate/hexane (1:2) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 2.05 g ) as a colorless foam.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{DMSO}-d_{6}\right): \delta 1.03(\mathrm{~m}, 28 \mathrm{H}), 3.92(\mathrm{~m}, 1 \mathrm{H}), 4.01(\mathrm{~m}, 1 \mathrm{H}), 4.12(\mathrm{~m}, 1 \mathrm{H})$, $4.24(\mathrm{~m}, 2 \mathrm{H}), 5.67(\mathrm{~m}, 1 \mathrm{H}), 5.89(\mathrm{~s}, 1 \mathrm{H}), 7.17$ (bs. 2H), $8.04(\mathrm{~s}, 1 \mathrm{H})$.

Step C: . 2-Amino-4-chloro-7-[2-O-methyl- $\beta$-D-ribofuranosyll-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile -67.

To a preacooled solution $\left(0^{\circ} \mathrm{C}\right)$ of the compound from Step B ( 1.70 g , 3.00 mmol ) in DMF ( 30 mL ) was added methyl iodide ( $426 \mathrm{mg}, 3.00 \mathrm{mmol}$ ) and then $\mathrm{NaH}(60 \%$.in mineral oil) ( $120 \mathrm{mg}, 3.00 \mathrm{mmol}$ ). The mixture was stirred at rt for 30 ninutes and then poured into a stirred mixture of saturated aqueous ammonium chloride ( 100 mL ) and ethyl acetate ( 100 mL ). The organic phase was washed with water ( 100 mL ), dried over magnesium sulfate, filtered and evaporated in vacuo. The resulting oily residue was co-evaporated three times from acetonitrile ( 10 mL ), taken up in THF ( 50 mL ) and tetrabutylammonium fluoride ( $1.1 \mathrm{mmol} / \mathrm{g}$ on silica) ( 4.45 g , 6.00 mmol ) was added. The mixture was stirred for 30 minutes, filtered and the filtrate evaporated in vacuo. The crude product was purified on silica using methanol/dichloromethane (7:93) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 359 mg ) as a colorless solid.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 3.30(\mathrm{~s}, 3 \mathrm{H}), 3.56(\mathrm{~m}, 2 \mathrm{H}) \cdot 3.91(\mathrm{~m}, 1 \mathrm{H}), 4.08(\mathrm{~m}, 1 \mathrm{H}), 4.23$
$(\mathrm{m}, 1 \mathrm{H}), 5.11(\mathrm{~m}, 1 \mathrm{H}), 5.23(\mathrm{~m}, 1 \mathrm{H}), 7.06(\mathrm{~m}, 1 \mathrm{H}), 7.16(\mathrm{bs}, 2 \mathrm{H}), 8.38(\mathrm{~s}, 1 \mathrm{H})$.

## Step D: 2-Amino-3,4-dihydro-4-oxo-7-[2-O-methyl- $\beta$-D-ribofuranosyll-7Hpyrrolof 2,3 -dlpyrimidine-5-carbonitrile <br> To a solution of the compound from Step D. in DMF ( 5.0 mL ) and

 dioxane ( 3.5 mL ) was added syn-pyridinealdoxime ( $336 \mathrm{mg}, 2.75 \mathrm{mmol}$ ) and then tetramethylguanidine ( $288 \mathrm{mg}, 2.50 \mathrm{mmol}$ ). The resulting solution was stirred overnight at rt , evaporated in vacuo and and co-evaporated three times from acetonitrile ( 20 mL ). The oily residue was purified on silica gel using methanol/dichloromethane ( $7: 93$ ) as eluent. Fractions containing the product were proled and evaporated in vacuo to give the desired product ( 103 mg ) as a colorless solid.${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 3.30(\mathrm{~s}, 3 \mathrm{H}), 3.57(\mathrm{~m}, 2 \mathrm{H}), 3.86(\mathrm{~m}, 1 \mathrm{H}), 4.00(\mathrm{~m}, 1 \mathrm{H}), 4.21$
$(\mathrm{m}, 1 \mathrm{H}), 5.07(\mathrm{~m}, 1 \mathrm{H}), 5.17(\mathrm{~m}, 1 \mathrm{H}), 5.94(\mathrm{~m}, 1 \mathrm{H}), 6.56(\mathrm{bs}, 2 \mathrm{H}), 7.93(\mathrm{~s}, 1 \mathrm{H}), 10.82$ (bs, 1 H ).

## EXAMPLE 14

2-Amino-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one


Step A: $\quad \begin{aligned} & \text { 2-Amino-4-chloro-5-methyl-7-(2-O-methyl- } \beta \text {-D-ribofuranosyl)- } 7 \mathrm{H} \text { - } \\ & : \quad \text { pyrrolo }[2,3-c l \text {-pyrimidine }\end{aligned}$
Into a solution of the compound from Example 12, Step B ( 188 mg ,
0.6 mmol ) in anhydrous DMF ( 6 mL ) was added NaH ( $60 \%$ in mineral oil; 26 mg , 0.66 mmol ). The mixture was stirred at room temperature for 0.5 h and then cooled. $\mathrm{MeI}(45 \mu \mathrm{~L})$ was added at $0^{\circ} \mathrm{C}$ and the reaction mixture allowed to warm to $15^{\circ} \mathrm{C}$ in 5 h. Then the mixture was poured into ice-water ( 20 mL ) and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ $(100+50 \mathrm{~mL})$. The combined organic extracts were washed with water $(50 \mathrm{~mL})$, brine ( 50 mL ) and dried ( $\mathrm{Na}_{2} \mathrm{SO}_{4}$ ): The evaporated residue was purified on a silica gel column with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 30 / 1$. Appropriate fractions were pooled and evaporated to yield the title compound ( 50 mg ) as a colorless glass.

Step B: : $\quad 2$-Amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-5-methyl-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one
A solution of the compound from Step A ( $50 \mathrm{mg}, 0.15 \mathrm{mmol}$ ) in 0.5 M $\mathrm{NaOMe} / \mathrm{MeOH}(4 \mathrm{~mL})$ was stirred at reflux temperature for 1.5 h . The mixture was cooled, mixed with silica gel and evaporated to dryness. The silica gel was loaded onto a silica gel column and eluted with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 30 / 1$. The fractions containing the product were collected and evaporated to yield 2-amino-7-(2-$O$-methyl- $\beta$-D-ribofuranosyl)-4-methoxy-5-methyl-7 H -pyrrolo[2,3- $d$ ]pyrimidine ( 40 $\mathrm{mg})$. This was mixed with 2 N aqueous $\mathrm{NaOH}(4 \dot{\mathrm{~m} L})$ and stirred at reflux temperature for 10 h . The mixture was cooled in ice bath, neutralized with 2 N aqueous HCl and evaporated. The solid residue was suspended in MeOH , mixed with silica gel and evaporated. The silica gel was loaded onto a silica gel column and eluted with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 5 / 1$. Appropriate fractions were pooled and evaporated to give the title compound ( 40 mg ) as a white solid.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 2.18(\mathrm{~s}, 3 \mathrm{H}), 3.26(\mathrm{~s}, 3 \mathrm{H}), 3.45,3.52(2 \mathrm{~m}, 2 \mathrm{H}), 3.82(\mathrm{~m}, 1 \mathrm{H})$, $3.97(\mathrm{dd}, 1 \mathrm{H}), 4.20(\mathrm{~m}, \mathrm{I} \mathrm{H}), 4.99((\mathrm{t}, 1 \mathrm{H}), 5.10(\mathrm{~d}, 1 \mathrm{H}), 5.94(\mathrm{~d}$, $1 \mathrm{H}, J=7.0 \mathrm{~Hz}), 6.19(\mathrm{bs}, 2 \mathrm{H}), 6.68(\mathrm{~s}, 1 \mathrm{H}), 10.60 \cdot(\mathrm{br}, 1 \mathrm{H})$.

2-Amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-dlpyrimidin-4(3H)-one


This compound was prepared following the procedures described in $J$.
Med. Chem. 38: 3957 (1995).

## EXAMPLE 16

15 2-Amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one


This compound was prepared following the procedures described in $J$.
Org. Chem. 47: 226 (1982).

20

## EXAMPLE 17

2-Amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile


Step A: 2-Amino-7-( 3 -D-arabinofuranosyl)-4-chloro-7H-pyrrolo[2,3-
d]pyrimidine-5-carbonitrile
This intermediate was prepared according to J. Chem. Soc. Perkin
Trans. 1, 2375 (1989).

Step B: $\quad$ 2-Amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
To a solution of the compound from Step A ( $163 \mathrm{mg}, 0.50 \mathrm{mmol}$ ) in DMF ( 5.0 mL ) and dioxane ( 3.5 mL ) was added syn-pyridinealdoxime ( $336 \mathrm{mg}, 2.75$ mmol ) and then tetramethylguanidine ( $288 \mathrm{mg}, 2.50 \mathrm{mmol}$ ). The resulting solution was stirred overnight at rt , evaporated in vacuo and and co-evaporated three times from acetonitrile ( 20 mL ). The oily residue was purified on silica using methanol/dichloromethane (1:4) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 72 mg ) as a colorless solid.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 3.60(\mathrm{~m} ; 2 \mathrm{H}), 3.73(\mathrm{~m}, 1 \mathrm{H}), 4.01(\mathrm{~m}, 2 \mathrm{H}), 5.06(\mathrm{~m}, 1 \mathrm{H}), 5.48$
$\left.(\mathrm{m}, 2 \mathrm{H}), 6.12(\mathrm{~m}, 1 \mathrm{H}), 6.52^{(\mathrm{bs}}, 2 \mathrm{H}\right), 7.70(\mathrm{~s}, 1 \mathrm{H}), 10.75(\mathrm{bs}, 1 \mathrm{H})$.

## EXAMPLE 18

## 2-Amino-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one



Step A 2-Amino-7-(2,3,5-tii-O-benzyl- $\beta$-D-arabinofuranosyl)-4-chloro-5-methyl-7H-pyrrolo[2,3-d]pyrimidine

To a solution of 1-O-p-nitrobenzyl-D-arabinofuranose ( $3.81 \mathrm{~g}, 6.70$ mmol ) in DCM was bubbled Br until TLC (hexane/ethylacetate (2:1)) showed complete reaction (about 30 min ). The reation mixture was filtered and evaporated in vacuo. The oily residue was taken up in acetonitrile ( 10 mL ) and added to a vigorously stirred suspension of 2-amino-4-chloro-5-methyl-7H-pyrrolo[2,3d] pyrimidine (Liebigs Ann. Chem. (1984), 4, 708) (1.11 g; 6.00 mmol ) KOH (1.12 g, 20.0 mmol ) and tris[2-(2-methox yethoxy)ethyl]amine ( $0.216 \mathrm{~g}, 0.67 \mathrm{mmol}$ ) in acetonitrile ( 80 mL ). The resulting suspension was stirred at rt for 30 min , filtered and evaporated in yacuo. The crude product was purified on silica using hexane/ethylacetate ( $3: 1$ ) as the eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 1.13 g ) as a colorless foam.

Step B: 2-Amino-7- 3 -D-arabinofuranosyl-4-chloro-5-methyl-7H-pyrrolol2,3-

To a precooled $\left(-78^{\circ} \mathrm{C}\right)$ solution of the compound from Step A $(0.99 \mathrm{~g}$, 1.7 mmol ) in dichloromethane ( 30 mL ) was added borontrichloride ( 1 M in dichloromethane) ( $17 \mathrm{miL}, 17.0 \mathrm{mmol}$ ) over a 10 min . The resulting solution was stirred at $-78^{\circ} \mathrm{C}$ for 1 h , allowed to warm to $-15^{\circ} \mathrm{C}$ and stirred for another 3 h . The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) ( 15 mL ), stirred at $-15^{\circ} \mathrm{C}$ for 30 min , and pH adjusted to 7.0 by addition of $\mathrm{NH}_{4} \mathrm{OH}$. The mixture was evaporated in vacuo and the resulting oil purified on silica using
methanol/dichloromehane (1:9) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 257 mg ) as a colorless foum.

Step C: 2-Amino-7-( $\beta$-D)-arabinofuranosyl)-5-methyl-7H-pyrrolo[2,3-dlpyrimidin-4(3H)-one
To the compound from Step B ( $157 \mathrm{mg}, 0.50 \mathrm{mmol}$ ) was added NaOH ( 2 M , aqueous) ( 2 mL ). The resulting solution was stirred at relux for lh , cooled and neutralized by addition of HCl ( 2 M , aqueous). The mixture was evaporated in vacuo and the crude product purified on silica using methanol/dichloromehane ( $2: 8$ ) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 53 mg ) as a colorless powder.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 2.13(\mathrm{~d}, 3 \mathrm{H}), 3.58(\mathrm{~m}, 2 \mathrm{H}), 3.71(\mathrm{~m}, 1 \mathrm{H}), 4.00(\mathrm{~m}, 2 \mathrm{H}), 5.09$
$(\mathrm{m}, 1 \mathrm{H}), 6.22(\mathrm{bs}, 2 \mathrm{H}), 5.50(\mathrm{~m}, 2 \mathrm{H}), 6.12(\mathrm{~m}, 1 \mathrm{H}) ; 6.64(\mathrm{~s}, 1 \mathrm{H}), 10.75(\mathrm{bs}, 1 \mathrm{H})$.

EXAMPLE 19

2-Amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one

A solution 1-O-acetyl-2-O-benzyl-5-O-(p-toluoyl)-3-deoxy-3-fluoro-D-ribofuranose ( $410 \mathrm{mg}, 1.01 \mathrm{mmol}$ ) (prepared by a modified method described for similar sugar derivatives, Helv. Chim. Acta 82: 2052 (1999) and J. Med. Chem.1991, 34,2195 ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(1.5 \mathrm{~mL})$ was cooled to $-15^{\circ} \mathrm{C}$ in a dry ice/ $\mathrm{CH}_{3} \mathrm{CN}$
5 bath. After cooling the reaction mixture for 10 min . under the argon atmosphere, $33 \%$ $\mathrm{HBr} / \mathrm{AcOH}(370 \mu \mathrm{~L}, 1.5$ equiv.) was added slowly over 20 min keeping the bath temperature around $-15^{\circ} \mathrm{C}$. After the addition was complete, the reaction mixture was stirred at $-10^{\circ} \mathrm{C}$ for 1 hr . The solvent was removed under reduced pressure and the

PCT/US02/01531
residue azeotroped with anhydrous toluene ( $5 \times 10 \mathrm{~mL}$ ). In a separate flask, 2 -amino-4-chloro- 7 H -pyrrolo[ 2,3 - $d$ ]pyrimidine ( $210 \mathrm{mg}, 1.2 \mathrm{mmol}$ ) was suspended in anhydrous $\mathrm{CH}_{3} \mathrm{CN}(10 \mathrm{~mL})$ and cooled to $-10^{\circ} \mathrm{C}$. To this was added $60 \% \mathrm{NaH}$ dispersion in oil ( 57 mg ) in two portions, and the reaction mixture was stirred for 45 min . during which time the solid dissolved and the bath temperature rose to $0^{\circ} \mathrm{C}$. The bath was removed and stirring was continued for about 20 additional min. It was cooled back to $-10^{\circ} \mathrm{C}$ and the bromo sugar, prepared above, was taken up in anhydrous $\mathrm{CH}_{3} \mathrm{CN}(1.5$ mL ) and added slowly to the anion of nucleubase. After the addition was complcte, the reaction mixture was stirred for an additional 45 min allowing the temperature of the reaction to rise to $0^{\circ} \mathrm{C}$. The bath was removed and the reaction allowed to stir at room temperature for 3 hr . Methanol was added carefully to the reaction mixture and the separated solid removed by filtration. The solvent was removed under reduced pressure and the residual oil dissolved in EtOAc $(50 \mathrm{~mL})$ and washed with water ( $3 \times 20 \mathrm{~mL}$ ). The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to give an oil. It was purified by column chromatography to furnish fully protected 2 -amino-7-(5-O-(p-toluoyl)-2-O-benzyl-3-de'oxy-3-fluoro- $\beta$-D-ribofuranosyl)-4-chloro-7H-pyrrolo[2,3- $d$ ]pyrimidine ( 190 mg ) as an $\alpha / \beta$ mixture ( $1: 1$ ) . After conversion of 4chloro to 4 -oxo by heating the compound with $2 \mathrm{~N} \mathrm{NaOH} /$ dioxane mixture at $105^{\circ} \mathrm{C}$ and after the usual workup the residue was debenzylated using $20 \mathrm{~mol} \% \mathrm{w} / \mathrm{w}$ of $10 \%$ $\mathrm{Pd} / \mathrm{C}$ and ammonium formate in refluxing methanol to give title compound after purification by HPLC; yield $\mathrm{i} 0 \%$. ESMS: calcd. for $\mathrm{C}_{11} \mathrm{H}_{13} \mathrm{FN}_{4} \mathrm{O}_{4} 284.24$, found $283.0(\mathrm{M}+1)$.

## EXAMPLE 20

## 2-Amino-3,4-dihydro-4-oxo-7-(2-deoxy- $\beta$-D-ribofuranosy])-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



## IPD DELHI 23-06-2015 15:55

This compound was prepared following.the procedures described in Synthesis 1327 (1998).

## EXAMPLE 21

5

## 6-Amino-1-( $\beta$-D-ribofuranosyl)-1 H -imidazo[4.5-c]pyridin-4(5H)-one



This compound was prepared following the conditions described in $J$. Am. Chem. Soc. 97: 2916 (1.975).

## EXAMPLE 22

## 2-Amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-5H-pyrrolo[3,2- $d$ ]pyrimidin-4-(3H)-one



To a suspension of 2 -amino- 5 H -pyrrolo[3,2- $d$ ]pyrimidin-4(3H)-one ( 9 deazaguanine) ( $0.454 \mathrm{~g}, 3.0 \mathrm{mmol}$ ) (prepared according to J.Org.Chem.1978, 43, 2536) and 2-O-methyl-1,3,5-tri-O-benzoyl- $\beta$-D-ribofuranose ( $1.54 \mathrm{~g}, 3.2 \mathrm{mmol}$ ) in dry nitromethane ( 23 mL ) at $60^{\circ} \mathrm{C}$ was added stannic chloride ( $0.54 \mathrm{~mL}, 4.5 \mathrm{mmol}$ ). The reaction mixture was maintained at this temperature for 0.5 hr ., cooled and poured onto ice-cold saturated sodium bicarbonate solution $(70 \mathrm{~mL})$. The insoluble material was filtered through florisil and washed with ethyl acetate ( $3 \times 50 \mathrm{~mL}$ ). The
filtrate was extracted with ethyl acetate ( $2 \times 50 \mathrm{~mL}$ ), and organic layer was washed with water ( $2 \times 50 \mathrm{~mL}$ ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. Chromatography of the resulting foam on silica gel with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(14: 1)$ afforded the benzoylated product $(0.419 \mathrm{~g}, 30 \%$ yield). To a suspension of the benzoylated product $(0.25 \mathrm{~g})$ in

6-Amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 1 -imidazo[4,5-clpyridine-4(5H)-one (3'-deoxy-3-deaza-guanosine)


Step A: $\quad \frac{\text { 3-Deoxy-4-O-p-toluoyl-2-O-acetyl- } \beta \text {-D-ribofuranosyl acetate }}{\text { A solution of 3-deoxy-4-O-p-toluoyl-1,2-O-isopropylidene- } \beta \text {-D- }}$ ribofuranose (Nucleosides Nucleotides 1994, 13, 1425 and Nucleosides Nucleotides $1992,11,787)(5.85 \mathrm{~g}, 20 \mathrm{mmol})$ in 64 mL of $80 \%$ acetic acid was stirred at $85^{\circ} \mathrm{C}$ overnight. The reaction mixture was concentrated and co-evaporated with toluene. The residue was dissolved in 90 mL of pyridine. Acetic anhydride ( 6 mL ) was added at $0^{\circ} \mathrm{C}$, and the reaction mixture was stirred at it for $6^{\circ} \mathrm{h}$. After condensation, the residue was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate solution, water and brine. The organic phase was dried and concentrated.

Chromatographic purification on a silica gel column using 3:1 and 2:1 hexanesEtOAc as eluent provided 5.51 g of the title compound as a clear oil. ${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.98(\mathrm{~s}, 3 \mathrm{H}), 2.09(\mathrm{~s}, 3 \mathrm{H}), 2.15-2.35(\mathrm{~m}, 2 \mathrm{H}), 2.41(\mathrm{~s}, 3 \mathrm{H}), 4.27-$ $4.42(\mathrm{~m}, \mathrm{H}), 4.46-4.58(\mathrm{~m}, \mathrm{H}), 4.65-4.80(\mathrm{~m}, 1 \mathrm{H}), 5.21-5.28(\mathrm{~m}, 1 \mathrm{H}), 6.20(\mathrm{~s}, 1 \mathrm{H})$, 7.19-7.31 (m, 2H), 7.90-8.01 (m, 2H).

Step B: Methyl 5-cyanomethyl-1-(3-deoxy-4-O-p-toluoyl-2-O-acetyl- $\beta$-D-ribofuranasyl)-1 H -imidazole-4-carboxylate A mixture of methyl 5(4)-(cyanomethyl)-1H-imidazole-4(5)carboxylate (J. Am. Chem. Soc.1976, 98, 1492 and J. Org. Chem.1963, 28, 3041) ( $1.41 \mathrm{~g}, 8.53 \mathrm{mmol}$ ), $1,1,1,3,3,3$-hexamethyldisilazane ( 20.5 mL ) and ammonium sulfate ( 4.1 mg ) was refluxed at $125^{\circ} \mathrm{C}$ under Ar atmosphere for 18 h . After evaporation, the residue was dissolved in 10 mL of dichloroethane. A solution of the compound from Step A ( $2.86 \mathrm{~g}, 8.5 \mathrm{mmol}$ ) in 10 mL of dichloroethane was added followed by addition of $\mathrm{SnCl}_{4}(1.44 \mathrm{~mL}, 3.20 \mathrm{~g})$. The resulted reaction mixture was stirred at it overnight and diluted with chloroform. The mixture was washed with aqueous sodium bicarbonate, water and brine. The organic phase was dried and concentrated. Chromatographic purification of the residue on a silica gel column using 1:1, 1:2, and 1:3 hexanes-EtOAc as eluent provided 2.06 g of the title compound as a white foam.
${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta 2.15(\mathrm{~s}, 3 \mathrm{H}), 2.28-2.40(\mathrm{~m}, 2 \mathrm{H}), 2.38(\mathrm{~s}, 3 \mathrm{H}), 3,87(\mathrm{~s}, 3 \mathrm{H}), 4.46$ (dd, $2 \mathrm{H}, \mathrm{J}=7.6,2.0 \mathrm{~Hz}$ ), $4.50-4.57(\mathrm{~m}, 1 \mathrm{H}), 4.68-4.75(\mathrm{~m}, 1 \mathrm{H}), 4.76-4.83(\mathrm{~m}, 1 \mathrm{H})$, $5.41(\mathrm{~d}, 1 \mathrm{H}, J=5.6 \mathrm{~Hz}), 5.91(\mathrm{~s}, 1 \mathrm{H}), 7.24-7.28(\mathrm{~m}, 2 \mathrm{H}), 7.80(\mathrm{~s}, 1 \mathrm{H}), 7.82-7.90(\mathrm{~m}$, $2 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta 13.1,20.7,21.6,31.5,51.8,63.5,77.9,79.2,89.8,115.1$, $126.2,129.3,129.5,131.7,135.1,144.3,163.1,166.1,170.3$.

${ }^{1} \mathrm{H}$ NMR ( $\mathrm{DMSO}_{\mathrm{d}}$ ): $\delta 2.41-2.46(\mathrm{~m}, \mathrm{IH}), 2.52-2.58(\mathrm{~m}, 1 \mathrm{H}), 3.48-3.55(\mathrm{~m}, 1 \mathrm{H})$, $3.60-3.70(\mathrm{~m}, 1 \mathrm{H}), 4.27-4.36(\mathrm{~m}, 2 \mathrm{H}), 4.97(\mathrm{t}, 1 \mathrm{H}, \mathrm{J}=5.6 \mathrm{~Hz}), 5.44(\mathrm{~s}, 1 \mathrm{H}), 5.47(\mathrm{~s}$, $1 \mathrm{H}), 5.60(\mathrm{~s}, 2 \mathrm{H}), 5.66,(\mathrm{~d}, 1 \mathrm{H}, J=4.4 \mathrm{~Hz}), 7.90(\mathrm{~s}, 1 \mathrm{H}), 10.33(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (DMSO $d_{6}$ ) $\delta 34.1,62.4,70.4,74.7,80.4,91.6,123.0,136.3,141.9,147.6,156.5$.

EXAMPLE 24

6-Amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofüranosyl)-1H-imidazo[4,5-c]pyridin-4(3H)one

This compound was prepared in a manner similar to the preparation of 2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one (Example 23).

## EXAMPLE 25

1-( $\beta$-D-Ribofuranosyl)-1H-pyrazolo[3,4- $d$ ]pyrimidin-4(3H)-one (Allopurinol riboside)

## EXAMPLE 26

9-( $\beta$-D-Arabinofuranosyl)-9 - -purin-6(1H)-one


This compound was prepared following the conditions described in $J$. Med. Chem. 18: 721 (1975).

## EXAMPLE 27

10
2-Amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $C$ ]pyrimidin-4(3H)thione


A solution of the compound from Example 11, Step C ( $1.5 \mathrm{~g}, 5 \mathrm{mmol}$ ), thiourea ( 0.4 g .5 .2 mmol .) in abs. EtCH was refluxed for 16 hrs. The solution was

## EXAMPL.E 28

2-Amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine


This compound was obtained from commercial sources.

## EXAMPLE 29

2-Amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-


This compound was prepared as described in Example 13, Steps A-C.

## EXAMPLE 30

15
2-Amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d]$ pyrimidine

$\begin{aligned} \text { Step A: } \quad & \frac{2 \text {-Amino-4-chloro-5-ethyl-7-[3,5-O-(tetraisopropyldisiloxane-1,3- }}{\text { diyl)- } \beta \text {-D-ribofuranosyl]-7H-pyrrolo }[2,3-d] \text { pyrimidine }} \\ & \text { To a solution of 2-amino-4-chloro-5-ethyl-7-( } \beta \text {-D-ribofuranosyl)-7H- }\end{aligned}$ pyrrolo $[2,3-d]$ pyrimidine $(0.300 \mathrm{~g}, 0.913 \mathrm{mmol})$ in pyridine ( 8 mL ) was added $1,3-$ dichloro-1,1,3,3-tetraisopropyldisiloxane ( $0.317 \mathrm{~g}, 1.003 \mathrm{mmol}$ ) dropwise. The solution stirred at it overmight, evaporated in vacuo to an oil, and evaporated repeatedly from acetonitrile. The crude product was purified on silica using $5 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 254 mg ) as a colorless solid.

| Step B: | 2-Amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H- |
| :---: | :---: |
|  | pyrrolo [2,3-d]pyrimidine |
|  | To a pre-cooled solution ( $0^{\circ} \mathrm{C}$ ) of the compound from step A ( 192 mg , | $0.337 \mathrm{mmol})$ in DMF ( 3 mL ) was added methyl iodide ( $45.4 \mathrm{mg}, 0.320 \mathrm{mmol}$ ) and then $\mathrm{NaH}(60 \%$ in minetal oil) $(8.10) \mathrm{mg}, 0.320 \mathrm{mmol})$. The mixture was stirred at rt for 45 minutes and then poured into a stirred mixture of saturated aqueous ammonium chloride ( 10 mL ) and ethyl acetate ( 10 mL ). The organic phase phase was washed with brine ( 10 mL ) and dried over $\mathrm{MgSO}_{4}$ and evaporated in vacuo. The resulting oily residue was taken up in THF ( 5 mL ) and tetrabutylammonium fluoride ( 1.1 $\mathrm{mmol} / \mathrm{g}$ on silica) $(0.529 \mathrm{~g}, 0.582 \mathrm{mmol})$ was added.'The mixture was stirred for 30 minutes, filtered and the filtrate evaporated in vacuo. The crude product was purified on silica using $10 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 66 mg ) as a colorless ṣolid.

${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ) $\boldsymbol{\delta} .1 .15(\mathrm{t}, 3 \mathrm{H}), 2.65(\mathrm{q}, 2 \mathrm{H}), 3.20(\mathrm{~s}, 3 \mathrm{H}), 3.51(\mathrm{~m}, 2 \mathrm{H}), 3.84$
$(\mathrm{m}, 1 \mathrm{H}), 4.04(\mathrm{~m}, 1 \mathrm{H}), 4.21(\mathrm{~m}, 1 \mathrm{H}), 4.99(\mathrm{~m}, 2 \mathrm{H}), 5.15(\mathrm{~m}, 2 \mathrm{H}), 6.07(\mathrm{~m}, 2 \mathrm{H}), 6.62$ (s br, 2H), 7.06. (s, 2H).

## EXAMPLE 31

2-Amino-4-chloro-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine

2-Amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine

|
This compound was.synthesized as described in Example, 11; Steps A-C.
15
This compound was prepared as described in Example 14, Step A.
${ }^{1} \mathrm{H}$ NMR ( $\mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 2.33(\mathrm{~s}, 3 \mathrm{H}), 3.39(\mathrm{~s}, 1 \mathrm{H}), 3.72,3.83(2 \mathrm{dd}, 2 \mathrm{H}), 4.03(\mathrm{~m}, 1 \mathrm{H})$, $4.17(\mathrm{t}, 1 \mathrm{H}), 4.39(\mathrm{dd}, 1 \mathrm{H}), 5.98(\mathrm{~d}, 1 \mathrm{H}, J=5.9 \mathrm{~Hz}), 6.7(\mathrm{bs}, 2 \mathrm{H}) ; 7.01(\mathrm{~s}, 1 \mathrm{H})$.

## EXAMPLE 32




EXAMPLE 33

2-Amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine


This compound was prepared following the procedures described in Helv. Chim. Acta 73: 1879 (1990).

2-Amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine

'The compound was prepared as described in Example 12, Steps A-B.
$10{ }^{1} \mathrm{H}$ NMR (DMSO-d $d_{6}$ ): $\delta 2.29(\mathrm{~s}, 3 \mathrm{H}), 3.54(\mathrm{~m}, 2 \mathrm{H}), 3.84(\mathrm{~m}, \mathrm{lH}), 4.04\left(\mathrm{dd}, 1 \mathrm{H}, J_{I}=\right.$ $\left.3.0, \mathrm{~J}_{2}=4.9 \mathrm{~Hz}\right), 4.80-5.50(\mathrm{bs}, 3 \mathrm{H}), 4.28(\mathrm{t}, 1 \mathrm{H}), 5.98(\mathrm{~d}, 1 \mathrm{H}, J=6.5 \mathrm{~Hz}), 6.7(\mathrm{bs}$, $2 \mathrm{H}), 7.13$ ( $\mathrm{s}, \mathrm{HI}$ ).

## EXAMPLE 35

15
2-Amino-4-chloro-5-ethyl-7-( $\beta$-D-ribofuranosyl):-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine


This compound was prepared as described in Example 9, Steps A-B. ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 2: 00(\mathrm{t}, 3 \mathrm{H}), 2.69(\mathrm{q}, 2 \mathrm{H}), 3.48\left(\mathrm{dd}, 1 \mathrm{H}, J_{J}=4.2 \mathrm{~Hz}, J_{2}=\right.$ $11.8 \mathrm{~Hz}), 3.56\left(\mathrm{dd}, 1 \mathrm{H}, J_{1}=4.3 \mathrm{~Hz}, J_{2}=11.8 \mathrm{~Hz}\right), 3.80(\mathrm{~m}, 1 \mathrm{H}), 4.02\left(\mathrm{dd}, 1 \mathrm{H}, J_{1}=\right.$

2-Amino-6-chloro-9-( $\beta$-D-ribofuranosyl)-9H-purine


This compound was obtained from commercial sources.

## EXAMPLE 37

PCT/US02/01531


This compound was prepared following the procedures described in $J$ : Chem. Soc. Perkin Trans. 1, 2375 (1989).

2-Amino-4-chloro-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolol2,3dlpyrimidine


10
This compound was prepared following the procedures described in $J$. Med. Chem. 38: 3957 (1995).

## EXAMPLE 39

2-Amino-4-chloro-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


The compound was prepared as described in Example 18, Steps A-B.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 2.24(\mathrm{~s}, 3 \mathrm{H}), 3.60(\mathrm{~m}, 3 \mathrm{H}), 3.98(\mathrm{~m}, 2 \mathrm{H}), 4.98(\mathrm{~m}, 1 \mathrm{H}), 5.43$ (bs, 2H), $6.25 .(\mathrm{s}, 1 \mathrm{H}), 6.57(\mathrm{bs}, 2 \mathrm{H}), 7,01(\mathrm{~s}, 1 \mathrm{H})$.
5
EXAMPLE 40

2'-O-Methylcytidine


10
This compound was obtained from commercial sources.
EXAMPLE 41

3'-Deoxy-3'-methylcytidine

15

-86-

WO 02/057425

This compound was prepared following the procedures described in U.S. Patent No. 3,654,262 (1972), which is incorporated by reference herein in its entirety.

## 3'-Deoxycytidine



This compound was obtained from commercial sources.

## EXAMPLE 43

3'-Deoxy-3'-fluorocytidine

15.

This compound was prepared following the procedures described in J. Med. Chem. 34: 2195 (1991).

EXAMPLE 44

20 1-( $\beta$-D-Arabinofuranosyl)-1H-cytosine


This compound was obtained from commercial sources.

## EXAMPLE 45

5
2'-Amino-2'-deoxycytidine


This compound was obtained from commercial sources.

EXAMPLE 46

3'-Deoxy-3'-methyluridine


This compound was prepared following procedures described in U.S Patent No. $3,654,262$, which is incorporated by reference herein in its entirety.

## EXAMPLE 47

5
3'-Deoxy-3'-fluorouridine


This compound was prepared following procedures described in $J$. Med. Chem. 34: 2195 (1991) a nd FEBS Lett. 250: 139 (1989).

3'-Deoxy-5-methyluridine


This compound was obtained from commercial sources.

## EXAMPLE 49

3'-Dcoxy-2'-O-(2-methoxyethyl)-3'-methyl-5-methyluridine

- 89 -

$\begin{aligned} & \text { Step A: }: \frac{5^{\prime}-Q \text {-(tert-butyldiphenylsilyl)-3'-O-(3-tert-butylphenoxythiocarbonyl)- }}{} \begin{array}{l}\text { 2'-O-(2-methoxyethyl)-5-methyluridine }\end{array} \\ & \text { This compound was synthesized by the reaction of the corresponding }\end{aligned}$
5 5'-protected-2'-substituted-5-methyluridine with 3'- $t$-butylphenoxy chlorothionoformate following the similar procedure for the preparation of 3 '-phenoxythiocarbonyl-2'-deoxy derivative (Synthesis 1994, 1163).

Step B: $\quad 5^{\prime}-0$-(tert-Butyldiphenylsilyl)-3'-deoxy-2'-O-(2-methoxyethyl)-3'-(2-phenylethenyl)-5-methyluridine
To a solution of 5'-O-(tert-butyldiphenylsilyl)-3'-O-(3-tert-butylphenoxythiocarbonyl)-2 - - -(2-methoxyethyl)-5-methyluridine ( $15.0 \mathrm{~g}, 20.0$ mmol ) in 150 mL of benzene was added $\mathrm{PhCH}=\mathrm{CHSnBu} 3(18.7 \mathrm{~g}, 50 \mathrm{mmol})$. The resulting solution was degassed three times with argon at rt and $45^{\circ} \mathrm{C}$. After ABN
$15(1.0 \mathrm{~g}, 6.1 \mathrm{mmol})$ was added, the resulting solution was refluxed for 2 h . Another portion of AIBN ( $1.0 \mathrm{~g}, 6.1 \mathrm{mmol}$ ) was added after cooling to about $40^{\circ} \mathrm{C}$ and refluxed for 2 h . This procedure was repeated until the starting material disappeared. The solvent was evaporated and the residue was purified by flash chromatography on a silica gel column using $10: 1$ and $5: 1$ hexanes-EtOAc as eluent to give 1.74 g of $5^{\prime}-$ O-(tert-butyldiphenylsilyl)-3'-deoxy-2'-O-(2-methoxyethyl)-3'-(2-phenylethenyl)5methyluridine as a white foam.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.13,(\mathrm{~s}, 9 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H}), 3.18-3.30(\mathrm{~m}, 1 \mathrm{H}), 3.37(\mathrm{~s}, 3 \mathrm{H})$, 3.58-3.62 (m, 2H), 3.79-3.80 (m, 2H), 4.06-4.37 (m, 4H), 4.95 (s, 1H), 6.25-6.40. $(\mathrm{m}, 1 \mathrm{H}), 6.62(\mathrm{~d}, 1 \mathrm{H}, J=16 \mathrm{~Hz}), 7.27-7.71(\mathrm{~m}, 16 \mathrm{H}), 9.21(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR
$25 .\left(\mathrm{CDCl}_{3}\right) \delta 11.9,19.6,27.2,45.3,59.0,62.1,70.2,72.0,84.6,87.1,90.2,110.4,122.8$, 126.4, 127.8, 128.0, 128.3, 128.6, 130.0, 132.7, 133.5, 134.7, 135.3, 135.4, 136.9, 150.3, 154.1; HRMS (FAB) $m / z 641.302\left(\mathrm{M}+\mathrm{H}^{+}\left(\mathrm{C}_{37} \dot{\mathrm{H}}_{45} \mathrm{~N}_{2} \mathrm{O}_{6}\right.\right.$ Si requires 641.304$)$.

Step C: $\quad \begin{aligned} & 5^{\prime}-O \text {-(tert-Buty }{ }^{\prime} \text { diphenylsilyl)-3'-deoxy-3'-(hydroxymethyl)-2'-O-(2- } \\ & \text { methoxyethyl)-5-methyluridine }\end{aligned}$
To a solution of 5'-O-(tert-butyldiphenylsilyl)-3'-deoxy-2'-O-(2-methoxyethyl)- $3^{\prime}$-( 2 -phenylethenyl) 5 -methyluridine. ( $5.0 \mathrm{~g}, 7.8 \mathrm{mmol}$ ) and $N$ - methylmorpholine $N$-oxide (NMO) $(1.47 \mathrm{~g}, 12.5 \mathrm{mmol})$ in 150 mL of dioxane was added a catalytic amount of osmium tetranxide ( $4 \%$ aquenus solution, $2.12 \mathrm{~mL}, 85$ $\mathrm{mg}, 0.33 \mathrm{mmol}$ ). The flask was covered by aluminum foil and the reaction mixture was stirred at it overnight. A solution of $\mathrm{NaIO}_{4}(5.35 \mathrm{~g}, 25 \mathrm{mmol})$ in 5 mL of water was added to the above stirred reaction mixture. The resulting reaction mixture was stirred for 1 h at $0^{\circ} \mathrm{C}$ and 2 h at t , followed by addition of 10 mL of ethyl acetate. The mixture was filtered through a celite pad and washed with ethyl acetate. The filtrate was washed 3 times with $1(1) \%$ aqueous $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ solution until the color of aqueous phase disuppeared. The organic phase was further washed with water and brine, dried ( $\mathrm{Na}_{2} \mathrm{SO}_{4}$ ) and concentrated. The aldchyde thus obtained was dissolved in 130 mL of cthanol-water ( $4: 1 \mathrm{l}, \mathrm{v} / \mathrm{v}$ ). Sodium boruhydride ( NaBH 4 ) $(1.58 \mathrm{~g}, 40 \mathrm{mmol})$ was added in portions at $0^{\circ} \mathrm{C}$. The resulting reaction mixture was stirred at rt for 2 h and then treated with 200 g of ice water. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated. The resulted residue was purified by flash chromatography on a silica gel column using 2:1, $1: 1$ and $1: 2$ hexanes-EtOAc as eluents to give 1.6 g of $5^{\prime}-O$-(tert-butyldiphenylsilyl)-3'-deoxy-3'-(hydroxymethyl)-2'-O-(2-methoxyethyl)-5methyluridine as a white foam.
${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 1.09(\mathrm{~s}, 9 \mathrm{H}), 1.50(\mathrm{~s}, 3 \mathrm{H}), 2.25(\mathrm{bs}, 1 \mathrm{H}), 2.52-2.78(\mathrm{~m}, 1 \mathrm{H}), 3.38$ $(\mathrm{s}, 3 \mathrm{H}), 3.52-4.25(\mathrm{~m}, 10 \mathrm{H}), 5.86(\mathrm{~s}, 1 \mathrm{H}), 7.38-7.70(\mathrm{~m}, 11 \mathrm{H}), 9.95(\mathrm{bs}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta 12.1,19.5,27.1 ; 43.1,58.2,58.8,63.1,69.5,71.6,82.3,86.1,89.8$, $110.5,128.0,130.2,132.5,133.2,135.1,135.3,136.5,150.5,164.4$; HRMS (FAB) $m / z 569.268(\mathrm{M}+\mathrm{H}){ }^{+} .\left(\mathrm{C}_{30} \mathrm{H}_{41} \mathrm{~N}_{2} \mathrm{O}_{7}\right.$ Si requires 569.268).

Step D: $\quad$ '-O-(tert-Butyldiphenylsilyl)-3'-deoxy-3'-(iodomethyl)-2'-O-(2-methoxyethyl)-5-methyluridine
To a solution of $5^{\prime}-\mathrm{O}$-(tert-butyldiphenylsilyl)-3'-deoxy-3'-(hydroxymethyl)-2'-O-(2-methoxyethyl)-5-methyluridine ( $1.34 \mathrm{~g}, 2.35 \mathrm{mmol}$ ) in 25 mL of anhydrous DMF under stirring was added sequentially at $0^{\circ} \mathrm{C} 2,6$-lutidine ( 0.55 $\mathrm{mL}, 0.51 \mathrm{~g}, 4.7 \mathrm{mmol}, 2.0$ equiv) and methyl triphenoxy-phosphonium iodide ( 1.28 g ,
2.83 mmol ). The resulting reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 1 h and at rt for 2 h . The reaction mixture was diluted with 10 mL of ethyl acetate and washed twice with $0.1 \mathrm{~N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ aqueous solution to remove iodine. The organic phase was further washed with aqueous $\mathrm{NaHCO}_{3}$ solution, water, and brine. The aqueous phases were back extracted with ethyl acetate. The combined organic phases were dried ( $\mathrm{Na}_{2} \mathrm{SO}_{4}$ ) and concentrated. The resulting residue was purified by flash chromatography on a silica gel column using 5:1, 3:1 and then $1: 1$ hexanes-EtOAc to provide 1.24 g of 5 '-$O$-(tert-butyldiphenylsilyl)-3'-deoxy-3'-(iodomethyl)-2'-O-(2-methoxyerhyl)-5methyluridine as a white foam.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.13(\mathrm{~s}, 9 \mathrm{H}), 1.62(\mathrm{~s}, 3 \mathrm{H}), 2.64-2.85(\mathrm{~m}, 2 \mathrm{H}), 3.20-3.35(\mathrm{~m}, 1 \mathrm{H})$, $3.38(\mathrm{~s}, 3 \mathrm{H}), 3.50-4.25(\mathrm{~m}, 8 \mathrm{H}), 5.91(\mathrm{~s}, 1 \mathrm{H}), 7.32-7.50(\mathrm{~m}, 6 \mathrm{H}), 7.60(\mathrm{~s}, 1 \mathrm{H}), 7.62-$ $7.78(\mathrm{~m}, 4 \mathrm{H}), 10.46(\mathrm{~s}, 1 \mathrm{H}){ }^{13}{ }^{3} \mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 12.4,19.5,27.2,45.0,58.0,62.5$, $70.3,71.9,83.3,85.6,88.9,110.5,128.1,128.2,130.1,130.3,132.4,132.9,135.0$, $135.4,135.6,150.7,164.7$; HRMS (FAB) $m / z 679.172(\mathrm{M}+\mathrm{H})^{+}\left(\mathrm{C}_{30} \mathrm{H}_{40} \mathrm{~N}_{2} \mathrm{O}_{6} \mathrm{Si}\right.$ requires 679.170).

Step E: . 3'-Deoxy-3'-(iodomethyl)-2'-O-(2-methoxyethyl)-5-methyluridine A solution of 5'-O-(tert-butyldiphenylsilyl)-3'-deoxy-3'-(iodomethyl)-$2^{\prime}-O$-(2-methoxyethyl)-5-methyluridine ( $1.12 \mathrm{~g}, i .65 \mathrm{mmol}$ ) and triethylamine trihydrofluoride ( $1.1 \mathrm{~mL}, 1.1 \mathrm{~g}, 6.7 \mathrm{mmol}$ ) in 20 mL of THF was stirred at rt for 24 h . The reaction mixture was diluted with 50 mL of ethyl acetate and washed with water and brine. The organic phase was dried ( $\mathrm{Na}_{2} \mathrm{SO}_{4}$ ) and concentrated. The residue was purified by flash chromatography on a silica gel column. Gradient elution with 2:1, $1: 2$ and then $1: 3$ hexanes-EtOAc provided 504 mg of the title compound as a white foam.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CD}_{3} \mathrm{OD}\right): \delta 1.87(\mathrm{~s}, 3 \mathrm{H}), 2.47-2.75(\mathrm{~m}, 1 \mathrm{H}), 3.18-3.37(\mathrm{~m}, 2 \mathrm{H}), 3.40(\mathrm{~s}$, $3 \mathrm{H}), 3.59-3.70(\mathrm{~m}, 2 \mathrm{H}), 3: 71-3.90(\mathrm{~m}, 2 \mathrm{H}), 3.92-4.17(\mathrm{~m}, 4 \mathrm{H}), 5: 87(\mathrm{~s}, 1 \mathrm{H}), 8.17(\mathrm{~s}$, $1 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(\mathrm{CD}_{3} \dot{\mathrm{OD}}\right): \delta 12.5,45.2,59.2,60.9,71.0,72.9,85.4,87.3,89.7,110.5$, 138.0, 152.1, 166.6; HRMS (FAB) $m / z 441.053 \cdot(\mathrm{M}+\mathrm{H})^{+}\left(\mathrm{C}_{14} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{O}_{6}\right.$. requires 441.052).

Step F: $\quad 3^{\prime}$-Deaxy-5'-O-(4-methoxytrityl)-3'-(iodomethyl)-2'-O-(2-methoxyethyl)-5-methyluridine

A mixture of $3^{\prime}$-deoxy-3'-(iodomethyl)-2'-O-(2-methoxyethyl)-5methyluridine ( $472 \mathrm{mg}, 1: 1 \mathrm{mmol}$ ), diisopropylethylamine $(0.79 \mathrm{~mL}, 0.586 \mathrm{~g}, 4.5$ mmol), and $p$-anisyl chlorodiphenyl methane (4'-methoxytrityl chloride, MMT-Cl) $(1.32 \mathrm{~g}, 4.27 \mathrm{mmol})$ in 6 mL of ethyl acetate and 4 mL of THF was stirred at rt for 48
5 h. The reaction mixture was diluted with ethyl acetate and washed with water, followed by brine. The organic phase was dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated. The crude product was purified by flash chromatography on a silica gel column. Gradient elution with 3:1, 2:1, 1:1, and then $1: 3$ hexanes-EtOAc provided 690 mg of the title compound as a white foam.
$10{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 1.46^{\circ}(\mathrm{s}, 3 \mathrm{H}), 2.70-2.89(\mathrm{~m}, 2 \mathrm{H}), 3.19-3.31(\mathrm{~m}, 2 \mathrm{H}), 3.39(\mathrm{~s}, 3 \mathrm{H})$, $3.58-3.70(\mathrm{~m}, 3 \mathrm{H}), 3.80(\mathrm{~s}, 3 \mathrm{H}), 3.80-3.94(\mathrm{~m}, 1 \mathrm{H}), 4.05-4.25(\mathrm{~m}, 3 \mathrm{H}), 5.89(\mathrm{~s}, 1 \mathrm{H})$, $6.85(\mathrm{~s}, 1 \mathrm{H}), 6.89(\mathrm{~s}, 1 \mathrm{H}), 7.24-7.48(\mathrm{~m}, 12 \mathrm{H}), 7.78(\mathrm{~s}, 1 \mathrm{H}), 9.69(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 12.3,45.3,55.3,58.9,61.6,70.2,71.9,82.6,85.6,87.1,89.1,110.5$, 113.4, 127.4, 128.2, 128.4, 130.5, 134.7, 135.3, 143.6, 143.7, 150.5, 158.9, 164.6.

15 HRMS (FAB) m/z $735.155(\mathrm{M}+\mathrm{Na})^{+}\left(\mathrm{C}_{34} \mathrm{H}_{37} \mathbb{N}_{2} \mathrm{O}_{7} \mathrm{Na}\right.$ requires 735.154).

Step G: $\quad 3^{\prime}$-Deoxy-5'-O-(4-methoxytrityl)-3'-methyl-2'-O-(2-methoxyethyl)-5methyluridine
A mixture of ammonium phosphinate ( $410 \mathrm{mg}, 5.1 \mathrm{mmol}$ ) and
$1,1,1,3,3,3$-hexamethyldisilazane ( $1.18 \mathrm{~mL}, 0.90 \mathrm{~g}, 5.59 \mathrm{mmol}$ ) was heated at 100 $110^{\circ} \mathrm{C}$ for 2 h under nitrogen atmosphere with condenser. The intermediate BTSP(bis[trimethylsilyl]phosphinate) was cooled to $0^{\circ} \mathrm{C}$ and 5 mL of dichloromethane was injected. To this mixture was injected a solution of $3^{\prime}$-deoxy-5'-$O$-(4-methoxytrityl)-3'-(iodomethyl)-2'-O-(2-methoxyethyl)-5-methyluridine $(0.78 \mathrm{~g}$, 1.1 mmol ) and diisopropylethylaminc ( $0.39 \mathrm{~mL}, 287 \mathrm{mg}, 2.23 \mathrm{mmol}$ ) in 7 mL of dichloromethane. After the reaction mixture was stirred at rt oveinight, a mixture of THF-MeOH-NEt3 (3/6/0.3 nLL) was added and continued to stir for 1 h . The reaction mixture was filtered through a pad of celite and washed with dichloromethane. Thesolvent wasievaporated and the residue was purified by flash chromatography on a silica gel column using 2:1, 1:1, and then $1: 2$ hexanes-EtOAc as eluent providing 380 mg of the title compound.
${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 0.97(\mathrm{~d}, 3 \mathrm{H}, \mathrm{J}=6.8 \mathrm{~Hz}), 1.41(\mathrm{~s}, 3 \mathrm{H}), 2.35-2.55(\mathrm{~m}, 1 \mathrm{H}), 3.27$
(dd, $1 \mathrm{H}, J=11.0,3.0 \mathrm{~Hz}$ ), $3.37(\mathrm{~s}, 31 \mathrm{f}), 3.54-3.68(\mathrm{~m}, 3 \mathrm{H}), 3.79(\mathrm{~s}, 3 \mathrm{H}), 3.75-3.87$
$(\mathrm{m}, 1 \mathrm{H}), 3.94(\mathrm{~d}, 1 \mathrm{H}, J=5.0 \mathrm{~Hz}), 4.03-4.16(\mathrm{~m}, 2 \mathrm{H}), 5.84(\mathrm{~s}, 1 \mathrm{H}), 6.83(\mathrm{~s}, 1 \mathrm{H}), 6.87$
$(\mathrm{s}, 1 \mathrm{H}), 7.20-7.37(\mathrm{~m}, 8 \mathrm{H}), 7.39-7.50(\mathrm{~m}, 4 \mathrm{H}), 7.86(\mathrm{~s}, 1 \mathrm{H}), 9.50(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 8.7,12.1,35.6,55.3,59.0,61.7,69.8,72.1,85.4,86.4,86.7,89.8,110.0$, 113.3, 127.2, 128.0, 128.4, 130.4, 135.0, 135.7, 143.9, 150.5, 158.8, 164.6 . HRMS (FAB) m/z $609.256\left(\mathrm{M}^{+}+\mathrm{Na}\right)^{+}\left(\mathrm{C}_{34} \mathrm{H}_{38} \mathrm{~N}_{2} \mathrm{O}_{7} \mathrm{Na}\right.$ requires 609.257).

Step H: 3'-Deoxy-3'-merhyl-2'-O-(2-methoxyethyl)-5-methyluridine Trifluoroacetic acid ( 1.5 mL ) was added dropwise to a stirred solution of 3'-deoxy-5'-O-(4-methoxytrityl)-3'-methyl-2'-O-(2-methoxyethyl)-5-methyluridine ( $370 \mathrm{mg}, 0.63 \mathrm{mmol}$ ) in 50 mL of chloroform at $0^{\circ} \mathrm{C}$. The mixture was stirred at rt for 30 min, concentrated, and then dissolved in ethyl acetate. The solution was washed with dilute sodium bicarbonate and brine. The organic phase was dried ( $\mathrm{Na}_{2} \mathrm{SO}_{4}$ ) and concentrated. The resulting residue was purified by flash chromatography on a silica gel column. Elution with $1: 1,1: 3$ and then $0: 1$ hexanesEtOAc provided 170 mg of the title compound as a white foam.
${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 1.03(\mathrm{~d}, 3 \mathrm{H}, \mathrm{J}=6.8 \mathrm{~Hz}), 1.83 \cdot(\mathrm{~s}, 3 \mathrm{H}), 2.20-2.40(\mathrm{~m}, 1 \mathrm{H}), 3.10-$ $3.28(\mathrm{~m}, 1 \mathrm{H}), 3.35(\mathrm{~s}, 3 \mathrm{H}), 3.50-4.15(\mathrm{~m}, 10 \mathrm{H}), 5.81(\mathrm{~s}, 1 \mathrm{H}), 7.89(\mathrm{~s}, 1 \mathrm{H}), 9.77(\mathrm{~s}$, $\left.{ }^{1 H}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right)$ : $\delta 8.9,12.4,34.7,59.0,60.6,69.7,72.0,86.3,89.8,109.7$, $136.9,150.4,164.7$. HRMS ( FAB ) $m / 2315.154\left(\mathrm{M}+\mathrm{H}^{+}\left(\mathrm{C}_{14} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{6}\right.\right.$ requires 315.155).

## 2'-Amino-2'-dcoxyuridine



This compound was prepared following the procedures described in $J$. Org. Chem.61: 781 (1996).

## EXAMPLE 51

## 3'-Deoxyuridine


'5. This compound was obtained from commercial sources.

## EXAMPLE 52

$\underline{2^{\prime}-C \text {-Methyladenosine }}$

10


This compound was prepared following the conditions described in J. Med. Chem. 41: 1708 (1998).

EXAMPLE 53
15
3'-Deoxyadenosine (Cordycepin)


This compound was obtained from commercial sources.

## EXAMPLE 54

5
3'-Amino-3'-deoxyadenosine


This compound was prepared following the conditions described in Tetrahedron Lett. 30: 2329.(1989).

## 8-Bromoadenosine



15
This compound was obtained from commercial sources.
-96-

## EXAMPLE 56

2'-O-Methyladenosine

5


This compound was obtained from commercial sources.

## EXAMPLE 57

10 3'-Deoxy-3'-fluoroadenosiné


This compound was prepared following the procedures described in $J$. Med. Chem. 34: 2195 (1991).

6-Methyl-9-( $\beta$-D-ribofuranosyl)-9H-purine


This compound was prepared following the procedures described in Nucleosides, Nucleotides, Nucleic Acids 19: 1123 (2000).

## EXAMPLE 59

## 2',3',5'-tri-O-acetyl-8-methylsulfonyladenosine



EXAMPLE 60

1-Methyl-9-[2,3,5-tri- $O$-(p-toluoyl)- $\beta$-D-ribofuranosyl]-9 H -purine-6(1H)-thione



## EXAMPLE 61

4-Amino-7-(2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


To chromium trioxide ( $1.57 \mathrm{~g}, 1.57 \mathrm{mmol}$ ) in dichloromethane (DCM) $(10 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ was added acetic anhydride ( $145 \mathrm{mg}, 1.41 \mathrm{mmol}$ ) and then pyridine ( $245 \mathrm{mg}, 3.10 \mathrm{mmol}$ ). The mixture was stirred for 15 min , then a solution of 7-[3,5-()-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]- $\beta$-D-ribofuranosyl]-7H-pyrrolo[2,3- $d$ ]pyrimidin-4-amine [for preparation, see J. Am. Chem. Soc. 105: 4059 (1983)] ( $508 \mathrm{mg}, 1.00 \mathrm{mmol}$ ) in $\mathrm{DCM}(3 \mathrm{~mL})$ was added. The resulting solution was stirred for 2 h and then poured into ethyl acetate ( 10 mL ), and subsequently filtered through silica gel using ethyl acetate as the eluent. The combined filtrates were evaporated in vacuo, taken up in diethyl ether/THF ( $1: 1$ ) ( 20 mL ), cooled to $-78^{\circ} \mathrm{C}$ and methylmagnesium bromide ( 3 M , in THF ) ( $3.30 \mathrm{~mL}, 10 \mathrm{mmol}$ ) was added dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 10 min , then allowed to come to room temperature ( rt ) and quenched by addition of saturated aqueous ammonium chloride $(10 \mathrm{~mL})$ and extracted with $\mathrm{DCM}(20 \mathrm{~mL})$. The organic phase was evaporated in -99 -
vacuo and the crude product purified on silica gel using $5 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo. The resulting oil was taken up in THF ( 5 mL ) and tctrabutylammonium fluoride (TBAF) on silica ( $1.1 \mathrm{mmol} / \mathrm{g}$ on silica) ( 156 mg ) was added. The mixture was stirred at rt for 30 min , filtered, and evaporated in vacuo. The crude product was purified on silica gel using $10 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired compound ( 49 mg ) as a colorless solid. lH NMR (DMSO- $d_{6}$ ): $\delta 1.08(\mathrm{~s}, 3 \mathrm{H}), 3.67(\mathrm{~m}, 2 \mathrm{H}), 3.74(\mathrm{~m}, 1 \mathrm{H}), 3.83(\mathrm{~m}, 1 \mathrm{H}), 5.19$ $(\mathrm{m}, 1 \mathrm{H}), 5.23(\mathrm{~m}, 1 \mathrm{H}), 5.48(\mathrm{~m}, 1 \mathrm{H}), 6.08(1 \mathrm{H}, \mathrm{s}), 6.50(\mathrm{~m}, 1 \mathrm{H}), 6.93(\mathrm{bs}, 2 \mathrm{H}), 7.33$ (m, 1H), 8.02 (s, lH).

## EXAMPLE 62

Step A.
3,5-Bis-O-(2,4-dichlorophenylmethyl)-1-O-methyl- $\alpha$-D-ribofuranose
A mixture of 2- O -acetyl-3,5-bis- O -(2,4-dichlorophenylmethyl)-1- O -methyl- $\alpha$-D-ribofuranose [for preparation, see: Helv. Whim. Acta 78: 486 (1995)] ( $52.4 \mathrm{~g}, 0.10 \mathrm{~mol}$ ) in methanolic $\mathrm{K}_{2} \mathrm{CO}_{3}(500 \mathrm{~mL}$, saturated at room temperature) was stirred at room temperature for 45 min . and then concentrated under reduced pressure. The oily residue was suspended in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(500 \mathrm{~mL})$, washed with water ( $300 \mathrm{~mL}+5$ $\times 200 \mathrm{~mL})$ and brine ( 200 mL ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated to give the title compound ( 49.0 g ) as colorless oil, which was used without further purification in Step B below.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 3.28\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.53\left(\mathrm{~d}, 2 \mathrm{H}, \mathrm{J}_{5,4}=4.5 \mathrm{~Hz}, \mathrm{H}-5 \mathrm{a}, \mathrm{H}-5 \mathrm{~b}\right)$, 3.72 (dd, $\left.1 \mathrm{H}, J_{3,4}=3.6 \mathrm{~Hz}, J_{3.2}^{1}=6.6 \mathrm{~Hz}, \mathrm{H}-3\right), 3.99$ (ddt, $1 \mathrm{H}, J_{2,1}=4.5 \mathrm{~Hz}, \mathrm{~J}_{2, \mathrm{OH}-2}=$ $9.6 \mathrm{~Hz}, \mathrm{H}-2), 4.07(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4), 4.50\left(\mathrm{~s}, 2 \mathrm{H}, \dot{\mathrm{C}} \mathrm{H}_{2} \mathrm{Ph}\right), 4.52,4.60\left(2 \mathrm{~d}, 2 \mathrm{H}, \mathrm{J}_{\mathrm{gem}}=13.6\right.$
$\left.\mathrm{Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 4.54(\mathrm{~d}, 1 \mathrm{H}, \mathrm{OH}-2), 4.75(\mathrm{~d}, 1 \mathrm{H}, \mathrm{II}=1), 7.32-7.45,7.52-7.57(2 \mathrm{~m}, 10 \mathrm{H}$, 2 Ph ).
${ }^{13} \mathrm{C}$ NMR ${ }^{\prime}\left(\mathrm{DMSO}-d_{6}\right) \delta 55.40,69.05,69.74,71.29,72.02,78.41,81.45,103.44$, $127.83,127.95,129.05,129.28,131.27,131.30,133.22,133.26,133.55,133.67$, 135.45, 135.92 .

Step B: $\quad 3,5$-Bis- $O$-(2,4-dichlorophenylmethyl):1- $O$-methyl- $\alpha$-D-erythro-pentofuranos-2-ulose
To an ice-cold suspension of Dess-Martin periodinane ( $50.0 \mathrm{~g}, 118$ mmol ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 350 mL ) under argon ( Ar ) was added a solution of the compound from Step A ( $36.2 \mathrm{~g}, 75 \mathrm{mmol}$ ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(200 \mathrm{~mL})$ dropwise over 0.5 h . The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 0.5 h and then at room temperature for 3 days. The mixture was diluted with anhydrous $\mathrm{Et}_{2} \mathrm{O}(600 \mathrm{~mL})$ and poured into an ice-cold mixture of $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \cdot 5 \mathrm{H}_{2} \mathrm{O}(180 \mathrm{~g})$ in saturated aqueous $\mathrm{NaHCO}_{3}(1400 \mathrm{~mL})$. The layers were separated, and the organic layer was washed with saturated aqueous $\mathrm{NaHCO}_{3}(600 \mathrm{~mL})$, water $(800 \mathrm{~mL})$ and brine $(600 \mathrm{~mL})$, dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and evaporated to give the title compound ( 34.2 g ) as a colorless oil, which was used without further purification in Step C below.
${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta 3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.79\left(\mathrm{dd}, 1 \mathrm{H}, J_{5 \mathrm{a}, 5 \mathrm{~b}}=11.3 \mathrm{~Hz}, J_{5 \mathrm{a}, 4}=3.5 \mathrm{~Hz}\right.$, $\mathrm{H}-5 \mathrm{a}), 3.94\left(\mathrm{dd}, 1 \mathrm{H}, J_{5 \mathrm{~b}, 4}=2.3 \mathrm{~Hz}, \mathrm{H}-5 \mathrm{~b}\right), 4.20\left(\mathrm{dd}, 1 \mathrm{H}, J_{3,1}=1.3 \mathrm{~Hz}, J_{3,4}=8.4 \mathrm{~Hz}\right.$, $\mathrm{H}-3), 4.37$ (ddt, $1 \mathrm{H}, \mathrm{H}-4$ ), $4.58,4.69$ ( $2 \mathrm{~d}, 2 \mathrm{H}, J_{\mathrm{gem}}=13.0 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}$ ), 4.87 (d, 1 H , $\mathrm{H}-1), 4.78,5.03\left(2 \mathrm{~d}, 2 \mathrm{H}, \mathrm{Jgem}_{\mathrm{m}}=12.5 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 7.19-7.26,7.31-7.42(2 \mathrm{~m}, 10 \mathrm{H}$, 2 Ph ).
${ }^{13} \mathrm{C}$ NMR (DMSO-d $d_{6}$ ) $\delta 55.72,69.41,69.81,69.98,77.49,78.00,98.54,127.99$, 128.06, 129.33, 129.38, 131.36, 131.72, 133.61, 133.63, 133.85, 133.97, 134.72, 135.32, 208.21.

Step C: 3,5-Bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl-1-O-methyl- $\alpha$-Dribofuranose
To a solution of MeMgBr in anhydrous $\mathrm{Et}_{2} \mathrm{O}(0.48 \mathrm{M}, 300 \mathrm{~mL})$ at $-55^{\circ} \mathrm{C}$ was added dropwise a solution of the compound from Step B (17.40 g, 36.2 $\mathrm{mmol})$ in anhydrous $\mathrm{Et}_{2} \mathrm{O}(125 \mathrm{~mL})$. The reaction mixture was allowed to warm. to $-30^{\circ} \mathrm{C}$ and stirred for 7 h at $-30^{\circ} \mathrm{C}$ to $-15^{\circ} \mathrm{C}$, then poured into ice-cold water ( 500 mL ) and the mixture vigorously stirred at room temperature for 0.5 h . The mixture was filtered through a Celite pad ( $10 \times 5 \mathrm{~cm}$ ) which was thoroughly washed with $\mathrm{Et}_{2} \mathrm{O}$.

The organic layer was dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentrated. The residue was dissolved in hexanes ( $\sim 30 \mathrm{~mL}$ ), applied onto a silica gel column ( $10 \times 7 \mathrm{~cm}$, prepacked in hexanes) and eluted with hexanes and hexanes/EtOAc (9/1) to give the title compound ( 16.7 g ) as a colorlcss syrup.
$51^{1} \mathrm{H} \mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.36\left(\mathrm{~d}, 3 \mathrm{H}, J_{\mathrm{Me}, \mathrm{OH}}=0.9 \mathrm{~Hz}, 2 \mathrm{C}-\mathrm{Me}\right), 3.33(\mathrm{q}, 1 \mathrm{H}, \mathrm{OH}), 3.41(\mathrm{~d}$, $\left.1 \mathrm{H}, J_{3,4}=3.3 \mathrm{~Hz}\right), 3.46(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH} 3), 3.66\left(\mathrm{~d}, 2 \mathrm{H}, J_{5,4}=3.7 \mathrm{~Hz}, \mathrm{H}-5 \mathrm{a}, \mathrm{H}-5 \mathrm{~b}\right), 4.18$ (apparent q, 1H, H-4), $4.52(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1), 4.60\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{Ph}\right), 4.63,4.81(2 \mathrm{~d}, 2 \mathrm{H}, \mathrm{Jggem}$ $\left.=13.2 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 7.19-7.26,7.34-7.43$ ( $2 \mathrm{mi}, 10 \mathrm{H}, 2 \mathrm{Ph}$ ).
${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right):=824.88,55.45,69.95,70.24,70.88,77.06,82.18,83.01,107.63$,
$10 \quad 127.32,129.36,130.01,130.32,133.68,133.78,134.13,134.18,134.45,134.58$.

## Step D: . 4-Chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyll-7H-pyrrolo[2,3-d]pyrimidine

To a solution of the compound from Step C ( $9.42 \mathrm{~g}, 19 \mathrm{mmol}$ ) in anhydrous dichloromethane ( 285 mL ) at $0^{\circ} \mathrm{C}$ was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid, 20 $\mathrm{mL}, 114 \mathrm{mmol}$ ) dropwise. The resulting solution was stirred at $0^{\circ} \mathrm{C}$ for 1 h and then at room temperature for 3 h , evaporated in vacuo and co-evaporated with anhydrous toluene $(3 \times 4 t) \mathrm{mL}$ ). The oily residue was dissolved in anhydrous acetonitrile ( 50 mL ) and added to a solution of sodium salt of 4 -chloro- 1 H -pyrrolo[2,3- $d$ ]pyrimidine
20 [for preparation, see J. Chem. Soc., 131 (1960)] in acetonitrile [generated in situ from 4-chloro- 1 H -pyrrolo[ $2,3-d$ ]pyrimidine ( $8.76 \mathrm{~g}, 57 \mathrm{mmol}$ ) in anhydrous acetonitrile ( 1000 mL ), and NaH ( $60 \%$ in mineral oil, $2.28 \mathrm{~g}, 57 \mathrm{mmol}$ ), after 4 h of vigorous stirring-at room temperature]. The combined mixture was stirred at room temperature for 24 h , and then evaporated to dryness. The residue was suspended in water ( 250 $\mathrm{mL})$ and extracted with $\mathrm{EtOAc}(2 \times 500 \mathrm{~mL})$. The combined extracts were washed with brine ( 300 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude product was purified on a silica gel colurmn ( $10 \mathrm{~cm} \times 10 \mathrm{~cm}$ ) using ethyl acetate/hexane (1:3 and $\mathrm{I}: 2$ ) as the eluent. Fractions containing the product were combined and evaporated in vacuo to give the desired product ( 5.05 g ) as a colorless foam.
$30{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 0: 93\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.09(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}), 3.78\left(\mathrm{dd}, 1 \mathrm{H}, J_{5^{\prime}, 5{ }^{\prime \prime}}=10.9\right.$ $\mathrm{Hz}, J_{5^{\prime}, 4}=2.5 \mathrm{~Hz}, \mathrm{H}-5^{\prime}$ ), 3.99 ( $\mathrm{dd}, 1 \mathrm{H}, J_{5^{\prime \prime}, 4}=2.2 \mathrm{~Hz}, \mathrm{H}-5^{\prime \prime}$ ), $4.23-4.34$ ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{H}-3^{\prime}$, $\left.\mathrm{H}-4^{\prime}\right), 4.63,4.70\left(2 \mathrm{~d}, 2 \mathrm{H}, \mathrm{Jgcm}_{\mathrm{gcm}}=12.7 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 4.71,4.80\left(2 \mathrm{~d}, 2 \mathrm{H}, J_{\mathrm{gem}}=12.1\right.$ $\left.\mathrm{Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 6.54\left(\mathrm{~d}, \mathrm{IH}_{,}, J_{5,6}=3.81 \mathrm{lz}, \mathrm{H}-5\right), 7.23-7.44(\mathrm{~m}, 10 \mathrm{H}, 2 \mathrm{Ph})$.
${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 21.31,69.10,70.41,70.77,79.56,80.41,81.05,91.11,100.57$, 118.21, 127.04, 127.46, 127.57, 129.73, 129.77, 130.57, 130.99, 133.51, 133.99, 134.33, 134.38. 134.74, 135.21, 151.07, 151.15 152.47.

## Step E: $\quad$ 4-Chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine

To a solution of the compound from Step $\mathrm{D}(5.42 \mathrm{~g}, 8.8 \mathrm{mmol})$ in dichloromethane $(175 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in dichloromethane, $88 \mathrm{~mL}, 88 \mathrm{mmol}$ ) dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2.5 h , then at $-30^{\circ} \mathrm{C}$ to $-20^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) $(90 \mathrm{~mL})$ and the resulting mixture stirred at $-15^{\circ} \mathrm{C}$ for 30 min ., then neutralized with aqueous ammonia at $0^{\circ} \mathrm{C}$ and stirred at room temperature for 15 min . The solid was filtered and washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(1 / 1$, 250 mL ). The combined filtrate was evaporated, and the residue was purified by flash

Step F: 4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3db pyrimidine
To the compound from Step E ( $1.54 \mathrm{~g}, 5.1 \mathrm{mmol}$ ) was added methanolic ammonia (saturated at $0^{\circ} \mathrm{C} ; 150 \mathrm{~mL}$ ). The mixture was heated in a stainless steel autoclave at $85^{\circ} \mathrm{C}$ for 14 h , then cooled and evaporated in vacuo. The crude mixture was purified on'a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(9 / 1)$ as eluent to give the title compound as a colorless foam ( 0.8 g ), which separated as an amorphous solid after treatment with MeCN . The amorphous solid was recrystallized from methanol/acetonitrile; mp. $222^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.62\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.57-3.67\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}\right), 3.75-3.97$ (m, $\left.3 \mathrm{H}, \mathrm{H}-5^{\prime \prime}, \mathrm{H}^{\prime} 4^{\prime}, \mathrm{H}-3^{\prime}\right), 5.00 \cdot\left(\mathrm{~s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}\right), 5.04\left(\mathrm{~d}, 1 \mathrm{H}, J_{3^{\prime} \mathrm{OH}, 3^{\prime}}{ }^{\prime}=6.8 \mathrm{~Hz}, 3^{\prime}-\mathrm{OH}\right)$,
$5.06\left(\mathrm{t}, 1 \mathrm{H}, J_{5^{\prime} \mathrm{OH}, 5^{\prime}, 5^{\prime \prime}}=5.1 \mathrm{~Hz}, 5^{\prime}-\mathrm{OH}\right), 6.11\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 6.54\left(\mathrm{~d}, 1 \mathrm{H}, J_{5,6}=3.6 \mathrm{~Hz}\right.$, $\mathrm{H}-5$ ), 6.97 (br s, $2 \mathrm{H}, \mathrm{NH}_{2}$ ), 7.44 ( $\mathrm{d}, 1 \mathrm{H}, \mathrm{H}-6$ ), 8.02 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-2$ ).
13C NMR (DMSO- $d_{6}$ ): $\delta 20.26,60.42,72.72,79.30,82.75,91.20,100.13,103.08$, 121.9G, 150.37, 152.33, 158.15.

LC-MS: Found: $279.10\left(\mathrm{M}-\mathrm{H}^{+}\right)$; calc. for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}$: 279.11 .

## EXAMPLE 63

4-Amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carboxamide


Step A: 4-Amino-6-bromo-7-(2- $O$-acetyl-5-O-benzoyl-3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile
BSA ( $0.29 \mathrm{~mL}, 2.0 \mathrm{mmol}$ ) was added into a stirred suspension of 4-amino-6-bromo-5-cyano-1 H -pyrrolo[2,3- $d$ ]pyrimidine ( $0.24 \mathrm{~g}, 1 \mathrm{mmol}$; prepared according to Nucleic Acid Chemistry, Part IV, Townsend, L. B. and Tipson, R. S.; Ed.; Wiley-Interscience: New York, 1991; pp. 16-17 and Synthetic Commun. 1998, 28,3835 ) in dry acetonitrile ( 10 mL ) at room temperature under argon. After 15 min , 1,2-di-O-acetyl-5-O-benzoyl-3-deoxy-3-methyl-D-ribofuranose (J. Med. Chem. (1976), 19, 1265) ( $0.36 \mathrm{~g}, 1.0 \mathrm{mmol}$ ) was added along with TMSOTf $(0.54 \mathrm{~g}, 3$ mmol ). The mixture was stirred at room temperature for 5 min and then at $80^{\circ} \mathrm{C}$ for 0.5 h . The solution was cooled, diluted with ethyl acetate ( 50 mL ) and poured into ice-cold saturated aqueous $\mathrm{NaFCO}_{3}(15 \mathrm{~mL})$. The layers were separated. The organic layer was washed with brine ( 15 mL ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and then evaporated. The residue was purified on silica:gel column using a solvent system of hexanes/ EtOAc: $3 / 1$. Appropriate fractions were collected and evaporated to provide the title compound as colorless foam ( 0.21 g ).

Step B: $\quad$ 4-Amino-7-(2-O-acetyl-5-O-benzoyl-3-deoxy-3-methyl- $\beta-1$ -ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile
To a suspension of the title compound from Step A ( $183 \mathrm{mg}, 0.35$ $\mathrm{mmol})$ in $\mathrm{EtOH}(9 \mathrm{~mL})$ were added ammonium formate $(0.23 \mathrm{~g}, 3.6 \mathrm{mmol})$ and $10 \%$ 5 palladium on activated carbon ( 20 mg ) and the mixture was heated at reflux for 1.5 h . The hot reaction mixture was filtered through Celite and washed with hot EtOH. The solvent was removed and the residue treated with MeOH . The pale yellow solid was filtered thus yielding 105 mg of pure title compound. The filtrate was evaporated and purified on a silica gel column with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 50 / 1$ to afford an additional 63 mg of title compound as a white solid.

Step C: 4-Amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-

## 7H-pyrrolo[2,3-c] pyrimidin-5-carboxamide

A mixture of the compound from Step B ( $51 \mathrm{mg}, 0.12 \mathrm{mmol}$ ),
ethanolic ammonia ( 5 mL , saturated at $0^{\circ} \mathrm{C}$ ), aqueous ammonia ( $5 \mathrm{~mL}, 30 \%$ ) and aqueous hydrogen peroxide ( $1 \mathrm{~mL}, 35 \%$ ) was stirred room temperature for 8 h . The solution was evaporated and the residue purified on silica gel column with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 10 / 1$ to give the title compound as a white solid ( 28 mg ): ${ }^{1} \mathrm{H}-\mathrm{MNR}\left(\mathrm{CD}_{3} \mathrm{OD}\right): \delta 1.12(\mathrm{~d} ; 3 \mathrm{H}, j=6.8 \mathrm{~Hz}), 2.40(\mathrm{~m}, 1 \mathrm{H}), 3.76\left(\mathrm{dd}, 1 \mathrm{H}, J_{I}=12.8\right.$
$\left.20 \mathrm{~Hz}, J_{2}=4.0 \mathrm{~Hz}\right), 3.94-4.04(\mathrm{~m}, 2 \mathrm{H}), 4.33(\mathrm{~d}, \mathrm{H}, \mathrm{J}=5.4 \mathrm{~Hz}), 6.13(\mathrm{~s}, 1 \mathrm{H}), 8.11(\mathrm{~s}$, $1 \mathrm{H}), 8.16$ ( $\mathrm{s}, 1 \mathrm{H}$ ).

## EXAMPLE $64^{\circ}$.

4-Amino-7-(3-deoxy- $\beta$-D-ribofuranosyll)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide


This compound was prepared following the procedures described in $J$.
Med. Chem. 26: 25 (1983).

4-Amino-7-( $\beta$-D-ribofuranosyl) $=71 / I$-pyrrolo[2,3-clpyrimidinc-5-carboxamide
(Sangivamycin)


This compound was obtained from commercial sources.

## EXAMPLE 66

7-(2-O-methyl- $\beta$-D-ribofuranosy])-7II-pyrrolo[2,3- $d$ ]pyrimidine


This compound was prepared following the procedures described in $J$. Org. Chem. 39: 1891 (1974).
15

## EXAMPLE 67

4-Amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[ 2,3 -d] pyrimidine-5carboxamide


This compound was prepared following the procedures described in Chem. Pharm. Bull. 41: 775 (1993).

4-Amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile


This compound was prepared following the procedures described in $J$.
10 Med. Chem. 30: 481 (1987).

EXAMPLE 69

4-Amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine

-107-

This compound was prepared following the procedures described in $J$. Org. Chem. 39: 1891 (1974).

## EXAMPLE 70

5
3'-Amino-3'-deoxy-2'-O-methyladenosine


This compound is obtained by the methylation of appropriately protected $3^{\prime}$-amino-3'-deoxyadenosine derivative (Example 54).
10

## EXAMPLE 71

4-Amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyirolo[2,3- $\alpha$ ]pyrimidine


15
This compound was prepared following the following procedure described in Can. J. Chem. 55: 1251 (1977).

EXAMPLE 72

General process to SATE prodrug moiety

S-Acyl-2-Thioethyl (SATE) pronucleotides are discussed in C.R. Wagner, V.V. lyer, and E.J. Mc̣Intee, "Pronucleotides: Toward the In Vivo Delivery of Antiviral and Anticancer Nucleotides," Med. Res. Rev., 20: 1-35 (2000), which is incorporated by reference herein in its entirety. SATE derivatives of nuclensides are also disclosed U.S. Patent Nos. 5,770,725; 5,849,905; and 6,020,482, the contents of each of which are incorporated by reference herein in their entirety.

Bis(S-ácetyl-2-thioethyl)-N,N-difsopropylphosphurumidite:
2-Mercaptoethanol ( $5 \mathrm{~g}, 64 \mathrm{mmol}$ ) was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 50 mL ).
To this solution was added triethylamine ( $7.67 \mathrm{~mL}, 57.6 \mathrm{mmol}$ ), and the reaction mixture was cooled in an ice bath to $0^{\circ} \mathrm{C}$. Acetic anhydride ( $4.54 \mathrm{~mL}, 48 \mathrm{mmol}$ ) was added dropwise in 10 min , and the reaction mixture was stirred for 1 h at $0^{\circ} \mathrm{C}$. The reaction mixture was then allowed to come to room temperature over a period of 2 h . The reaction mixture was diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$, washed with water ( 75 mL ), $5 \%$ aqueous $\mathrm{NaHCO}_{3}(75 \mathrm{~mL})$ and brine ( 75 mL ). The organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo to give an oil. The oil was then dissolved in anhydrous THF: $(40 \mathrm{~mL})$ and anhydrous triethylamine ( 7.76 mL ) was added. To this mixture was added activated molecular sieves $(4 \AA)$ and was kept at room temperature for 10 min . The reaction mixture was cooled in an ice bath to $0^{\circ} \mathrm{C}$ and diisopropylphosphoramidous dichloride $(6.47 \mathrm{~g}, 32.03 \mathrm{mmol})$ was added. The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 2 h under inert atmosphere. Hexane ( 40 mL ) was added to the reaction mixture and the precipitate formed was filtered. The filtrate was concentrated to one fourth of the volume, purified by loaded silica gel column chromatography and eluted with hexane containing $3 \%$ triethylamine and incremental amount of ethyd acetate ( 0 to $7 \%$ ) to give the title compound as an oil ( 2.36 g ). ${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.17(\mathrm{~s} ; 6 \mathrm{H}), 1.2 \mathrm{l}(\mathrm{s}, 6 \mathrm{H}), 2.36(\mathrm{~s}, 6 \mathrm{H}), 3.14(\mathrm{t}, J=6.44 \mathrm{~Hz})$, $3.51-3.84(\mathrm{~m}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 24.47,24.61,30.48,42.85,43.1,61.88$, 62.23, 195.26; ${ }^{13} \mathrm{P}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 146.96$.

2'-O-Methylguanosine-5'-fbis-( $S$-acetyl-2-thioethyl)phosphate]


 was mixed with 1 H -tetrazole ( $0.061 \mathrm{~g}, 0.87 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuo overnight. To this mixture was added anhydrous acetonitrile ( 8 mL ). To the turbid solution, bis( $S$-acetyl-2-thivethyl) $N, N$-diisopropylphosphoramidite ( $0.3 \mathrm{~g}, 0.87 \mathrm{mmol}$ ) was added slowly and the reaction mixture was stirred at ambient temperature under inert atmosphere for 2 h . Solvent was removed in vacuo. The residue was cooled to $40^{\circ} \mathrm{C}$ and a solution of 3 -chloroperbenzoic acid $(0.2 \mathrm{~g})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(7 \mathrm{~mL})$ was added. The solution was allowed to warm up to room temperature over 1 h . Sodium hydrogensulfite ( $10 \%$ aqueous solution, 2 mL ) was added to reduce the excess of 3chloroperbenzoic acid. The organic phase separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL})$, washed with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}(10 \mathrm{~mL})$, water $(10 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue was purified by silica gel column chromatography and eluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ containing incremental amount of MeOH (5 to $10 \%$ ) as eluent to yield the title compound $(0.36 \mathrm{~g})$ as a foam.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ); $\delta 2.35(\mathrm{~s}, 6 \mathrm{H}), 2.97(\mathrm{~s}, 3 \mathrm{H}), 3.11(\mathrm{t}, 4 \mathrm{H}, J=6.0 \mathrm{~Hz}), 3.5(\mathrm{~m}, 1$
$\mathrm{H}), 3.74(\mathrm{~s}, 3 \mathrm{H}), 3.72-3.83(\mathrm{~m}, 2 \mathrm{H}), 3.97-4.11(\mathrm{~m}, 6 \mathrm{H}), 5.1(\mathrm{~d}, 1 \mathrm{H}, J=6.4 \mathrm{~Hz}), 5.29$ (d, $1 \mathrm{H}, J=3.1 \mathrm{~Hz}), 6.89(\mathrm{~d}, 2 \mathrm{H}, J=8.8 \mathrm{~Hz}), 7.15-7.37(\mathrm{~m}, 12 \mathrm{H}), 7.68(\mathrm{~s}, 1 \mathrm{H}), 7.73$ (s, 1 H ), $10.72(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 30.36,55.38,57.99,66.08,66.19,67.22$, $69.15,70.49,81.18,81.57,86.64,113.04,117.99,126.66,127.71,128.67,130.04$, $136.09,136.56,144.51,144.82,149.52,151.29,158.15,194.56 ;{ }^{13} \mathrm{P}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta$ -2.04; MS (API-ES) $852.10[\mathrm{M}-\mathrm{H}]^{+}$.

Step B: $\quad$ '- $O$-methylguanosinc-5'-fbis-( $S$-acetyl-2-thioethyl)phosphate] $N^{2 \cdot}$ (4-monomethoxytrityl)-2'-O-methylguanosine-5'-[bis-( $S$-acetyl-2thioethyl)phosphate] ( $0.2 \mathrm{~g}, 0.23 \mathrm{mmol}$ ) was dissolved in acetic acid: $\mathrm{MeOH}: \mathrm{H}_{2} \mathrm{O}, 3$
: $6: 1$ and heated at $55^{\circ} \mathrm{C}$ for 24 h . Solvent was removed and the residue was purified by HPLC on reverse phase column (Hamilton PRP-1, $250 \times 22 \mathrm{~mm}, \mathrm{~A}=$ Acetonitrile, $B=\mathrm{H}_{2} \mathrm{O} 20$ to 100 B in 65 min , flow $10 \mathrm{~mL} \mathrm{~min}^{-1}$ ). Fractions containing the product were pooled together and evaporated to give the title compound ( $40 \%$ yield). ${ }^{13} \mathrm{P}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta-0.72$; MS (API-ES) $\mathrm{m} / \mathrm{z} 582.1[\mathrm{M}+\mathrm{H}]^{+}$..

## EXAMPLE 74

## 2'-O-Methylguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]

Step A: $\quad$ Bis(S-pivaloyl-2-thioethyl)- $N, N$-diisopropylphosphoramidite $S$-pivaloyl:2-thioethanol ( $6.3 \mathrm{~g}, 39.6^{\circ} \mathrm{mmol}$ ) was dissolved in anhydrous THF ( 100 mL ). To this solution was added activated molecular sieves ( $4 \mathrm{~A}^{\circ}$ ) and kept at room temperature for 30 min . Anhydrous triethylamine ( 7.9 mL , 59.4 mmol ) was added and the reaction mixture was cooled in an ice bath to $0^{\circ} \mathrm{C}$. To this mixture diisopropylphosphoramidous dichloride $(4 \mathrm{~g}, 19.8 \mathrm{mmol})$ was added dropwise. The mixture was stirred the reaction mixture at $0^{\circ} \mathrm{C}$ for 2 h under inert gas atmosphere. Hexane ( 100 mL ) was added to the reaction mixture, and the precipitate formed was filtered. The filtrate was concentrated to one fourth of the volume. This was purified by flash silica.gel column chromatography using hexane containing $2 \%$ triethylamine and incremental amount of ethyl acetate (0 to $3 \%$ ) as eluent to give the title compound as an oil ( 5.23 g ).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.13-1.31(\mathrm{~m}, 30 \mathrm{H}), 1.21(\mathrm{~s}, 6 \mathrm{H}), 3.09(\mathrm{t}, \mathrm{J}=6.6 \mathrm{~Hz}, 4 \mathrm{H}), 3.51-$ $3.84(\mathrm{~m}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 24.47,24.61,27.32,30.00,42.85,43.1,46.32$, 61.98, 62.33, 206.1; ${ }^{13} \mathrm{P}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta 148.51$.

## Step B: $\quad$ 2'-O-methylguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]

$N^{2}$-(4-monomethoxytrityl)-2'-O-methylguanosine ( $0.6 \mathrm{~g}, 1.05 \mathrm{mmol}$ ) was mixed with 1 H -tetrazole ( $0.05 \mathrm{~g}, 0.7 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuo overnight. To this mixture anhydrous acetonitrile ( 13.8 mL ) was added. The reaction mixture was cooled to $0^{\circ} \mathrm{C}$ in an ice bath and bis( $\$$-pivaloyl-2-thioethyl) $N, N$ - diisopropylphosphoramidite ( $0.32 \mathrm{~g}, 0.7 \mathrm{mmol}$ ) was added slowly. The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 5 minutes. The ice bath was removed and the reaction mixture was allowed ta stir at room temperature under an inert atmosphere for 2 h . Solvent was removed in vacuo. The residue was cooled to $-40^{\circ} \mathrm{C}$ and a solution of 3chloroperbenzoic acid ( $0.24 \mathrm{~g}, 1.4 \mathrm{mmol}, 57-80 \%$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ was added. The solution was allowed to warm up to $-10^{\circ} \mathrm{C}$ over $\mathrm{l}^{\prime} \mathrm{h}$. Sodium hydrogensulfite ( $10 \%$ aqueous solution, 10 mL ) was added to reduce the excess of 3-chloroperbenzoic acid. The organic phase separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$, washed with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}(40 \mathrm{~mL})$, water ( 40 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue was chromatographed on a flash silica gel column using a $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ containing incremental amount of $\mathrm{MeOH}(0$ to $5 \%)$ as eluent. Fractions containing the product were pooled together and evaporated. The residue was dissolved in a solution of acetic acid/water/methanol ( $10 \mathrm{~mL}, 3: 1: 6$ ) and heated at $55^{\circ} \mathrm{C}$ for 24 h . Evaporated the solution in vacuum to get an oil. The oil was dissolved in $20 \% \mathrm{MeOH}$ in water and purified by HPLC on C-18 column (Luna C-18, $250 \times 2.12 \mathrm{~mm}, \mathrm{~A}=$ water, $\mathrm{B}=$ acetonitrile, 20 to $10 \% \mathrm{~B}$ in 65 min ., flow 10 mL $\left.\mathrm{min}^{-1}, \lambda 260 \mathrm{~nm}\right)$ to yield the title compound ( 0.082 g ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $\mathrm{d}_{6}$ ): $\delta 1.18(\overline{\mathrm{~s}}, 18 \mathrm{H}), 3.08(\mathrm{~m}, 4 \mathrm{H}), 3.33(\mathrm{~s}, 3 \mathrm{H}) 3.94-4.10(\mathrm{~m}, 6 \mathrm{H})$, $4.14-4.21(\mathrm{~m}, 2 \mathrm{H}), 4.29(\mathrm{~m}, 1 \mathrm{H}), 5.42(\mathrm{~d}, 1 \mathrm{H}, J=5.4 \mathrm{~Hz}), 5.81(\mathrm{~d}, 1 \mathrm{H}, J=5.8 \mathrm{~Hz})$, 6.49 (bs, 2 H ), $7.86(\mathrm{~s}, 1 \mathrm{H}), 10.66(\mathrm{bs}, 1 \mathrm{H}) ;{ }^{13} \mathrm{P}$ NMR ( $\mathrm{DMSO}-d_{6}$ ): $\delta$-0.71; MS (APIES) $m / z 664.2[\mathrm{M}-\mathrm{H}]^{\circ}$.

```
EXAMPLE 75
```


## 8-Bromo-2'-O-methylguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]



This compound was synthesized according to the procedure used for the synthesis of Example 74 starting with 8 -bromo- $N^{2}$-(4-monomethoxytrityl)-2'-O,methylguanosine $(0.46 \mathrm{~g}, 0.63 \mathrm{mmol})$. Other reagents used were 1 H -tetrazole $(0.034 \mathrm{~g}$,

## 2-Amino-3,4-dihydro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5'-[bis-(S-yivaloyl-2-thioethyl)phosphate]



This compound was synthesized according to the procedure used for the synthesis of Example 74 starting with 7-deaza- $N^{2}$-(4-monomethoxytrityl)-2'-O'methylguanosine ( $0.47 \mathrm{~g}, 0.82 \mathrm{mmol}$ ). Other reagents used were 1 H -tetrazole ( 0.044
g, 0.63 mmol ), bis( $S$-pivaloyl-2-thioethyl) $N, N$-diisopropylphosphoramidite $(0.29 \mathrm{~g}$, 0.63 mmol ), acetonitrile ( 11 mL ), 3-chloroperbenzoic acid ( $0.21 \mathrm{~g}, 1.26 \mathrm{mmol}, 57-80$ \%) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5.2 \mathrm{~mL})$. The title conipound was isolated in $29 \%$ yield $(0.158 \mathrm{~g})$. ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.14(\mathrm{~s}, 18 \mathrm{H}), 3.06(\mathrm{~m}, 4 \mathrm{H}), 3.31(\mathrm{~s}, 3 \mathrm{H}) 3.96-4.26(\mathrm{~m}, 9 \mathrm{H})$,

3'-Deoxyguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]

$N^{2}$-(4-Monomethoxytrityl)-3'-deoxyguanosine ( $0.20 \mathrm{~g}, 0.35 \mathrm{mmol}$ ) was mixed with 1 H -tetrazole ( $0.019 \mathrm{~g}, 0.27 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuo overnight. To this mixture anhydrous acetonitrile ( 4.7 mL ) was added to give a turbid solution. The reaction mixture was cooled to $0^{\circ} \mathrm{C}$ in an ice bath and bis( $S$-pivaloyl-2thioethyl) $N, N$-diisopropylphosphoramidite ( $0.12 \mathrm{~g} ; 0.27 \mathrm{mmol}$ ) was added slowly. The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 5 minutes. The ice bath was removed and the reaction mixture was allowed to come to room temperature. The reaction mixture was stirred at room temperature under an inert gas atmosphere for 2 h . Solvent was removed in vacuo. The residue was cooled to $-40^{\circ} \mathrm{C}$ and a solution of 3chloroperbenzoic acid ( $0.12 \mathrm{~g}, 0.7 \mathrm{mmol}, 57-80 \%$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2.2 \mathrm{~mL})$ was added. The solution was allowed to warm up to $-10^{\circ} \mathrm{C}$ òver 1 h . Sodium hydrogensulfite ( $10 \%$ aqueøus solution, 2 mL ) was added to reduce the excess of 3-chloroperbenzoic acid. The organic phase was separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL})$, washed with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}(20 \mathrm{~mL})$, water $(20 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue was chromatographed on a flash silica gel column
using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ containing incremental amount of MeOH ( 0 to $5 \%$ ) as eluent. Fractions containing the product were pooled and evaporated. The residue was dissolved in a solution of acetic acid/water/methanol ( $5 \mathrm{~mL}, 3: 1: 6$ ) and heated at $55^{\circ} \mathrm{C}$ for 24 h . Evaporated the solution in vacuum to get an oil. The oil was dissolved in $20 \% \mathrm{MeOH}$ in water and purified by HPLC on C-18 column (Luna C-18, $250 \times 2.12 \mathrm{~mm}, \mathrm{~A}=$ water, $\mathrm{B}=$ acctonitrile, 20 to $10 \% \mathrm{~B}$ in 65 min ., flow $10 \mathrm{~mL} \mathrm{~min}^{-1}, \lambda 260 \mathrm{~nm}$ ) to yield the title compound ( 0.027 g ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.15(\mathrm{~s}, 18 \mathrm{H}), 1.92-2.01(\mathrm{~m}, 1 \mathrm{H}), 2.17-2.28(\mathrm{~m}, \mathrm{lH}), 3.04(\mathrm{t}$, $4 \mathrm{H}, \mathrm{J}=6.2 \mathrm{~Hz}$ ), 3.91-4.23 (m, 6 H$), 4.37-4.55(\mathrm{~m}, 2 \mathrm{H}), 5.67(\mathrm{~m}, 2 \mathrm{H}), 6.45(\mathrm{bs}, 2 \mathrm{H})$, $7.75(\mathrm{~s}, 1 \mathrm{H}), 10.61(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{P}$ NMR (DMSO- $d_{6}$ ): $\delta-0.75$; MS (API-ES) m/z 634.2 , [M-H].

## EXAMPLE 78

2-Amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]


2-(4-Monomethoxytrityl)amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one ( $0.30 \mathrm{~g}, 0.52 \mathrm{mmol}$ ) was mixed with 1 H -tetrazole ( $0.028 \mathrm{~g}, 0.40 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuo overnight. To this mixture anhydrous acetonitrile ( 7 mL ) was added, and the solution was cooled to $0^{\circ} \mathrm{C}$ in an ice bath. Bis( $S$-pivaloyl-2-thioethyl)- $N, N$-diisopropylphosphoramidite ( $0.18 \mathrm{~g}, 0.40^{-}$ mmol ) was added slowly. The reaction mixture was allowed to come to at room temperature and stirred at room temperature under an inert atmosphere for 2 h . The solvent was removed in vacuo. The residue was cooled to $-40^{\circ} \mathrm{C}$, and a solution of 3chloroperbenzoic acid ( $0.14 \mathrm{~g}, 0.8 \mathrm{mmol}, 57-80 \%$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ was added. The solution was allowed to warm up to $-10^{\circ} \mathrm{C}$ over 2 h . Sodium hydrogensulfite ( $10 \%$
aqueous solution, 5 mL ) was added to reduce the excess of 3-chloroperbenzoic acid. The organic phase was separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$, washed with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}(40 \mathrm{~mL})$, water $(40 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue was chromatographed on a flash silica gel column using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ containing incremental amount of $\mathrm{MeOH}(0$ to $5 \%)$ as eluent. Fractions containing the product were pooled and evaporated. The residue was dissolved in a solution of acetic acid/water/ methanol ( $10 \mathrm{~mL}, 3: 1: 6$ ) and heated at $55^{\circ} \mathrm{C}$ for 24 h . The solution was evaporated to give an oil. The oil was dissolved in $20 \% \mathrm{MeOH}$ in water and purified by HPLC on C-18 column (Luna C18,250 X $2.12 \mathrm{~mm}, \mathrm{~A}=$ water,
$10 \mathrm{~B}=$ acetonitrile 20 to $10 \%$ B in 65 mL , flow $10 \mathrm{~mL} / \mathrm{min}, \lambda 260 \mathrm{~nm}$ ) to give the title compound ( 0.053 g ).
${ }^{\mathrm{I}} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.16(\mathrm{~s}, 18 \mathrm{H}), 1.91-2.01(\mathrm{~m}, 1 \mathrm{H}), 2.17-2.25(\mathrm{~m}, 1 \mathrm{H}), 3.05(\mathrm{t}$, $4 \mathrm{H}, J=6.2 \mathrm{~Hz}), 3.92-4.2(\mathrm{~m}, 6 \mathrm{H}), 4.35(\mathrm{bs}, 2 \mathrm{H}), 5.56(\mathrm{~d}, 1 \mathrm{H}, J=4.2 \mathrm{~Hz}), 5.86(\mathrm{~d}$; $1 \mathrm{H}, J=2.4 \mathrm{~Hz}), 6.24(\mathrm{~m}, 3 \mathrm{H}), 6.77(\mathrm{~d}, 1 \mathrm{H}, J=3.6 \mathrm{~Hz}), 10.36(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{P} \cdot \mathrm{NMR}$
15 (DMSO-d ${ }^{2}$ ): $\delta-0.89$; HRMS (MALDI) Calcd for $\mathrm{C}_{25} \mathrm{H}_{39} \mathrm{~N}_{4} \mathrm{O}_{9} \mathrm{PS}_{2} .635 .1969$ found 635.1964.

## EXAMPLE 79

2-Amino-5-bromo-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5'-[bis-( $S$-pivaloyl-2-thioethyl)phosphate]


2-(4-Monomethoxytrityl)amino-5-bromo-7-(3-deoxy- $\beta$-Dribofuranosyl). 7 H -pyrrolo $2,3-d]$ pyrimidin- $4(3 H)$-one ( $0.066 \mathrm{~g}, 0.17 \mathrm{mmol}$ ) was mixed with imidazole triflate ( $0.017 \mathrm{~g}, 0.17 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuo overnight. To this mixture anhydrous acetonitrile ( 7 mL ) and bis( $S$-pivaloyl-2thioethyl) $N, N$-diisopropylphosphoramidite ( $0.97 \mathrm{~g}, 0.24 \mathrm{mmol}$ ) were added slowly.

The reaction mixture was stirred under an inert atmosphere for 18 h . Solvent was removed in vacuo. The residue was cooled to $-40^{\circ} \mathrm{C}$ and a solution of 3chloroperbenzoic acid ( $0.059 \mathrm{~g}, 0.34 \mathrm{mmol}, 57-80 \%$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{~mL})$ was added. The solution was allowed to warm up to $-10^{\circ} \mathrm{C}$ over 2 h . Sodium hydrogensulfite ( 10 $\%$ aqueous solution, 5 mL ) was added to reduce the excess of 3 -chloroperbenzoic acid. The organic phase was separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL})$, washed with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}(20 \mathrm{~mL})$, water ( 20 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue was chromatographed on flash silica gel column using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ containing incremental amount of $\mathrm{MeOH}(0$ to $5 \%)$ as eluent. Fractions containing the product were pooled and evaporated. The residue was dissolved in a solution of acetic acid/water/ methanol ( $3 \mathrm{~mL}, 3: 1: 6$ ) and heated at $55^{\circ} \mathrm{C}$ for 24 h . The solution was evaporated to give an oil. The oil was dissolved in $20 \% \mathrm{MeOH}$ in water and purified by HPLC on C-18 column (Luna C18,250 X $2.12 \mathrm{~mm}, \mathrm{~A}=$ water, $\mathrm{B}=$ acetonitrile 20 to $10 \% \mathrm{~B}$ in 65 mL , flow $10 \mathrm{~mL} \mathrm{~min}^{-1}, \lambda 260 \mathrm{~nm}$ ) to afford the title compound ( 0.036 g ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{0}$ ): $\delta 1.17(\mathrm{~s}, 18 \mathrm{H}), 1.87-2.03(\mathrm{~m}, 1 \mathrm{H}), 2.17-2.26(\mathrm{~m}, 1 \mathrm{H}), 3.05(\mathrm{t}$, $4 \mathrm{H}, J=6.4 \mathrm{~Hz}), 3.92-4.2(\mathrm{~m}, 6 \mathrm{H}), 4.37(\mathrm{bs}, 2 \mathrm{H}), 5.70(\mathrm{~d}, 1 \mathrm{H}, J=4.4 \mathrm{~Hz}), 5.85(\mathrm{~d}$, $1 \mathrm{H}, J=2.6 \mathrm{~Hz}), 6.36(\mathrm{bs}, 2 \mathrm{H}), 6.93(\mathrm{~s}, 1 \mathrm{H}), 10.51(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{P}$ NMR (DMSO- $\left.\mathrm{d}_{6}\right): \delta-$ 0.89; MS (AP-ES) $n / z 711.11$ and 713.09 [M-H]; HRMS (MALDI) Calcd for $\mathrm{C}_{25} \mathrm{H}_{38} \mathrm{BrN}_{4} \mathrm{O}_{9} \mathrm{PS}_{2} .713 .1074$ and 715.1074 found 713.1081 and 715.102.

## EXAMPLE 80

## 2'-O-Methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]


${ }^{\prime} \mathrm{N}^{4}$-( $4,4^{\prime}$ '- Dimethoxytrityl)-2'-O-methylcytidine ( $0.49 \mathrm{~g}, 0.86^{\circ} \mathrm{mmol}$ ) was mixed with 1 H -tetrazole ( $0.06 \mathrm{~g}, 0.86 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuo
overnight. To this mixture anhydrous acetonitrile ( 6 mL ) and bis-( $(S$-pivaloyl-2i thioethyl)- $N, N$.diisopropylphosphoramidite ( $0.39 \mathrm{~g}, 0.86 \mathrm{mmol}$ ) were added at $0^{\circ} \mathrm{C}$. The reaction mixture was allowed to come to room temperature and stirred under an inert atmosphere fur 18 h . Solvent was removed in vacuo. The residue was cooled to $-40^{\circ} \mathrm{C}$ and a solution of 3-chloroperbenzoic acid ( $0.3 \mathrm{~g}, 1.72 \mathrm{mmol}, 57-80 \%$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5.5 \mathrm{~mL})$ was added. The solution was allowed to warm up to $-10^{\circ} \mathrm{C}$ over 2 h . Sodium hydrogensulfite ( $10 \%$ aqueous solution, 5 mL ) was added to reduce the excess of 3 -chloroperbenzoic acid. The organic phase was separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL})$, washed with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}(20 \mathrm{~mL})$, water ( 20 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue was chromatographed on a flash silica gel column using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ containing incremental amount of MeOH ( 0 to $10 \%$ ) as eluent. Fractions containing the product were pooled and evaporated. The residue was dissolved in a solution of acetic acid/water/ methanol ( $10 \mathrm{~mL}, 3: 1: 6$ ) and heated at $55^{\circ} \mathrm{C}$ for 24 h . The solution was evaporated to give an oil. The oil was dissolved in $20 \% \mathrm{MeOH}$ in water and purified by HPLC on $\mathrm{C}-18$ column (Luna $\mathrm{C} 18,250 \times 2.12 \mathrm{~mm}, \mathrm{~A}=$ water, $\mathrm{B}=$ acetonitrile 20 to $10 \% \mathrm{~B}$ in 65 ML , flow 10 mL $\left.\mathrm{min}^{-1}, \lambda 260 \mathrm{~nm}\right)$ to yield the title compound ( 0.076 g ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.18(\mathrm{~s}, 18 \mathrm{H}), 3.12(\mathrm{t}, 4 \mathrm{H}, J=6.4 \mathrm{~Hz}), 3.39(\mathrm{~s}, 3 \mathrm{H}), 3.69(\mathrm{t}$, $1 \mathrm{H}, J=4.2 \mathrm{~Hz}), 3.93-4.3(\mathrm{~m}, 8 \mathrm{H}), 5.29(\mathrm{~d}, 1 \mathrm{H}, J=6.2 \mathrm{~Hz}), 5.72(\mathrm{~d}, 1 \mathrm{H}, J=7.4 \mathrm{~Hz})$, $5.86(\mathrm{~d}, 1 \mathrm{H}, J=4 \mathrm{~Hz}), 7.21(\mathrm{bs}, 2 \mathrm{H}), 7.58(\mathrm{~d}, 1 \mathrm{H}, J=7.4 \mathrm{~Hz}) ;{ }^{13} \mathrm{P}$ NMR $\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta-$ 0.64 ; MS (AP-ES) $m / z 625.69[\mathrm{M}+\mathrm{H}]^{+}$; HRMS (MALDI) Calcd for $\mathrm{C}_{24} \mathrm{H}_{4} \mathrm{~N}_{3} \mathrm{O}_{10} \mathrm{PS}_{2} \mathrm{Na} 648.1785$ found 648.1804 .

## EXAMPLE 81

## 5-Bromo-2'-O-methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]


-118-

Step A: 5-Bromo-3'-O-(t-butyldimethyl)silyl-2'-O-methylcytidine
2'-O-Methylcytidine ( $1.5 \mathrm{~g}, 5.83 \mathrm{mmol}$ ) was mixed with imidazole ( $3.97 \mathrm{~g}, 58.32 \mathrm{mmol}$ ) and dried in vacuo. This mixture was dissolved in anhydrous DMF ( 4 mL ) and t-butyldimethylsilyl chloride ( $4.41 \mathrm{~g}, 29.25 \mathrm{mmol}$ ) was added and the reaction mixture was stirred for 18 h at room temperature under an inert atmosphere. Reaction mixture was diluted with water $(100 \mathrm{~mL})$ and extracted with ethyl acetate ( $2 \times 60 \mathrm{~mL}$ ). The organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. The residue was purified by silica gel column chromatography and eluted with ethyl acetate/hexane, $6: 4$. Fractions containing the product were pooled and evaporated. The product obtained ( 2.76 g ) was dissolved in acetonitrile ( 19.43 mL ), $\mathrm{LiBr}(0.623 \mathrm{~g}, 7.18 \mathrm{mmol})$ and stirred to get a clear solution. To this ammonium ceric (IV) nitrate ( $6.24 \mathrm{~g}, 11.37 \mathrm{mmol}$ ) was added and the reaction mixture was allowed to stir at room temperature for 3 h . Solvent was removed in vacuum. The residue obtained was taken in ethyl acetate ( 100 mL ) and washed with water ( 80 mL ). The organic phase was separated, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. Residue purified by silica gel column chromatography and eluted with $5 \% \mathrm{MeOH}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The product obtained ( $2.66 \frac{\mathrm{~g}}{\mathrm{~g}}$ ) was dissolved in $80 \%$ 'acetic acid in water and heated at $50^{\circ} \mathrm{C}$ for 6 h . The solvent was removed and the residue purified on a silica gel column and eluted with $5 \% \mathrm{MeOH}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give the title compound ( 0.85 g ). ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.78(\mathrm{~s}, 6 \mathrm{H}), 0.85(\mathrm{~s}, 9 \mathrm{H}), 3.31(\mathrm{~s}, 3 \mathrm{H}), 3.44-3.6(\mathrm{~m}, 2 \mathrm{H})$, $3.69-3.9(\mathrm{~m}, 2 \mathrm{H}), 4.24(\mathrm{~m}, 1 \mathrm{H}), 5.29(\mathrm{t}, 1 \mathrm{H}, J=4.4 \mathrm{~Hz}), 5.76(\mathrm{~d}, 1 \mathrm{H}, J=3.2 \mathrm{~Hz})$, 7.06 (b s,1H), 7.88 (bs, 1H), 8.39 (s, 1H).

Step B: $\quad$ 5-Bromo-2'-O-methylcytidine-5'-rbis-(S-pivaloyl-2thioethyl)phosphate]
5-Bromo-3'-O-(t-butyldimethyl)silyl-2'-O-methylcytidine ( 0.093 g , 0.21 mmol ) was mixed with 1 H -tetrazole ( $0.03 \mathrm{~g}, 0.42 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuo overnight. To this mixture anhydrous acetonitrile ( 2 mL ). Bis-( $S$-pivaloyl-2-thioethyl)- $N, N$-diisopropylphosphoramidite ( $0.2 \mathrm{~g}, 0.42 \mathrm{mmol}$ ) was added at $0^{\circ} \mathrm{C}$. The reaction mixture was allowed to come to room temperature and stirred under an inert atmosphere for 4 h . Solvent was removed in vacuo. The residue was cooled to $-40^{\circ} \mathrm{C}$ and a solution of 3-chloroperbenzoic acid ( $0.072 \mathrm{~g} ; 0.42 \mathrm{mmol}, 57-80 \%$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2$ mL ) was added. The solution was allowed to warm up to $-10^{\circ} \mathrm{C}$ over 2 h . Sodium hydrogensulfite ( $10 \%$ aqueous solution, 2 mL ) was added to reduce the excess of 3 chloroperbenzoic acid..The organic phase separated, diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL})$,
washed with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}(20 \mathrm{~mL})$, water $(20 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue was dissolved in THF ( 2.1 mL ) and triethylamine trihydrofluoride ( $0.17 \mathrm{~g}, 1.1 \mathrm{mmol}$ ). The reaction mixture was stirred at room temperaiure for 18 h . The solution was evaporated to give an oil. The oil was dissolved in ethyl acetate ( 30 mL ) and washed with water ( 20 mL ), $5 \%$ aqueous $\mathrm{NaHCO}_{3}$ and brine ( 20 mL ). Thc organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated.'The residue was dissolved in $20 \% \mathrm{MeOH}$ in water and purified by HPLC on $\mathrm{C}-18$ column (Luna C18, 250 X 2.12 mm , $\mathrm{A}=$ water, $\mathrm{B}=$ acetonitrile 20 to $10 \% \mathrm{~B}$ in 65 mL , flow $10 \mathrm{~mL} \mathrm{~min}{ }^{-1}, \lambda 260 \mathrm{~nm}$ ) to give the title compound ( 0.054 g ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.17(\mathrm{~s}, 18 \mathrm{H}), 3.11(\mathrm{t}, 4 \mathrm{H}, J=6.2 \mathrm{~Hz}), 3.39(\mathrm{~s}, 3 \mathrm{H}), 3.75(\mathrm{t}$, $1 \mathrm{H}, J=4.8 \mathrm{~Hz}), 3.93-4.3(\mathrm{~m}, 8 \mathrm{H}), 5.23(\mathrm{~d}, 1 \mathrm{H}, J=6.4 \mathrm{~Hz}), 5.8(\mathrm{~d}, 1 \mathrm{H}, J=3.8 \mathrm{~Hz})$, 7.07 (bs, 1H), $7.89(\mathrm{~s}, 1 \mathrm{H}) 7.94$ (bs, 1 H$) ;{ }^{13} \mathrm{P}$ NMR ( $\mathrm{CD}_{3} \mathrm{CN}$ ): $\delta-0.34$; MS (AP-ES). $m / z 702.00$ and $704.00[\mathrm{M}-\mathrm{H}] ;$ HRMS (MALDI) Calcd for $\mathrm{C}_{24} \mathrm{H}_{39} \mathrm{BrN}_{3} \mathrm{O}_{10} \mathrm{PS}_{2} \mathrm{Na}$ 726.0890 and 728.0890 found 726.0893 and 728.086 .

EXAMPLE 82

3'-Deoxycytidine-5'-[bis-(S-pivaloyil-2-thioethyl)phosphate]


Step A:
$N^{4}$-(4,4'-dimethoxytrityl)-3'-deoxycytidine
3'-Deoxycytidine ( $0.8 \mathrm{~g}, 3.54 \mathrm{mmol}$ ) was mixed with imidazole ( 2.41 $\mathrm{g}, 35.4 \mathrm{mmol}$ ) and dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuum overnight at $40^{\circ} \mathrm{C}$. The mixture was dissolved in anhydrous DMF and $t$-butyldimethylsilyl chloride ( $2.68 \mathrm{~g}, 17.78 \mathrm{mmol}$ ) was added and the reaction mixture was stirred under an argon atmosphere for 18 h at room temperature. The reaction mixture was diluted with water $(100 \mathrm{~mL})$ and extracted with ethyl acetate ( $2 \times 75 \mathrm{~mL}$ ). The organic phase was separated, dried over
anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. The residue was purified by silica gel column chromatography and eluted with ethyl acetate/hexane (6:4) to yield 2 ', 5 '-bis'(t-butyldimethylsilyl)-3'-deoxycytidine ( 1.27 g ). This was then mixed with DMAP ( 0.34 $\mathrm{g}, 2.79 \mathrm{mmol}$ ) and dricd in vacuum. This mixture was dissolved in anhydrous pyridine $(8 \mathrm{~mL})$ and 4,4 '-dimethoxytrityl chloride ( $1.89 \mathrm{~g}, 5.58 \mathrm{mmol}$ ) was added. The reaction mixture was stirred at room.temperature under an argon atmosphere for 18 h . Solvent was removed in vacuo. The residue obtained was taken in ethyl acetate ( 100 mL ) and washed with $5 \% \mathrm{NaHCO}_{3}$ in water ( 75 mL ) and brine ( 75 ml ). The organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. The residue obtained was dissolved in THF ( 28 mL ). To this triethylamine trihydrofluoride ( $2.26 \mathrm{~mL}, 13.74 \mathrm{mmol}$ ) and triethylamine ( $0.95 \mathrm{~mL}, 6.87 \mathrm{mmol}$ ) were added and stirred at room temperature for 18 h . Solvent was removed and the residue dissolved in ethyl acetate ( 50 mL ), washed with water ( 50 mL ) and $5 \% \mathrm{NaHCO}_{3}$ in water ( 50 mL ). The organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. The residue obtained was purified by silica gel column chromatography and eluted with $5 \% \mathrm{MeOH}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to yield the title compound ( 0.66 g ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.66(\mathrm{~m}, 1 \mathrm{H}), 1.85(\mathrm{~m}, 1 \mathrm{H}), 3.47(\mathrm{~m}, 1 \mathrm{H}), 3.63(\mathrm{~m}, 1 \mathrm{H}), 3.71$
$(\mathrm{s}, 6 \mathrm{H}), 4.00(\mathrm{bs}, 1 \mathrm{H}), 4.19(\mathrm{~m}, 1 \mathrm{H}), 4.96(\mathrm{t}, 1 \mathrm{H}, \mathrm{J}=5.2 \mathrm{~Hz}), 5.39(\mathrm{bs}, 1 \mathrm{H}), 5.53(\mathrm{~s}$, $1 \mathrm{H}), 6.17(\mathrm{bs}, 1 \mathrm{H}), 6.83(\mathrm{~d}, 4 \mathrm{H}, J=8.8 \mathrm{~Hz}), 7.04-7.22(\mathrm{~m}, 9 \mathrm{H}), 7.77(\mathrm{~d}, 1 \mathrm{H}, J=7.6$ Hz ), 8.27 (bs, 1 H ); MS (AP-ES) $m / z 528.1$ [M-H].

## Step B: $\quad$ 3'-Deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate] This compound was synthesized following the similar synthetic

 procedure used for the synthesis of Example 80 starting with $N^{4}$-(4,4'-dimethoxytrityl)-3'-deoxycytidine ( $0.3 \mathrm{~g}, 0.57 \mathrm{mmol}$ ). Other reagents used for the synthesis were 1 H -tetrazole ( $0.04 \mathrm{~g}, 0.57 \mathrm{mmol}$ ), acetonitrile ( 4 mL ), bis-( $S$-pivaloyl-2-thioethyl)- $N, N$-diisopropylphosphoramidite ( $0.52 \mathrm{~g}, 1.14 \mathrm{mmol}$ ) and 3chloroperbenzoic acid $(0.2 \mathrm{~g}, 1.14 \mathrm{mmol}, 57-80 \%)$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3.6 \mathrm{~mL})$. The product was isolated in $22 \%$ yield ( 0.073 g ) after HPLC purification.'H NMR ( 200 MHz , DMSO- $\mathrm{d}_{6}$ ): $\delta 1.17(\mathrm{~s}, 18 \mathrm{H}), 1.84(\mathrm{~m}, 2 \mathrm{H}), 3.11(\mathrm{t}, 4 \mathrm{H}, J=6.4$ $\mathrm{Hz}), 3.93-4.31(\mathrm{~m}, 8 \mathrm{H}), 4.39(\mathrm{~m}, 1 \mathrm{H}), 5.55(\mathrm{~d}, 1 \mathrm{H}, J=4.2 \mathrm{~Hz}), 5.67(\mathrm{dd}, 2 \mathrm{H}, J=7.4$ and 1.8 Hz ), 7.1 (bs, 2 H$), 7.56(\mathrm{~d}, 1 \mathrm{H}, J=7.4 \mathrm{~Hz}) ;{ }^{13} \mathrm{P} \operatorname{NMR}\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta-0.71 ; \mathrm{MS}$ (AP-ES) $\mathrm{m} / \mathrm{z} \cdot 596.1[\mathrm{M}+\mathrm{H}]^{+}$; HRMS (MALDI) Calcd for $\mathrm{C}_{23} \mathrm{H}_{38} \mathrm{~N}_{3} \mathrm{O}_{9} \mathrm{PS}_{2} \mathrm{Na} 618.1679$. found 618.1600 .

## EXAMPLE 83

## 2'-O-Methylcytidine-5'-Ibis(isopropyloxycarbonyloxymethyl)]phosphate



Phosphonomethoxy nucleoside analogs are discussed in C.R. Wagner, V.V. Iyer, and E.J. McIntee, "Pronucleotides: Toward the In Vivo Delivery of Antiviral and Anticancer Nucleotides," Med. Res. Rev., 20: 1-35 (2000), which is incorporated by reference herein in its entirety. They are also disclosed U.S. Patent Nos. $5,922,695 ; 5,977,089 ; 6,043,230$; and $6,069,249$, the contents of each of which are incorporated by reference herein in their entirety.

Step A: iso-Propyl chloromethyl carbonate
This was prepared according to Antiviral Chemistry \& Chemotherapy
8: 557 (1997).
Step B:- 2'-O-Methylcytidine-5'-phosphate
This intermediate was prepared as described in Tetrahedron Lett. 50:
5065 (1967).
Step C: $\quad$ 2'-O-Methyloytidine-5'-[bis(isopropyloxycarbonyloxy methyl)]phosphate
2'-O-Methylcytidine-5'-phosphate ( $0.4 \mathrm{~g}, 1.19 \mathrm{mmol}$ ) was dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ in vacuum overnight at $40^{\circ} \mathrm{C}$. It was then suspended in anhydrous DMF ( 4 mL ). To this mixture was added diisopropylethylamine ( $0.86 \mathrm{~mL}, 4.92 \mathrm{mmol}$ ) and isopropyl chloromethyl carbonate ( $1.56 \mathrm{~g}, 7.34 \mathrm{mmol}$ ). The mixture was heated at $50^{\circ} \mathrm{C}$ for 1 h . The reaction mixture was then allowed to come to room temperature. The reaction mixture was stirred at room temperature for 48 h and then filtered. The

- 122 -
filtrate was diluted with water ( 100 mL ) and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 50 \mathrm{~mL})$. The organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. The residue was dissolved in $20 \% \mathrm{McOH}$ in water and purified by HPLC on $\mathrm{C}-18$ column (Luna $\mathrm{C} 18,250 \times 2.12 \mathrm{~mm}, \mathrm{~A}=$ water, $\mathrm{R}=$ acetonitrile 20 to $10 \% \mathrm{~B}$ in 65 ML , flow 10 mL $\mathrm{min}^{-1}, \lambda 260 \mathrm{~nm}$ ) to give the title compound ( 2.5 mg ).
${ }^{13} \mathrm{P}$ NMR $\left(\mathrm{CD}_{3} \mathrm{CN}\right)$ : $\delta-3.09 ; \mathrm{MS}(\mathrm{AP}-\mathrm{ES}) \mathrm{m} / \mathrm{z} 570.1[\mathrm{M}+\mathrm{H}]{ }^{+}$.


## EXAMPLE 84

0 2'-O-Methylcytidine-5?-[(2-decyloxy-3-dodecylthio-1-propyl)phosphate]


The procedure is described for similar nucleoside analogs in German Patent 408366 (1992) and J. Acquired Immune Defic. Syndr. 2000, 23, 227. The reaction of the appropriately protected 2'-O-methylcytidine with (2-decyloxy-3-dodecylthio-1-propyl)phosphate [prepared by the reaction of 2-decyloxy-3-dodecylthio-1-propanol with $\mathrm{POCl}_{3}$ in ether in presence of triethylamine] under refluxing conditions in a toluene-ether mixture furnishes the desired compound.

## EXAMPLE 85

 12'-O-Methylcytidine-5'-[rac-(3-octadecylthio-2-palmitoyloxy-1-propyl)phosphate] ,

PCT/US02/01531


This compound is synthesized by the reaction of 2'O-methylcytidine-5'-monophosphoromorpholidate with rac-1-S-octadecyl-2-O-palmitoyl-1-thioglycerol in pyridine following the similar procedure described for AZT and ddS in J. Med: 5. Chem. 39: 1771 (1996).

EXAMPLE 86
Nucleoside 5'-Triphosphates
The nucleoside 5'-triphosphates of the present invention were prepared according to the general procedures described in Chem. Rev.100: 2047 (2000).

## EXAMPLE 87

## Purification and Purity Analysis of Nucleoside 5'-Triphosphates

Triphosphates were purified by anion exchange (AX) chromatography using a $30 \times 100 \mathrm{~mm}$ Mono $Q$ column (Pharmacia) with a buffer system of 50 mM This, pH 8 . Elution gradients were typically from 40 mM NaCl to 0.8 M NaCl in two column volumes at $6.5 \mathrm{~mL} / \mathrm{min}$. Appropriate fractions from anion exchange chromatography were collected and desalted by reverse-phase (RP) chromatography using a Luna C18 $250 \times 21 \mathrm{~mm}$ column (Phenomenex) with a flow rate of $10 \mathrm{ml} / \mathrm{min}$. Elution gradients were generally from $1 \%$ to $95 \%$ methanol in 14 min at a constant. concentration of 5 mM triethylammonium acetate (TEAA).

Mass spectra of the purified triphosphates were determined using online HPLC mass spectrometry on a Hewlett-Packard (Pablo Alto, CA) MSD 1100. A Phenomenex Luna (C18(2)), $150 \times 2 \mathrm{~mm}$, plus $30 \times 2 \mathrm{~mm}$ guard column, $3-\mu \mathrm{m}$. particle size was used for RP HPLC. A 0 to $50 \%$ linear gradient ( 15 min ) of . acetonitrile in 20 mM TEAA (triethylammonium acetate) pH 7 was performed in

PCT/US02/01531
series with mass spectral detection in the negative ionization mode. Nitrogen gas and a pneumatic nebulizer were used to generate the electrospray. The mass range of 150900 was sampled. Molecular masses were determined using the HP Chemstation analysis package. RP and AX:HPLC. RP HPLC with a Phenomonex luna or Jupiter column ( $250 \times$ 4.6 mm ), $5-\mu \mathrm{m}$ particle size was typically run with a $2-70 \%$ acetonitrile gradient in 15 min in 100 mM TEAS, pH 7 . AX HPLC was performed on a $1.6 \times 5 \mathrm{~mm}$ Mono
1 Q column (Pharmacia). Triphosphates were eluted with a gradient of 0 to 0.4 M
10 NaCl at constant concentration of 50 mM Tris, pH 8 . Purity of the triphosphates was generally $>80 \%$.

## EXAMPLE 88

## 15 Nucleoside 5'-Monophosphates

The nucleoside 5'-monophosphates of the present invention were prepared according to the general procedure described in Tetrahedron Lett. 50: 5065 (1967).

## EXAMPLE 89

## 2-Amino-9-( $\beta$-D-arabinofuranosyl)-9 H -purin-6(1 H$)$-one



This compound was obtained from commercial sources.

EXAMPLE 90.
3'-Deoxy-3'-methylguanosine


This compound was prepared following procedures described in U.S. Patent No. 3,654,262 (1972).

## 2'-O-[4-(Imidazolyl-1)butyllguanosine



10 Step A:- 2'-O-[4-(Imidazolyl-1)butyll-2-aminoadenosine
A solution 2-aminoadenosine ( $7.36 \mathrm{~g}, 26 \mathrm{mmol}$ ) in dry DMF ( 260 mL ) was treated portionwise with $60 \% \mathrm{NaH}(3.92 \mathrm{~g}, 1000 \mathrm{mmol})$. After 1 hr ., a solution of bromobutylimidazole ( $9.4 \mathrm{~g}, 286 \mathrm{mmol}$ ) in DMF ( 20 ml ) was added. After 16 hrs., the solution was conc. in vacua, partitioned between $\mathrm{H}_{2} \mathrm{O} / \mathrm{EtOAc}$ and separated. The aqueous layer was evaporated, and the residue was chromatographed on silica gel $\left(\mathrm{CHCl}_{3} / \mathrm{MeOH}\right)$ to afford the title nucleoside as a white solid; yield 4.2 g .
${ }^{1}$ H NMR (DMSO- $d_{6}$ ): $\delta 1.39(\mathrm{t}, 2 \mathrm{H}), 1.67(\mathrm{t}, 2 \mathrm{H}), 3.3-3.7(\mathrm{~m}, 4 \mathrm{H}), 3.93(\mathrm{~m}, 3 \mathrm{H}), 4.29$ $(\mathrm{m}, 2 \mathrm{H}), 4.40(\mathrm{~d}, \mathrm{H}), 5.50(5,1 \mathrm{H}), 5.72(\mathrm{~d}, 1 \mathrm{H}), 5.82(\mathrm{bs}, 2 \mathrm{H}), 6.72(\mathrm{bs}, 2 \mathrm{H}), 6.86(\mathrm{~s}$, $1 \mathrm{H}), 7.08(\mathrm{~s}, 1 \mathrm{H}), 7.57(\mathrm{~s}, 1 \mathrm{H}) .7 .91(\mathrm{~s}, 1 \mathrm{H})$.

Step B:
2'-O-[4-(Imidazolyl-1)butyllguanosine

A mixture of the intermediate from Step. A ( $3.2 \mathrm{~g}, 8 \mathrm{mmol}$ ) in $\mathrm{H}_{2} \mathrm{O}$ $(200 \mathrm{~mL})$, DMSO ( 10 mL ), trisodium phosphate ( 10 g ), and adenosine deaminase ( 0.3 g) was stirred at room temperature and pH 7 . The solution was filtered and and then evaporated. The resulting solid was crystallized from $\mathrm{EtOAc} / \mathrm{MeOH}$ to afford the title compound as a white solid; yield 2.6 g .
${ }^{1} \mathrm{H}$ NMR (DMSO-d $d_{6}$ ): $8.1 .139(\mathrm{t}, 2 \mathrm{II}), 1.67(\mathrm{t}, 2 \mathrm{II}), 3.3-3.7(\mathrm{~m}, 4 \mathrm{H}), 3.93(\mathrm{~m}, 3 \mathrm{II}), 4.29$ $(\mathrm{m}, 2 \mathrm{H}), 5.10(\mathrm{t}, 1 \mathrm{H}), 5.20(\mathrm{~d}, 1 \mathrm{H}), 5.79(\mathrm{~d}, 1 \mathrm{H}), 6.50(\mathrm{bs}, 2 \mathrm{H}), 6.86(\mathrm{~s}, 1 \mathrm{H}), 7.08(\mathrm{~s}$, $1 \mathrm{H}), 7.57(\mathrm{~s}, 1 \mathrm{H}) 7.9(\mathrm{~s}, 1 \mathrm{H})$.

## 2'-Deoxy-2'-fluoroguanosine .



This compound was prepared following the conditions described in

## 2'-Deoxyguanosine

EXAMPLE 92
 Chem. Pharm. Bull. 29: 1034 (1981).

## EXAMPLE 93




This compound was obtained from commercial sources.

## EXAMPLE 94

2-Amino-7-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-4(3H)one

Step A: 2-Amino-4-chloro-7-(2,3,5-tri-O-benzyl- $\beta$-D-arabinofuranosyl)-7Hpyrrolo $[2,3-d]$-pyrimidine
To a suspension of 2-amino-4-chloro-i H -pyrrolo[2,3- $d$ ]pyrimidine. [Liebigs Ann. Chem.1: 137 (1983)] ( $3.03 \mathrm{~g}, 18 \mathrm{mmol}$ ) in anhydrous $\mathrm{MeCN}(240 \mathrm{~mL})$, powdered $\mathrm{KOH}(85 \% ; 4.2 \mathrm{~g}, 60 \mathrm{mmol})$ and tris[2-(2-methoxyethoxy)-ethyl]amine $(0.66 \mathrm{~mL}, 2.1 \mathrm{mmol})$ were added and the mixture was stirred at room temperature for 10 min . Then a solution of 2,3,5-tri-O-benzyl-D-arabinofuranosyl bromide [prepared from correspouding $1-O-p$-nitrobenzoate ( $11.43 \mathrm{~g}, 20.1 \mathrm{mmol}$ ) according to Seela et al., J. Org. Chem. (1982), 47, 226] in MeCN ( 10 mL ) was added and stirring continued for another 40 min . Solid was filtered off, washed with $\mathrm{MeCN}(2 \times 25 \mathrm{~mL}$ ) and combined filtrate evaporated. The residue was purified on a silica gel column with a solvent system of hexancs/EtOAc: 7/1, 6/1 and 5/1. Two main zones were separated. From the more rapidly migrating zone was isolated the $\alpha$ anomer ( 0.74 g ) and from the slower migrating zone the desired $\beta$ anomer ( 4.01 g ). ${ }^{\text {. }}$

Step B: . 2-Amino-7-( $\beta$-D-arabinofuranosyl)-4-chloro-7H-pyrrolo[2,3d]pyrimidine
To a solution of the compound from Step A ( $4.0 \mathrm{~g}, 7 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 150 ml ) at $-78^{\circ} \mathrm{C}$ was added a solution of $1.0 \mathrm{M} \mathrm{BCl}_{3}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(70 \mathrm{~mL}, 70 \mathrm{mmol})$ during 45 min . The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 3 h and at $-20^{\circ} \mathrm{C}$ for 2.5 h . $\mathrm{MeOH}-\mathrm{CH}_{2} \mathrm{Cl}_{2}(70 \mathrm{~mL}, 1: 1)$ was added to the mixture, which was then stirred at $-20^{\circ} \mathrm{C}$ for 0.5 h and neutralized with conc. aqueous $\mathrm{NH}_{3}$ at $0^{\circ} \mathrm{C}$. The mixture was stirred at room temperature for 10 min . and then filtered. The solid was washed with
$\mathrm{MeOH}-\mathrm{CH}_{2} \mathrm{Cl}_{2}(70 \mathrm{~mL}, \mathrm{l}: 1)$ and the combined filtrate evaporated. The residue was purified on a silica gel column with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 20 / 1$ to give the desired nucleoside ( 1.18 g ) as a white solid.
 5.8 mmol were dissolved in DMF ( 3.5 mL ). 1,3-Dichloro-1,1,3,3tetraisopropyldisiloxane ( 1.0 mL ) was added to the solution. The reaction mixture was stirred at room temperature for 1 h and then evaporated. The residue was partitioned between $\mathrm{CH}_{2} \mathrm{Cl}_{2}(150 \mathrm{~mL})$ and water $(30 \mathrm{~mL})$. The layers were separated. The organic layer was dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated. The residue was purified on a silica gel column with a solvent system of hexanes/EtOAc: $7 / 1$ and $5 / 1$ to give the title compound ( 1.04 g ).

Step D: $\quad$ - -Amino-7-[2-O-acetyl-3,5-0-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)- $\beta$-D-arabinofuranosyll-4-chloro-7H-pyrrolo[2,3-d]pyrimidine A mixture of the compound from Step C ( $0.98 \mathrm{~g}, 1.8 \mathrm{mmol}$ ) in MeCN ( 12 mL ), $\mathrm{Et}_{3} \mathrm{~N}(0.31 \mathrm{~mL}) \mathrm{Ac}_{2} \mathrm{O}(0.21 \mathrm{~mL})$ and DMAP ( $5 \mathrm{mg}, 0.25 \mathrm{eq}$.) was stirred at room temperature for 5 h and then evaporated. The oily residue was dissolved in EtOAc $(200 \mathrm{~mL})$, washed with water ( $2 \times 20 \mathrm{~mL}$ ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated to yield pure title compound ( 1.12 g ).

Step E: 2-Amino-7-[2-O-acetyl- $\beta$-D-arabinofuranosyll-4-chloro-7H-pyrrolo[2,3- $d$ ]pyrimidine
To an ice-cold solution of the compound from Step $D(0.95 \mathrm{~g}, 1.63$ $\mathrm{mmol})$ in THF ( 10 mL ) and $\mathrm{AcOH}(0.19 \mathrm{~mL})$ was added dropwise $1: 0 \mathrm{M}$ tetrabutylammonium fluoride solution in THF ( 3.4 mL ) and stirred at $0^{\circ} \mathrm{C}$ for 15 min . The solution was concentrated and the oily residue applied onto a silica gel column packed in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and elufed with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 50 / 1,25 / 1$ and 20/1. Appropriate fractions were pooled and ejaporated to give the title nucleoside ( 0.56 g ) as a white solid.

Step F: 2-Amino-7-[2-O-acetyl-3,5-di-O-(tetrahydro-2-pyiranyl)- $\beta$-D-arabinofuranosyll-4-chloro-7 H -pyrrolo [2,3-d]pyrimidine - 129 -

IPO DELHI 23-05-2015 15:55

To a solution of the compound from Step $\mathrm{E}(0.5 \mathrm{~g}, 1.46 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ and 3;4-dihydro-2- H -pyrane ( 0.67 mL ) was added dropwise TMSI ( $30 \mu \mathrm{~L}, 0.2 \mathrm{mmol}$ ). The reaction mixture was stirred at room temperature for 1 l h and then evaporated. The oily residue was purified on a silica gel column packed in a solvent system of hexanes/EtOAc/Et $\mathrm{N}: 75 / 25 / 1$ and eluted with a solvent system of hexancs/EtOAc: $3 / 1$. The fractions containing the product were collected and evaporated to give the desired compound $(0.60 \mathrm{~g})$.

Step G: 2-Amino-7-[3,5-di-O-(tetrahydro-2-pyranyl)-ß-D-arabinofuranosyll]-4-chloro- 7 H -pyrrolo $2,3-d$ ]pyrimidine A mixture of the compound from Step $\mathrm{F}(0.27 \mathrm{~g}, 0.53 \mathrm{mmol})$ and methanolic ammonia (saturated at $0^{\circ} \mathrm{C} ; 10 \mathrm{~mL}$ ) was kept overnight at $0^{\circ} \mathrm{C}$. Evaporation of the solvent yielded the desired compound ( 0.25 g ).

Step H: 2-Amino-9-[2-deoxy-2-fluoro-3,5-di-O-(tetrahydro-2-pyranyl)- $\beta$-D-ribofuranosyll-4-chloro-7H-pyrrolo[2,3-d]pyrimidine To a solution of the compound from Step G ( $0.24 \mathrm{~g}, 0.51 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ and pyridine $(0.8 \mathrm{~mL})$ at $-60^{\circ} \mathrm{C}$ was added diethylaminosulfur trifluoride (DAST; 0.27 mL ) dropwise under Ar. The solution was stirred at $-60^{\circ} \mathrm{C}$ for 0.5 h , at $0^{\circ} \mathrm{C}$ overnight and at room temperature for 3 h . The mixture was diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(25 \mathrm{~mL})$ and poured into saturated aqueous $\mathrm{NaHCO}_{3}(15 \mathrm{~mL})$. The organic layer was washed with water ( 10 mL ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated. The residue was purified on a silica gel column with a solvent system of hexanes/EtOAc: $5 / 1$ to give the title compound ( 45 mg ) as a pale yellow foam.


Step J: $\quad$ 2-Amino-7-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl) 7 H -pyrrolo[2,3-d]pyrimidin-4 $(3 H)$-one

```
i - 130.
```

A mixture of the compound from Step I ( $4 \mathrm{mg}, 0.08 \mathrm{mmol}$ ) in 2 N aqueous $\mathrm{NaOH}(1.2 \mathrm{~mL})$. was stirred at reflux temperature for 1.5 h . The solution was cooled in an ice-bath, neutralized with 2 N aqueous HCl and evaporated to dryness. The residue was suspended in MeOH , mixed with silica gel and evaporated. The solid residue was placed onto a silica gel column (packed in a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}: 10 / 1$ ) which was eluted with a solvent system of $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ : $10 / 1$. The fractions containing the product were collected and evaporated to dryness to yield the title compound ( 20 mg ) as a white solid.
${ }^{1} \mathrm{H}$ NMR (CD ${ }_{3} \mathrm{OD}$ ): $\delta 3.73,3.88(2 \mathrm{dd}, 2 \mathrm{H}, J=12.4,3.8,2.6 \mathrm{~Hz}), 4.01(\mathrm{~m}, 1 \mathrm{H}), 4.47$
(ddd, $1 \mathrm{H} J^{\prime}=16.5,6.6 \mathrm{~Hz}$ ), 5.14 (ddd, $\left.1 \mathrm{H}, J=5.3,4.7 \mathrm{~Hz}\right), 6.19(\mathrm{dd}, 1 \mathrm{H}, J=17.8$, $3.0 \mathrm{~Hz}), 6.39(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}=3.6 \mathrm{~Hz}), 6.95(\mathrm{~d}, \mathrm{iH})$.
${ }^{19} \mathrm{~F}$ NMR $\left(\mathrm{CD}_{3} \mathrm{OD}\right): \delta-206.53$ ( dt).

## EXAMPLE 95

2-Amino-7-( $\beta$-D-ribofuranosyll)-7H-pyrrolo(2,3- $d$ lpyrimidin-4(3H)-one


This compound was prepared following the procedures described in J. Chen. Soc. Perkin Trans. 1, 2375 (1989).

## EXAMPLE 96

2-Amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one


This compound was prepared following the procedures in Tetrahedron Lett. 28: 5107 (1987).

6-Amino-1-(2-O-methyl- $\beta$-D-ribofuranosyl)-1 $H$-imidazo $[4,5-c]$ pyridin-4(5H)-one


This compound was prepared in a manner similar to the preparation of
10 2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one (Example 23).

## EXAMPLE 98

15 6-Amino-1-(2-deoxy- $\beta$-D-ribofuranosyl)-1 $H$-imidazo[4,5-c]pyridin-4(5H)-one


This compound was prepared following the procedures described in $J$. Med. Chem. 26: 286(1983).

## EXAMPLE 99

6-Amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1H-imidazol4.5-clpyridin-4(5H)one


10 2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one (Example 23).

EXAMPLE 100
15
6-Amino-1-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-clpyridin-4(5H)one


This compound was prepared in a manner similar to the preparation of 2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one (Example 23).

5
EXAMPLE 101

6-Amino-1-( $\beta$-D-arabinofuranosyl)-1 $H$-imidazo[4,5-c]pyridin-4(5H)-one


10 A preparation of this compound is given in Eur. Pat. Appln. 43722 Al (1982).

## EXAMPLE 102

15 2'-O-[2-(N,N-diethylaminooxy)ethyl]-5-methyluridine


Step A: $\quad \because$ 5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine In a 2 L stainless steel, unstirred pressure reactor was added borane in tetrahydrofuran ( $1.0 \mathrm{M}, 2.0 \mathrm{eq}, 622 \mathrm{~mL}$ ). In the fume hood and with manual stirring, ethylene glycol ( 350 mL , excess) was added cautiously at first until the evolution of hydrogen gas subsided. 5'-O-tert-Butyldiphenylsilyl- $\mathrm{O}^{2}-2^{\prime}$-anhydro- 5 -methyluridine ( $149 \mathrm{~g}, 0.311 \mathrm{~mol}$ ) and sodium bicarbonate ( 0.074 g ) were added with manual stirring. The reactor was sealed and heated in an oil bath until an internal temperature of $160^{\circ} \mathrm{C}$ was reached and then maintained for 16 h (pressure < 100 psig ). The reaction vessel was cooled to ambient and opened. The reaction mixture was concentrated under reduced pressure ( 10 to 1 mm Hg ) in a warm water bath $\left(40-100^{\circ} \mathrm{C}\right)$ with the more extreme conditions used to remove the ethylene glycol. The residue was purified by column chromatography ( 2 kg silica gel, ethyl acetate:hexanes gradient $1: 1$ to $4: 1$ ). The appropriate fractions were combined, stripped and dried to product as white crisp foam ( 84 g ), contaminated starting material ( 17.4 g ) and pure reusable starting materiat ( 20 g ). TLC and NMR were consistent with $99 \%$ pure product. ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 1.05(\mathrm{~s}, 9 \mathrm{H}), 1.45(\mathrm{~s}, 3 \mathrm{H}), 3.5-4.1(\mathrm{~m}, 8 \mathrm{H}), 4.25(\mathrm{~m}, 1 \mathrm{H})$, $4.80(\mathrm{t}, 1 \mathrm{H}), 5.18(\mathrm{~d}, 2 \mathrm{H}), 5.95(\mathrm{~d}, 1 \mathrm{H}), 7.35-7.75(\mathrm{~m}, 11 \mathrm{H}), 11.42(\mathrm{~s}, 1 \mathrm{H})$.

Step B: $\quad{ }^{\prime}-$-O-I2-(2-phthalimidoxy)ethyll-5'-t-butyldiphenylsilyl-5methyluridine
5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine ( $20 \mathrm{~g}, 36.98 \mathrm{mmol}$ ) was mixed with triphenylphosphine ( $11.63 \mathrm{~g}, 44.36 \mathrm{mmol}$ ) and $N$ hydroxyphthalimide ( $7.24 \mathrm{~g}, 44.36 \mathrm{mmol}$ ). It was then dried over $\mathrm{P}_{2} \mathrm{O}_{5}$ under high vacuum for two days at $40^{\circ} \mathrm{C}$. The reaction mixture was flushed with argon and dry THF ( 369.8 mL ) was added to get a clear solution. Diethyl azodicarboxylate-( 6.98 $\mathrm{mL}, 44.36 \mathrm{mmol})$ was added dropwise to the reaction mixture. The rate of addition
was maintained such that resulting deep red coloration is just discharged before adding the next drop. After the addition was complete, the reaction was stirred for 4 h. By that time TLC showed the completion of the reaction (ethyl acetate/hexane, 60:40). The solvent was evaporaled under vacuum. Residue obtained was placed on

Slep D: $\quad$ '-O-tert-Butyldiphenylsilyl-2'-O-[2-( $N, N$-diethylaminooxy)ethyll -5 methyluridine

5'-O-tert-Butyldiphenylsilyl-2'-O-[2-(acetaldoximinooxy)ethyl]-5methyluridine ( $4.5 \mathrm{~g}, 7.74 \mathrm{mmol}$ ) was dissolved in 1 M pyridinium $p$-toluenesulfonate (PPTS) in $\mathrm{MeOH}\left(77.4 \mathrm{~mL}\right.$ ). It was then cooled to $10^{\circ} \mathrm{C}$ in an ice bath. To this mixture $\mathrm{NaBH}_{3} \mathrm{CN}(0.97 \mathrm{~g}, 15.5 \mathrm{mmol})$ was added and the mixture was stirred at $10^{\circ} \mathrm{C}$ for 10 minutes. Reaction mixture was allowed to come to room temperature and stirred for 4 h. Solvent was removed in vacuo to give an oil. Diluted the oil with ethyl acetate ( 100 mL ), washed with water ( 75 mL ), $5 \% \mathrm{NaHCO}_{3}(75 \mathrm{~mL}$ ) and brine ( 75 mL ). The orgànic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. Residue obtained was dissolved in 1M PPTS in MeOH ( 77.4 mL ), acetaldehyde ( 0.48 mL , 8.52 mmol ) was added and stirred at ambient temperature for 10 minutes. Then reaction mixture was cooled to $10^{\circ} \mathrm{C}$ in an ice bath and $\mathrm{NaBH}_{3} \mathrm{CN}(0.97 \mathrm{~g}, 15.50$ mmol) was added and stirred at $10{ }^{\circ} \mathrm{C}$ for 10 minutes. Reaction mixture was allowed to come to room temperature and stirred for 4 h . Solvent was removed in vacuo to get an oil. The oil was dissolved in ethyl acetate ( 100 mL ), washed with water ( 75 mL ), $5 \% \mathrm{NaHCO}_{3}(75 \mathrm{~mL})$ and brine ( 75 mL ). The organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated to dryness. The residue obtained was purified by silica gel column chromatography and eluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} / \mathrm{NEt}_{3}, 94: 5: 1$ to give title compound ( 3.55 g ) as a white foam.
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.95(\mathrm{t}, 6 \mathrm{H}, J=7.2 \mathrm{~Hz}), 1.03(\mathrm{~s}, 9 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H}), 2.58(\mathrm{q}$, $4 \mathrm{H}, J=7.2 \mathrm{~Hz}), 3.59(\mathrm{~m}, 1 \mathrm{H}), 3.73(\mathrm{~m}, 3 \mathrm{H}), 3.81(\mathrm{~m}, 1 \mathrm{H}), 3.88(\mathrm{~m}, 1 \mathrm{H}), 3.96(\mathrm{~m}$, $2 \mathrm{H}), 4.23(\mathrm{~m}, 1 \mathrm{H}), 5.21(\mathrm{~d}, 1 \mathrm{H}, J=5.6 \mathrm{~Hz}), 5.95 .(\mathrm{d}, 1 \mathrm{H}, J=6.4 \mathrm{~Hz}), 7.43(\mathrm{~m}, 7 \mathrm{H})$, $7.76(\mathrm{~m}, 4 \mathrm{H}), 11.39(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 11.84,19.35,26.97,52.27,63.27$, $68.81,70.27,72.27,82.64,84.47,86.77,111.04,127.87,130.01,135.11,135.41$, 141.32, $150.48,164.04$; $\mathrm{HR} M \mathrm{MS}$ (FAB), Calcd for $\mathrm{C}_{32} \mathrm{H}_{45} \mathrm{~N}_{3} \mathrm{O}_{7} \mathrm{SiCs}^{\oplus}, 744.2081$, found 744.2067.

## Step E: $\quad$ 2'-O-[2-( $N, N$-diethylaminooxy)cthyll]-5-methyluridine <br> A mixture of triethlyamine trihydrogenfluoride ( $4.39 \mathrm{~mL}, 26.81 \mathrm{mmol}$ ) and triethylamine ( $1.87 \mathrm{~mL}, 13.41 \mathrm{mmol}$ ) in THF ( 53.6 mL ) was added to $5^{\prime}$ - - -tert-

 butyldiphenylsilyl-2'-O-[2-(N,N-diethylaminooxy)ethyl]-5-methyluridine ( 3.28 g , $5.36 \mathrm{mmol})$. The reaction mixture was stirred at room temperature for 18 h . Solvent was removed in vacuo. The residue was placed on a silica gel column and eluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} / \mathrm{NEt}_{3}, 89: 10: 1$, to yield the title compound ( 1.49 g ). ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.97(\mathrm{t}, 6 \mathrm{H}, J=7.2 \mathrm{~Hz}), 1.75(\mathrm{~s}, 3 \mathrm{H}), 2.58(\mathrm{q}, 4 \mathrm{H}, J=7.2$ $\mathrm{Hz}), 3.55(\mathrm{~m}, 4 \mathrm{H}), 3.66(\mathrm{~m}, 2 \mathrm{H}), 3.83(\mathrm{bs}, 1 \mathrm{H}), 3.95(\mathrm{t}, 1 \mathrm{H}, J=5.6 \mathrm{~Hz}), 4.11(\mathrm{q}, 1 \mathrm{H}, J$ - 137 -$=4.8 \mathrm{~Hz}$ and 5.6 Hz$), 5.05(\mathrm{~d}, 1 \mathrm{H}, J=5.6 \mathrm{~Hz}), 5.87(\mathrm{~d}, 1 \mathrm{H}, J=6.0 \mathrm{~Hz}), 7.75(\mathrm{~s}, 1 \mathrm{H})$, $11.31(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 11.75,12.27,52.24,61.31,68.86,70.19,72.25$, 81.49, 85.10, 90.29, 110.60, 137.79, 150.57, 164.37; HRMS (FAB) Calcd for $\mathrm{C}_{16} \mathrm{H}_{28} \mathrm{~N}_{3} \mathrm{O}_{7}{ }^{\oplus} \cdot 374.1927$, found 374.1919 .
5

## 1-(2-C-Methyl- $\beta$-D-arabinofuranosyl)uracil



5-Methyl-3'-deoxycytidine


This compound was prepared following the procedures described in Chem. Pharm. Bull. 30: 2223 (1982).

## EXAMPLE 105

## 2-Amino-2'-O-methyladenosine



This compound was obtained from commercial sources.
i
EXAMPLE 106

2'-Deoxy-2'-fluoroadenosine

10


This compound was obtained from commercial sources.

## EXAMPLE 107

15 3'-Deoxy-3'-fluoroadenosine


This compound was prepared following the procedures described in Nucleosides Nucleotides 10: 719 (1991).

5

## EXAMPLE 108

3'-Deoxy-3'-methyladenosine


This compound was prepared following the procedures described in $J$. 10 Med. Chem. 19: $1265^{\circ}$ (1976).

## EXAMPLE 109

2-Amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine

15


- 140 -

This compound was prepared following the procedures described in $J$. Am. Chem. Soc. 106: 6379 (1984).

## EXAMPLE 110

5
4-Amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine


This compound is described in U.S. Patent 4,439,604, which is incorporated ' by reference hcrein in its entirety.
10 described for the preparation of Example 24 except the nucleobase is 3-deazaadenine.

## EXAMPLE 112



This compound was obtained from commercial sources.

## EXAMPLE 113

5
4-Amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine


This compound is described in Acta Crystallogr., Sect. C: Cryst. Struct. Commun. C43: 1790 ( 1987 ).

## EXAMPLE 114

4-Amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine


The procedure described earlier for Example 23 is used to synthesize this example by reacting the appropriately substituted 3-C-methyl-sugar intermediate with a protected 3-deazaadenine derivative.

4-Amino-1- $\beta$-D-ribofuranosyl-1 H -imidazo 4,5 -clpyridine


This compound was obtained from commercial sources.
EXAMPLE 115


## 2-(2-C-Methyl- $\beta$-D-arabinofuranosyl)adenine



This compound is prepared from 4-amino-9-(3,5-bis- O -tert-butyldimethylsilyl- $\beta$-D-erythro-pentofuran-2-ulosyl)purine (J. Med. Chem. 1992, 35, 2283) by reaction with MeMgBr and deprotection as described in Example 61.

## EXAMPLE 117

4-Amino-7-(2-C-ethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


Step A: $\quad \begin{aligned} & \text { 3,5-Bis- } O \text {-(2,4-dichlorophenylmethyl)-2-C-ethyl-1-O-methyl- } \alpha \text {-D. } \\ & \\ & \\ & \text { Iibofuranose }\end{aligned}$
To diethyl ether $(300 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$ was slowly added $\operatorname{EtMgBr}(3.0 \mathrm{M}$,
16.6 mL ) and then dropwise the compound from Step B of Example $62(4.80 \mathrm{~g}, 10.0$ $\mathrm{mmol})$ in anhydrous $\mathrm{Et}_{2} \mathrm{O}(100 \mathrm{~mL})$. The reaction mixture was stirred at $-78^{\circ} \mathrm{C}$ for 15 min , allowed to warm to $-15^{\circ} \mathrm{C}$ and stirred for another 2 h , and then poured into a stirred mixture of water $(300 \mathrm{~mL})$ and $\mathrm{Et}_{2} \mathrm{O}(600 \mathrm{~mL})$. The organic phase was separated, dried $\left(\mathrm{MgSO}_{4}\right)$, and evaporated in vacuo. The crude product was purified on silica gel using ethyl acetate/hexane (1:2) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 3.87 g ) as a colorless oil.

Step B: : 4-Chloro-7-[3,5-bis- $O$-(2,4-dichlorophenylmethyl)-2-C-ethyl- $\beta$-D-ribofuranosyll-7 H -pyrrolo $2,3-d]$ pyrimidine To a solution of the compound from Step A ( $1.02 \mathrm{mg}, 2.0 \mathrm{mmol}$ ) in dichloromethane ( 40 mL ) was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid) ( $1.75 \mathrm{~mL}, 10.0 \mathrm{mmol}$ ) dropwise at $0^{\circ} \mathrm{C}$. The resulting solution was stirred at It for 2 h , evaporated in vacuo and co-evaporated twice from toluene ( 10 mL ). The oily residue was dissolved in acetonitrile ( 10 mL ) and added to a vigorously stirred mixture of 4-chloro-1 H pyrrolo[ $2,3-d$ ]pyrimidine ( $307 \mathrm{mg}, 2.0 \mathrm{mmol}$ ), potassium hydroxide ( $337 \mathrm{mg}, 6.0$ mmol ) and tris[2-(2-methoxyethoxy)ethyl]amine ( $130 \mathrm{mg}, 0.4 \mathrm{mmol}$ ) in acetonitrile $(10 \mathrm{~mL})$. The resulting mixture was stirred at room temperature overnight, and thenpoured into a stirred mixture of saturated ammonium chloride ( 100 mL ) and ethyl acetate ( 100 mL ). The organic layer was separated, washed with brine ( 100 mL ), dried over $\mathrm{MgSO}_{4}$, filtered and evaporated in vacuo. The crude product was purified on silica gel using ethyl acetate/hexane (1:2) as eluent to give the desired product (307 mg ) as a colorless foam.

WO 02/057+25
PCT/US02/01531

Step C: 4-Chloro-7-(2-C-ethyl- 3 -D-ribofuranosyl)- $\overline{7} \mathrm{H}$-pyrrolof2,3-
d]pyrimidine
To a solution of the compound from Step B ( $307 \mathrm{mg}, 0.45 \mathrm{mmol}$ ) in dichloromethane ( 8 mL ) was added boron trichloride ( 1 M in dichloromethane) (4.50 $\mathrm{mL}, 4.50 \mathrm{mmol}$ ) at $-78^{\circ} \mathrm{C}$. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 1 h , then at $-10^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) ( 10 mL ), stirred at $-15^{\circ} \mathrm{C}$ for 30 min , and neutralized by addition of aqueous ammonium hydroxide. The mixture was evaporated in vacuo and the resulting oil purified on silica gel using methanol/dichloromethane (1:9) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 112 mg ) as a colorless foam.

Step D: 4-Amino-7-(2-C-ethyl-ß-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine
To the compound from Step C ( $50 \mathrm{mg}, 0.16 \mathrm{mmol}$ ) was added saturated ammonia in methanol ( 4 mL ). The mixture was stirred at $75^{\circ} \mathrm{C}$ for 72 h in a closed container, cooled and'evaporated in vacuo. The crude mixture was purified on silica gel using methanol/dichloromethane ( $1: 9$ ) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 29 mg ) as a colorless powder.
${ }^{1} \mathrm{H}$ NMR ( 200 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta 0.52(\mathrm{t}, 3 \mathrm{H}), 1.02(\mathrm{~m}, 2 \mathrm{H}), 4.01-3.24(\mathrm{~m}, 6 \mathrm{H})$, $5.06(\mathrm{~m}, 1 \mathrm{H}), 6.01(\mathrm{~s}, 1 \mathrm{H}), 6.51(\mathrm{~d}, 1 \mathrm{H}), 6.95(\mathrm{~s} \mathrm{br}, 2 \mathrm{H}), 6.70(\mathrm{~d}, 1 \mathrm{H}), 7.99(\mathrm{~s}, 1 \mathrm{H})$. LC-MS: Found: 295.2 ( $\mathrm{M}+\mathrm{H}^{+}$); calc. for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 295.14$.

## EXAMPLE 118

2-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one


- 145 -


Step C: . 2-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3$d$ ]pyrimidin- $4(3 \mathrm{H})$-one
A mixture of product from Step B ( $90 \mathrm{mg}, 0.3 \mathrm{mmol}$ ) in aqueous $\mathrm{NaOH}(2 \mathrm{~N}, 9 \mathrm{~mL})$ was heated at reflux temperature for 5 h , then neutralized $\mathrm{at}^{\circ} 0^{\circ} \mathrm{C}$.. with 2 N aqueous HCl and evaporated to dryness. Purification on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}, 5 / 1$ as eluent afforded the title compound as a white solid (70 mg ).
${ }^{1} \mathrm{H}$ NMR ( $200 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 0.86(\mathrm{~s}, 3 \mathrm{H}), 3.79(\mathrm{~m} \mathrm{1H}), 3.90-4.05(\mathrm{~m}, 3 \mathrm{H}), 6.06$ (s, 1 H ), $6.42(\mathrm{~d}, J=3.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.05(\mathrm{~d}, J=3.7 \mathrm{~Hz}, 1 \mathrm{H})$.

## EXAMPLE 119

2-Amino-4-cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine


A solution of 2-amino-4-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidine (Example 118 , Step B) ( $21 \mathrm{mg}, 0.07 \mathrm{mmol}$ ) in cyclopropylamine ( 0.5 mL ) was heated at $70^{\circ} \mathrm{C}$ for two days, then evaporated to an oily residue and purified on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}, 20 / 1$, as eluent to give the title compound as a white solid ( 17 mg ).
$1 \mathrm{H} \operatorname{NMR}\left(200 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right): \delta 0.61(\mathrm{~m}, 2 \mathrm{H}), 0.81(\mathrm{~m}, 2 \mathrm{H}), 0.85(\mathrm{~s}, 3 \mathrm{H}), 2.83(\mathrm{~m}$, $1 \mathrm{H}), 3.74-3.86(\mathrm{~m}, 1 \mathrm{H}), 3.93-4.03(\mathrm{~m}, 2 \mathrm{H}), 4.11(\mathrm{~d}, \mathrm{~J}=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.02(\mathrm{~s}, 1 \mathrm{H})$, $6.49(\mathrm{~d}, J=3.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.00(\mathrm{~d}, J=3.7 \mathrm{~Hz}, 1 \mathrm{H})$.

## EXAMPLE 120

3',5'-Bis-[ $O$-(1-oxooctyl)]-2'-O-methylcytidine


- 147 -

1,3-Dicyclohexylcarbodiimide ( $21.48 \mathrm{~g}, 104 \mathrm{mmol}$ ) was dissolved in anhydrous dichloromethane ( 100 mL ). To the solution was added octanoic acid ( 5.49 $\mathrm{mL}, 34.5 \mathrm{mmol}$, made anhydrous by keeping over molecular sieves, $4 \mathrm{~A}^{\circ}$ overnight at room temperature), and the resulting reaction mixture was stirred under argon atmosphere for 6 h . The white precipitate which formed was filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was dissolved in anhydrous pyridine and added to $\mathrm{N}^{4}$-(4,4'-dimethoxytrityl)-2'-O-methylcytidine ( 0.43 $\mathrm{g}, 0.77)$. DMAP $(0.09 \mathrm{~g}, 0.77 \mathrm{mmol})$ was added and the resulting mixture was stirred at room temperature under argon atmosphere for 12 h . The solvent was removed under reduced pressure and the residue obtained was dissolved in ethyl acetate ( 100 mL ). The organic phase was washed with aqueous sodium bicarbonate ( $5 \%, 50 \mathrm{~mL}$ ), dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography and eluted with $5 \% \mathrm{MeOH}$ in dichloromethane. The. product obtained was dissolved in a mixture of acetic acid: $\mathrm{MeOH}: \mathrm{H}_{2} \mathrm{O}(20 \mathrm{~mL}, 3: 6: 1)$. The resulting mixture was heated at $50^{\circ} \mathrm{C}$ for 24 h . The solvent was removed under reduced pressure. The residue obtained was purified by flash silica gel column chromatography and eluted with dichloromethane containing 0 to $5 \%$ of MeOH to give the title compound ( 0.22 g ).
${ }^{1} \mathrm{H}$ NMR ( 200 MHz , DMSO-d6) $\delta 0.83(\mathrm{~m}, 6 \mathrm{H}), 1.23$ (br s, 16 H ), 1.51 (m, 4H), 2.33 $(\mathrm{m}, 4 \mathrm{H}), 3.26(\mathrm{~s}, 3 \mathrm{H}), 4.06(\mathrm{t}, \mathrm{J}=5.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.21(\mathrm{~m}, 3 \mathrm{H}), 5.11(\mathrm{t}, \mathrm{J}=5.2 \mathrm{~Hz}, 1 \mathrm{H})$, $5.75(\mathrm{~d}, \mathrm{~J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.84(\mathrm{~d}, \mathrm{~J}=4.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.26(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 7.61(\mathrm{~d}, \mathrm{~J}=7.4 \mathrm{~Hz}$, 1H).
MS (ES): $m / z 510.3\left[\mathrm{M}+\mathrm{H}^{+}\right.$; HRMS (FAB) Calcd for $\mathrm{C}_{26} \mathrm{H}_{4} 4 \mathrm{~N}_{3} \mathrm{O} 7$ : 510.3179 ;
found 510.3170 .

## EXAMPLE 121

## 4-Amino-1-( $\beta$-D-ribofuranosyl)-1 H -pyrazolo $3.4-d$ pyrimidine



- 148 -

This compound was prepared following procedures described in Nucleic Acids Res., 11: 871-872 (1983).

## EXAMPLE 122

5
2'C-Methyl-cytidine


This compound was prepared following procedures described in L . Beigelman et al., Carbohyd.. Res. 166: 219-232 (1987) or X-Q Tang, et al., J. Org. 10 Chem. 64: 747-754 (1999). !

## EXAMPLE 123

4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5carbonitrile


This compound was prepared following procedures described by Y . Murat et al. in Heterocycles 33: 391-404 (1992).

## EXAMPLE 124

4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5carboxamide

## 8-Aminoadenosine



This compound was prepared following the procedure described in M . Ikehara and S. Yamada, Chem. Pharm. Bull., 19: 104 (1971).

This compound was prepared following procedures described by Y .
Murai et al: in Heterocycles 33: 391-404 (1992).

## EXAMPLE 125

EXAMPLE 126

## Mass Spectral Characterization of Nucleoside 5'-Triphosphates

Mass spectra of nucleoside $5^{\prime}$-triphosphates were determined as described in
 Example 87. Listed in the following table are the calculated and experimental masses
for the nucleoside 5'-triphosphates prepared according to the procedures of Example 86. The example numbers correspond to the parent nucleoside of the nucleoside 5;triphosphate.

| Example | Calculated | Found |
| :---: | :---: | :---: |
| 1 | 507.0 | 506.9 |
| 2 | 525.0 | 524.9 |
| 5 | 537.0 | 537.0 |
| 6 | 539.0 | 539.0 |
| 7 | 565.0 | 565.0 |
| 8 | 547.0 | 546.9 |
| 9 | 550.0 | 550.0 |
| 10 | 506.0 | 505.9 |
| 11 | 536.0 | 535.9 |
| 12 | 536.0 | 536.0 |
| 13 | 561.0 | 560.9 |
| 14 | 550.0 | 550.0 |
| 15 | 524.0 | 524.0 |
| 16 | 522.0 | 521.9 |
| 17 | 547.0 | $: 546.9$ |
| 18 | 536.0 | 536.0 |
| 20 | 531.0 | 530.9 |
| 21 | 522.0 | 522.0 |
| 22 | 536.0 | 536.0 |
| 23 | 506.0 | 506.1 |
| 24 | 524.0 | 524.0 |
| 25 | 508.0 | 508.0 |
| 26 | 508.0 | 508.0 |
| 27 | 552.0 | 552.0 |
| 28 | 506.0 | 506.0 |
| 29 | 579.0 | 578.9 |
| 30 | 582.0 | 582.0 |
| 31 | 568.0 | 567.9 |
|  |  |  |

PCT/US02/01531

| 32 | 554.0 | 553.9 |
| :---: | :---: | :---: |
| 33 | 540.0 | 539.9 |
| 34 | 554.0 | 553.9 |
| 35 | 568.0 | 567.9 |
| 36 | 541.0 | 541.0 |
| 37 | 565.0 | 564.9 |
| 38 | 542.0 | 541.9 |
| 39 | 554.0 | 553.9 |
| 41 | 481.0 | 481.0 |
| 42 | 467.0 | 467.0 |
| 43 | 485.0 | 484.8 |
| 46 | 482.0 | 482.0 |
| 47 | 486.0 | 485.8 |
| 48 | 482.0 | 482.0 |
| 49 | 554.0 | 554.0 |
| 51 | 468.0 | 468.1 |
| 52 | 521.0 | 521.0 |
| 53 | 491.0 | 491.2 |
| 55 | 584.9 | 585.1 |
| 56 | 521.0 | 521.2 |
| 58 | 506.0 | 506.0 |
| 61 | 520.0 | 519.9 |
| 62 | 520.0 | 520.0 |
| 63 | 547.0 | 547.0 |
| 64 | 533.0 | 533.0 |
| 65 | 549.0 | 549.0 |
| 67 | 551.0 | 551.0 |
| 68 | 515.0 | 514.9 |
| 69 | 520.0 | 520.1 |
| 71 | 490.0 | 489.9 |
| .89 | 523.0 | 522.9 |
| 90 | 521.0 | 520.9 |
| 91 | 645.1 | 645.0 |
|  |  |  |
| 63 |  |  |
| 63 |  |  |

- 152 -

IPO OELHT 23-06-2015 15:56

| 94 | 524.0 | 523.9 |
| :---: | :---: | :---: |
| 95 | 522.0 | 521.8 |
| 98 | 536.0 | 535.9 |
| 99 | 520.0 | 520.0 |
| 102 | 613.1 | 613.0 |
| 103 | 498.0 | 497.9 |
| 104 | 481.0 | $\cdot 481.0$ |
| $\vdots 105$ | 536.0 | 536.2 |
| 106 | 509.0 | 508.9 |
| 108 | 505.0 | 505.0 |
| 112 | 506.0 | 506.1 |
| 113 | 490.0 | 490.0 |
| 117 | 534.0 | 534.0 |
| 118 | 536.0 | 536.0 |

## EXAMPLE 127

[4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]-pyrimidine]-5'monophosphate


To the compound from Step F of Example 62 ( $14 \mathrm{mg}, 0.05 \mathrm{mmol}$ ) (dried by coevaporation with pyridine and several times with toluene) was added trimcthyl phosphate ( 0.5 mL ). The mixture was stirred overnight in a sealed container. It was then cooled to $0^{\circ} \mathrm{C}$ and phosphorous oxychloride ( $0.0070 \mathrm{~mL}, 0.075$ mmol ) was added via a syringe. The mixture was stirred for 3 h at $0^{\circ} \mathrm{C}$, then the reaction was quenched by addition of tetraethylammonium bicarbonate (TEAB) (1M)
$(0.5 \mathrm{~mL})$ and water ( 5 mL ). The reaction mixture was purified and analyzed according to the procedure described in Example 87.
Electron spray mass spectrum (ES-MS): Found: $359.2\left(\mathrm{M}-\mathrm{H}^{+}\right)$, calc. for $\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{~N}_{4} \mathrm{O}_{7} \mathrm{P}-\mathrm{H}^{+}: 359.1$.

## EXAMPLE 128

[4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]-pyrimidine]-5’diphosphate

To the compound from Step F of Example 62 ( $56 \mathrm{mg}, 0.20 \mathrm{mmol}$ ) (dried by coevaporation with pyridine and several times with toluene) was added: trimethyl phosphate (stored over sieves) ( 1.0 mL ). The mixture was stirred overnight in a sealed container. It was then cooled to $0^{\circ} \mathrm{C}$ and phosphorous oxychloride ( 0.023 $\mathrm{mL}, 0.25 \mathrm{mmol}$ ) was added via a syringe. The mixture was stirred for 2 h at $0^{\circ} \mathrm{C}$, then tributylamine $(0.238 \mathrm{~mL}, 1.00 \mathrm{mmol})$ and tributylammionium phosphate (generated from phosphoric acid and tributylamine in pyridine, followed by repeated azeotropic evaporation with pyridine and acetonitrile) ( 1.0 mmol in 3.30 mL acetonitrile) was added. The mixture was stirred for an additional 30 min at $0^{\circ} \mathrm{C}$, the sealed vial was then opened and the reaction quenched by addition of TEAB (1M) ( 1.0 mL ) and water $(5 \mathrm{~mL})$. The reaction mixture was purified and analyzed according to the procedure described in Example 87.
ES-MS: Found: $439.0\left(\mathrm{M}-\mathrm{H}^{+}\right)$, calc. for $\mathrm{C}_{12} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{10} \mathrm{P}_{2}-\mathrm{H}^{+}: 439.04$.

EXAMPLE 129
[4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolö[2,3- $d$ ]-pyrimidine]-5'triphosphate


To the compound from Step F of Example 62 ( $20 \mathrm{mg}, 0.07 \mathrm{mmol}$ ) (dried by coevaporation with pyridine and several times with toluene) was added trimethyl phosphate (stored over sieves) ( 0.4 mL ). The mixture was stirred overnight

## 7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one



To the compound from Step E of Example $62(59 \mathrm{mg}, 0.18 \mathrm{mmol})$ was added aqueous sodium hydroxide (IM). The mixture was heated to reflux for 1 hr , cooled, neutralized with qqueous HCl (2M) and evaporated in vacuo. The residue was purified on silica gel using dichloromethane/methanol (4:1) as eluent. Fractions - 155 .
containing the product were pooled and evaporated in vacuo to give the desired product ( 53 mg ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathrm{CD}_{3} \mathrm{CN}$ ): $\delta 0.70(\mathrm{~s}, 3 \mathrm{H}), 3.34-4.15$ (overlapping m, 7 H ), $6.16(\mathrm{~s}, 1 \mathrm{H}), 6.57$ (d, $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{~d}, 3.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.83(\mathrm{~s}, 1 \mathrm{H})$.

## 4-Amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolol2,3-d]pyrimidine



## EXAMPLE 131

Amine


To a pre-cooled solution $\left(0^{\circ} \mathrm{C}\right)$ of the compound from Step F of Example 62 ( $140 \mathrm{mg}, 0.50 \mathrm{mmol}$ ) in DMF ( 2.5 mL ) was added $N$-chlorosuccinimide ( $0.075 \mathrm{~g}, 0.55 \mathrm{mmol}$ ) in DMF ( 0.5 mL ) dropwise. The solution was stirred at rt for lh and the reaction quenched by addition of methanol ( 4 mL ) and evaporated in vacuo. The crude product was purified on silica gel using methanol/dichloromethane (1:9) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 55 mg ) as a colorless solid.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta 0.80(\mathrm{~s}, 3 \mathrm{H}), 3.65-4.14$ (overlapping $\mathrm{m}, 7 \mathrm{H}$ ), $5.97(\mathrm{~s} \mathrm{br}, 2 \mathrm{H})$, 6.17 (s, 1H), $7.51(\mathrm{~s}, 1 \mathrm{H}), 8.16(\mathrm{~s}, 1 \mathrm{H})$.

ES-MS: Found: 315.0 $\left(\mathrm{M}+\mathrm{H}^{+}\right)$, calc.for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{ClN}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}$: 315.09.

EXAMPLE 132

4-Amino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


To a pre-cooled solution ( $0^{\circ} \mathrm{C}$ ) of the compound from Step F of Example $62(28 \mathrm{mg}, 0.10 \mathrm{mmol})$ in DMF ( 0.5 mL ) was added $N$-bromosuccinimide $(0.018 \mathrm{~g}, 0.10 \mathrm{mmol})$ in $\mathrm{DMF}(0.5 \mathrm{~mL})$ dropwise. The solution was stirred at $0^{\circ} \mathrm{C}$ for 20 min , then at It for 10 min : The reaction was quenched by addition of methanol ( 4 mL ) and evaporated in vacuo. The crude product was purified on silica gel using " methanol/dichloromethane (1:9) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 13.0 mg ) as a colorless solid.
101 H NMR $\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta 0.69(\mathrm{~s}, 3 \mathrm{H}), 3.46-4.00$ (overlapping m, 7 H ), $5.83(\mathrm{~s} \mathrm{br}, 2 \mathrm{H}$ ), 6.06 (s, 1H), 7.45 (s, 1H), 8.05 (s, 1HI).

ES-MS: Found: $359.1\left(\mathrm{M}+\mathrm{H}^{+}\right)$, calc.for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{BrN}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 359.04$.

EXAMPLE 133

2-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyirrolo[2,3- $d$ ]pyrimidine


A mixture of 2-amino-4-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7Hpyrrolo[ $2,3-d]$ pyrimidine (Example 118, Step B) $(20 \mathrm{mg}, 0.07 \mathrm{mmol})$ in EtOH ( 1.0 mL ), pyridine ( 0.1 mL ) and $10 \% \mathrm{Pd} / \mathrm{C}(6 \mathrm{mg})$ under $\mathrm{H}_{2}$ (atmospheric pressure) was stirred overnight at room temperature. The mixture was.filtered through a Celite pad which was thorougly washed with EtOH. The combined filtrate was evaporated and

PCT/US02/01531
purified on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}, 20 / 1$ and $10 / 1$, as eluent to give the title compound as a white solid ( 16 mg ).
${ }^{1} \mathrm{H}$ NMR ( $200 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 0.86\left(\mathrm{~s}, 3 \mathrm{H}, 2^{\prime} \mathrm{C}-\mathrm{Me}\right), 3.82\left(\mathrm{dd}, J_{5^{\prime} 4^{\prime}}=3.6 \mathrm{~Hz}, J_{5^{\prime}, 5{ }^{\prime \prime}}=\right.$ $\left.12.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}\right), 3.91-1.03\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5^{\prime}, \mathrm{H}-4^{\prime}\right), 4.10\left(\mathrm{~d}, \mathrm{~J}_{3^{\prime} 4^{\prime}}=8.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3^{\prime}\right)$,

2-Amino-5-methyl-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-dlpyrimidin-4(3H)-one

## EXAMPLE 134

 6.02 (s, $1 \mathrm{H}, \mathrm{H}-1$ '), 6.41 ( $\mathrm{d}, \mathrm{J}_{\mathrm{s} .6}=3.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5$ ), 7.39 (d, 1H, H-6), 8.43 (s, 1H, H4). ES MS: $281.4\left(\mathrm{MH}^{+}\right)$.

Step A: 2-Amino-4-chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyl]-5-methyl- 7 H -pyrrolo[2,3-d]pyrimidine
To an ice-cold solution of the product from Step C of Example 62 ( $1.57 \mathrm{~g}, 3.16 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 50 mL ) was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid; 3.3 mL ) dropwise. The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 1 h and then at room temperature for 2 h , concentrated in vacuo and co-evaporated with toluene ( $2 \times 20$ mL ). The resulting oil was dissolved in $\mathrm{MeCN}(20 \mathrm{~mL})$ and added dropwise to a solution of the sodium salt of 2-amino-4-chloro-5-methyl-1 H -pyrrolo[2,3d] pyrimidine in acetonitrile [generated in situ from 2-amino-4-chloro-5-methyl-1 H -pyrrolo[2,3-d]pyrimidine [for preparation, see Liebigs Ann. Chem. 1984: 708-721] ( $1.13 \mathrm{~g}, 6.2 \mathrm{mmol}$ ) in anhydrous acetonitrile ( 150 mL ), and NaH ( $60 \%$ in mineral oil, $248 \mathrm{mg}, 6.2 \mathrm{mmol}$ ), after 2 h of vigorous stirring at ft$]$ : The combined mixture was stirred at rt for 24 h and then evaporated to dryness. The residue was suspended in water ( 100 mL ) and extracted with EtOAc $(300+150 \mathrm{~mL})$. The combined extracts were washed with brine $(100 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude product was purified on a;silica gel column ( $5 \times 7 \mathrm{~cm}$ ) using ethyl
acetate/hexane ( 0 to $30 \% \mathrm{EtOAc}$ in $5 \%$ step gradient) as the eluent. Fractions containing the product were combined and evaporated in vacuo to give the desired product $(0.96 \mathrm{~g})$ as a colorless foam.

Step B: , 2-Amino-4-chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl]-5-methyl-7H-pyrrolo[2,3-d]pyrimidine To an ioe-cold mixture of the product from Step A ( $475 \mathrm{mg}, 0.7 \mathrm{mmol}$ ) in THF ( 7 mL ) was added $\mathrm{NaH}\left(60 \%\right.$ in mineral oil, 29 mg ) and stirred at $0^{\circ} \mathrm{C}$ for 0.5 h. Then $\mathrm{MeI}(48 \mu \mathrm{~L})$ was added and reaction mixture stirred at rt for 24 h . The reaction was quenched with MeOH and the mixture evaporated. The crude product was purified on a silica gei column ( $5 \times 3.5 \mathrm{~cm}$ ) using hexane/ethyl acetate ( $9 / 1,7 / 1$, $5 / 1$ and $3 / 1$ ) as eluent. Fractions containing the product were combined and evaporated to give the desired compound ( 200 mg ) as a colorless foam.

Step C: 2-Amino-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl-$\beta$-D-ribofuranosyll]-5-methyl-7 H -pyrrolo[ 2,3 - $d$ ]pyrimidine- $4(3 \mathrm{H})$-one A. mixture of the product from Step B ( $200 \mathrm{mg}, 0.3 \mathrm{mmol}$ ) in $1,4-$ dioxane ( 15 mL ) and aqueous $\mathrm{NaOH}(2 \mathrm{~N}, 15 \mathrm{~mL})$ in a pressure bottle was heated overnight at $135^{\circ} \mathrm{C}$. The mixture was then cooled to $0^{\circ} \mathrm{C}$, neutralized with 2 N aqueous HCl and evaporated to dryness. The crude product was suspended in MeOH , filtered, and the solid thoroughly washed with MeOH . The combined filtrate was concentrated, and the residue purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) using. $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(40 / 1,30 / 1$ and $20 / 1$ ) as eluent to give the desired compound ( 150 mg ) as a colorless foam.

Step D: 2-Amino-5-methyl-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7Hpyrrolo[ 2,3 -d] pyrimidin-4(3H)-one
A mixture of the product from Step C ( $64 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) in MeOH ( 5 $\mathrm{mL})$ and $\mathrm{Et}_{3} \mathrm{~N}(0.2 \mathrm{~mL})$ and $10 \% \mathrm{Pd} / \mathrm{C}(24 \mathrm{mg})$ was hydrogenated on a Parr hydrogenator at 50 psi at r.t. for 1.5 days, then filtered through a Celite pad which was thoroughly washed with MeOH . The combined filtrate was evaporated and the residue purified on a silica gel column ( $3 \times 4 \mathrm{~cm}$ ) with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(30 / 1,20 / 1)$ as eluent to yield 2 -amino-5-methyl-7-(5-O-benzyi-2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3-d]pyrimidin-4(3H)-one. The compound ( 37 mg ) was
further hydrogenated in $\mathrm{EtOH}(2 \mathrm{~mL})$ with $10 \% \mathrm{Pd} / \mathrm{C}$ and under atmospheric pressure of hydrogen. After stirring 2 days at r.t., the reaction mixture was filtered through Celite, the filtrate evaporated and the crude product purified on a silica gel column (1 $\times 7 \mathrm{~cm}$ ) with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(30 / 1,20 / 1$ and $10 / 1)$ as eluent to yield the title
5 compound ( 12 mg ) after freeze-drying.
${ }^{1} \mathrm{H}$ NMR ( $200 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 0.81\left(\mathrm{~s}, 3 \mathrm{H}, 2^{\prime} \mathrm{C}-\mathrm{Me}\right), 2.16\left(\mathrm{~d}, J_{\mathrm{H}-6 . \mathrm{C} 5 \cdot \mathrm{Me}}=1.3 \mathrm{~Hz}\right.$, $3 \mathrm{H}, \mathrm{C} 5-\mathrm{Me}), 3.41\left(\mathrm{~s}, 3 \mathrm{H}, 2^{\prime}-\mathrm{OMe}\right), 3.67\left(\mathrm{dd}, J_{5^{\prime} 4^{\prime}}=3.4 \mathrm{~Hz}, \mathrm{~J}_{5^{\prime}, 5^{\prime \prime}}=12.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}\right)$, 3.81-3.91 (m, 3H, H-5', H-4', H-3'), 6.10 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-\mathrm{l}^{\prime}$ ), 6.66 ( $\mathrm{d}, 1 \mathrm{H}, \mathrm{H}-6$ ). ES MS: 323.3 ( $\mathrm{M}-\mathrm{H})^{+}$.

## 4-Amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine



Step A: $\quad$ 4-Chloro-7-13,5-bis- $O$-(2,4-dichlorophenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyll-5-methyl-7H-pyrrolo $2,3-d]$ pyrimidine
To an ice-cold solution of the product from Step C of Example 62 ( $1.06 \mathrm{~g}, 2.1 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL}$ ) was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid; 2.2 mL ) dropwise. The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 1 h and then at room temperature for 2 h , concentrated in vacuo and co-evaporated with toluene ( $2 \times 15$ $\mathrm{mL})$. The resulting oil was dissolved in $\mathrm{MeCN}(10 \mathrm{~mL})$ and added dropwise into a solution of the sodium salt of 4 -chloro-5-methyl- 1 H -pyrrolo[2,3-d]pyrimidine in acetonitrile [generated in situ from 4-chloro-5-methyl-1H-pyrrolo[2,3-d]pyrimidine [for preparation, see J. Med. Chem. 33: 1984 (1990)] ( $0.62 \mathrm{~g}, 3.7 \mathrm{mmol}$ ) in anhydrous acetonitrile ( 70 mL ), and NaH ( $60 \%$ in mineral oil, $148 \mathrm{mg}, 3.7 \mathrm{mmol}$ ), after 2 h of vigorous stirring at rt ]. The combined mixture was stirred at rt for 24 h and then evaporated to dryness. The residue was suspended in water ( 100 mL ) and extracted with EtOAc $(250+100 \mathrm{~mL})$. The combined extracts were washed with brine ( 50
mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude product was purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) using hexane/ethyl acetate $(9 / 1,5 / 1,3 / 1)$ gradient as the eluent. Fractions containing the product were combined and evaporated in vacuo to give the desired product $(0.87 . \mathrm{g})$ as a colorless foam. .

Step B: 4-Chloro-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine
To a solution of the compound from Step $\dot{A}\left(0.8^{\prime \prime} / \mathrm{g}, 0.9 \mathrm{mmol}\right)$ in dichloromethane ( 30 mL ) at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in dichloromethane, $9.0 \mathrm{~mL}, 9.0 \mathrm{mmol}$ ) dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2.5 h , then at $-30^{\circ} \mathrm{C}$ to $-20^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) ( 9 mL ) and the resulting mixture stirred at $-15^{\circ} \mathrm{C}$ for 30 min ., then neutralized with aqueous ammonia at $0^{\circ} \mathrm{C}$ and stirred at it for 15 min . The solid was filtered and washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(1 / 1,50 \mathrm{~mL})$. The combined filtrate was evaporated, and the residue was purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(40 / 1$ and $30 / 1$ ) gradient as the eluent to furnish the desired compound $(0.22 \mathrm{~g})$ as a colorless foam.

Step C: 4-Amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3dlpyrimidine
To the compound from Step B $(0.2 \mathrm{~g}, 0.64 \mathrm{mmol})$ was added methanolic ammonia (saturated at $0^{\circ} \mathrm{C} ; 40 \mathrm{~mL}$ ). The mixture was heated in a stainless steel autoclave at $100^{\circ} \mathrm{C}$ for 14 h , then cooled and evaporated in vacuo. The crude mixture was purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ ( $50 / 1$, $30 / 1,20 / 1$ ) gradient as eluent to give the title compound as a white solid ( 0.12 g ). ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.60$ ( $\mathrm{s}, 3 \mathrm{H}, 2^{\prime} \mathrm{C}-\mathrm{Me}$ ), 2.26 ( $\mathrm{s}, 3 \mathrm{H}, 5 \mathrm{C}-\mathrm{Me}$ ), $3.52-3.61$ ( m , 1H, H-5'), 3.70-3.88 (m, 3H, H-5', H-4', H-3'), 5.00 ( $\mathrm{s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}$ ), 4.91-4.99 (m, $\left.3 \mathrm{H}, 2^{\prime}-\mathrm{OH}, 3^{\prime}-\mathrm{OH}, 5^{\prime}-\mathrm{OH}\right), 6.04\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-\mathrm{l}^{\prime}\right), 6.48$ (br s, $2 \mathrm{H}, \mathrm{NH}_{2}$ ), 7.12 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-$ 6), $7.94(\mathrm{~s}, \mathrm{lH}, \mathrm{H}-2)$. ES MS: $295.2\left(\mathrm{MH}^{+}\right)$.

EXAMPLE 136

4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine-5carboxylic acid


The compound of Example 123 ( $0.035 \mathrm{~g}, 0.11 \mathrm{mmol}$ ) was dissolved in a mixture of aqueous ammonia ( $4 \mathrm{~mL}, 30 \mathrm{wt} \%$ ) and saturated methanolic ammonia ( 2 mL ), and a solution of $\mathrm{H}_{2} \mathrm{O}_{2}$ in water ( $2 \mathrm{~mL}, 35 \mathrm{wt} \%$ ) was added. The reaction

Step A: $\quad$ 3,5-Bis- $O$-(2,4-dichlorophenylmethyl)-2-C-vinyl-1-O-methyl- $\alpha$ - - solid. mixture was stirred at room temperature for 18 h . Solvent was removed under reduced pressure, and the residue obtained was purified by HPLC on a reverse phase column (Altech Altima C-18, 10x $299 \mathrm{~mm}, \mathrm{~A}=$ water, $\mathrm{B}=$ acetonitrile, 10 to $60 \% \mathrm{~B}$ in 50 min , flow $2 \mathrm{~mL} / \mathrm{min}$ ) to yield the title compound $(0.015 \mathrm{~g}, 41 \%)$ as a white
${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CD}_{3} \mathrm{OD}\right): 80.85(\mathrm{~s}, 3 \mathrm{H}, \mathrm{Mc}), 3.61(\mathrm{~m}, 1 \mathrm{H}), 3.82(\mathrm{~m}, 1 \mathrm{H}) 3.99-4.86(\mathrm{~m}$, $2 \mathrm{H}), 6.26(\mathrm{~s}, 1 \mathrm{H}), 8.10(\mathrm{~s}, 2 \mathrm{H}) 8.22(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\mathrm{CD}_{3} \mathrm{OD}$ ): 20.13, 61.37, 73.79, 80.42, 84.01, 93.00, 102.66, 112.07, 130.07, 151.40, 152.74, 159.12, 169.30. HRMS (FAB) Calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{~N}_{4} \mathrm{O}_{6}{ }^{7} 325: 1148$, found 325.1143 .

## EXAMPLE 137.

4-Amino-7-(2-C-vinyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d]$ pyrimidine
 ribofuranose

Cerium chloride heptahydrate ( $50 \mathrm{~g}, 134.2 \mathrm{mmol}$ ) was finely crushed in a pre-heated mortar and transferred to a round-bottom flask equipped with a mechanical stirrer. The flask was heated under high vacuum overnight at $160^{\circ} \mathrm{C}$. The vacuum was released under argon and the flask was cooled to room temperature. Anhydrous THF ( 300 mL ) was cannulated into the flask. The resulting suspension was stirred at room temperature for 4 h and then cooled to $-78^{\circ} \mathrm{C}$. Vinylmagnesium bromide ( 1 M in THF, $122^{\circ} \dot{\mathrm{mL}}, 120 \mathrm{mmol}$ ) was added and stirring continued at $-78^{\circ} \mathrm{C}$ for 2 h . To this suspension was added a solution of 3,5-bis- O -( $2,4-$ dichlorophenylmethyl)-1- $O$-methyl- $\alpha$-D-erythro-pentofuranose-2-ulose ( $14 \mathrm{~g}, 30$ mmol) [from Example 2, Step B] in anhydrous THF ( 100 mL ), dropwise with constant stirring. The reaction was stirred at $-78^{\circ} \mathrm{C}$ for 4 h . The reaction was quenched with saturated ammonium chloride solution and allowed to come to room temperature. The mixture was filtered through a celite pad and the residue washed with $\mathrm{Et}_{2} \mathrm{O}(2 \times 500 \mathrm{~mL})$. The organic layer was separated and the aqueous layer extracted with $\mathrm{Et}_{2} \mathrm{O}(2 \times 200 \mathrm{~mL})$. The combined organic layers were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to a viscous yellow oil. The oil was purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \% \mathrm{EtOAc}$ in hexanes). The title compound ( 6.7 g , 13.2 mmol ) was obtained as a pale yellow oil.

Step B: 4-Chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-vinyl- $\beta$-D-ribofuranosyll-7 H -pyrrolo $[2,3-d]$ pyrimidine
To a solution of the compound from Step A $(6.4 \mathrm{~g}, 12.6 \mathrm{mmol})$ in anhydrous dichloromethane ( 150 mL ) at $-20^{\circ} \mathrm{C}$ was added $\mathrm{HBr}(30 \%$ solution in $\mathrm{AcOH}, 20 \mathrm{~mL}, 75.6 \mathrm{mmol}$ ) dropwise. The resulting solution was stirred between $-10^{\circ} \mathrm{C}$ and $0^{\circ} \mathrm{C}$ for 4 h , evaporated in vacuo and co-evaporated with anhydrous toluene ( $3 \times 40 \mathrm{~mL}$ ). The oily residue was dissolved in anhydrous acetonitrile ( 100 mL ) and added to a solution of the sodium salt of 4-chloro- 1 H -pyirolo[2,3d]pyrimidine ( $5.8 \mathrm{~g}, 37.8 \mathrm{mmol}$ ) in acctonitrile (generated in situ as described in Example 62) at $-20^{\circ} \mathrm{C}$. The resulting mixture was allowed to come to room temperature and stirred at room temperature for 24 h . The mixture was then evaporated to dryness, taken up in water and extracted with EtOAc ( $2 \times 300 \mathrm{~mL}$ ). The combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude mixture was purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \%$ EtOAc in hexanes) and the title compound ( 1.75 g ) isolated as a white foam.

Step C: 4-Amino-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-vinyl- $\beta$-D. ribofuranosyl]-7 H -pyrrolo [2,3- $d$ ]pyrimidine
The compound from Step B ( $80, \mathrm{mg}$ ) was dissolved in the minimum amount of 1,4 -dioxane and placed in a stainless steel bomb. The homb was cooled to $-78^{\circ} \mathrm{C}$ and liquid ammonia was added. The bomb was sealed and heated at $90^{\circ} \mathrm{C}$ for 24 h . The ammonia was allowed to evaporate and the residue concentrated to a white solid which was used in the next step without further purification.

Step D: 4-Amino-7-(2-C-vinyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine
To a solution of the compound from Step C $(60 \mathrm{mg})$ in dichloromethane at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in dichloromethane) dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2.5 h , then at $-30^{\circ} \mathrm{C}$ to $-20^{\circ} \mathrm{C}$ for 3h. The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) and 15 the resulting mixture stirred at $-15^{\circ} \mathrm{C}$ for 0.5 h , then neutralized with aqueous. ammonia at $0^{\circ} \mathrm{C}$ and stirred at room temperature for 15 min . The solid was filtered and washed with methanol/dichloromethane (1:1). The combined filtrate was evaporated and the residue purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \%$ methanol in ElOAc containing $0.1 \%$ triethylamine). The fractions containing the product were evaporated to give the title compound as a white solid ( 10 mg ). $1 /$ NMR (DMSO- $\mathrm{d}_{6}$ ): $\delta 3.6\left(\mathrm{~m}, \mathrm{H}, \mathrm{H}-5^{\prime}\right), 3.8\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}\right) ; 3.9\left(\mathrm{~m} \mathrm{~d}, 1-\mathrm{H}, \mathrm{H}-4^{\prime}\right)$, $4.3\left(\mathrm{t}, 1 \mathrm{H}, \mathrm{H}-3^{\prime}\right), 4.8-5.3\left(\mathrm{~m}, 6 \mathrm{H}, \mathrm{CH}=\mathrm{CH}_{2}, 2^{\prime}-\mathrm{OH}, 3^{\prime}-\mathrm{OH}, 5^{\prime}-\mathrm{OH}\right) 6.12\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-\mathrm{l}^{\prime}\right)$, 6.59 (d, 1H, H-5), 7.1 (br s, 1H, NH2), 7.43 (d, 1H, H-6); 8.01 (s, 1H, H-2).

ES-MS: Found: 291.1 (M-H); calc. for $\mathrm{C}_{13} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{4}-\mathrm{H}: 291.2$.

## EXAMPLE $138^{\circ}$

4-Amino-7-(2-C-hydroxymethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine


Step A: 4-Chloro-7-[3,5-bis-Q-(2,4-dichlorophenylmethyl)-2-C-hydroxymethyl- $\beta$-D-ribofuranosyll-7H-pyrrolo[2,3- $d$ ]pyrimidine To a solution of the compound from Example 137, Step B ( 300 mg , 0.48 mmol ) in 1,4-dioxane ( 5 mL ) were added $N$-methylmorpholine- $N$-oxide ( 300 mg , 2.56 mmol ) and osmium.tetroxide ( $4 \%$ solution in water, 0.3 mL ). The mixture was stirred in the dark for 14 h . The precipitate was removed by filtration through a celite plug, diluted with water ( $3 \times$ ), and extracted with EtOAc. The EtOAc layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The oily residue was taken up in dichloromethane ( 5 mL ) and stirred over $\mathrm{NaIO}_{4}$ on silica gel ( $3 \mathrm{~g}, 10 \% \mathrm{NaIO}_{4}$ ) for 12 h. The silica gel was removed by filtration and the residue was evaporated and taken up in absolute ethanol ( 5 mL ). The solution was cooled in an ice bath and sodium borohydride ( $300 \mathrm{mg}, 8 \mathrm{mmol}$ ) was added in small portions. The resulting mixture was stirred at room temperature for 4 h and then diluted with EtOAc. The organic layer was washed with water ( $2 \times 20 \mathrm{~nL}$ ), brine ( 20 mL ) and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The solvent was evaporated and the residue purified by flash chromatography $\left(\mathrm{SiO}_{2}, 2: 1\right.$ hexanes/EtOAc) to give the title compound ( $160 \mathrm{mg}, 0.25 \mathrm{mmol}$ ) as white flakes.

Sep B: $\quad$ 4-Amino-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C hydroxymethyl- $\beta$-D-ribofuranosyll-7 H -pyrrolo[2,3-d]pyrimidine The compound from Step A ( $150 \mathrm{mg}, 0.23 \mathrm{mmol}$ ) was dissolved in the minimum amount of 1,4 -dioxane ( 10 mL ) and placed in a stainless steel bomb. The bomb was cooled to $-78^{\circ} \mathrm{C}$ and liquid ammonia was added. The bomb was sealed and heated at $90^{\circ} \mathrm{C}$ for 24 h . The ammonia was allowed to evaporate and the residue concentrated to a white solid which was used in the next step without further purification.

## Step C: 4-Amino-7-(2-C-hydroxymethyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3dlpyrimidine

The compound from Step B ( $120 \mathrm{mg}, 0.2 \mathrm{mmol}$ ) was dissolved in $1: 1$ methanol/dichloromethane, $10 \% \mathrm{Pd}-\mathrm{C}$ was added, and the suspension stirred under an $\mathrm{H}_{2}$ atmosphere for 12 h . The catalyst was removed by filtration through a celite pad and washed with copious amounts of methanol. The.combined filtrate was evaporated in vacuo and the residue was purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \%$ methanol in EtOAc containing $0.1 \%$ triethylamine) to give the title compound ( 50 nug) as a white powder.
$10{ }^{1} \mathrm{H}$ NMR ( $\mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 3.12\left(\mathrm{~d} ; 1 \mathrm{H}, \mathrm{CH}_{2}{ }^{\prime}\right), 3.33\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{CH}_{2}{ }^{\prime \prime}\right)$ ), $3.82\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}\right)$, 3.99-4.1(m, $\left.2 \mathrm{H}, \mathrm{H}-4^{\prime}, \mathrm{H}-5^{\prime \prime}\right), 4.3$ (d, $\left.1 \mathrm{H}, \mathrm{H}-3^{\prime}\right), 6.2$ (s, $1 \mathrm{H}, \mathrm{H}-1^{\prime}$ ), 6.58 (d, $1 \mathrm{H}, \mathrm{H}-5$ ), 7.45 (d, 1H, H-6), 8.05 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-2$ ).

LC-MS: Found: $297.2\left(\mathrm{M}+\mathrm{H}^{+}\right)$; calc. for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{5}+\mathrm{H}^{+}: 297.3$.

## 4-Amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidine



Step A: ! 4-Chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-fluoromethyl-B-D-ribofuranosyll-7H-pyrrolo[2,3-d]pyrimidine
To a solution of the compound from Example 138, Step A ( $63 \mathrm{mg}, 0.1$ mmol ) in anhydrous dichloromethane ( 5 mL ) under argon, were added 4 dimethylaminopyridine (DMAP) ( $2 \mathrm{mg}, 0.015 \mathrm{mmol}$ ) and triethylamine ( $62 \mu \mathrm{~L}, 0.45$ mmol ). The solution was cooled in an ice bath and p-toluenesulfonyl chloride ( 30 $\mathrm{mg}, 0.15 \mathrm{mmol}$ ) was added. The reaction was stirred at room temperature overnight, washed with $\mathrm{NaHCO}_{3}(2 \times 10 \mathrm{~mL})$, water ( 1.0 mL ), brine $(10 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to a pink solid in vacuo. The solid was dissolved in anhydrous THF ( 5 mL ) and cooled in an icebath. Tetrabutylammonium fluoride ( 1 M solution in THF, - 166 -

$1 \mathrm{~mL}, 1 \mathrm{mmol}$ ) was added and the mixture stirred at room temperature for 4 h . The solvent was removed in vacuo, the residue taken up in dichloromethane, and washed with $\mathrm{NaHCO}_{3}(2 \times 10 \mathrm{~mL})$, water ( 10 mL ) and brine $(10 \mathrm{~mL})$. The dichloromethane layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, concentrated in vacuo, and purified by flash chromatography ( $\mathrm{SiO}_{2}, 2: 1$ hexanes/EtOAc) to afford the title compound ( 20 mg ) as a white solid.

Step B: 4-Aminu-7-[3,5-bis-O-(2,4-dichluruphenylmethyl)-2-C-fluoromethyl-B-D-ribofuranosyll-7H-pyrrolo 2,3 - $d$ lpyrimidine
The compound from Step A ( $18 \mathrm{mg}, 0.03 \mathrm{mmol}$ ) was dissolved in the minimum amount of 1,4 -dioxane and placed in a stainless steel bomb. The bomb was cooled to $-78^{\circ} \mathrm{C}$ and liquid ammonia was added. The bomb was sealed and heated at $90^{\circ} \mathrm{C}$ for 24 h . The ammonia was allowed to evaporate and the residue concentrated to a white solid which was used in the next step without further purification.

Step C: $\quad$ 4-Amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3d]pyrimidine: -
The compound from Step B ( 16 mg ) was dissolved in $1: 1$ methanol/dichloromethane, $10 \% \mathrm{Pd}-\mathrm{C}$ was added, and the suspension stirred under an $\mathrm{H}_{2}$ atmosphere for 12 h . The catalyst was removed by filtration through a celite pad and washed with copious amounts of methanol. The combined filtrate was evaporated in vacuo and the residue was purified by flash chromatography $\left(\mathrm{SiO}_{2}, 10 \%\right.$ methanol in EtOAc containing $0.1 \%$ triethylamine) to give the title compound ( 8 mg ) as a white powder.
${ }^{1}{ }^{H}$ NMR (DMSO-d ${ }_{6}$ ): $\delta 3.6-3.7$ ( $\mathrm{m}, \mathrm{IH}, \mathrm{H}-5^{\prime}$ ), 3.8 -4.3 (m, 5H, H-5', H-4', H-3', $\left.\mathrm{CH}_{2}\right) 5.12\left(\mathrm{t}, 1 \mathrm{H}, 5^{\prime}-\mathrm{OH}\right), 5.35\left(\mathrm{~d}, 1 \mathrm{H}, 3^{\prime}-\mathrm{OH}\right), 5.48\left(\mathrm{~s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}\right), 6.21\left(\mathrm{~s},{ }^{\prime} 1 \mathrm{H}, \mathrm{H}-\right.$ $\left.1^{\prime}\right), 6.52$ (d, $1 \mathrm{H}, \mathrm{H}-5$ ), 6.98 (br s, 2H, NH2), 7.44 (d, $1 \mathrm{H}, \mathrm{H}-6$ ), 8.02 (s, $1 \mathrm{H}, \mathrm{H}-2$ ) 19F NMR (DMSO-d6): $\delta-230.2$ (t).
ES-MS: Found: $299.1\left(\mathrm{M}^{+\mathrm{H}^{+}}\right)$, calc.for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{FN}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}:$299.27.

EXAMPLES 140 and 141

4-Amino-7-(3-deoxy-2-C-methyl- -D -ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine and 4-amino7-(3-deoxy-2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo [2,3- $\alpha$ ]pyrimidine



Step A: $\quad 7$-[2,5-Bis- $O$-(tert-butyldimethylsilyl)- $\beta$-D-ribofuranosyll]-7Hpyrrolo $2,3-\alpha]$ pyrimidine and $7-[3,5-$ Bis- $O$-(tert-butyldimethylsilyl) $-\beta$ -D-ribofuranosyll-7H-pyrrolo[2,3-d]pyrimidine
To a stirred solution of tubercidin ( $5.0 \mathrm{~g}, 18.7 \mathrm{mmol}$ ) in a mixture of pyridine ( 7.5 mL ) and DMF: $(18.5 \mathrm{~mL})$ was added silver nitrate $(6.36 \mathrm{~g}, 38.8 \mathrm{mmol})$. This mixture was stirred at room temperature for 2 h . It was cooled in an ice bath and THF ( 37.4 mL ) and tert-butyldimethylsilyl chloride ( $5.6 \mathrm{~g}, 37 \mathrm{mmol}$ ) was added and the mixture was stirred at room temperature for 2 h . The mixture was then filtered through a pad of celite and washed with THF. The filtrate and washings were diluted with ether containing a small amount of chloroform. The organic layer was washed successively with sodium bicarbonate and water ( $3 \times 50 \mathrm{~mL}$ ), dried over anhydrous sodium sulfate and concentrated. The pyridine was removed by coevaporation with toluene and the residue was purified by flash chromatography on silica gel using $5-7 \%$ MeOH in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ as the eluent; yield 3.0 g .

Step B: $\quad$ 7-[2,5-Bis- $O$-(tert-butyldimethylsily 1$)-\beta$-D-ribofuranosyl)]-4-[di-(4-methoxyphenyl)phenylmethyl]amino- 7 H -pyrrolo[2,3- $d]$ pyrimidine and 7-[3,5-bis-O-(tert-butyldimethylsilyl)- $\beta$-D-ribofuranosyl]-4-[di-(4-methoxyphenyl)phenylmethyl]amino- 7 H -pyrrolo $[2,3-d]$ pyrimidine To a solution of mixture of the compounds from Step A $(3.0 \mathrm{~g}, 6.0$ mmol ) in anhydrous pyridine ( 30 mL ) was added 4, $4^{\prime}$-dimethoxytrityl chloride ( 2.8 g , 8.2 mmol ) and the reaction mixture was stirred at room temperature overnight. The muxture was then triturated with aqueous pyridine.and extracted with ether. The organic layer was washed with water, dried over anhydrous sodium sulfate and

PCT/US02/01531
concentrated to a yellow foam ( 5.6 g ). The residue was purified by flash chromatography over silica gel using $20-25 \%$ EtOAc in hexanes as the eluent. The appropriate fractions were collected and concentrated to furnish $2^{\prime}, 5^{\prime}-\mathrm{O}$-bis-O-(tert-butyldimethylsilyl)- and $3^{\prime}, 5^{\prime}$-bis-O-(tert-butyldimethylsilyl) protected nucleosides as colorless foams ( 2.2 g and 1.0 g , respectively).

> Step Ci $\quad$ 7-[2,5-Bis-O-(tert-butvidimethylsilyl)-3-O-tosyl- 3 -D-ribofurannsyl)]-4-[di-(4-methoxyphenyl)phenylmethyl]amino-7 H -pyrrolo 2,3 d] pyrimidine
> To an ice-cooled solution of 2 ', 5 '-bis-O-(tert-butyldimethylsilyl)protected nucleoside from Step B ( $2.0 \mathrm{~g}, 2.5 \mathrm{mmol}$ ) in pyridine ( 22 mL ) was added ptoluenesulfonyl chloride ( $1.9 \mathrm{~g}, 9.8 \mathrm{mmol}$ ). The reaction mixture was stirred at room temperature for four days: It was then triturate with aqueous pyridine ( $50 \%, 10 \mathrm{~mL}$ ) and extracted with ether ( $3 \times 50 \mathrm{~mL}$ ) containing a small amount of $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$. The organic layer was washed with sodium bicarbonate and water ( $3 \times 30 \mathrm{~mL}$ ). The organic layer was dried over? anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated. Pyridine was removed by co-evaporation with toluene ( $3 \times 25 \mathrm{~mL}$ ). The residual oil was filtered through a pad of silica gel using hexane:ethyl acetate ( $70: 30$ ) as eluent; yield 1.4 g .

Step D: 4-Idi-(4-methox yphenyl)phenylmethyllamino-7-[3-O-tosyl- $\beta$-D-ribofuranosyl-7H-pyrrolo[2,3-d]pyrimidine
A solution of the compound from Step C $(1.0 \mathrm{~g}, 1.1 \mathrm{mmol})$ and THF ( 10 mL ) was stirred with tetrabutylammonium fluoride ( 1 M solution in THF, 2.5 mL ) for 0.5 h . The mixture was cooled and diluted with ether ( 50 mL ). The solution was washed with water ( $3 \times 50 \mathrm{~mL}$ ), dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated to an oil. The residue was purified by passing through a pad of silica gel using hexane: ethyl acetate ( $1: 1$ ) as eluent; yield 780 mg .

Step E: $\quad$-Amino-7-(3-dcoxy-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]-pyrimidine and 4 -amino-7-(3-deoxy-2-C-methyl- $\beta$-D. arabinofuranosyl)-7 7 -pyrrolo-[2,3- $d]$ pyrimidine
A solution of $\mathrm{CH}_{3} \mathrm{MgI}$ ( 3.0 M solution in ether, 3.0 mL ) in anhydrous toluene ( 3.75 mL ) was cooled in an ice bath. To this was added a solution of thecompound from Step D ( $500 . \mathrm{mg}, 0.8 \mathrm{mmol}$ ) in anhydrous toluene ( 3.7 mL ). The resulting mixture was stirred at room temperature for 3.5 h . It was cooled and treated
with aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ solution and extracted with ether ( 50 mL containing 10 mL of $\left.\mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$. The organic layer was separated and washed with brine $(2 \times 30 \mathrm{~mL})$ and water ( $2 \times 25 \mathrm{~mL}$ ), dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to an oil which was purified by flash chromatography on silica gel using $4 \% \mathrm{MeOH}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to

## 4-Amino-7-(2,4-C-dimethyl- 3 tD-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


-170.

## Step A: 5-Deoxy-1,2-O-isopropylidene-D-xylofuranose

I,2-O-Isopropylidene-D-xylofuranose ( $38.4 \mathrm{~g}, 0.2 \mathrm{~mol}$ ), 4 dimethylaminopyridine ( 5 g ), triethylamine ( $55.7 \mathrm{~mL}, 0.4 \mathrm{~mol}$ ) were dissolved in dichloromethane ( 300 mL ). p-Toluenesulfonyl chloride ( $38.13 \mathrm{~g}, 0.2 \mathrm{~mol}$ ) was added and the reaction mixture was stirred at room temperature for 2 h . The reaction mixture was then poured into saturated aqueous sodium bicarbonate ( 500 mL ) and the two layers were separated. The organic layer was washed with aqueous citric acid solution ( $20 \%, 200 \mathrm{~mL}$ ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated to give a solid $(70.0 \mathrm{~g})$. The solid was dissolved in dry THF ( 300 mL ) and $\mathrm{LiAlH}_{4}(16.0 \mathrm{~g}, 0.42 \mathrm{~mol})$ was added in portions over 30 min . The mixture was stirred at room temperature for 15 h . Ethyl acetate $(100 \mathrm{~mL})$ was added dropwise over 30 min and the mixture was filtered through a silica gel bed. The filltrate was concentrated and the resulting oil was chromatographed on silica gel (EtOAc/hexane 1/4) to afford the product as a solid ( 32.5 g ).

## Step B: $\quad$ 3,5-Bis-O-(2,4-dichlorophenylmethyl)-1-O-methyl-4-methyl- $\alpha$-Dribofuranose <br> Chromium oxide ( $50 \mathrm{~g}, 0.5 \mathrm{~mol}$ ), acetic anhydride ( $50 \mathrm{~mL}, 0.53 \mathrm{~mol}$ )

 and pyridine ( $100 \mathrm{~mL}, 1.24 \mathrm{~mol}$ ) were added to dichloromethane ( 1 L ) in an ice water bath and the mixture was stirred for 15 min . 5 -Deoxy-1,2-O-isopropylidene-Dxylofuranose ( $32 \mathrm{~g}, 0.18 \mathrm{~mol}$ ) in dichloromethane ( 200 mL ) was added, and the mixture was stirred at the same temperature for 30 min . The reaction solution was diluted with ethyl acetate ( 1 L ) and filtered through a silica gel bed. The filtrate was concentrated to give a yellow oil. The oil was dissolved in 1,4-dioxane ( 1 L ) and formaldehyde ( $37 \%, 200 \mathrm{~mL}$ ). The solution was cooled to $0^{\circ} \mathrm{C}$ and solid $\mathrm{KOH}(50 \mathrm{~g})$ was added. The mixture was stirred at room temperature overnight and was then extracted with ethyl acetate $(6 \times 200 \mathrm{~mL})$. After concentration, the residue was chromatographed on silica gel (EtOAc) to afford the product as an oil ( 1.5 g ). The oil was dissolved in 1-methyl-2-pyrrolidinone ( 20 mL ) and 2,4-dichlorophenylmethyl chloride ( $4 \mathrm{~g}, 20.5 \mathrm{mmol}$ ) and $\mathrm{NaH}(60 \%, 0.8 \mathrm{~g})$ were added. The mixture was stirred ovemight and diluted with toluene ( 100 mL ). The mixture was then washed with saturated aqueous sodium bicarbonate ( $3 \times 50 \mathrm{~mL}$ ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated. The residue was dissolvẹd in methanol ( 50 mL ) and HCl in dioxane ( $4 \mathrm{M}, 2 \mathrm{~mL}$ ) was added. The solution was stirred overnight and evaporated. The residue waschromatographed on silica gel (EtOAc/hexane:1/4) to afford the desired product as an oil ( 2.01 g ).

Step C: $\quad$ 3,5-Bis- $O$-(2,4-dichlorophenylmethyl)-2,4-di- $C$-methyl-1- $O$-methyl- $\alpha$ -

## D-ribofuranose

The product ( $2.0 \mathrm{~g}, 4.0 \mathrm{mmol}$ ) from Step B and Dess-Martin . periodinane ( 2.0 g ) in dichloromethane ( 30 mL ) were stirred overnight at room temperature and was then concentrated under reduced pressure. The residue was triturated with ether ether ( 50 mL ) and filtered. The filtrate was washed with a solution of $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} .5 \mathrm{H}_{2} \mathrm{O}(2.5 \mathrm{~g})$ in saturated aqueous sodium bicarbonate solution ( 50 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and evaporated. The residue was dissolved in anhydrous $\mathrm{Et}_{2} \mathrm{O}(20 \mathrm{~mL})$ and was added dropwise to a solution of $\mathrm{MeMgBr}^{\mathrm{M}} \mathrm{Et}_{2} \mathrm{O}$ (3 $\mathrm{M}, 10 \mathrm{~mL}$ ) at $-78^{\circ} \mathrm{C}$. The reaction mixture was allowed to warm to $-30^{\circ} \mathrm{C}$ and stirred at $-30^{\circ} \mathrm{C}$ to $-15^{\circ} \mathrm{C}$ for 5 h , then poured into saturated aqueous ammonium chloride ( 50 $\mathrm{mL})$. The two layers were separated and the organic layer was dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentrated. The residue was chromatographed on silica gel (EtOAc/hexane: $1 / 9$ ) to afford the title compound as a syrup ( 1.40 g ).

Step D: $\quad$ 4-Chloro-7-[3,5-bis- $O$-(2,4-dichlorophenylmethyl)-2,4-di- $C$-methyl- $\beta$ -D-ribofuranosyll-7H-pyrrolo[2,3-d]pyrimidine
To the compound from Step $\mathrm{C}(0.70 \mathrm{~g}, 1.3 \mathrm{mmol})$ was added $\mathrm{HBr}(5.7$ M in acetic acid, 2 mL ). The resulting solution was stirred at room temperature for 1 h , evaporated in vacuo and co-evaporated with anhydrous toluene ( $3 \times 10 \mathrm{~mL}$ ). 4-Chloro- 1 H -pyrrolo $[2,3-d]$ pyrimidine ( $0.5 \mathrm{~g}, 3.3 \mathrm{mmol}$ ) and powdered $\mathrm{KOH}(85 \%$, $150 \mathrm{mg}, 2.3 \mathrm{mmol}$ ) were stirred in 1-methyl-2-pyrrolidinone ( 5 mL ) for 30 min and the mixture was co-evaporated with toluene ( 10 mL ). The resulting solution was poured into the above bromo sugar residue and the mixture was stirred overnight. The mixture was diluted with toluene ( 50 mL ), washed with water ( $3 \times 50 \mathrm{~mL}$ ) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with (EtOAc/ Hexane 15/85) to afford a solid ( 270 mg ).

Sep E: 4-Amino-7-(2,4-di-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine

The compound from Step D ( 270 mg ) was dissolved in dioxane ( 2 mL ) and liquid ammonia $(20 \mathrm{~g})$ was added in a stainless steel autoclave. The mixture was heated at $100^{\circ} \mathrm{C}$ for 15 h , then cooled and evaporated. The residue was chromatographed on silica gel (EtOAc) to afford a solid ( 200 mg ). The solid ( 150 mg ) and $\mathrm{Pd} / \mathrm{C}(10 \% 150 \mathrm{mg})$ in methanol ( 20 mL ) were shaken under $\mathrm{H}_{2}$ ( 30 psi ) for 3 h , filtered and evaporated. The residue was chromatographed on silica gel ( $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}: 1 / 9$ ) to afford the desired product as a solid ( 35 mg ). ${ }^{1} \mathrm{H}$ NMR (DMSO- $\mathrm{d}_{6}$ ): $80.65(\mathrm{~s}, 3 \mathrm{H}), 1.18(\mathrm{~s}, 3 \mathrm{H}), 3.43(\mathrm{~m}, 2 \mathrm{H}), 4.06(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J} 6.3$ $\mathrm{Hz}), 4.87(\mathrm{~s}, 1 \mathrm{H}), 5.26^{\circ}(\mathrm{br}, 1 \mathrm{H}), 5.08(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J} 6.3 \mathrm{~Hz}), 5.25(\mathrm{t}, 1 \mathrm{H}, J 3.0 \mathrm{~Hz}), 6.17(\mathrm{~s}$, 1 H ), $6.54(\mathrm{~d}, \mathrm{lH}, J 3.5 \mathrm{~Hz}), 6.97(\mathrm{~s}, \mathrm{br}, 2 \mathrm{H}), 7.54(\mathrm{~d}, 1 \mathrm{H}, J 3.4 \mathrm{~Hz}), 8.02$ (s, 1H). ${ }^{13} \mathrm{C}$ NMR (DMSO- $d_{6}$ ): $\delta 18.19,21.32,65.38,73.00,79.33,84.80,90.66,99.09$, 102.41, 121.90, 149.58, 151.48, 157.38.

LC-MS: Found: $295.1\left(\mathrm{M}^{+} \mathrm{H}^{+}\right)$; calculated for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 295.1$

4-Amino-7-(3-deoxy-3-fluoro-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine

EXAMPLE 143
-


Step A: 3-Deoxy-3-fluoro-1-O-methyl-5-O-toluoyl- $\alpha$-D-ribofuranose 1,2-O-Isopropylidene-D-xylofuranose ( $9.0 \mathrm{~g}, 50 \mathrm{mmol}$ ) and p-toluoyl chloride ( $7.0 \mathrm{~mL}, 50 \mathrm{mmol}$ ) in pyridine ( 50 mL ) were stirred for 30 min . Water ( 10 mL ) was added and the mixture was concentrated under reduced pressure. The residue was dissolved in toluene ( 500 mL ) and the solution was washed with water $(200 \mathrm{~mL})$ and saturated aqueous sodium bicarbonate $(200 \mathrm{~mL})$. The two layers were separated and the organic layer was evaporated. The residue was dissolved in methanol ( 100 mL ) and HCl in dioxane ( $4 \mathrm{M}, 10 \mathrm{~mL}$ ) was added. The mixture was
stirred at room temperature overnight and was then evaporated under reduced pressure. The resulting oil was chromatographed on silica gel (EtOAc/hexane: 1/1) to afford an oil ( 10.1 g ). The oil was dissolved in dichloromethane ( 100 mL ) and diethylaminosulfur trifluoride (DAST) ( 5.7 mL ) was added. The mixture was stirred overnight and was then poured into saturated aqueous sodium bicarbonate solution $(100 \mathrm{~mL})$. The mixture was extracted with toluene $(2 \times 50 \mathrm{~mL})$ and the combined organic layers were concentrated. The residue was chromatographed on silica gel (EtOAc/hexane: $15 / 85$ ) to afford the title compound as an oil ( 1.50 g ).

Step B: $\quad \frac{\text { 3-Deoxy-3-fluoro-2-C-methyl-1-O-methyl-5-O-toluoyl- } \alpha \text {-D. }}{}$
$\frac{\text { ribofuranose }}{\text { The product from Step A }(1.0 \mathrm{~g}, 3.5 \mathrm{mmol}) \text { and Dess-Martin }}$ periodinane ( 2.5 g ) in dichloromethane ( 20 mL ) were stirred overnight at room temperature and was then concentrated under reduced pressure. The residue was triturated with diethyl ether $(50 \mathrm{~mL})$ and filtered. The filtrate was washed with a solution of $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} .5 \mathrm{H}_{2} \mathrm{O}$ ( 12.5 g ) in saturated aqueous sodium bicarbonate ( 100 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$; filtered and evaporated. The residue was dissolved in anhydrous WHF ( 50 mL ). $\mathrm{TiCl}_{4}(3 . \mathrm{mL})$ and methyl magnesium bromide in ethyl ether ( $3 \mathrm{M}, 10$ mL ) were added at $-78^{\circ} \mathrm{C}$ and the mixture was stirred at -50 to $-30^{\circ} \mathrm{C}$ for 2 h . The mixture was poured into saturated aqueous sodium bicarbonate solution ( 100 mL ) and filtered through Celite. The filtrate was extracted with toluene ( 100 mL ) and evaporated. The residue was chromatographed on silica gel (EtOAc/hexane: 15/85) to afford the title compound as and oil ( 150 mg ).

Step C: 4-Amino-7-(3-deoxy-3-fluoro-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d ]pyrimidine
The product from Step B ( $150 \mathrm{mg}, \dot{0} .5 \mathrm{mmol}$ ) was dissolved in HBr ( $30 \%$ ) in acetic acid ( 2 ml ). After one hour, the mixture was evaporated under reduced pressure and co-evaporated with toluene ( 10 mL ). 4-Chloro-1H-pyrrolo[2,3d] pyrimidine ( $0.5 \mathrm{~g}, 3.3 \mathrm{mmol}$ ) and powdered $\mathrm{KOH}(85 \%, 150 \mathrm{mg}, 2.3 \mathrm{mmol}$ ) were stirred in DMF ( 3 mL ) for 30 min and the mixture was co-evaporated with toluene ( 2 $\mathrm{mL})$. The resulting solution was poured into the above bromo sugar and the mixture was stirred ovemight. The mixture was diluted with toluene $(50 \mathrm{~mL})$, washed with water ( $3 \times 50 \mathrm{~mL}$ ) and concentrated under reduced pressure. The residue was
chromatographed on silica gel (EtOAc/hexane 15/85) to afford an oil ( 60 mg ). The oil was dissolved in dioxane ( 2 mL ) and liquid ammonia ( 20 g ) was added in a stainless steel autoclave. The mixture was heated at $85^{\circ} \mathrm{C}$ for 18 h , then cooled and evaporated. The residue was chromatographed on silica gel

8-Amino-2'-C-methyladenosine


Step A: 8-Bromo-2'-C-methyladenosine
To a solution of $2^{\prime}$ - C-methyladenosine [for preparation, see J. Med.
Chem. 41: 1708 ( 1998 )] ( $138 \mathrm{mg}, 0.5 \mathrm{mmol}$ ) in DMF ( 4 mL ) was added $N$ bromosuccinimide ( $231 \mathrm{mg}, 1.35 \mathrm{mmol}$ ). The solution was stirred protected from light at rt for 2 d and then evaporated in vacuo. The crude product was purified on a silica gel column ( $3 \times 9 \mathrm{~cm}$ ) using dichloromethane/methanol ( $25 / 1,20 / 1$ and $15 / 1$ ) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 38 mg ) as a white solid.

Step B:
8-Amino-2'-C-methyladenosine

A solution of the compound from Step A ( $38 \mathrm{mg}, 0.11 \mathrm{mmol}$ ) in liquid ammonia ( 10 mL ) was heated in a stainless steel autoclave at $105^{\circ} \mathrm{C}$ for 1 d , then cooled and evaporated. The residue was purified by HPLC [C-18 Phenomenex Luna ( $10 \mu ; 250 \times 2.1 .2 \mathrm{~mm}$ ) RP-column; solvents: (A) water, (B) acetonitrile; Linear gradient: $2-35 \% \mathrm{~B}$ in 76 min .] to yield the title compound ( 12 mg ) as a white fluffy material after freeze-drying.
'H NMR (DMSO-d ${ }^{\text {) }}$ : $\delta 0.70$ (s, 3H, Me), 3.55-3.75 (m, 3H, H-5', H-5', H-4'), 4.03 (m, 1H, H-3'), $4.81\left(\mathrm{~s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}\right), 5.10\left(\mathrm{~d}, 1 \mathrm{H}, 3^{\prime}-\mathrm{OH}\right), 5.45\left(\mathrm{t}, 1 \mathrm{H}, 5^{\prime}-\mathrm{OH}\right), 5.86(\mathrm{~s}$, 1H, H-1'), 6.30, 6.39 ( $2 \mathrm{~s}, 6 \mathrm{H}, 2 \mathrm{NH}_{2}$ ), 7.78 (s, 1H, H-2).
ES-MS: Found: $295.0\left(\mathrm{M}-\mathrm{H}^{+}\right)$.

## EXAMPLE 145

4-Amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d$ ]pyrimidine


Step A: 4-chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl-

## $\beta$-D-ribofuranosyl]-7 H -pyrrolo[2,3-d]pyrimidine

To a pre-cooled $\left(0^{\circ} \mathrm{C}\right)$ solution of the compound from Example 62,
Step D ( $618 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) in THF ( 8 mL ) was added methyl iodide ( $709 \mathrm{mg}, 5.0$ mmol) and NaH ( $60 \%$ in mineral oil) $(44 \mathrm{mg}, 1.1 \mathrm{mmol})$. The resulting mixture was stirred overnight at rt and then poured into a stirred mixture of saturated aqueous ammonium chloride ( 50 mL ) and dichloromethane ( 50 mL ). The organic layer was washed with water ( 50 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$ and evaporated in vacuo. The resulting crude product was purified on silica gel using ethyl acetate/hexane as the eluent.
Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 735 mg ) as a colorless foam.

Step B: $\quad$-amino-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl-$\beta$-D-ribofuranosyl]-7H-pyrrolo[2,3-d]pyrimidine
To the compound from Step A ( $735 \mathrm{mg}, 1.16 \mathrm{mmol}$ ) was added methanolic ammonia (saturated at $\left.0^{\circ} \mathrm{C}\right)(20 \mathrm{~mL})$. The mixture was heated in a stainless steel autoclave at $80^{\circ} \mathrm{C}$ overnight, then cooled and the content evaporated in vacuo. The crude mixture was purified on silica gel using ethyl acetate/hexane as the eluent. Fractions containing the product were pooled'and evaporated in vacuo to give the desired product ( 504 mg ) as colorless foam.

| Step $\mathrm{C}: \quad \frac{4 \text {-amino-7-(2-C,2-O-dimethyl- } \beta \text {-D-ribofuranosyl)-7 }}{}$d]-pyrrolo[2,3- |  |
| ---: | :--- |
|  | A mixture of the product from Step $\mathrm{C}(64 \mathrm{mg}, 0.1 \mathrm{mmol}), \mathrm{MeOH}(5$ | $\mathrm{mL}), \mathrm{Et}_{3} \mathrm{~N}(0.2 \mathrm{~mL})$ and $10 \% \mathrm{Pd} / \mathrm{C}(61 \mathrm{mg})$ was hydrogenated on a Parr hydrogenator at 50 psi at room temperature overnight. The mixture was filtered throught celite, evaporated in vacuo and filtered through a pad of silica gel using $2 \%$ methanol in dichloromethane as eluent. The desired product was collected and evaporated in vacuo. The compound was redissolved in methanol ( 10 mL ) and $10 \% \mathrm{Pd} / \mathrm{C}(61 \mathrm{mg})$ was added. The mixture was hydrogenated on a Parr hydrogenator at 55 psi at room temperature for two weeks. The mixture was filtered through elite, evaporated in yacuo and purified on silica gel using $10 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 110 mg ) as a colorless foam.

lH NMR (DMSO- $d_{6}$ ): $\delta 0.68(\mathrm{~s}, 3 \mathrm{H}$ ), $3.40(\mathrm{~s}, 3 \mathrm{H}$ ), 3.52-3.99 (overlapping m, 4 H ), $4.92(\mathrm{~d}, 1 \mathrm{H}), 5.07(\mathrm{t}, 1 \mathrm{H}), \dot{6} .26(\mathrm{~s}, 1 \mathrm{H}), 6.55(\mathrm{~d}, 1 \mathrm{H}), 7.00 \mathrm{~s}$ br, 2 H$), 7.46(\mathrm{~d}, 1 \mathrm{H}), 8.05$ (s, 1H).

LC-MS: Found: 293:1 (M-H+); call. for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{4}-\mathrm{H}^{+}$: 293.12.

EXAMPLE 146

4-Methylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine


The compound from Step E of Example $62(200 \mathrm{mg}, 0.67 \mathrm{mmol})$ was added to methylamine ( 5 mL condensed in a small stainless steel autoclave) and warmed at $85^{\circ} \mathrm{C}$ for 48 h , then cooled and evaporated in vacuo. The crude mixture which separated as an amorphous solid after treatment with MeN. The amorphous solid was dissolved in water and lyophilized to give a colorless powder ( 144 mg ). ${ }^{1} \mathrm{H} \mathrm{NMR}$ ( $\mathrm{DMSO}-d_{6}$ ): $\delta 0.63\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.32\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{N} \mathrm{CH}_{3}\right), 3.58-3.67(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-$ $5^{\prime}$ ), 3.79-3.39 (m, 3H, H-5', H-4', H-3'), 5.03 ( $\left.\mathrm{s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}\right), 5.04-5.11$ ( $1 \mathrm{H}, 3^{\prime}-\mathrm{OH}$, $\left.101 \mathrm{H}, 5^{\prime}-\mathrm{OH}\right), 6.14\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 6.58\left(\mathrm{~d}, 1 \mathrm{H}, J_{\mathrm{s}, 6}=3.6 \mathrm{~Hz}, \mathrm{H}-5\right), 7.46(\mathrm{~d}, 1 \mathrm{H}, \mathrm{H}-6)$, 7.70 (br s, 1H, NH), 8.14 (s, $1 \mathrm{H}, \mathrm{H}-2$ ).

LC-MS: Found: 295.1 (M-H ${ }^{+}$); call. for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 294.3$.

## EXAMPLE 147

## 4-Dimethylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine



The compound from Step E of Example $62(200 \mathrm{mg}, 0.67 \mathrm{mmol})$ was added to dimethylamine ( 5 mL condensed in a small stainless steel autoclave) and warmed at $85^{\circ} \mathrm{C}$ for 48 h , then cooled and evaporated in vacuo. The crude mixture was purified on a silica gel with ethanol as the eluent to give the title compound
which separated as an amorphous solid after treatment with MeCN . The amorphous solid was dissolved in water and lyophilized to give a colorless powder ( 164 mg ). ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.64$ ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ), 3.29 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{NCH}_{3}$ ), 3.32 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{N} \mathrm{CH}_{3}$ ), 3.60-3.66 (m, 1H, H-5'), 3.77-3.97 (m, 3H, H-5", H-4', H-3'), 5.04 ( $\mathrm{s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}$ ), $5.06-5.11\left(1 \mathrm{H}, 3^{\prime}-\mathrm{OH}, 1 \mathrm{H}, 5^{\prime}-\mathrm{OH}\right), 6.21\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 6.69\left(\mathrm{~d}, 1 \mathrm{H}, J_{5,6}=3.6 \mathrm{~Hz}, \mathrm{H}-\right.$ 5), 7.55 (d, 1H, H-6), 8.13 (s, 1H, H-2).

LC-MS: Found: 309.3 (M- $\mathrm{H}^{+}$); calc. for $\mathrm{C}_{14} \mathrm{H}_{20} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 308.33$.

## EXAMPLE 148

4-Cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


The compound from Step E of Example $62(200 \mathrm{mg}, 0.67 \mathrm{mmol})$ was added to cyclopropylamine ( 5 mL condensed in a small stainless steel autoclave) and

EXAMPLE 149

## 4-Amino-7-(3-C-methyl- $\beta$-D-xylofuranosyl)-7H-pyrrolof 2,3- $\alpha$ ]pyrimidine



Step A: $\quad 7-[2,5$-Bis-O-(tert-butyldimethylsilyl)- $\beta$-D-ribofuranosyl)]-4-[(4-methoxyphenyl)diphenylmethyllamino- 7 H -pyrrolo $[2,3-d]$ pyrimidine and $7-[3,5$-bis- $O$-(tert-butyldimethylsilyl)- $\beta$-D-ribofuranosyl]-4-[(4- methoxyphenyl)diphenylmethyllamino- 7 H -pyrrolo $[2,3-d]$ pyrimidine To a solution of mixture of the compounds from Step A of Examples 140 and $141(0.32 \mathrm{~g}, 0.65 \mathrm{mmol})$ in anhydrous pyridine ( 6 mL ) was added monomethoxytrityl chloride ( $0.30 \mathrm{~g}, 0.98 \mathrm{mmol}$ ) and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated and the residue was partitioned between $\mathrm{CH}_{2}^{3} \mathrm{Cl}_{2}(70 \mathrm{~mL})$ and water $(20 \mathrm{~mL})$. The organic layer was washed with water and brine, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated. The residue was purified on silica gel column using 5-13\% EtOAc in hexanes as the eluent. The appropriate fractions were collected and concentrated to furnish $2^{\prime}, 5^{\prime}$-bis-O-(tert-butyldimethylsilyl)- and $3^{\prime}, 5^{\prime}$-bis-O-(tert-butyldimethylsilyl) protected nucleosides as colorless foams ( 343 mg and 84 mg , respectively).

Step B: $\quad 7-[2,5-$ Bis-O-(tert-butyldimethylsilyl)- $\beta$-D-erythro-pentofuranos-3-ulosyll-4-[(4-methoxyphenyl)diphenylmethyllamino-7H-pyrrolo [2,3dI pyrimidine
To a well-stirred suspension of chromium trioxide ( $91 \mathrm{mg}, 0.91 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ were added pyridine ( $147 \mu \mathrm{~L}, 1.82 \mathrm{mmol}$ ) and then acetic anhydride ( $86 \mu \mathrm{~L}, 0.91 \mathrm{mmol}$ ). The mixture was stirred at room temperature for 0.5 h. Then the 2 ', 5 '-bis-O-(fert-butyldimethylsilyl) protected nucleoside from step A ( 343 mg 0.45 mmol ) in $\mathrm{C}_{2} \mathrm{H}_{2} \mathrm{Cl}_{2}(2.5 \mathrm{~mL})$ was added and the mixture stirred at room temperature 2 h . The mixture was then poured into ice-cold EtOAc ( 10 mL ) and filtered through a short silica gel column using EtOAc as the eluent. The filtrate was evaporated and the residue purified on a silica gel column with hexanes and hexanes/EtỌAc ( $7 / 1$ ) as the eluent to give the title compound ( 180 mg ).

Step C: 7-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-C-methyl- $\beta$-D-ribofuranosyl)-4-[(4-methoxyphenyl)diphenylmethyllamino-7 H -pyrrolo [2,3-
d pyrimidine and $7-\int 2,5$-Bis- $O$-(tert-butyldimethylsilyl)-3-C-methyl- $\beta$ -D-xylofuranosyl)-4-[(4-methoxyphenyl)diphenylmethyllamino-7H- pyrrolo $2,3-d]$ pyrimidine To a mixture of MeMgBr ( 3.0 M solution in ether; $0.17 \mathrm{~mL}, 0.5 \mathrm{mmol}$ ) in anhydrous hexanes ( 1.5 mL ) at room temperature was added dropwise a solution of the compound from Step B ( $78 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) in anhydrous hexanes ( 0.5 mL ). After 2 h stirring at room temperature, the reaction mixture was poured into ice-cold water ( 10 mL ) and diluted with EtOAc ( 20 mL ), then filtered through Celite which was then thoroughly washed with EtOAc. The layers were separated and the organic layer was washed with brine, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated. The residue was purified on a silica gel column using $8 \cdot$ to $25 \%$ EtOAc in hexanes as eluent to give the 3-C-methyl xylo- ( 60 mg ) and the $3-\dot{C}$-methyl ribo-isomer ( 20 mg ).

## Step D: $\quad$ 4-Amino-7-(3-C-methyl- $\beta$-D-xylofuranosyl)-7H-pyrrolo[2,3d] pyrimidine <br> To an ice-cold solution of 3-C-methyl-xylo isomer from Step C ( 60

 $\mathrm{mg}, 0.08 \mathrm{mmol}$ ) in THF ( 2 mL ) was added TBAF ( 1 M in THF; $0.32 \mathrm{~mL}, 0.32 \mathrm{mmol}$ ). The reaction mixture was stirred at room temperature for 5 h , then diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 50 mL ), washed with water ( $3 \times 15 \mathrm{~mL}$ ), dried, and evaporated. The residue was dissolved in dioxane ( 0.3 mL ) and $80 \%$ acetic acid ( 3 mL ) was added. The reaction mixture was stirred at room temperature for $1 d$ and then evaporated. The residue was co-evaporated with dioxane, taken up in water ( 50 mL ) and washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 10 \mathrm{~mL})$. The aqueous layer was concentrated and then freeze-dried. The residue was purified on silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(20 / 1$ and $10 / 1$ ) as the eluent to give the title compound as a white fluffy compound after freeze drying ( 10 mg ).${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta 1.28\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.56(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 3.78\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{H}-4^{\prime}, \mathrm{H}-\right.$ $\left.5^{\prime}, \mathrm{H}-5^{\prime \prime}\right), 4.10(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 4.44\left(\mathrm{~d}, 1 \mathrm{H}, J_{2^{\prime}} \mathrm{p}=3.9 \mathrm{~Hz}, \mathrm{H}-2^{\prime}\right), 5.58\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right)$, 5.85 (br s, $2 \mathrm{H}, \mathrm{NH}_{2}$ ), $6.15(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 6.48\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{s}, 6}=3.7 \mathrm{~Hz}, \mathrm{H}-5\right.$ ), $7.23(\mathrm{~d}, .$. $1 \mathrm{H}, \mathrm{H}-6), 811(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-2)$. ES-MS: $281[\mathrm{MH}]^{+}$.

## EXAMPLE 150.

4-Amino-7-(3-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine

The ribo-isomer ( 20 mg ) from Step C of Example 149 was deprotected using the procedure described in Step D of Example 32 to yield the title compound (4 mg ).
$1_{1} \mathrm{NMR}\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta 1.43\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.2 \dot{8}(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 3.58(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5$, $\mathrm{H}-$ $\left.5^{\prime \prime}\right), 3.99\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4^{\prime}\right), 4.10(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 4.62\left(\mathrm{~d}, 1 \mathrm{H}, J_{2^{\prime}} 1^{\prime}=8.1 \mathrm{~Hz}, \mathrm{H}-2^{\prime}\right), 5.69$ (d, $1 \mathrm{H}, \mathrm{H}-1^{\prime}$ ), 5.88 (br s, $3 \mathrm{H}_{:} \mathrm{OH}, \mathrm{NH}_{2}$ ), 6.45 (br s, $1 \mathrm{H}, \mathrm{OH}$ ), $6.51\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{5,6}=3.7\right.$ $\mathrm{Hz}, \mathrm{H}-5), 7.19$ (d, 1H, H-6), 8.12 (s, 1H, H-2). ES-MS: $281[\mathrm{MH}]^{+}$.

## EXAMPLE 151

I
2,4-Diamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d]$ pyrimidine


A mixture of the product from Step B of Example 118 ( 24 mg ) in aqueous ammonia $(30 \%, 10 \mathrm{~mL})$ was heated in a stainless steel autoclave at $100^{\circ} \mathrm{C}$ ovemight, then cooled and evaporated. The residue was purified on a silica gel
 column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(10 / 1$ and $5 / 1)$ as the eluent to afford the title compound ( 15 mg ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.68\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.48-3.58(\mathrm{~m} \mathrm{IH}, \mathrm{H}-5$ ) , 3.68-3.73 (m, 2 H , H-5', H-4'), 3.84 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}-3^{\prime}$ ), 4.72 ( $\mathrm{s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}$ ), 4.97-5.03 (m, 2H, $3^{\prime}-\mathrm{OH}, 5^{\prime}-$ OH ), 5.45 ( $\mathrm{br} \mathrm{s}, 2 \mathrm{H}, \mathrm{NH}_{2}$ ), $6.00\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1{ }^{\prime}\right), 6.28(\mathrm{~d}, 1 \mathrm{H}, J=3.7 \mathrm{~Hz}, \mathrm{H}-5$ ), 6.44 (br $\left.\mathrm{s}, 2 \mathrm{H}, \mathrm{NH}_{2}\right) 6.92(\mathrm{~d}, 1 \mathrm{HJ}=3.7 \mathrm{~Hz}, \mathrm{H}-6)$. ES MS: $294.1\left(\mathrm{M}-\mathrm{H}^{+}\right)$.

## EXAMPLE 152

4-Amino-2-fluoro-7-(2-C-methyl- $\beta$ - P -ribofuranosyl)-7H-pyrrolof2,3-d]pyrimidine

To a solution of $\mathrm{HF} /$ pyridine $(70 \%, 2 \mathrm{~mL}$ ) diluted with pyridine ( 1 mL ) at $-30^{\circ} \mathrm{C}$ is added the compound of Example $151(60 \mathrm{mg}, 0.2 \mathrm{mmol})$ in 0.5 mL pyridine followed by tert-butyl nitrite ( $36 \mu \mathrm{~L}, 0.3 \mathrm{mmol}$ ). Stirring is continued for 5 $\min -25^{\circ} \mathrm{C}$. Then the solution is poured into ice-water ( 5 mL ), neutralized with 2 N aqueous NaOH , and evaporated to dryness. The residue is purified on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ (20/1 and 10/1) as the fluent to afford the title compound.

## EXAMPLE 153

4-Amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


- 183. 

Step A: $\quad \frac{\text { 4-Acetylamino-7-(2,3,5-tri-O-acetyl-2-C-methyl- } \beta \text {-D-ribofuranosyl)- }}{\frac{7 H \text {-pyrrolo } 2,3-d \text { pyrimidine }}{\text { To a solution of the compound from step F of Example } 62(280 \mathrm{mg},}}$
$1.00 \mathrm{mmol})$ in pyridine is added acetic anhydride ( $613 \mathrm{mg}, 6.0 \mathrm{mmol}$ ). The resulting solution is stirred overnight at ambient temperature cvaporated in vacuo and the resulting crude mixture is purified on silica gel using ethyl acetate/hexane as the eluent. Fractions containing the desired product are pooled and evaporated in vacuo to give the desired product.

## Step B: . 4-Acetylamino-5-bromo-7-(2,3,5-tri-O-acetyl-2-C-methyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo[ $2,3-d$ ]pyrimidine

To a pre-cooled $\left(0^{\circ} \mathrm{C}\right)$ solution of the compound from Step A ( 460 mg , 1.00 mmol ) in DMF is added $N$-bromosuccinimide ( $178 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) in DMF. The resulting solution is stirred at $0^{\circ} \mathrm{C}$ for 30 min then at room temperature for another 30

Step C:
4-Amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine
To a pre-cooled $\left(-78^{\circ} \mathrm{C}\right)$ solution of the compound from Step B (529 $\mathrm{mg}, 1.00 \mathrm{mmol}$ ) in THF is added butyl lithium ( 2 M in hexanes) ( $0.5 \mathrm{~mL}, 1.00 \mathrm{mmol}$ ). The resulting solution is stirred at $-78^{\circ} \mathrm{C}$ for 30 min and then quenched with $N-$ fluorobenzensulfonimide ( $315 \mathrm{mg}, 1.00 \mathrm{mmol}$ ) in THF. The resulting solution is very slowly allowed to come to ambient temperature and then poured into a stirred mixture of saturated aqueous ammonium chloride and dichloromethane. The organic phase is evaporated in vacuo and treated with ammonium hydroxide at $55^{\circ} \mathrm{C}$ in a closed container overnight. The resulting crude mixture is purified on silica gel using dichloromethane/methanol as the eluent. Fractions containing the desired product are pooled and evaporated in vacuo to give the desired product.

## EXAMPLE 154

## 4-Amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1H-pyrazolo[3,4- $d$ ]pyrimidine



5 Step A:
4-Aminó-1--13,5-bis-O-(2,4-dichloraphenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyll-1H-pyrazolo 3,4 -d ]pyrimidine
To the compound from Step C of Example $62(1.00 \mathrm{~g}, 2.02 \mathrm{mmol})$ in dichloromethane ( 20 mL ) was bubbled HBr gas for 5 min until it was saturated. The resulting solution was stirred at room temperature for 10 min , evaporated in vacuo and coevaporated with anhydrous toluene ( 10 mL ). 4-Amino- $1 H$-pyrazolo[3,4d] pyrimidine (Aldrich, 0.43 g .3 .18 mmol ) and $\mathrm{NaH}(60 \%, 150 \mathrm{mg}, 3.8 \mathrm{mmol})$ were stirred in 1 -methyl-2-pyrrolidinone ( 10 mL ) for 30 min . The resulting solution was poured into the above bromo sugar residue and the mixture was stirred overnight. The mixture was diluted with toluene ( 50 mL ), washed with brine ( $10 \%, 3 \times 50 \mathrm{~mL}$ ) and concentrated under reduced pressure. The residue was chromatographed on. silica gel (EtOAc as eluent) to afford a solid ( 400 mg ).

## Step B: $\quad$ 4-Amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1 H -pyrazole 3 3,4d pyrimidine

To a solution of the compound from Step A $(0.20 \mathrm{~g}, 0.33 \mathrm{mmol})$ in dichloromethane ( 10 mL ) at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in dichloromethane) ( $3 \mathrm{~mL}, 3 \mathrm{mmol}$ ) dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 0.5 h , then at $-45^{\circ} \mathrm{C}$ to $-30^{\circ} \mathrm{C}$ for 2 h . The reaction was quenched by addition of sodium acetate $(1.0 \mathrm{~g})$ and methanol $(10 \mathrm{~mL})$. The solution was evaporated and the residue was purified by flash chromatography over silica gel using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and $\mathrm{CH}_{2} \mathrm{Cl}_{2} \mathrm{MeOH}$ (95:5-90:10) gradient as the eluent to furnish the desired compound ( 60 mg ) as a solid, which was recrystallized from methanol and acetonitrile to give the title compound as an off-white solid ( 40 mg ).
${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.75(\mathrm{~s}, 3 \mathrm{H}), 3.59(\mathrm{~m}, 1 \mathrm{H}), 3.69(\mathrm{~m}, 1 \mathrm{H}), 3.91(\mathrm{~m}, 1 \mathrm{H}), 4.12$ $(\mathrm{m}, \mathrm{lH}), 4.69(\mathrm{t}, 1 \mathrm{H}, \mathrm{J} 5.1 \mathrm{~Hz}), 5.15(\mathrm{~m}, 2 \mathrm{H}), 6.13(\mathrm{~s}, 1 \mathrm{H}), 7.68(\mathrm{~s}, \mathrm{br}, 1 \mathrm{H}), 7.96(\mathrm{~s}, \mathrm{br}$, $1 \mathrm{H}), 8.18(\mathrm{~s}, 1 \mathrm{H}), 8.21(\mathrm{~s}, 1 \mathrm{H})$.
${ }^{13}$ C NMR ' ${ }^{(\text {DMSO }}-d_{6}$ ): 19.32, 62.78, 74.11, 78.60, 83.65, 90.72, 99.79, 133.50,

The assays employed to meașure the inhibition of HCV NS5B polymerase and HCV 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.

## A. Assay for Inhibition of HCV NS5B Polymerase:

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

## Procedure:

Assay Buffer Conditions: ( $50 \mu \mathrm{~L}$-total/reaction)
20 mM Tris, pH 7.5
$50 \mu \mathrm{MEDTA}$
5 mM DTT
$2 \mathrm{mM} \mathrm{MgCl}_{2}$
80 mM KCl
$0.4 \mathrm{U} / \mu \mathrm{L}$ RNAsin (Promega, stock is 40 units $/ \mu \mathrm{L}$ )
$0.75 \mu \mathrm{~g}$ t500 (a $500-\mathrm{nt}$ RNA made using 77 runoff transcription with a sequence from the NS $2 / 3$ region of the hepatitis C genome)
$1.6 \mu \mathrm{~g}$ purified hepatitis C NS5B (form with 21 amino acids C-terminally truncated)
$1 \mu \mathrm{M} \mathrm{A,C,U,GTP}$ (Nucleoside triphosphate mix)

# [alpha- ${ }^{32} \mathrm{P}$ ]-GTP or [alpha- ${ }^{33} \mathrm{P}$ ]-GTP 

The compounds were tested at various concentrations up to $100 \mu \mathrm{M}$ final concentration.

An appropriate volume of reaction buffer was made including enzyme

The assay was an in situ Ribonuclease protection, Scintillation Proximity based-plate asșay (SPA). . 10,000-40,000 cells were plated in 100-200 $\mu \mathrm{L}$ - 187 .
of media containing $0.8 \mathrm{mg} / \mathrm{mL} \mathrm{G418}$ in 96 -well cytostar plates (Amersham). Compounds were added to cells at various concentrations up to $100 \mu \mathrm{M}$ in $1 \%$ DMSO at time 0 to 18 h and then cultured for $24-96 \mathrm{~h}$. Cells were fixed ( $20 \mathrm{~min}, 10 \%$ formalin), permeabilized ( $20 \mathrm{~min}, 0.25 \%$ Triton $\mathrm{X}-100 / \mathrm{PBS}$ ) and hybridized (overnight, $50^{\circ} \mathrm{C}$ ) with a single-stranded ${ }^{33} \mathrm{P}$ 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 $65^{\circ} \mathrm{C}$ and counted in a Trperount. 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' nontranslated 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.

Representative compounds tested in the replication assay exhibited $\mathrm{EC}_{50}$ 's less than 100 micromolar.

The nucleoside derivatives 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 nucleoside derivatives of the present invention to inhibit human DNA polymerases was measured in the following assays.
a. Inhibition of Human DNA Polymerases alpha and beta:

## Reaction Conditions:

$50 \mu \mathrm{~L}$ reaction volume

Reaction buffer components:
20 mM Tris-HCl, pH 7.5
$200 \mu \mathrm{~g} / \mathrm{mL}$ bovine serum albumin
100 mM KCl
$2 \mathrm{mM} \beta$-mercaptoethanol
$10 \mathrm{mM} \mathrm{MgCl}_{2}$
$1.6 \mu \mathrm{M} \mathrm{dA}, \mathrm{dG}, \mathrm{dC}, \mathrm{dTTP}$

IPODEHHI.23-06-2015 15:56

PCT/US02/01531
$\alpha^{3}{ }^{33} \mathrm{P}$-dATE

## Enzyme and template:

$0.05 \mathrm{mg} / \mathrm{mL}$ gaped fish sperm DNA template
$50.01 \mathrm{U} / \mu \mathrm{L}$ DNA polymerase $\alpha$ or $\beta$.

Preparation of gaped fish sperm DNA template:
Add $5 \mu \mathrm{~L} \mathrm{MM} \mathrm{MgCl}_{2}$ to $500 \mu \mathrm{~L}$ activated fish sperm DNA (USB 70076);
Warm to $37^{\circ} \mathrm{C}$ and add $30 \mu \mathrm{~L}$ of $65 \mathrm{U} / \mu \mathrm{L}$ of exonuclease III (GibcoBRL 18013-011);
Incubate 5 min at $37^{\circ} \mathrm{C}$;
Terminate reaction by heating to $65^{\circ} \mathrm{C}$ for 10 min ;
Load 50-100 $\mu \mathrm{L}$ aliquots onto Bio-spin 6 chromatography columns (Bio-Rad 7326002) equilibrated with 20 mM This- $\mathrm{HCl}, \mathrm{pH} 7.5$;

Elute by centrifugation at $1,000 \mathrm{Xg}$ for 4 min ;
. 15 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 $2 \mathrm{mM} \beta$-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 $37^{\circ} \mathrm{C}$. The reaction was quenched by the addition of $20 \mu \mathrm{~L}$ 0.5 M EDTA. $50 \mu \mathrm{~L}$ of the quenched reaction was spotted onto Whatman DE81 filter disks and air dried. The filter disks, were repeatedly washed with 150 mL 0.3 M ammonium formate, pH 8 until $l_{j} \mathrm{~mL}$ of wash is $<100 \mathrm{cpm}$. 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 $=[1-(\mathrm{cpm}$ in test reaction -cpm in blank $) /(\mathrm{cpm}$ in control . reaction - chm in blank)] $x 100$.

## b. Inhibition of Human DNA Polymerase gamma:

The potential for inhibition of human DNA polymerase gamma was measured in reactions that included $0.5 \mathrm{ng} / \mu \mathrm{L}$ enzyme; $10 \mu \mathrm{M} \mathrm{dATP}$, dGTP, dTP, and TTP; $2 \mu \mathrm{Ci} /$ reaction [ $\alpha{ }^{33} \mathrm{P}$ ]-dATP, and $0.4 \mu \mathrm{~g} / \mu \mathrm{L}$ activated fish sperm DNA (purchased from US Biochemical) in a buffer containing 20 mM Iris $\mathrm{pH} 8,2 \mathrm{mM} \beta$ - mercaptoethanol, $50 \mathrm{mM} \mathrm{KCl}, 10 \mathrm{mM} \mathrm{MgCl} 2$, and $0.1 \mu \mathrm{~g} / \mu \mathrm{L}$ BSA. Reactions were allowed to proceed for 1 h at $37^{\circ} \mathrm{C}$ and were quenched by addition of 0.5 M EDTA to a final concentration of 142 mM . Product formation was quantified by anion exchange filter binding and scintillation counting. Compounds were tested at up-to-50 $\mu \mathrm{M}$.

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

The ability of the nucleoside derivatives 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 $\beta$-galactosidase ( $\beta$-gal) expression. Cells were infected for 48 h , and $\beta$-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 $100 \mu \mathrm{M}$; 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 immunedeficiency 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 nucleoside derivatives of the present invention were also screened
for cytotoxicity against cultured hematoma ( $\mathrm{HuH}-7$ ) 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 $1.5 \times 10^{5}$ cells $/ \mathrm{mL}$ for suspension cultures in 3 day incubation and 5.0 $\times 10^{4}$ cells $/ \mathrm{mL}$ for adherent cultures in 3 day incubation. $99 \mu \mathrm{~L}$ of cell culture was transferred to wells of a 96 -well tissue culture treated plate, and $1 \mu \mathrm{~L}$ of 100 -times final concentration of the test compound in DMSO was added. The plates were incubated at $37^{\circ} \mathrm{C}$ and $5 \% \mathrm{CO}_{2}$ for a specified period of time. After the incubation period, $20 \mu \mathrm{~L}$ of CellTiter 96 Aqueous One Solution Cell Proliferation Assay reagent (MTS) (Promega) was added to each well and the plates were incubated at $37^{\circ} \mathrm{C}$ and $5 \% \mathrm{CO}_{2}$ for an additional period of time up to 3 h . 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 wast 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):Assay conditions are described in the article by Sidwell and Huffman, "Use of disposable microtissue culture plates for antiviral and interferon induction studies," Appl. Microbial. 22: 797-801 (1971).

## Viruses:

Rhinovirus type 2 (RV-2), strain HGP, was used with KB cells and media $(0.1 \%$ $\mathrm{NaHCO}_{3}$, 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 çells. MEM (Eagle's minimum essential medium) with 5\% Fetal Bovine serum (FBS) and $0.1 \% \mathrm{NaHCO}_{3}$ was used as the growth medium.
Antiviral test medium for all three virus types was MEM with $5 \% \mathrm{FBS}, 0.1 \%$ $\mathrm{NaHCO}_{3}, 50 \mu \mathrm{~g}$ gentamicin $/ \mathrm{mL}$, and 10 mM MgCl 2 .
$2000 \mu \mathrm{~g} / \mathrm{mL}$ 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 $5 \% \mathrm{CO}_{2}$ at $37^{\circ} \mathrm{C}$. 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 $\div$ ED50.

1. 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 $5 \% \mathrm{FBS}$ and $0.1 \% \mathrm{NaHCO}_{3}$ and without antibiotics.

Assay medium for dengue, yellow fever, and Bạnzi viruses was MEM, $2 \%$ FBS, $0.18 \% \mathrm{NaHCO}_{3}$ and $50^{\circ} \mathrm{\mu g}$ gentamicin $/ \mathrm{mL}$.

Antiviral testing of the compounds of the present irvention 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, $0.1 \% \mathrm{NaHCO}_{3}$ and $50 \mu \mathrm{~g}$ gentamicin $/ \mathrm{mL}$.

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. Adequatecytopathic 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 El 309 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 61 or Example 62 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O 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 -theemployed, 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 $I$ which is of the stereochemical configuration:

(I)
or a pharmaceutically acceptable salt thereof;
wherein B is selected from the group consisting of





$\mathrm{A}, \mathrm{G}$, and L are each independently CH or N ;
D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, C-NHCONH2, C-CONR11R11, C-CSNR IIRII, C-COOR ${ }^{11}$, C-C( $=\mathrm{NH}$ ) $\mathrm{NH}_{2}$, C-hydroxy, C- Cl-3 alkoxy, C-amino, C- C1-4 alkylamino, C-di(C1-4 alkyl) amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with
one to three groups independently selected from halogen, amino, hydroxy, carboxy, and $\mathrm{C}_{1}-3$ alkoxy;
E is N or $\mathrm{CR}^{5}$;
W is O or S ;

Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}{ }^{9} \mathrm{R} 10$;
$\mathrm{R}^{1}$ is hydrogen, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is hydrusy or $\mathrm{C}_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
halogen,
$C_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms,
$\mathrm{C}_{1}^{\prime}-10$ alkoxy, optionally substituted with $\left.\mathrm{C}_{1-}\right\}$ alkoxy or 1 to 3 fluorine atoms,
C2-6 alkenyloxy,
C1-4 alkylthio,
C1-8 alkylcarbonyloxy,
aryloxycarbonyl, .
azido;
amino,
$\mathrm{C}_{1-4}$ alkylamino, and di( $\mathrm{C}_{1-4}$ alkyl)amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $\mathrm{R}^{1}$ and $\mathrm{R}^{3}$ is hydroxy or $\mathrm{C}_{1-4}$
alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
halogen,
$\mathrm{C}_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms, $\mathrm{C}_{1-10}$ alkoxy, optionally substituted with hydroxy, $\mathrm{C}_{1-3}$ alkoxy, carboxy;-or 1 to 3 fluorine atoms,
C2-6 alkenyloxy,
$\mathrm{C}_{1-4}$ alkylthio, $\mathrm{C}_{1-8}$ alkylcarbonyloxy, ? aryloxycarbonyl,

> azido,
> amino,
> $\mathrm{C}_{1-4}$ alkylamino, and di( $\mathrm{C}_{1-4}$ alkyl)amino; or
$5 \quad R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NG}_{0-4}$ alkyl;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, C3-6 cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; $\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2}-6$ alkenyl, $\mathrm{C}_{2}-6$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen; R14 is $\mathrm{H}, \mathrm{CF}_{3}, \mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di(C1-4 alkyl)amino;
R 7 is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, C3-6 cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl)amino;
each $\mathrm{Rll}^{11}$ is independently- H or $\mathrm{C}_{1-6}$ alkyl;
R 8 is H , hallogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl;
R12 and R13 are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl; and $\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{Cl}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{QCH}\left(\mathrm{C}_{1-4}\right.$ alkyl $) \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,

with the provisos that (a) when $R^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is fluoro, then the other of $\mathrm{R}^{3}$ and $\mathrm{R}^{4}$ is not hydrogen, halogen, azido, trifluoromethyl, $C_{1-4}$ alkyl, amino, $C_{1-4}$ alkylamino, di( $C_{1-4}$ alkyl)amino, or $\mathrm{C}_{1-10}$ alkoxy; (b) when $R^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is halogen, hydroxy, $C_{1-6}$ alkoxy, or $\mathrm{C}_{2-6}$ alkenyloxy, then the other of $\mathrm{R}^{3}$ and $\mathrm{R}^{4}$ is not hydrogen, fluoro, or azido; and (c) when $R^{1}$ and $R^{3}$ are hydrogen and $R^{2}$ is hydroxy, then $R^{4}$ is not hydroxy.

## 2. A method of treating RNA-dependent RNA viral infection in a mammal in need thereof comprising administering a therapeutically effective amount

 of a compound of Claim 1 .5 structural formula II of the indicated stereochemical configuration:

(II)
wherein B is


Or


D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR}{ }^{11} \mathrm{R}^{11}$, C-CSNR 11R11, C-COOR 11, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C -di( $\mathrm{C}_{1-4}$ alkyl)amino, C -halogen, C -(1,3-oxazol-2-yl), C -(1,3-thiazol-2yl ), or C -(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and Cl-3 alkoxy;
E is N or $\mathrm{C}-\mathrm{R}$;
W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O} 9 \mathrm{H} 4$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{9} \mathrm{R} 10$;
$20 R^{1}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
halogen, Cl-3 alkyl, trifluoromethyl, C 1-4 alkoxy, $\mathrm{C}_{1-4}$ alkylthio, $\mathrm{C}_{1: 8}$ alkylcarbonyloxy, aryloxycarbonyl, azido, amino $_{r}$ $\mathrm{C}_{1-4}$ alkylamino, and di(C1-4 alkyl)amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{Rl}^{\text {and }} \mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $R 1$ and $R^{3}$ is selected from the group consisting of
hydrogen,
hydroxy,
fluoro, C1-4 alkyl; trifluoromethyl, C1-4 alkoxy, C1-4 alkylthio, $\mathrm{C}_{1}-8$ alkylcarbonyloxy, azido, amino, $\mathrm{C}_{1-4}$ alkylamino, and ' di( $\mathrm{C}_{1-4}$ alkyl)amino; or
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC} 0-4$ alkyl;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$
alkyl)amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$;
$\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2-6}$ alkenyl, $\mathrm{C}_{2}-6$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen;
R 7 is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or
di( $\mathrm{C}_{1-4}$ alkyl)amino;
each R11 is independently H or $\mathrm{C}_{1-6}$ alkyl;
$\mathbf{R}^{8}$ is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl;
R12 and R13 are each independently hydrogen or methyl; and
$\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1}-4$ alkyl, or $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl;
with the provisos that (a), when $R^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is fluoro, then the other of $\mathrm{R}^{3}$ and $\mathrm{R}^{4}$ is not hydrogen, halogen, trifluoromethyl, $\mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamind, di( $\mathrm{C}_{1-4}$ alkyl)amino, or $\mathrm{C}_{1-4}$ alkoxy; (b) when R 1 is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is halogen, hydroxy, or $C_{1-4}$ alkoxy, then the other of $R^{3}$ and $R^{4}$ is not hydrogen, fluoro, or azido; and (c) when $R^{1}$ and $R^{3}$ are hydrogen and $R^{2}$ is hydroxy, then $R^{4}$ is not hydroxy.
4. The method of Claim 2 wherein the compound is of the structural formula $I I$ of the indicated stereochemical configuration:

(II)
wherein $B$ is



D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ ulkyl, C-NHCONH2, C-CONR 11 R ${ }^{11}$; C-CSNR11R11, C-COORL1, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C -di( $\mathrm{C}_{1-4}$ alkyl)amino, C -halogen, C -(1,3-oxazol-2-yl), C-(1,3-thiazol-2-
yl ), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and Cl-3 alkoxy;
E is N or $\mathrm{C}-\mathrm{R}$;
5 W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H} 4$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{9} \mathrm{R}^{10}$;
$\mathrm{Rl}^{1}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
halogen, C1-3 alkyl, trifluoromethyl, Cl-4 alkoxy, $\mathrm{C}_{1-4}$ alkylthio, $\mathrm{C}_{1-8}$ alkylcarbonyloxy, aryloxycarbonyl, azido, amino; $C_{1-4}$ alkylamino, and di(Cl-4 alkyl)anino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of R 1 and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $R$ ! and $R^{3}$ is selected from the group consisting of hydrogen,
hydrọxy, fluoro, Cl-4 alkyl, trifluoromethyl, Cl-4 alkoxy, $\mathrm{C}_{1-4}$ alkylthio, $\mathrm{C}_{1-8}$ alkylcarbónyloxy, azido, amino, Cl-4 alkylamino, and di(Cl-4 alkyl)amino; or
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC}_{0-4}$ alkyl; $\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di $\left(\mathrm{C}_{1-4}\right.$
$10 \mathrm{R}^{8}$ is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1}-4$ alkyl)0-2 aminomethyl; R12 and R13 are each independently hydrogen or methyl; and $\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{C}_{1-4}$ alkyl, or then the other of $R^{3}$ and $R^{4}$ is not hydrogen, fluoro, or azido; and (c) when $R^{1}$ and $R^{3}$ are hydrogen and $\mathrm{R}^{2}$ is hydroxy, then $\mathrm{R}^{4}$ is not hydroxy.
5. The method of Claim 3 wherein the compound is of the structural formula II of the indicated stereochemical configuration: $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl; with the provisos that (a) when $R^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is fluoro, then the other of $R^{3}$ and $R^{4}$ is not hydrogen, halogen, trifluoromethyl, $C_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, or $\mathrm{C}_{1-4}$ alkoxy; (b) when $\mathrm{R}^{1}$ is hydrogen, one of $R^{3}$ and $R^{4}$ is hydrogen, and $R^{2}$ is halogen, hydroxy, or $C_{1-4}$ alkoxy, alkyl)amino, C3-6 cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; $\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, C2-6 alkenyl, $\mathrm{C}_{2-6}$ alkynyl,. $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen; R7 is hydrogen, amino, C1-4 alkylanino, C3-6 cycinalkylamino, or di(C1-4 alkyl)aminu; each $\mathrm{R}^{11}$ is independently H or $\mathrm{C}_{1-6}$ alkyl;

(III)
wherein $B$ is

- 202-




D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C} 1-3$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR}{ }^{11} \mathrm{R} 11$, C-CSNR 11 R11, C-COOR11, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C -di( $\mathrm{C}_{1}-4$ alkyl) amino, C -halogen, C -( 1,3 -oxazol-2-yl), C -(1,3-thiazol-2- yl ), or C-(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;
W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R} 9 \mathrm{R} 10$;
$\mathrm{R}^{1}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy, fluors, Cl 43 alkyl, trifluoromethyl, $\mathrm{C}_{1-8}$ alkylcarbonyloxy, Cl-3 alkoxy, and amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{1}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1-4}$ alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy, fluors, Cl-3 alkyl, trifluoromethyl, $\mathrm{C}_{1-8}$ alkylcarbonyloxy, C1-3 alkoxy, and amino; or
$\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC} 0-4$ alkyl;
$\mathrm{R}^{6}$ is $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \dot{\mathrm{C}}_{1-4}$ alkylamino, di(C1-4 alkyl) amino,
$\mathrm{C}_{3}-6$ cycloálkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; $\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2}-6$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen; $R 7$ is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3-6}$ cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl) amino;
each R11 is independently H or C $1-6$ alkyl;
$\mathrm{R}^{8}$ is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomettryl; and.
$\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{t}$-butyl, or $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{iPr}$;
with the provisos that (a) when $R 1$ is hydrogen and $R^{2}$ is fluors, then $R^{3}$ is not hydrogen, trifluoromethyl, fluoro, $\mathrm{C}_{1-3}$ alkyl, amino, or $\mathrm{C}_{1-3}$ alkoxy; (b) when $R 1$ is hydrogen and $\mathrm{R}^{2}$ is fluoro, hydroxy, or $\mathrm{C}_{1-3}$ alkoxy, then R 3 is not hydrogen or fluoro; and (c) when $R^{1}$ is hydrogen and $R^{2}$ is hydroxy, then $R^{3}$ is not $\beta$-hydroxy.
6. The method of Claim 4 wherein the compound is of the structural formula III of the indicated stereochemical configuration:

(III)
wherein $B$ is

or


D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} 11_{\mathrm{R}} 11$, C-CSNR11R11, C-COUR11, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C -di( $\mathrm{C}_{1-4}$ alkyl)àmino, C -halogen, C -(1,3-oxazol-2-yl), C-(1,3-thiazol-2-
yl ), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selectẹd from halogen, amino, hydroxy, carboxy, and C1-3 alkoxy;
W is O or S ;
Y is $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl; $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{9} \mathrm{R}{ }^{10}$;
$10 \mathrm{R}^{1}$ is hydrogen, $\mathrm{CF}_{3}$, or $\mathrm{C}_{1-4}$ alkyl and one of $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ is OH or $\mathrm{C}_{1}-4$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen,
hydroxy,
fluoro,
C1-3 alkyl,
trifluoromethyl,
C1.8 alkylcarbonyloxy, C1-3 alkoxy, and amino; or the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy,
fluoro,
C1-3 alkyl,
trifluoromethyl,
$\mathrm{C}_{1-8}$ alkylcarbonyloxy,
C 1-3 alkoxy, and
amino; or
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC}_{0-4}$ alkyl;
$\mathrm{R}^{6}$ is $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino,
i 5 C3-6 cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$;
$\mathbf{R}^{5}$ is $\mathrm{H}_{1} \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2}-6$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen;
$R 7$ is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cymloallcylamino, or di( $\mathrm{C}_{1-4}$ alkyl)amino; each R11 is. independently H or $\mathrm{C}_{1-6}$ alkyl;
$10 \mathrm{R}^{8}$ is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1}-4$ alkyl)0-2 aminomethyl; and $\mathrm{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{t}$-butyl, or $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{iPr}$;
with the provisos that (a) when $R^{1}$ is hydrogen and $R^{2}$ is fluoro, then $R^{3}$ is not hydrogen, trifluoromethyl, fluoro, $\mathrm{C}_{1}-3$ alkyl, amino, or $\mathrm{C}_{1-3}$ alkoxy; (b) when $\mathrm{R}^{1}$ is hydrogen and $\mathrm{R}^{2}$ is fluoro, hydroxy, or $\mathrm{C}_{1-3}$ alkoxy, then $\mathrm{R}^{3}$ is not hydrogen or fluoro; and (c) when $R^{1}$ is hydrogen and $R^{2}$ is hydroxy, then $R^{3}$ is not $\beta$-hydroxy.
7. The method of Claim 5 wherein B is

8. The method of Claim 6 wherein $B$ is

9. The method of Claim 5 wherein $B$ is

- 206 -

IPO. DELHI 23-06-2015 15:56

10. The method of Claim 6 wherein B is

11. The method of Claim 6 wherein the compound is selected from the group consisting of:

2'-O-methyl-cytidine,
2'-C-methyl-cytidine,
3',5'-di-O-octanoyl-2'-O-methyl-cytidiné,
3'-O-octanoyl-2'-O-methyl-cytidine,
2'-C-methyl-adenosine,
2'-C-methyl-8-amino-adenosine,
4-amino-5-cyano-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,
4-amino-5-(aminocarbonyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
3'-deoxy-3'-methyl-cytidine,
4-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2;3-
$d$ ]pyrimidin-5-carboxamide,
4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
4-amino-7-(3-deoxy- $\beta_{-}$D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-5-
carboxamide,
3'-amino-3'-deoxyadenosine,
-207 -
$i$
IPO DELHI 23-06-2015.15:56

2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranośyl)-7H-pyrrolo[2,3d] pyrimidin-5-carboxamide, 4-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d]$ pyrimidin-5-carboxamide, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidin-5-carbonitrile, 2-amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
6-amino-1-( $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5H)-one, 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
2'-O-methylguanosine;
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin$4(3 H)$-one,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-5H-pyrrolo[3,2- $d$ ]pyrimidin$4(3 \mathrm{H})$-one,
7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine,
2-amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo-[2,3- $d$ ]pyrimidin-5-carbonitrile, 2-amino-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one,
8 -azidoguanosine,
8 -aminoguanosine,
8 -bromoadenosine,
8-uminoadenosine,
8 -bromoguanosine,
4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7 $H$-pyrrolo[2,3- $d$ ]pyrimidin-5-carboxamide,
2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidin-5-carbonitrile,
2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,

WO 02/057+25
PCT/US02/01531

2-amino-4-chloro-5-methyl-7-(2-O-méthyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidine,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-thione,

2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
2-amino-7-( $\beta$-D-ribofuranhsyl)-7H-pyrrolo[2,3- $\not$ ] pyrimidine,
2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2;3-
d]pyrimidine,
1-( $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d]$ pyrimidin-4(3H)-one,
4-amino-1-( $\beta$-D-ribofuranosyl)-1H-pyrazolo[3,4- $d$ ]pyrimidine,
2 -amino-6-chloro-9-( $\beta$-D-ribofuranosyl)-9H-purine,
2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carbonitrile,
6-methyl-9-( 3 -D-ribofuranosyl)-9H-purine,
2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one,
2-amino-4-chloro-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7 H -pyrrolo[2,3d]pyrimidine,
2-amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, 2-amino-7-( $\beta$-D-arabinofuranosyl)=3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-cärbonitrile,
2-amino-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one,
9-( $\beta$-D-arabinofuranosyl)-9 H -purin-6( 1 H )-one,
1-( $\beta$-D-arabinofuranosyl)-1 H -cytosine,
2-amino-4-chloro-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
3'-deoxy-3'-(fluoromethyl)-guanosine,
2'-amino-2'-deoxycytidine,
4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carbonitrile,
2'-O-methyladenosine,
: $\quad 4$-aminu-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine, 3'-amino-3'-deoxy-2'-O-methyl-adenosine, 3'-deoxy-3'-methyl-uridine, 6-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 $H$-imidazo[4,5-c]pyridin-4(5H)-one, 6 -amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin$4(3 H)$-one,
2-amino-7-(2-deoxy- $\beta$-D-ribofurannsyl)-3,4-dihydro-1 oxo-7H-pyrrole[2,3= $d]$ - pyrimidin-5-carbonitrile,
3'-deoxy-2'-O-(2-methoxyethyl)-3'-methyl-5-methyluridine,
2'-amino-2'-deoxy-uridine,
2-amino-9-( $\beta$-D-arabinofuranosyl)-9H-purin-6( 1 H )-one,
3'-deoxy-3'-methylguanosine,
2'-O-[4-(imidazolyl-1)butyl]guanosine,
2'-deoxy-2'-fluoroguanosine,
2'-deoxyguanosine,
2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one,

2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3d] pyrimidin-5-carbonitrile,
2-amino-5-iodo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-
d]pyrimidin-5-carbonitrile,
2-amirio-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one,
2-amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7.H-pyrrolo[2,3-d]pyrimidin-4(3H)-
one,
2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-
d] pyrimidin-4(3.H)-one,
2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidin-4(3H)-one,
6-amino-1-(2-O-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)one,
6-amino-1-(2-deoxy- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one,

6-amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 $H$-imidazo[4,5-c]pyridin-4(5H)-one,
6-amino-1-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin4( $5 H$ )-one,

6-amino-1-( $\beta$-D-arabinofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 2'-O-[2-(N,N-diethylaminooxy)ethyl]-5-methyluridine, 5-ethynyl-2'-O-(2-methox yethyl)-cytidine.
1-(2-C-methyl- $\beta$-D-arabinofuranosyl)uracil,
2-amino-2'-O-methyladenosine,
2'-deoxy-2'-fluoroadenosine,
3'-deoxy-3'-methyladenosine,
2-amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide,
4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carboxamide, 4-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
4-amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine, 4-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine (tubercidin), 4,6-diamino-7-( $\beta$-D-ribofuranosyl):7H-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-7-(3-deoxy-3-fluoro- $\beta_{3}$-D-ribofuranosyl)-7H-pyrrolo-[2,3$d$ ]pyrimidin-5-ciarboxamide, 4-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 $H$-imidazo[4,5-c]pyridine, 4-amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine, 4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine, 4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $\alpha$ ]pyrimidine, 4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3d] pyrimidine; and the corresponding 5'-triphosphates, 5 '[bis(isopropyloxycarbonyloxymethyl)]monophosphates, 5'-mono-(S-Cl-4 alkanoyl-2-thioethyl)monophosphates, and 5'-bis-(S-Cl-4 alkanoyl-2thioethyl)monophosphates thereof;
or a pharmaceutically acceptable salt thereof.
12. The method of Claim 2 wherein the compound is selected from the group consisting of:

2'-O-methyl-cytidine,

2'-C-methyl-cytidine, 3',5i-di-O-octanoyl-2'-O-methyl-cytidine, 3'-Q-octanoyl-2'-O-methyl-cytidine, 2'-C-methyl-adenosine, 2'-C-methyl-8-amino-adenosine, 4-amino-5-cyano-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
4-amino-5-(aminocarbonyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine, 3'-deoxy-3'-methyl-cytidine,
4-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carboxamide, 3'-amino-3'-deoxyadenosine, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide,
4-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-5-carboxamide, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile,
2-amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
6-amino-1-( $\beta$-D-ribofuranosyl)-1 $H$-imidazo[4,5-c]pyridin-4(5H)-one,
2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
2'-O-methylguanosine,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2;3- $d$ ]pyrimidin-4(3H)-one,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-5H-pyrrolo[3,2- $d$ ]pyrimidin-4(3H)-one,

# 7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine, 

 2-amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-
[2,3- $d$ ]pyrimidin-5-carbonitrile,
2-amino-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3FI)-one, 8 -azidoguanosine, 8 -aminoguanosine, 8 -bromoadenosine, 8-aminoadenosine, 8 -bromoguanosine,
4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-5-carboxamide,
2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile, 2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine,
2-amino-4-chloro-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo-[2,3- $d$ ]pyrimidine,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-thione,
2-amiño-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
2-amino-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidine,
2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo $[2,3-\alpha]$ pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,
1-( $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d$ ]pyrimidin-4(3H)-one,
4-amino-1-( $\beta$-D-ribofuranosyl)-1H-pyrazolo[3,4- $d$ ]pyrimidine, 2-amino-6-chloro-9-( $\beta$-D-ribofuranosyl)-9H-purine, 2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d] pyrimidin-5carbonitrile,
6-methyl-9-( $\beta$-D-ribofuranosyl)-9 H -purine,

2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-4(3H)-one, 2-amino-4-chloro-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3$d$ ]pyrimidine,
5 2-amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, 2-amino-7-( 3 -D-arabinofuranosyl)-3,4-dihydro-4-oxo-7 H -pyrrolo[2,3d] pyrimidin-5-carbonitrile,
2-amino-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin$4(3 H)$-one,
9-( $\beta$-D-arabinofuranosyl)-9H-purin-6(1H)-one, 1-( $\beta$-D-arabinofuranosyl)-1 $H$-cytosine,
2-amino-4-chloro-5-methyl-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3d] pyrimidine,
3'-deoxy ${ }^{\prime} 3^{\prime}$-(fluoromethyl)-guanosine, 2'-amino-2'-deoxycytidine, 4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-5carbonitrile, 2'-O-methyladenosine, 4-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
3'-amino-3'-deoxy-2'-O-methyl-adenosine, 3'-deoxy-3'-methyl-uridine, 6-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 6-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin$4(3 H)$-one, d]-pyrimidin-5-carbonitrile, 3'-deoxy-2'-O-(2-methox yethyl)-3'-methyl-5-methyluridine, 2'-amino-2'-deoxy-uridine,
2-amino-9-( $\beta$-D-arabinofuranosyl)-9H-purin-6( 1 H )-one, 3'-deoxy-3'-methylguanosine, 2'-O-[4-(imidazolyl-1)butyl]guanosine, 2'-deox y-2'-fluoroguanosine, 2'-deoxyguanosine, 2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one,

$$
-214-
$$

IPO DELHI 23-06-2015 15:56

2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3- . d]pyrimidin-5-carbonitrile, 2-amino-5-iodo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,

2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-5-carbonitrile,
2-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrmin[2-3- $\pi]$ pyrimidin $1(3 H)$-onc; 2-amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
2-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidin-4(3H)-one,
2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one,
6-amino-1-(2-〇-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)one,
6-qmino-1-(2-deoxy- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 6-amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one,
6-amino-1-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5H)-one,
6-amino-1-( $\beta$-D-arabinofuranosyl)-1 H -imidazo[4,5-c]pyridin-4( 5 H )-one, 2'-O-[2-( $N, N$-diethylaminooxy)ethyl]-5-methyluridine,
5-ethynyl-2'-O-(2-methoxyethyl)-cytidine,
1-(2-C-methyl- $\beta$-D-arabinofuranosyl)uracil,
2-amino-2'-O-methyladenosine,
2'-deoxy-2'-fluoroadenosine,
3'-deoxy-3'-methyladenosine,
2-amino-7-(2-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(3-deoxy-3-fluóro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-5carboxamide,
4-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,

4-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridine, 4-amino-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine (tubercidin), 4,6-diamino-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $\alpha$ ]pyrimidine, 2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-
d]pyrimidin-5-carboxamide,
4-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine,
4-amino-1-(3-deoxy-3-methyl- $\beta$ - n -rihofuranosyl) 1 H imidazo[4,5-c]pyridine,
4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine, 4-amino-1-(2-C-methy[- $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d$ ]pyrimidine,
4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine; and
the corresponding 5'-triphosphates, 5'-
[bis(isopropyloxycarbonyloxymethyl)]monophosphates, 5 '-mono-(S-C1-4
alkanoyl-2-thioethyl)monophosphates, and 5'-bis-(S-C1-4 alkanoyl-2-
thioethyl)monophosphates thereof;
or a pharmaceutically acceptable salt thereof.
13. The method of Claim 11 wherein the compound is selected from the group consisting of:

2'-O-methyl-cytidine,
2'-C-methyl-cytidine,
3',5'-di. $O$-octanoyl-2'-O-methyl-cytidine,
3'-O-octanoyl-2'-O-methyl-cytidine,
4-amino-1-( $\beta$-D-ribofuranosyl)-1H-pyrazolo[3,4- $d$ ]pyrimidine,
4-amino-5-cyano-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-
d]pyrimidine,
4-amino-5-(aminocarbonyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-
pyrrolo[2,3-d]pyrimidine,
2'-C-methyladenosine,
2'-C-methyl-8-amino-adenosine,
3'-deoxy-3'-methyl-cytidine,
4-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidin-5-carboxamide,
4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine,

4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidin-5carboxamide,
3'-amino-3'-deox yadenosine, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-5-carboxamide, 4-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidin-5-carboxamide, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofurannosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile,
2-amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)one,
6-amino-1-( $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidin-4(3H)one, 2'-O-methylguanosine, 2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin4(3H) :one,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-5H-pyrrolo[3,2-d]pyrimidin-4-(3H)-one,
7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo-[2,3- $d$ ] pyrimidine-5-carbonitrile,
2-amino-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidin-4(3H)-one, 8 -uzidoguanosine,
8 -aminoguanosine, 8 -bromoadenosine, 8 -aminoadenosine, 8 -bromoguanosine, 4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]-pyrimidin-5-carboxamide,
2-amino-4-chloró-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbónitrile,

2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine; -
2-amino-4-chloro-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidine;

2-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine,
2-amino-4-chloro-\%-( $\beta$ - D -ribofuranosyl)-7 H -pyrrolo [2;3- $\alpha$ ] pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine, 2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidin-4(3H)-one,
2-amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, 4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d$ ]pyrimidine, and
2-amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3$d$ ]pyrimidin-5-carbonitrile; and the corresponding $5^{\prime}$-triphosphates, $5^{\prime}$ -
[bis(isopropyloxycarbonyloxymethyl)]monophosphates, 5'-mono-(S-pivaloyl-2-thioethyl)monophosphates, and 5'-bis-(S-pivaloyl-2thioethyl)monophosphates thereof; or a pharmaceutically acçeptable salt thereof.
14. The method of Claim 12 wherein the compound is selected from the group consisting of:

2'-O-methyl-cytidiné,
2'-C-methyl-cyitidine, $3^{\prime}$,5'-di-O-octanoyl-2'-O-methyl-cytidine, 3'-O-octanoyl-2'-O-methyl-cytidine, 4-amino-1-( $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d$ ]pyrimidine, 4-amino-5-cyano-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
4-amino-5-(aminocarbonyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
2'-C-methyladenosine,
2'-C-methyl-8-amino-ạdenosine,

3'-deoxy-3'-methyl-cytidine,
4-amino-7-(3-deoxy-3-methy]- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 4-amino-7-(3-deox $\dot{y}$ - $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3- $d$ ]pyrimidine,
4-amino-7-(3-deọ́xy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2;3- $d$ ]pyrimidin-5carboxamide, 3'-amino-3'-deoxyadenosine, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidin-5-carboxamide,
10 4-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile,
2-amino-5-ethyl-7-( $\dot{\beta}$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha]$ pyrimidin-4(3H)one,
6-amino-1-( $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridin-4(5H)-one, 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
2'-O-methylguanosine,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin$4(3 H)$-one,
2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)- $5 H$-pyrrolo[3,2-d]pyrimidin-4-(3H)-one,
7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
2-amino-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo $2,3-d]$ pyrimidin-4(3H)one,
2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidine-5-carbonitrile,
2-amino-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one,
8 -azidoguanosine,
8-aminoguanosine,
8 -bromoadenosine,
8-aminoadenosine,
8 -bromioguanosine,

4-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]-pyrimidin-5-carboxamide, 2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile,

2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine,
2-amino-4-chloro-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidine,
2-amino-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d]$ pyrimidine', 2-amino-4-chloro-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha]$ pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one,
4-amino-1-(2-C-rnethyl- $\beta$-D-ribofuranosyl)-1 H -pyrazolo[3,4-d]pyrimidine, 2-amino-7-( $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one, and
2-amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-
d]pyrimidin-5-carbonitrile; and the corresponding 5'-triphosphates, 5'-
t[bis(isopropyloxycarbonyloxymethyl)]monophosphates, 5'-mono-(S-pivaloyl-
2-hioethyl)monophosphates, and 5'-bis-(S-pivaloyl-2-
thioethyl)monophosphates thereof; or a pharmaceutically acceptable salt thereof.
15. The method of Claim 13 wherein the compound is selected from the group consisting of:

2'-O-methyl-cytidine,
2'-C-methyl-cytidine,
3',5'-di-O-octanoyl-2'-O-methyl-cytidine, 3'-O-octanoyl-2'-O-methyl-cytidine,
4-amino-1-( $\beta$-D-ribofuranosyl)-1H-pyrazolo[3,4- $d]$ pyrimidine,
4-amino-5-cyano-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,

4-amino-5-(aminocarbonyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $c$ ] pyrimidine, 2'-C-methyladenosine, 2'-C-mdthyl-8-amino-adenosine,
8-bromoguanosine, 8 -aminoguanosine, 8 -aminoadenosine, 4-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3- $d$ ]pyrimidine, 2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3d] pyrimidine,
2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3$d$ ]pyrimidin-5-carboxamide;
4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d$ ]pyrimidine, 2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3--
d]pyrimidin-5-carbonitrile;
and the corresponding 5 '-triphosphates thereof;
2'-O-methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate],
2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3$d]$ pyrimidine-5'-[bis-( $S$-pivaloyl-2-thioethyl)phosphate],
3'-deoxy.guanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], and 3'-deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]; or a pharmaceutically acceptable salt thereof.
16. The method of Claim 14 wherein the compound is selected from the group consisting of:

2'O-methyl-cytidine,
$2^{\prime} \cdot$ C-methyl-cytidine,
3',5'-di-O-octanoyl-2'-O-methyl-cytidine; •
3'-O-octanoyl-2'- $\dot{O}$-methyl-cytidine,
4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -pyrazolo[3,4- $d$ ]pyrimidine,
4-amino-5-cyamo'7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,
4-amino-5-(aminocarbonyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,

2'-C-methyladenosine, 2'-C-methyl-8-amino-adenosine, 8 -bromoguanosine, 8 -aminoguanosine, 8-aminoadenosine, 4-artino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[ $[2,3-d$ ]pyrimidine, 2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3d] pyrimidine,
4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)- $\mathrm{i} H$-pyrazolo $[3,4-d]$ pyrimidine, 2-amino-3,4-dihydro-4-oxo-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carboxamide, 2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile; and the corresponding $5^{\circ}$-triphosphates thereof;

2'-O-methylcytidine-5'-[bis-( $S$-pivaloyl-2-thioethyl)phosphate], 2-amino-7-(3-de'oxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5'-[bis-( $S$-pivaloyl-2-thioethyl)phosphate], 3'-deoxyguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], and 3'-deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]; or a pharmaceutically acceptable salt thereof.
17. The method of Claim 15 wherein the compound is selected from the group consisting of:

2 '- $O$-methylcytidine,
2'-C-methylcytidine, $3^{\prime}, 5^{\prime}$-di- $O$-octanoyl-2'-O-methyl-cytidine, 3'-O-octanoyl-2'-O-methyl-cytidine,
4-amino-1-( $\beta$-D-ribofuranosyl)-1 H -pyrazolo[ $3,4-d]$ pyrimidine,
4-amino-5-cyano-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
d]pyrimidine,
4-amino-5-(aminocarbonyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-d]pyrimidine,
2'-C-methyladenosiné,
2'-O-methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], - 222 -

2-amino-7-(3-de ${ }^{\text {xx }} \dot{y}$ - $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], and 3'-deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate]; or a pharmaceutically acceptable salt thereof.
18. The method of Claim 16 wherein the compound is selected from the group consisting of;

2'-O-methylcytidine,
2'-C'-methylcytidine,
3',5'-di-O-octanoyl-2'-O-methyl-cytidine, 3'-O-octanoyl-2'-O-methyl-cytidine, 4-amino-1-( $\beta$-D-ribofuranosyl)-1H-pyrazolo[3,4- $d$ ]pyrimidine, 4-amino-5-cyano-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine,
4-amino-5-(aminocarbipnyl)-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-
pyrrolo[2,3- $d$ ]pyrimidine,
2'-C-methyladenosine,
2'-O-methylcytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate],
2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-
d] pyrimidine-5'-[bis-( $S$-pjualoyl-2-thioethyl)phosphate], and
3'-deoxycytidine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate];
or a pharmaceutically acceptable salt thereof.
19. The method of Claim I wherein said RNA-dependent RNA viral polymerase is Flaviviridae viral polymerase or Picomaviridae viral polymerase and said RNA-dependent RNA viral replication is Flaviviridae viral replication or Picornaviridae viral replication.
20. The method of Claim 19 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, Banzi 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

WO 02/057425
replication, dengue virus replication, West Nile virus replication, Japanese encephalitis virus replication, Banzi virus replication, and bovine viral diarrhea virus replication. infection is hepatitis C virus infection.
25. A compound of structural formula IV of the indicated stereochemical configuration:

(IV)
21. The method of Claim 20 wherein said Flaviviridae viral polymerase is hepatitis $C$ virus polymerase and said Flaviviridae viral replication is hepatitis C virus replication.
22. The method of Claim 2 wherein said RNA-dependent RNA viral infection is Flaviviridae viral infection or Picomaviridae viral infection.
23. The method of Claim 22 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, Banzai virus infection, and bovine viral diarrhea virus infection.
24. The method of Claim 23 wherein said Flaviviridae viral

wherein B is selected from the group consisting of

$\mathrm{A}, \mathrm{G}$, and L are each independently CH or N ;
D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} 11_{\mathrm{R}} 11$, C-CSNR 11R11, C-COOR11, C-C(=NH)NH2, C-hydroxy, C-C1-3 alkoxy, C-amino,

C- C1-4 alkylamino, C-di(C1-4 alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and $\mathrm{C}_{1-3}$ alkoxy;
E is N or $\mathrm{CR}^{5}$;
W is O or S ;
X is $\mathrm{O}, \mathrm{CH}_{2}$, or $\mathrm{CF}_{2}$;
$\mathrm{Rl}^{1}$ is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{2}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy, halogen,
$\mathrm{C}_{1-4}$ alkyl, optionally substituted with 1 to 3 fluorine atoms, $\mathrm{C}_{1-10}$ alkoxy, optionally substituted with $\mathrm{C}_{1-3}$ alkoxy or 1 to 3 fluorine atoms,
C2-6 alkenyloxy,
$\mathrm{C}_{1-4}$ alkylthio,
$\mathrm{C}_{1}$-8 alkylcarbonyloxy,
aryloxycarbonyl, azido, amino, $\mathrm{C}_{1-4}$ alkylamino, and
di( $\mathrm{C}_{1}-4$ alkyl)amino; or
$\mathrm{R}^{2}$ is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{1}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of
hydrogen,
hydfoxy,
halogen,
$\mathrm{C}_{1-4}$ alkyl, optiopally substituted with 1 to 3 .fluorine atoms,
$\mathrm{C}_{1-10}$ alkoxy, optionally substituted with hydroxy, $\mathrm{C}_{1-3}$ alkoxy, carboxy, or 1
to 3 fluorine atoms,
C2-6 alkenyloxy,
$\mathrm{C}_{1-4}$ alkylthio,
$\mathrm{C}_{1-8}$ alkylcarbonyloxy,
aryloxycarbonyl,
azido,
amino,
$\mathrm{C}_{1-4}$ alkylamino, and
di(C1-4 alkyl)amino; or
Rl and $\mathrm{R}^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and NCO 04 alkyl;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independentitly $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, $\mathrm{C}_{3-6}$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$;
$\mathrm{R}^{5}$ is $\mathrm{H}_{,} \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2-6}$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen;
$\mathrm{R}^{14}$ is $\mathrm{H}, \mathrm{CF}_{3}, \mathrm{C}_{1-4}$ alkyl, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or
di( $\mathrm{C}_{1-4}$ alkyl)amino;
$\mathrm{R}^{7}$ is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or
di(C1-4 alkyl)amino;
each Rl 11 is independently H or $\mathrm{C}_{1-6}$ alkyl;

R8 is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl;
R12 and R13 are each independently hydrogen, methyl, hydroxymethyl, or
5 fluoromethyl; and
$\mathrm{R}^{9} 9$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C} 1-4$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl) $\mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,

provided that at least one of R 9 and R 10 is not hydroxy.
10
wherein $B$ is

or


D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, $\mathrm{C}-\mathrm{NHCONH}_{2}, \mathrm{C}-\mathrm{CONR} .11 \mathrm{R} 11$, C-CSNR 11R11, C-COOR11, C-hydroxy, C-Cl-3 alkoxy, C-amino, C-C1-4 alkylamino, C -di( $\mathrm{C}_{1-4}$ alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-

# yl), or C-(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; <br> W is $\overline{\mathrm{O}}$ or S ; 

E is N or $\mathrm{C}-\mathrm{R}^{5}$;
R1 is hydrogen, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with: amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{2}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{2}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy. halogen. C1-3 alkyl, trifluoromethyl, C1-4 alkoxy, $C_{1-4}$ alkylthio, $\mathrm{C}_{1-8}$ alkylcarbonyloxy, aryloxycarbonyl, azido, amino, C 1-4 alkylạmino, and di (C1-4 alkyl)amino; or $\mathrm{R}^{2}$ is hydrogen, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of $R^{1}$ and $R^{3}$ is hydroxy or $C_{1-4}$ alkoxy and the other of $R^{1}$ and $R^{3}$ is selected from the group consisting of hydrogen, hydroxy, fluor, C1-4 alkyl, trifluoromethyl, C1-4 alkoxy, $\mathrm{C}_{\text {l-4 }}$ alkylthio, C1-8 alkylcarbonyloxy, azido, amino, C1-4 alkylamino, and -228- :
di (C1-4 alkyl) amino; or
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC} 0-4$ alkyl;
$\mathrm{R}^{4}$ and $\mathrm{R}^{6}$ are each independently $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$;
 $R 7$ is hydrogen, amino, $C_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl) amino;
each $\mathrm{R}^{11}$ is independently H or $\mathrm{C}_{1-6}$ alkyl;
$\mathrm{R}^{8}$ is H , halogen, CN , carboy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, or ( $\mathrm{C}_{1-4}$ alkyl)0-2 aminomethyl; and $\mathbf{R}^{9}$ and $\mathrm{R}^{10}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=0) \mathrm{C}_{1-4}$ alkyl, or $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl, provided that at least one of $\mathrm{R}^{9}$ and R 10 is not hydroxy.
27. The compound of Claim 26 of structural formula VI:

(VI)
wherein B is

or


D is $\mathrm{N}, \mathrm{CH}, \mathrm{C}-\mathrm{CN}, \mathrm{C}-\mathrm{NO}_{2}, \mathrm{C}-\mathrm{C}_{1-3}$ alkyl, C-NHCONH2, C-CONR11R11,

C-CSNR11R11, C-COOR11, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C1-4 alkylamino, C-di(C1-4 alkyl) amino, C-halogen, C-(1;3-oxazol-2-yl), C-(1,3-thiazol-2yl ), or C -(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboy, and
$R^{1}$ and $R^{2}$ together with the carbon atom to which they are attached form a 3- to 6membered saturated monocyclic ring system optionally containing a heteroatom selected from $\mathrm{O}, \mathrm{S}$, and $\mathrm{NC}_{0-4}$ alkyl;
$\mathrm{R}^{6}$ is $\mathrm{H}, \mathrm{OH}, \mathrm{SH}, \mathrm{NH}_{2}, \mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, $\mathrm{C}_{3}-6$ cycloalkylamino, halogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{CF}_{3}$; $\mathrm{R}^{5}$ is $\mathrm{H}, \mathrm{C}_{1-6}$ alkyl, $\mathrm{C}_{2-6}$ alkenyl, $\mathrm{C}_{2-6}$ alkynyl, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{CF}_{3}$, or halogen;

$$
\text { - } 230-
$$

$\mathrm{R}^{7}$ is hydrogen, amino, $\mathrm{C}_{1-4}$ alkylamino, $\mathrm{C}_{3}-6$ cycloalkylamino, or di( $\mathrm{C}_{1-4}$ alkyl)amino;
each R11 is independently H or $\mathrm{C}_{1-6}$ alkyl;
$\mathrm{R}^{8}$ is H , halogen, CN , carboxy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, $\mathrm{N}_{3}$, amino, $\mathrm{C}_{1-4}$ alkylamino, of:
2'-O-methylcytidine-5'-[bis-( $S$-pivaloyl-2-thioethyl)phosphate], 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5'-[bis-(S-pivaldyl-2-thioethyl)phosphate], 15 3'-deoxyguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], 2'-O-methylguanosine-5'-[bis-(S-acetyl-2-thioethyl)phosphate], 2'-O-methylguanosine-5'-[bis̈-( $S$-pivaloyl-2-thioethyl)phosphate], 8 -bromo-2'-O-methylguanosine-5'-[bis-(S-pivaloyl-2-thioethyl)phosphate], 2-amino-3,4-dihydro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-4-oxo-7H-pyrrolo[2,3-
29. A pharmaceutical composition comprising a compound of Claim 27 and a pharmaceutically acceptable carrier.
30. The pharmaceutical composition of Claim 29 useful for inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection.
31. The pharmaceutical composition of Claim 31 wherein said RNA-dependent RNA viral polymerase is HCV NS5B polymerase, said RNAdependent RNA viral replication is HCV replication, and said RNA-dependent RNA viral infection is HCV infection. i,
32. The pharmaceutical composition of Claim 31 in combination with a therapeutically effective amount of another agent active against HCV.
33. The pharmaceutical composition of Claim 32 wherein said agent active against HCV is ribavirin; levovirin; thymosin alphas; an inhibitor of NS3 serine protease; an inhibitor of inosine monophosphate dehydrogenase; interferon- $\alpha$ or pegylated interferon- $\alpha$, alone or in combination with ribavirin or levovirin.
34. A method of inhibiting HCV NS5B polymerase, inhibiting HCV replication, and/or treating HCV 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 HCV .
35. The method of Claim 34 wherein said agent active against HCV is ribavirin; levovirin; thymosin alpha-1; an inhibitor of NS3 serine protease; an inhibitor of inosine monophosphate dehydrogenase; interferon- $\alpha$ or pegylated interferon- $\alpha$, alone or in combination with ribavirin or levovirin.
36. Use of a compound of any one of Claims $1,3,5,7,9,11,13$, 15, 17, and 25-29 in the manufacture of a medicament for inhibition of RNAdependent RNA viral polymerase or inhibition of RNA-dependent RNA viral replication in a mammal.
37. Use of a compound of any one of Claims $2,4,6,8,10,12,14$, 16, 18 , and 25-29 in the manufacture of a medicament for treatment of RNAdependent RNA viral infection in a mammal.
38. Use according to Claim 36 for the manufacture of a medicament for inhibition of HCV polymerase or inhibition of HCV replication in a mammal.
39. Use according to Claim 37 for the manufacture of a medicament for treating HCV infection in a mamal.
40. Use according to Claim 39 in combination interferon- $\alpha$ or pegylated interferon- $\alpha$, alone or in combination with ribavirin or levovirin.
41. A compound selected from the group consisting of:

3',5'-di-O-octanoyl-2'-O-methyl-cytidine,
4-amino-7-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidin-5carboxamide,
2-amino-5-ethyl-7-( $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 2-amino-7-(3-deoxy- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 2-amino-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-5H-pyrrolo[3,2- $d$ ]pyrimidin-4(3H)-one, 7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine, 2-amino-3,4-dihydro-4-oxo-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo-[2,3-d]pyrimidin-5-carbonitrile,
2-amino-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one,
2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-5carbonitrile,
2-amino-4-chloro-5-ethyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine,
2-amino-4-chloro-5-methyl-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3d] pyrimidine,
2-amino-7-(2-O-methyl- $\beta$ - $\dot{\text { D }}$-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidin-4(3H)thione,
2-amino-4-chloro-7-(2-O-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-4-chloro-5-methyl-7-( $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2-amino-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one,

2-amino-4-chloro-7-(2-deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3$d]$ pyrimidine,
2-amino-7-( $\beta$-D-arabinofuranosyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2,3- $d$ ]pyrimidin-5- ${ }^{\text {' }}$ carbonitrile,
5 9-( $\beta$-D-arabinofuranosyl)-9H-purin-6(1 $1 H$ )-one, 3'-amino-3'-deoxy-2'-O-methyl-adenosine,
6 -amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1H-imidazn[4,5-c]pyridin-4(5H) ono, 6-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 $H$-imidazo[4,5-c]pyridin-4(3H)one, one;
2-amino-7-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidin-4(3H)one,
6-amino-1-(2-O-methyl- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5H)-one, 6-amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5H)one,
6-amino-1-(2-deoxy-2-fluoro- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4(5H)one,
1-(2-C-methyl- $\beta$-D-arabinofuranosyl)uracil,
4-amino-1-(3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine, 2-amino-7-(-3-deoxy-3-fluoro- $\beta$-D-ribofuranosyl): 7 H -pyrrolo-
[2,3- $d$ ] pyrimidin-5-carboxamide,
4-amino-1-(2-C-methyl- $\beta$-D-ribofuranosyl)-1 $H$-pyrazolo[3,4- $d$ ]pyrimidine, 4-amino-1-(3-deoxy- $\beta$-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridine, and 4-amino-1-(3-deoxy-3-methyl- $\beta$-D-ribofuranosyl)-1 H -imidazo[4,5-c]pyridine; and the corresponding 5 '-triphosphates; or a pharmaceutically acceptable salt thereof.
ORTIINAS-KOCIV

## BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND
IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND
IN THE MATTER OF:

INDIA CARES

VS.

Pharmasset, Inc.
... RESPONDENTS/APṖLICANTS

PRE-GRANT OPPOSITION BY INDIA CARES
Volume -IV of IV
(Page Nos. 679 to 957 )

| S. No. | Particulars | Page No. |
| :--- | :--- | :--- |
| $1 . \ddots$ | Annexure-7 <br> Copy of WO 2002/057287 | $958-1042$ |
|  |  |  |

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND
IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND
IN THE MATTER OF:

INDIA CARES
... PETITIONER/OPPONENT

VS.

Pharmasset, Inc.
... RESPONDENTS/APPLICANTS

PRE-GRANT OPPOSITION BY INDIA CARES
Volume-IV of IV
(Page Nos. 679 to 957)

| S. No. | Particulars | Page No. |
| :--- | :--- | :--- |
| 1. | $\frac{\text { Annexure-7 }}{\text { Copy of WO 2002/057287 }}$ | $958-1042$ |

IPO DELHI 23-06-2015 15:59

| 2. | $\begin{aligned} & \hline \text { Annexure-8 } \\ & \hline \text { WO 1999/43691 } \end{aligned}$ | 1043-1151 |
| :---: | :---: | :---: |
| 3. | Annexure-9 <br> Park BK and Kitteringham NR (1994), "Effects of fluorine substitution on drug metabolism: pharmacological and toxicological implications", Drug Metab. Rev., 26, 605. | 1152-1190 |
| 4. | Annexure-10 <br> Gumina, G ct al, (2001), "Synthesis and potent anti-HIV activity of L-3'-fluoro-2', 3'-unsaturated cytidine", ORGANIC LETTERS, 3 (26), 4177-4180. | 1191-1194 |
| 5. | ```Annexure-11 Pankiewicz (2000), "Fluorinated Nucleosides", Carbohydrate Research, 327, 87-105.``` | 1195-1213 |
| 6. | Annexure-12 <br> W.J. Middleton, (1975) "New Fluorinating Reagents. Dialylaminosulfur Fluorides", J. Org. Chemi., 40, 574-578. | 1214-1218 |
| 7. | Annexure-13 <br> P Herdewijn et al (1989), "The Application of diethylaminosulfur trifluoride to the synthesis of fluorinated nucleosides, Nucleosides and Nucleotides", 8(1), 65-96. | 1219-1250 |
| 8. | Annexure-14 <br> J. Wachtmeister et al (1999), "Synthesis of 4-substituted carbocyclic 2,3-dideoxy-3-C-hydroxymethyl mucleoside analogues as potential ant-viral agents", Tetrahedron, 55, 10761-10770. | 1251-1260 |
| 9. | Annexure-15 <br> K. Harada,J et al (1987), "Synthcsis and Anticytomegalovirus and Antiherpes Simplex Virus Activity of 5'-Modified Analogues of 2'-Fluoroarabinosylpyrimidine Nucleosides", J. Med. Chem., 30, 226-229. | 1261-1264 |
| 10. | Annexure-16 <br> Akira Matsuda et al (1987), "Radical deoxygenation of tertalcohols in 2'-branched-chain sugar pyrimidine nucleosides: synthesis and antileukemic activity of $2^{\prime}$-deoxy- $2^{\prime}$ (S)methylcytidine" Chemical \& Pharmaceutical Bulletin, 35(9):3967-70. | 1265-1274 |


| 11. | Affidavit of Dr. Otto Orlean Yang | $1275-1286$ |
| :--- | :--- | :--- |
| 12. | Power of Attorney-Form 26 | To follow |

Dated this $23^{\text {rd }}$ day of June, 2015.

## CHITRA ARVIND

FOR RAJESHWARI \& ASSOCIATES
AGENT FOR THE OPPONENT
T"o,
The Controller of Patents
The Patent Office, Delhi

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PITENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau

(43) International Publication Date 25 July 2002 (25.07.2002)

PCT
(10) International Publication Number WO 02/057287 A2
(51) International Patent Classification': $\cdot$ C07H 19/00
(21) International Application Number: PCTIUSO2/03086
(22) International Filing Date: 18 January 2002 (18.01.2002)
(25) Fillug Language:
(26) Publication Language:
(30) Priority Data:

60/263,313
60/282,069
60/299,320
60/344,528

English
English
$\vdots$
22 January 2001 (22.01.2001) US " 6 April 2001 (06.04.2001) US 19 June 2001 (19.06.2001) US
25 October 2001 (25.10.2001) US
(71) Applicants (for all designated States except US): MERCK \& CO., INC. [US/US]; I26 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). ISIS PHARMACE.UTICALS, INC. [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92(108 (US).
(72) Inventors; and
(75) Inventors/Applicunts (for US only): CARROLL L, Steven, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). MACCOSS, Malcolm [GB/US]; 126 East Lincoln Avenue. Rahway, NJ 07065.0907 (US). OLSEN, David, B. [US'/US]; 126 East Lincoln Avenue, Kahway, NJ 07065-0907 (LS). BHAT, Balkristent [IN/US]; 2292 Faraway Avenue, Carl shad, C $\wedge$ ソ2008 (US). BHAT, Neelima (IN/US): 2292 Faraday Avenue, Curlsbad, CA 92008 (US). COOK, Phillip Dan [Us/US $\left.\right|_{;} 2292$ Faraday Avenue, Carlsbad, CA 92008 (US), ELDRUP,
। Anne, B. [DK/US]; 242 Faraday Avenue, Carlsbad,

CA 92008 (US). PRAKASH, Thazha, P. [IN/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). PRHAVC, Marija [SUUS]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). SONG, Quanlai [CN/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (LIS).
(74) Common Representative: DURETTE, Philippe, L.; Merck \& Co., Inc., 126 East Lincoln Avenue, Kahway, NJ $07065-0907$ (US).
(81) Designated States (national): $\mathrm{AE}, \mathrm{AG}, \mathrm{AI}, \mathrm{AM}, \mathrm{AT}, \mathrm{Al}$, $\mathrm{A} Z, \mathrm{BA}, \mathrm{BB}, \mathrm{BG}, \mathrm{BR}, \mathrm{BY}, \mathrm{B} \ell, \mathrm{CA}, \mathrm{CH}, \mathrm{CN}, \mathrm{CO}, \mathrm{CR}, \mathrm{CU}$, $\mathrm{CZ}, \mathrm{DE}, \mathrm{DK}, \mathrm{DM}, \mathrm{DZ}, \mathrm{EC}, \mathrm{EE}, \mathrm{ES}, \mathrm{F}, \mathrm{GB}, \mathrm{GD} ; \mathrm{GE}, \mathrm{GH}$, GM, HR, HI, ID, II., TN, IS, IP, KR, KG, KR, KT, IC. I. K, LR, LS, LIT, LU, LV, MA, MD, MG, MK, MN, MW, MK, MU, NO, NZ, OM, PH, PL, PT, RD, RU, SD, SE, SG, SI, SK, SI, TI, TM, TN, TR; TM, TV, JA, VG, US, JJ, UN, YO, LA, LM, ZS.
(84) Designated States (regional): ARIPO patent (GH, GM, KB, LS, MW, MK, SD, SL, SQ, TX, JG, RM, KW), Eurasian patent ( $\mathrm{AM}, \mathrm{AZ}, \mathrm{BY}, \mathrm{KG}, \mathrm{KZ}, \mathrm{MD}, \mathrm{RU}, \mathrm{TJ}, \mathrm{TM}$ ), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent ( $B F, B J, C F, C G, C I, C M, G A, G N, G Q, G W, M L, M R$, NE, SN, 'TD, TB).

Published:

- without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidonce Notes on Codes and Abbreviations" appearing at the beginming of each regular issue of the PCT Gazette. pendent 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. They are particularly useful as inhibitors of hepatitis C virus (IICV) NSSB polymerase, ats inhibitors of HCV replication, and/or for the treatment of hepatitis C infection. The invention also describes pharmaceutical compositions containing such nucleoside compounds alone or in combination with other agents active against RNA -dependent RNA viral infection, in particular HCV infection. Also disclosed are methods of inhibiting RNA-dependent RNA polymerase, inhibiting RNA-dependent RNA viral replic:aisn, and/ur treating RNA-dependent RNA viral infection with the nucleoside compounds of the present invention.

NUCLEOSIDE DERIVATIVES AS INHIBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE

FIELD OF THE INVENTION
The present invention is concerned with nucleoside compounds and certain derivatives thereof, their synthesis, and their use as inhibitors of RNAdependent RNA viral polymerase. The compounds of the present invention are inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependeny RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and for the treatment of hepatitis C infection.

## BACKGROUND OF THE INVENTION

 infection, which are restricted to immunotherapy with recombinant interferon- $\alpha$ alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection. The 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); H. Rosen, et al, "Hepatitis C virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5: 393--1-399 (1999); D. Moradpour, et al., "Current and evolving therapies for hepatitis C," European J. Gastroenterol. Hepatol., 11: 1189-1202 (1999); R. Bartenschlager, "Candidate-Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40: 378-393 (1997); G.M. Lauer and B.D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345: 41-52 (2001); B.W. Dymock, "Emerging therapies for hepatitis C virus infection," Emerging Drugs, 6: 13-42 (2001); and C. Crabb, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001); the contents of 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.

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 $\mathrm{C}, \mathrm{E}$, and E 2 , and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS). proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in.the replication cycle of HCV. NS5B polymerase is therefore considered to be an essential component in the HCV replication complex [see K. Ishi, et al., "Expression of Hepatitis C Virus NS5B Protein: Characterization of Its RNA Polymerase Activity and RNA Binding," Hepatology, 29: 1227-1235 (1999) and V. Lohmann, et al., "Biochemical and Kinetic Analyses of NS5B RNA-Dependent RNA Polymerase of the Hepatitis C Virus," Virology, 249: 108-118 (1998)]. Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of.HCV-specific antiviral therapies.

It has now been found that nucleoside compounds of the present invention and certain derivatives thereof are potent inhibitors of RNA-dependent RNA viral replication and in particular HCV replication. The 5'-triphosphate derivatives of these nucleoside compounds are inhibitors of RNA-dependent RNA viral polymerase and in particular HCV NS5B polymerase. The instant nucleoside compounds and derivatives thereof are useful to treat RNA-dependent RNA viral infection and in particular HCV infection.

It is therefore an object of the present invention to provide nucleoside compounds and certain derivatives thereof which are useful as inhibitors of RNAdependent RNA viral polymerase and in particular as inhibitors of HCV NS5B polymerase.

It is another object of the present invention to provide nucleoside compounds and certain derivatives thereof which are useful as inhibitors of the replication of an RNA-dependent RNA virus and in particular as inhibitors of the replication of hepatitis C virus.

It is another object of the present invention to provide nucleoside compounds and certain derivatives thereof which are useful in the treatment of RNAdependent RNA viral infection and in particular in the treatment of HCV infection.
lt is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside 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 nucleoside compounds and derivatives thereof of the present invention for use as inhibitors of RNA-dependent RNA viral polymerase and in particular as inhibitors of HCV NS5B polymerase.

It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside compounds and derivatives thereof of the present invention for use as inhibitors of RNA' -dependent RNA viral replication and in particular as inhibitors of HCV replication.

It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside compounds and derivatives thereof of the present invention for use in the treatment of RNA-dependent RNA viral infection and in particular in the treatment of HCV infection.

It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside compounds and derivatives thereof of the. present invention in combination with other agents active against an RNA-dependent RNA virus and in particular against HCV.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral polymerase and in particular for the inhibition of HCV NS5B polymerase.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral replication and in particular for the inhibition of HCV replication.

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

It is another object of the present invention to provide nucleoside compounds and certain derivatives thereof 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 and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

It is another object of the present invention to provide for the use of the nucleoside compounds and certain derivatives thereof 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 RNAdependent RNA viral infection and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

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

## SUMMARY•OF THE INVENTION

The present invention relates to compounds of structural formula $I$ of the indicated stereochemical configuration:

(I)
or a pharmaceutically acceptable salt thereof; wherein $\mathrm{R}^{1}$ is $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{1-4}$ alkylthio, or one to three fluorine atoms; •
$\mathrm{R}^{2}$ is hydrogen, fluorine, hydroxy, mercapto, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{C}_{1-4}$ alkyl; or $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ together with the carbon atom to which they are attached form a 3- to 6 -membered saturated monocyclic ring system optionally containing a heteroatom selected from O , S , and $\mathrm{NC}_{0}-4$ alkyl;
$10 R^{3}$ and $R^{4}$ are each independently selected from the group consisting of hydrogen, cyano, azido, halogen, hydroxy, mercapto, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, and $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{1-4}$ alkylthio, or one to three fluorine atoms; $\mathrm{R}^{5}$ is hydrogen, $\mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{13} \mathrm{R} 14$;
R6 and R7 are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl; $\mathrm{R}^{8}$ is hydrogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{2-4}$ alkynyl, halogen, cyano, carboy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, azide, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, hydroxy, $C_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, ( $\mathrm{C}_{1-4}$ alkyl )0-2 aminomethyl, or C4-6 cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, $\mathrm{C}_{1-4}$ alkyl, and $\mathrm{C}_{1-4}$ alkoxy; R 9 is hydrogen, cyano, nitro, $\mathrm{C}_{1-3}$ alkyl, $\mathrm{NHCONH}_{2}, \mathrm{CONR} 12 \mathrm{R} 12, \mathrm{CSNR} 12 \mathrm{R} 12$, TOR ${ }^{12}, \mathrm{C}(=\mathrm{NH}) \mathrm{NH}_{2}$, hydroxy, $\mathrm{C}_{1-3}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ 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
25 from halogen, amino, hydroxy, carboxy, and C.1-3 alkoxy; R10 and R11 are each independently hydrogen, hydroxy, halogen, $\mathrm{C}_{1-4}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di(C1-4 alkyl)amino, $\mathrm{C}_{3}-6$ cycloalkylamino, di(C3-6

PCT/US02/03086
cycloalkyl)amino, or C4-6 cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, C1-4 alkyl, and C1-4 alkoxy;
each R12 is independently hydrogen or $\mathrm{C}_{1}-6$ alkyl; and

R13 and R 14 are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl)O$(\mathrm{C}=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl,


with the proviso that when $R 1$ is $\beta$-methyl and $R^{4}$ is hydrogen or $R^{4}$ is $\beta$-methyl and $R^{1}$ is hydrogen, $R^{2}$ and $R^{3}$ are $\alpha$-hydroxy, $R^{10}$ is amino, and $R^{5}, R^{6}, R^{7}, R^{8}$, and $\mathrm{R}^{11}$ are hydrogen, then $\mathrm{R}^{9}$ is not cyano or $\mathrm{CONH}_{2}$.

The compounds of formula $I$ are useful as inhibitors of RNAdependent RNA viral polymerase and in particular of.HCV NS5B polymerase. They are also inhibitors of RNAं-dependent RNA viral replication and in particular of HCV replication and are useful for the treatment of RNA-dependent RNA viral infection and in particular for the treatment of HCV infection.

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 and in particular against HCV as well as methods for the inhibition of RNA-dependent RNA viral replication and for the treatment of RNA-dependent RNA viral infection.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of structural formula I of the indicated stereochemical configuration:

(I)
or a pharmaceutically acceptable salt thereof;
wherein R 1 is $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{1-4}$ alkylthio, or one
5 to three fluorine atoms;
$\mathrm{R}^{2}$ is hydrogen, fluorine, hydroxy, mercapto, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{C}_{1-4}$ alkyl; or $\mathrm{R}^{1}$ and R2 together with the carbon atom to which they are attached form a 3 - to 6 -membered saturated monocyclic ring system optionally containing a heteroatom selected from O , S , and $\mathrm{NC} 0-4$ alkyl;
$10 R^{3}$ and $R^{4}$ are each independently selected from the group consisting of hydrogen, cyano, azide, halogen, hydroxy, mercapto, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2}-4$ alkynyl, and ' $\mathrm{C}_{1-4}$ alkyl, wherein alky! is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{1-4}$ alkylthio, or one to three fluorine atoms;
$\mathrm{R}^{5}$ is hydrogen, $\mathrm{C}_{1-10}$ alkylcarbonyi, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{P}(\mathrm{O}) \mathrm{R} 13 \mathrm{R} 14$;
R6 and R7 are each independently' hydrogen, methyl, hydroxymethyl, or fluoromethyl; $\mathrm{R}^{8}$ is hydrogen, $\mathrm{C}_{1-4}$ alkyl, $\mathrm{C}_{2-4}$ alkynyl, halogen, cyano, carboy, $\mathrm{C}_{1-4}$ alkyloxycarbonyl, azide, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, hydroxy, $C_{1-6 ~ a l k o x y ; ~} C_{1-6}$ alkylthio, $C_{1-6}$ alkylsulfonyl, ( $C_{1-4}$ alkyl )0-2 aminomethyl, or C4-6 cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, $\mathrm{C}_{1-4}$ alkyl, and $\mathrm{C}_{1-4}$ alkoxy; R 9 is hydrogen, cyano, nitro, $\mathrm{C}_{1-3}$ alkyl, $\mathrm{NHCONH}_{2}, \mathrm{CONR} 12 \mathrm{R} 12, \mathrm{CSNR} 12 \mathrm{R} 12$, TOR ${ }^{12}, \mathrm{C}(=\mathrm{NH}) \mathrm{NH}_{2}$, hydroxy, $\mathrm{C}_{1-3}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazoi-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 $\mathrm{C}_{1-3}$ alkoxy; $\mathrm{R}^{10}$ and $\mathrm{R}^{11}$ are each independently hydrogen, hydroxy, halogen, $\mathrm{C}_{1-4}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, $\mathrm{C}_{3}-6$ cycloalkylamino, di (C3-6
cycloalkyl)amino, or $\mathrm{C}_{4}-6$ cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, $\mathrm{C}_{1-4}$ alkyl, and C1-4 alkoxy;
each $\mathrm{R}^{12}$ is independently hydrogen or $\mathrm{C}_{1-6}$ alkyl; and R13 and R14 are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl)O(C=O)C1-4 alkyl,

with the proviso that when $R^{1}$ is $\beta$-methyl and $R^{4}$ is hydrogen or $R^{4}$ is $\beta$-methyl and $\cdot R 1$ is hydrogen, $R^{2}$ and $R^{3}$ are $\alpha$-hydroxy, $\mathrm{R}^{10}$ is amino, and $\mathrm{R}^{5}, \mathrm{R}^{6}, \mathrm{R}^{7}$, $\mathrm{R}^{8}$, and $\mathrm{R}^{11}$ are hydrogen, then $\mathrm{R}^{9}$ is not cyano or $\mathrm{CONH}_{2}$.
:The compounds of formula I are useful as inhibitors of RNAdependent RNA viral polymerase. They are also inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. compounds of structural formula II:

(II)
or a pharmaceutically acceptable salt thereof;
wherein
$\mathrm{Rl}^{1}$ is $\mathrm{C}_{1-3}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-3}$ alkoxy, $\mathrm{C}_{1-3}$ alkylthio, or one to three fluorine atoms;
$\mathrm{R}^{2}$ is hydroxy, fluoro, or C $\mathrm{C}_{1-3}$ alkoxy;
$\mathrm{R}^{3}$ is hydrogen, halogen, hydroxy, amino, or $\mathrm{C}_{1-3}$ alkoxy;
$\mathrm{R}^{5}$ is hydrogen, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{PO}_{3} \mathrm{H}_{2}$;
$\mathrm{R}^{8}$ is hydrogen; amino, or $\mathrm{C}_{1-4}$ alkylamino;
R 9 is hydrogen, cyano, methyl, halogen, or $\mathrm{CONH}_{2}$; and
R10 and R11 are each independently hydrogen, halogen, hydroxy, amino,
$\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, or $\mathrm{C}_{3}-6$ cycloalkylamino;
with the proviso that when $\mathrm{R}^{1}$ is $\beta$-methyl, $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are $\alpha$-hydroxy, $\mathrm{R}^{10}$ is amino, and $\mathrm{R}^{5}, \mathrm{R}^{8}$, and $\mathrm{R}^{11}$ are hydrogen, then $\mathrm{R}^{9}$ is not cyan or $\mathrm{CONH}_{2}$.

In a second embodiment of the compounds of structural formula I are the compounds of structural formula II wherein:
10 R1 is methyl, fluoromethyl, hydroxymethyl, difluoromethyl, trifluoromethyl, or aminomethyl;
$\mathrm{R}^{2}$ is hydroxy, fluoro, or methoxy;
$\mathrm{R}^{3}$ is hydrogen, fluoro, hydroxy, amino, or methoxy;
$\mathrm{R}^{5}$ is hydrogen or $\mathrm{P}_{3} \mathrm{O} 9 \mathrm{H}_{4}$;
$15 \quad \mathrm{R}^{8}$ is hydrogen or amino;
R 9 is hydrogen, cyano, methyl, halogen, or $\mathrm{CONH}_{2}$; and
R10 and R11 are each independently hydrogen, fluoro, hydroxy, or amino; with the proviso that when $\mathrm{R}^{1}$ is $\beta$-methyl, $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are $\alpha$-hydroxy, $\mathrm{R}^{10}$ is amino, and $R^{5}, R^{8}$, and $R^{11}$ are hydrogen, then $\mathrm{R}^{9}$ is not cyan or $\mathrm{CONH}_{2}$. 4-amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-mcthyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine-5carboxylic acid. 4-amino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,

4-amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)- $7 H$-pyrrolo[2,3- $d$ ]pyrimidine, 2,4-diamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine, 2-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 2-amino-4-cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine,
2-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3F)-one, 4-umino-7-(2-C-ethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one, 2-amino-5-methyl-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidin $\angle 4(3 H)$-one,
4-amino-7-(3-deoxy-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ] pyrimidine, 4-amino-7-(3-deoxy-2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]-. pyrimidine,
4-amino-2-fluoro-7-(2-C-meṭhyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(3-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(3-C-methyl- $\beta$-D-xylofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2,4-di-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, and 4-amino-7-(3-deoxy-3-fluoro-2:C-methyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo[2,3d]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

Further illustrative of the present invention are the compounds selected from the group consisting of:
4-amino-7-(2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, and
4-amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, and the corresponding 5 '-triphosphates;
or a pharmaceutically acceptable salt thereof.
In one embodiment of the present invention, the nucleoside 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 Picomaviridae virus is a rhinovirus, a poliovirus, 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, Banzi virus, and bovine viral diarrhea virus (BVDV). In a subclass of this subclass, the Flaviviridae virus is hepatitis $\mathbb{C}$ virus.

Another aspect of the present invention is concerned with a method for inhibiting RNA-dependent RNA viral polymerase, a method for inhibiting RNAdependent 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 $I$.

In one embodiment of this aspect of the present invention, the RNAdependent RNA viral polymerase is a positive-sense single-stranded RNA-dependent RNA viral polymerase. In a class of this embodiment, the positive-sense singlestranded RNA-dependent RNA viral polymerase is a Flaviviridae viral polymerase or a Picomaviridae viral polymerase. In a subclass of this class, the Picornaviridae viral polymerase is rhinovirus polymerase, poliovirus 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, Banzi 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 second embodiment of this aspect of the present invention, the RNA-dependent RNA viral replication is a positive-sense single-stranded RNAdependent RNA viral replication. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral replication is Flaviviridae viral replication or Picomaviridae viral replication. In a subclass of this class, the Picomaviridae
viral replication is rhinovirus replication, poliovirus 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, Banzi 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 third embodiment of this aspect of the present invention, the RNAdependent 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 rhinovirus infection, poliovirus infection, or 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, Banzi virus infection, and bovine viral diarrhea virus infection. In a subclass of this subclass, the Flaviviridae viral infection is hepatitis C virus infection.

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, isohexyl, 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 (ie., cyclopropyl, cyclobutyl, cyc̀lopentyl, cyclohexyl, cycloheptyl, or cyclooctyl).

The term "cycloheteroalkyl" is intended to include non-aromatic heterocycles containing one or two heteroatoms selected from nitrogen, oxygen and
sulfur. Examples of 4-6-membered cycloheteroalkyl include azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl, imidazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, piperazinyl, and the like.

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 "alkylthio" refers to straight or branched chain alkylsulfides of the number of carbon atoms specified (e.g., $\mathrm{C}_{1-4}$ alkylthio), or any number within this range [ie., methylthio (MeS-), ethylthio, isopropylthio, etc.].

The term "alkylamino" refers to straight or branched alkylamines of the number of carbon atoms specified (e.g., $\mathrm{C}_{1-4}$ alkylamino), or any number within this range [ie., methylamino, ethylamino, isopropylamino, $t$-butylamino, etc.].

The term "alkylsulfonyl" refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e.g., $\mathrm{C}_{1-6}$ alkylsulfonyl), or any number within this range [ie., methylsulfonyl ( $\mathrm{MeSO}_{2}-$ ), 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., $\mathrm{C}_{1-4}$ alkyloxycarbonyl), or any number within this range [ie., methyloxycarbonyl (MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl].

The term "aryl" includes both phenyl, naphthyl, and pyridyl. The aryl group is optionally substituted with one to three groups independently selected from $\mathrm{C}_{1-4}$ alkyl, halogen, cyan; nitro, trifluoromethyl, $\mathrm{C}_{1-4}$ alkoxy, and $\mathrm{C}_{1-4}$ alkylthio.

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 plurally.

The term " 5 '-triphosphate" refers to a triphosphoric acid ester derivative of the 5 '-hydroxyl group of a nucleoside compound of the present invention having the following general structural formula M :

wherein R1-R11 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 5 '-monophosphate and 5 '-diphosphate ester derivatives of the structural formulae IV and V , respectively,


The term " 5 '-(S-acyl-2-thioethyl)phosphate" or "SATE" refers to a mono- or di-ester derivative of a 5 '-monophosphate nucleoside derivative of the present invention of structural formulae VI and VII, respectively, as well as pharmaceutically acceptable salts of the mono-ester,


VI


The term "composition", as in "pharmaceutical composition," is intended to encompass a product comprising the active ingredients) and the inert ingredients) 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 concemed 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- $\alpha$, pegylated interferon- $\alpha$ (peginterferon- $\alpha$ ), a combination of interferon- $\alpha$ and ribavirin,
a combination of peginterferon- $\alpha$ and ribavirin, a combination of interferon- $\alpha$ and levovirin, and a combination of peginterferon- $\alpha$ and levovirin. Interferon- $\alpha$ includes, but is not limited to, recombinant interferon- $\alpha 2 \mathrm{a}$ (such as Rofernn interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon- $\alpha 2$ a (Pegasys ${ }^{\text {TM }}$ ), interferon- $\alpha 2 b$ (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ ), pegylated interferon- $\alpha 2 \mathrm{~b}$ (PegIntron ${ }^{\mathrm{TM}}$ ), a recombinant consensus interferon (such as interferon alphacon-1), and a purified interferon- $\alpha$ product. Amgen's recombinant consensus interferon has the brand name Infergen®. Levovirin is the L-enantiomer of ribuvirin 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, and GB2337262. 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 - 16 -
intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in de nova 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)].

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 nucleoside compounds and derivatives thereof 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 NS 5B 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 treating 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, levovirin, viramidine, thymosin alpha-1, an inhibitor of HCV NS3 serine protease,
(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, com 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 injertable use include otorile 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 0.01 to 1000 $\mathrm{mg} / \mathrm{kg}$ body weight in divided doses. In one embodiment the dosage range is 0.1 to $100 \mathrm{mg} / \mathrm{kg}$ body weight in divided doses. In another embodiment the dosage range is 0.5 to $20 \mathrm{mg} / \mathrm{kg}$ 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.

$$
-20-
$$

The compounds of the present invention contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend nucleoside compounds having the $\beta-\mathrm{D}$ encompassed with compounds of structural formula I. An example of keto-enol tautomers which are intended to be encompassed within the compounds of the present invention is illustrated below:


- 21 -

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 chromatography 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 stereochemistry of the substituents at the C-2 and C-3 positions of the furanose ring of the compounds of the present invention of structural formula $I$ is denoted by squiggly lines which signifies that substituents $R 1, R^{2}, R^{3}$ and $R^{4}$ can have either the $\alpha$ (substituent "down") or $\beta$ (substituent "up") configuration independently of one another. Notation of stereochemistry by a bold line as at C-1 and $\mathrm{C}-4$ of the furanose ring signifies that the substituent has the $\beta$-configuration (substituent "up").

(I)

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 encompussed 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, camsylate; carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate,
glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N -methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stẹarate, sulfate, subacetate, succinate, tännate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitahle 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 basés include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, $\mathrm{N}, \mathrm{N}$-dibenzylethylenediamine, diethylamine, 2diethylaminoethianol, 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 Nucleoside Compounds and Derivatives of the Invention <br> The nucleoside compounds and derivatives thereof of the present

 invention can be prepared following synthetic methodologies well-established in the practice of nucleoside and nucleotide chemistry. Reference is made to the following text for a description of synthetic methods used in the preparation of the compounds of the present invention: "Chemistry of Nucleosides and Nucleotides," L.B. Townsend, ed., Vols. 1-3, Plenum Press, 1988, which is incorporated by reference herein in its entirety.A representative general method for the preparation of compounds of the present invention is outlined in Scheme 1 below. This scheme illustrates the synthesis of compounds of the present invention of structural formula 1-7 wherein the furanose ring has the $\beta$-D-ribo configuration. The starting material is a 3,5 -bis-O- protected alkyl furanoside, such as methyl furanoside, of structural formula 1-1. The C- 2 hydroxyl group is then oxidized with a suitable oxidizing agent, such as a chromium trioxide or chromate reagent, Dess-Martin perindinane, or by Swern oxidation, to afford a C-2 ketone of structural formula 1-2. Addition of a Grignard reagent, such as an alkyl, alkenyl, or alkynyl magnesium halide (for example, $\mathrm{MeMgBr}, \mathrm{EtMgBr}$, vinylMgBr, allylMgBr, and ethynylMgBr) or an alkyl, alkenyl, or alkynyl lithium, such as MeLi , across the carbonyl double bond of $1-2$ in a suitable organic solvent, such as tetrahydrofuran, diethyl ether, and the like, affords the C-2 tertiary alcohol of structural formula 1-3. A good leaving group (such as $\mathrm{Cl}, \mathrm{Br}$, and I ) is next introduced at the $\mathrm{C}-1$ (anomeric) position of the furanose sugar derivative by treatment of the furanoside of formula $1-3$ with a hydrogen halide in a suitable organic solvent, such as hydrogen bromide in acetic acid, to afford the intermediate furanosyl halide 1-4. A C-1 sulfonate, such methanesulfonate ( $\mathrm{MeSO}_{2} \mathrm{O}$-), trifluoromethanesulfonate ( $\mathrm{CF}_{3} \mathrm{SO}_{2} \mathrm{O}$-), or p-toluenesulfonate ( -OTs ), may also serve as a useful leaving group in the subsequent reaction to generate the glycosidic (nucleosidic) linkage. The nucleosidic linkage is constructed by treatment of the intermediate of structural formula 1-4 with the metal salt (such as lithium, sodium, or potassium) of an appropriately substituted $1 H$-pyrrolo[2,3-d]pyrimidine $1-5$, such as an appropriately substituted 4-halo-1H-pyrrolo[2,3-d]pyrimidine, which can be generated in situ by treatment with an alkali hydride (such as sodium hydride), an alkali hydroxide (such as potassium hydroxide), an alkali carbonate (such as potassium carbonate), or an alkali hexamethyldisilazide (such as NaHMDS) in a suitable anhydrous organic solvent, such as acetonitrile, tetrahydrofuran, 1-methyl-2pyrrolidinone, or $\mathrm{N}, \mathrm{N}$-dimethylformamide (DMF). The displacement reaction can be catalyzed by using a phase-transfer catalyst, such as TDA-1 or triethylbenzylammonium chloride, in a two-phase system (solid-liquid or liquid-liquid). The optional protecting groups in the protected nucleoside' of structural formula 1-6 are then cleaved following established deprotection methodologies, such as those described in T.W. Greene and P.G.M. Wats, "Protective Groups in Organic Synthesis," $3^{\text {rd }}$ ed., John Wiley \& Sons, 1999. Optional introduction of an amino group at the 4-position of the pyrrolo[2,3-d]pyrimidine nucleus is effected by
treatment of the 4-halo intermediate $1-6$ with the appropriate amine, such as alcoholic ammonia or liquid ammonia, to generate a primary amine at the $\mathrm{C}-4$ position $\left(-\mathrm{NH}_{2}\right)$, an alkylamine to generate a secondary amine (-NHR), or a dialkylamine to generate a teniary amine (-NRR'). A 7H-pyrrolo[2,3-d]pyrimidin-4(3H)one compound may be derived by hydrolysis of 1-6 with aqueous base, such as aqueous sodium hydroxide. Alcoholysis (such as methanolysis) of $1-6$ affords a C-4 alkoxide (-OR), whereas treatment with an alkyl mercaptide affords a C-4 alkylthio (-SR) derivative. Subsequent chemical manipulations well-known to practitioners of ordinary skill in the art of organic/medicinal chemistry may be required to attain the desired compounds of the present invention.

## Scheme 1





The examples below provide citations to literature publications, which contain details for the preparation of final compounds or intermediates employed in the preparation of final compounds of the present invention. The nucleoside compounds of the present invention were prepared according to procedures detailed in the following examples. The examples 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 appreciate 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 ${ }^{\circ}$

4-Amino-7-(2- $\dot{C}$-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine


To chromium trioxide ( $1.57 \mathrm{~g}, 1.57 \mathrm{mmol}$ ) in dichloromethane (DCM) $(10 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ was added acetic anhydride ( $145 \mathrm{mg}, 1.41 \mathrm{mmol}$ ) and then pyridine ( $245 \mathrm{mg}, 3.10 \mathrm{mmol}$ ). The mixture was stirred for 15 min , then a solution of $7-[3,5-$ O-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl1]- $\beta$-D-ribofuranosyl]-7H-
pyrrolo[2,3-d]pyrimidin-4-amine. [for preparation, see J. Am. Chem. Soc. 105: 4059' (1983)] ( $508 \mathrm{mg}, 1.00 \mathrm{mmol}$ ) in DCM ( 3 mL ) was added. The resulting solution was stirred for 2 h and then poured into ethyl acetate ( 10 mL ), and subsequently filtered through silica gel using ethyl acetate as the eluent. The combined filtrates were evaporated in vacuo, taken up in diethyl ether/THF ( $1: 1$ ) ( 20 mL ), cooled to $-78^{\circ} \mathrm{C}$ and methylmagnesium bromide ( 3 M , in TFFF) $\left(3.30^{\circ} \mathrm{mL}, 10 \mathrm{mmol}\right)$ was added dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 10 min , then allowed to come to room temperature ( rt ) and quenched by addition of saturated aqueous ammonium chloride ( 10 mL ) and extracted with DCM ( 20 mL ). The organic phase was evaporated in vacuo and the crude product purified on silica gel using: $5 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo. The resulting oil was taken up in THF ( 5 mL ) and tetrabutylammonium fluoride (TBAF) on silica ( $1.1 \mathrm{mmol} / \mathrm{g}$ on silica) ( 156 mg ) was added. The mixture was stirred at rt for 30 min , filtered, and evaporated in vacuo. The crude product was purified on silica gel using $10 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired compound ( 49 mg ) as a colorless solid.
$1^{1}$ NMR (DMSO-d $\left.d_{6}\right): \delta 1.08(\mathrm{~s}, 3 \mathrm{H}), 3.67(\mathrm{~m}, 2 \mathrm{H}), 3.74(\mathrm{~m}, 1 \mathrm{H}), 3.83(\mathrm{~m}, 1 \mathrm{H}), 5.19$
$(\mathrm{m}, 1 \mathrm{H}), 5.23(\mathrm{~m}, 1 \mathrm{H}), 5.48(\mathrm{~m}, 1 \mathrm{H}), 6.08(1 \mathrm{H}, \mathrm{s}), 6.50(\mathrm{~m}, 1 \mathrm{H}), 6.93(\mathrm{bs}, 2 \mathrm{H}), 7.33$ $(\mathrm{m}, 1 \mathrm{H}), 8.02(\mathrm{~s}, 1 \mathrm{H})$.

## EXAMPLE 2

## 4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine



Step A: $\quad 3,5$-Bis- $O$-(2,4-dichlorophenylmethyl)-1- $O$-methyl- $\alpha$-D-ribofuranose A mixture of 2-O-acetyl-3,5-bis-O-(2,4-dichlorophenylmethyl)-1-O-methyl- $\alpha$-D-ribofuranose [for preparation, see: Helv. Chim. Acta 78: 486 (1995)]

$$
-27-
$$

( $52.4 \mathrm{~g}, 0.10 \mathrm{~mol}$ ) in methanolic $\mathrm{K}_{2} \mathrm{CO}_{3}(500 \mathrm{~mL}$, saturated at rt ) was stirred at room temperature for 45 min . and then concentrated under reduced pressure. The oily residue was suspended in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(500 \mathrm{~mL})$, washed with water ( $300 \mathrm{~mL}+5 \times 200$ mL ) and brine ( 200 mL ), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated to give the title compound ( 49.0 g ) as colorless oil, which was used without further purification in Step B below.
$1_{\text {H NMR ( }}$ (SO- $d_{6}$ ): $\delta 3.28\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.53\left(\mathrm{~d}, 2 \mathrm{H}, J_{5,4}=4.5 \mathrm{~Hz}, \mathrm{H}-5 \mathrm{a}, \mathrm{H}-5 \mathrm{~b}\right)$, 3.72 (dd, $\left.1 \mathrm{H}, J_{3,4}=3.6 \mathrm{~Hz}, J_{3,2}=6.6 \mathrm{~Hz}, \mathrm{H}-3\right), 3.99$ (ddd, $1 \mathrm{H}, J_{2,1}=4.5 \mathrm{~Hz}, J_{2, \mathrm{OH}-2}=$ $9.6 \mathrm{~Hz}, \mathrm{H}-2), 4.07(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4), 4.50\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{Ph}\right), 4.52,4.60\left(2 \mathrm{~d}, 2 \mathrm{H}, J_{\mathrm{gem}}=13.6\right.$ $\left.\mathrm{Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 4.54(\mathrm{~d}, 1 \mathrm{H}, \mathrm{OH}-2), 4.75(\mathrm{~d}, 1 \mathrm{H}, \mathrm{H}-1), 7.32-7.45,7.52-7.57(2 \mathrm{~m}, 10 \mathrm{H}$, 2Ph).
${ }^{13} \mathrm{C}$ NMR (DMSO- $d_{6}$ ): $\delta 55.40,69.05,69.74,71.29,72.02,78.41,81.45,103.44$, 127.83, 127.95, 129.05, 129.28, 131.27, 131.30, 133.22, 133.26, 133.55, 133.67, 135.45, 135.92.

Step B: 3,5-Bis- $O$-(2,4-dichlorophenylmethyl)-1-O-methyl- $\alpha$-D-erythro-pentofuranos-2-ulose
To an ice-cold suspension of Dess-Martin periodinane ( $50.0 \mathrm{~g}, 118$ mmol ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 350 mL ) under argon ( Ar ) was added a solution of the compound from Step A ( $36.2 \mathrm{~g}, 75 \mathrm{mmol}$ ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(200 \mathrm{~mL})$ dropwise over 0.5 h . The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 0.5 h and then at room temperature'for 3 days. The mixture was diluted with anhydrous $\mathrm{Et}_{2} \mathrm{O}(600 \mathrm{~mL})$ and poured into an ice-cold mixture of $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \cdot 5 \mathrm{H}_{2} \mathrm{O}(180 \mathrm{~g})$ in saturated aqueous $\mathrm{NaHCO}_{3}(1400 \mathrm{~mL})$. The layers were separated, and the organic layer was washed with saturated aqueous $\mathrm{NaHCO}_{3}(600 \mathrm{~mL})$, water $(800 \mathrm{~mL})$ and brine ( 600 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and evaporated to give the title compound ( 34.2 g ) as a colorless oil, which was used without further purification in Step C below.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 3.50\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.79\left(\mathrm{dd}, 1 \mathrm{H}, J_{5 \mathrm{a}, 5 \mathrm{~b}}=11.3 \mathrm{~Hz}, J_{5 \mathrm{a}, 4}=3.5\right.$ $\mathrm{Hz}, \mathrm{H}-5 \mathrm{a}), 3.94\left(\mathrm{dd}, 1 \mathrm{H}, J_{5 \mathrm{~L}, 4}=2.3 \mathrm{~Hz}, \mathrm{H}-5 \mathrm{~b}\right), 4.20\left(\mathrm{dd}, 1 \mathrm{H}, J_{3,1}=1.3 \mathrm{~Hz}, J_{3,4}=8.4\right.$ $\mathrm{Hz}, \mathrm{H}-3), 4.37$ (cd, 1H, H-4), 4.58, 4.69 ( $2 \mathrm{~d}, 2 \mathrm{H}, J_{\text {gem }}=13.0 \mathrm{~Hz}, \mathrm{CH} 2 \mathrm{Ph}$ ), 4.87 (d, $1 \mathrm{H}, \mathrm{H}-1), 4.78,5.03\left(2 \mathrm{~d}, 2 \mathrm{H}, J_{\mathrm{gem}}=12.5 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 7.19-7.26,7.31-7.42(2 \mathrm{~m}, 10 \mathrm{H}$, 2 Ph).
${ }^{13} \mathrm{C}$ NMR (DMSO- $d_{6}$ ): $\delta 55.72,69.41,69.81,69.98,77.49,78.00,98.54,127.99$, 128.06, 129.33, 129.38, 131.36, 131.72, 133.61, 133.63, 133.85, 133.97, 134.72, 135.32, 208.21 .

Step C: 3,5-Bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl-1-O-methyl- $\alpha$-Dribofuranose
To a solution of MeMgBr in anhydrous $\mathrm{Et}_{2} \mathrm{O}(0.48 \mathrm{M}, 300 \mathrm{~mL})$ at $-55^{\circ} \mathrm{C}$ was added dropwise a solution of the compound from Step B $(17.40 \mathrm{~g}, 36.2$ mmol ) in anhydrous $\mathrm{Et}_{2} \mathrm{O}$ ( 125 mL ). The reaction mixture was allowed to warm to $-30^{\circ} \mathrm{C}$ and stirred for 7 h at $-30^{\circ} \mathrm{C}$ to $-15^{\circ} \mathrm{C}$, then poured into ice-cold water ( 500 mL ) and the mixture vigorously stirred at room temperature for 0.5 h . The mixture was filtered through a Celite pad ( $10 \times 5 \mathrm{~cm}$ ) which was thoroughly washed with $\mathrm{Et}_{2} \mathrm{O}$. The organic layer was dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentrated. The residue was dissolved in hexanes ( $\sim 30 \mathrm{~mL}$ ), applied onto a silica gel column ( $10 \times 7 \mathrm{~cm}$, prepacked in hexanes) and eluted with hexanes and hexanes/EtOAc (9/1) to give the title compound ( 16.7 g ) as a colorless syrup.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.36\left(\mathrm{~d}, 3 \mathrm{H}, J_{\mathrm{Me}, \mathrm{OH}}=0.9 \mathrm{~Hz}, 2 \mathrm{C}-\mathrm{Me}\right), 3.33(\mathrm{q}, 1 \mathrm{H}, \mathrm{OH}), 3.41(\mathrm{~d}$, $\left.1 \mathrm{H}, J_{3,4}=3.3 \mathrm{~Hz}\right), 3.46\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.66\left(\mathrm{~d}, 2 \mathrm{H}, J_{5,4}=3.7 \mathrm{~Hz}, \mathrm{H}-5 \mathrm{a}, \mathrm{H}-5 \mathrm{~b}\right), 4.18$ (apparent $\mathrm{q}, 1 \mathrm{H}, \mathrm{H}-4), 4.52(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1), 4.60\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{Ph}\right), 4.63,4.81\left(2 \mathrm{~d}, 2 \mathrm{H}, \mathrm{Jg}_{\mathrm{gem}}\right.$ $\left.=13.2 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 7.19-7.26,7.34-7.43$ ( $2 \mathrm{~m}, 10 \mathrm{H}, 2 \mathrm{Ph}$ ).
${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right)$ : $\delta 24.88,55.45,69.95,70.24,70.88,77.06,82.18,83.01,107.63$, $127.32,129.36,130.01, .130 .32,133.68,133.78,134.13,134.18,134.45,134.58$.

Step D: $\quad$ 4-Chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyl]-7H-pyrrolo[2,3-d]pyrimidine

1. To a solution of the compound from Step C ( $9.42 \mathrm{~g}, 19 \mathrm{mmol}$ ) in anhydrous dichloromethane $(285 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid, 20 $\mathrm{mL}, 114 \mathrm{mmol}$ ) dropwise. The resulting solution was stirred at $0^{\circ} \mathrm{C}$ for 1 h and then at it for 3 h , evaporated in vacuo and co-evaporated with anhydrous toluene ( $3 \times 40$ $\mathrm{mL})$. The oily residue was dissolved in anhydrous acetonitrile $(50 \mathrm{~mL})$ and added to a solution of the sodium salt of 4-chlorp-1 H -pyrrolo $[\dot{2}, 3-d]$ pyrimidine in acetonitrile [generated in situ from 4-chloro-1H-pyrrolo[2,3- $d$ ]pyrimidine [for preparation, see: $\mathbf{J}$. Chem. Soc.: 131 (1960)] ( $8.76 \mathrm{~g}, 57 \mathrm{mmol}$ ) in anhydrous acetonitrile ( 1000 mL ), and NaH ( $60 \%$ in mineral oil, $2.28 \mathrm{~g}, 57 \mathrm{mmol}$ ), after 4 h of vigorous stirring at rt . The combined mixture was stirred at rt for 24 h , and then evaporated to dryness. The residue was suspended in water ( 250 mL ) and extracted with EtOAc ( $2 \times 500 \mathrm{~mL}$ ). The combined extracts were washed with brine ( 300 mL , dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude product was purified on a silica gel column ( $10 \mathrm{~cm} \times 10$
cm ) using ethyl acetate/hexane ( $1: 3$ and $1: 2$ ) as the eluent. Fractions containing the product were combined and evaporated in vacuo to give the desired product ( 5.05 g ) as a colorless foam.
${ }^{1} \mathrm{H}^{2}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta 0.93\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.09(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}), 3.78\left(\mathrm{dd}, 1 \mathrm{H}, J_{5^{\prime}, 5^{n}}=10.9\right.$

Step E: 4-Chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d lpyrimidine
To a solution of the compound from Step D ( $5.42 \mathrm{~g}, 8.8 \mathrm{mmol}$ ) in dichloromethane ( 175 mL ) at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in dichloromethane, $88 \mathrm{~mL}, 88 \mathrm{mmol}$ ) dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2.5 h , then at $-30^{\circ} \mathrm{C}$ to $-20^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) $(90 \mathrm{~mL})$ and the resulting mixture stirred at $-15^{\circ} \mathrm{C}$ for 30 min ., then neutralized with aqueous ammonia at $0^{\circ} \mathrm{C}$ and stirred at rt for 15 min. The solid was filtered and washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(1 / 1,250 \mathrm{~mL})$. The combined filtrate was evaporated, and the residue was purified by flash chromatography over silica gel using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and $\mathrm{CH}_{2} \mathrm{Cl}_{2}: \mathrm{MeOH}$ (99:1, $98: 2,95: 5$ and $90: 10$ ) gradient as the eluent to furnish desired compound $(1.73 \mathrm{~g})$ as a colorless foam, which turned into an amorphous solid after treatment with MeCN .
${ }^{1}{ }^{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.64\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right.$ ), $3.61-3.71$ ( $\mathrm{m}, \mathrm{lH}, \mathrm{H}-5^{\prime}$ ), 3.79-3.88 (m, $1 \mathrm{H}, \mathrm{H}-5^{\prime \prime}$ ), 3.89-4.01 (m, 2H, H-3', H-4'), 5.15-5.23 (m, 3H, $2^{\prime}-\mathrm{OH}, 3^{\prime}-\mathrm{OH}, 5^{\prime}-\mathrm{OH}$ ), 6.24 (s, 1H, H-1'), 6.72 (d, 1H, J5,6 = $3.8 \mathrm{~Hz}, \mathrm{H}-5$ ), 8.13 (d, 1H, H-6), 8.65 (s, 1H, H2).
${ }^{13} \mathrm{C}$ NMR (DMSO-d $\mathrm{d}_{6}$ ): $\delta$ 20.20, $59.95,72.29,79.37,83.16,91.53,100.17,117.63$, 128.86, 151.13, 151.19, 151.45.

Step F: 4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3Clpyrimidine
To the compound from Step $\mathrm{E}(1.54 \mathrm{~g}, 5.1 \mathrm{mmol})$ was added methanolic ammonia (saturated at $0^{\circ} \mathrm{C} ; 150 \mathrm{~mL}$ ). The mixture was heated in a - 30 -
stainless steel autoclave at $85^{\circ} \mathrm{C}$ for 14 h , then cooled and evaporated in vacuo. The crude mixture was purified on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ (9/1) as eluent to give the title compound as a colorless foam ( 0.8 g ), which separated as an amorphous solid after treatment with MeCN . The amorphous solid was recrystallized 5 from methanol/acetonitrilc; m.p. $222^{\circ} \mathrm{C}$. IHI NMR (DMSO-d ${ }^{\text {) }} \delta 0.62\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right.$ ), 3.57-3.67 (m, 1H, H-5'), 3.75-3.97 (m, 3H, $\left.\mathrm{H}-5^{\prime \prime}, \mathrm{H}-4^{\prime}, \mathrm{H}-3^{\prime}\right), 5.00\left(\mathrm{~s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}\right), 5.04\left(\mathrm{~d}, 1 \mathrm{H}^{\prime}, \mathrm{J}_{3}{ }^{\prime} 0 \mathrm{H}, 3^{\prime}=6.8 \mathrm{~Hz}, 3^{\prime}-\mathrm{OH}\right), 5.06(\mathrm{t}$, $\left.1 \mathrm{H}, \mathrm{J}_{5^{\prime} \mathrm{OH}, 5^{\prime} .5^{\prime \prime}}=\mathbf{S}^{\prime} .1 \mathrm{~Hz}, 5^{\prime}-\mathrm{OH}\right), 6.11\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 6.54\left(\mathrm{~d}, 1 \mathrm{H}, J_{5,6}=3.6 \mathrm{~Hz}, \mathrm{H}-5\right)$, 6.97 (br s, 2H, $\mathrm{NH}_{2}$ ), 7.44 (d, 1H, H-6), 8.02 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-2$ ).
10. 13C NMR (DMSO- $d_{\sigma}$ ) $\delta 20.26,60.42,72.72,79.30,82.75,91.20,100.13,103.08$, 121.96, 150.37, 152.33, 158.15.

LC-MS: Found: $279.10\left(\mathrm{M}-\mathrm{H}^{+}\right)$; calc. for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}$: 279.11 .

EXAMPLE 3

## 4-Amino-7-(2-C-ethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolö[2,3-d]pyrimidine



Slep A: - 3,5-Bis-O-(2,4-dichlorophenylmethyl)-2-C-ethyl-1-O-methyl- $\alpha$-Dribofuranose
To diethyl ether ( 300 mL ) at $-78^{\circ}{ }^{\circ} \mathrm{C}$ was slowly added $\mathrm{EtMgBr}(3.0 \mathrm{M}$, 16.6 mL ) and then dropwise the compound from Step B of Example $2(4.80 \mathrm{~g}, 10.0$ mmol) in anhydrous $\mathrm{Et}_{2} \mathrm{O}(100 \mathrm{~mL})$. The reaction mixture was stirred at $-78^{\circ} \mathrm{C}$ for 15 min , allowed to warm to $-15^{\circ} \mathrm{C}$ and stirred for another 2 h , and then poured into a stirred mixture of water $(300 \mathrm{~mL})$ and $\mathrm{Et}_{2} \mathrm{O}(600 \mathrm{~mL})$. The organic phase was separated, dried $\left(\mathrm{MgSO}_{4}\right)$, and evaporated in vacuo. The crude product was purified on silica gel using ethyl acetate/hexane (1:2) as eluent. Fractions containing the product were pooled and exaporated in vacuo to give the desired product ( 3.87 g ) as a colorless oil.

# Step B: 4-Chloro-7-[3,5-bis-Q-(2,4-dichlorophenylmethyl)-2-C-ethyl- $\beta$-D-ribofuranosyll- 7 H -pyrrolo [2,3- $d$ ]pyrimidine <br> To a solution of the compound from Step A ( $1.02 \mathrm{mg}, 2.0 \mathrm{mmol}$ ) in dichloromethane ( 40 mL ) was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid) ( $1.75 \mathrm{~mL}, 10.0 \mathrm{mmol}$ ) 

 dropwise at $0^{\circ} \mathrm{C}$. The resulting solution was stirred at room temperature for 2 h , evaporated in vacuo and co-evaporated twice from toluene ( 10 mL ). The oily residue was dissolved in acetonitrile ( 10 mL ) and added to a vigorously stirred mixture of 4 -chloro- $1 H$-pyrrolo $[2,3-d]$ pyrimidine ( $307 \mathrm{mg}, 2.0 \mathrm{mmol}$ ), potassium hydroxide ( 337 $\mathrm{mg}, 6.0 \mathrm{mmol}$ ) and tris[2-(2-methoxyethoxy)ethyl]amine ( $130 \mathrm{mg}, 0.4 \mathrm{mmol}$ ) in acetonitrile ( 10 mL ). The resulting mixture was stirred at it overnight, and then poured into a stirred mixture of saturated ammonium chloride ( 100 mL ) and ethyl acetate ( 100 mL ). The organic layer was separated, washed with brine ( 100 mL ), dried over $\mathrm{MgSO}_{4}$, filtered and evaporated in vacuo. The crude product was purified on silica gel using ethyl acetate/hexane (1:2) as eluent to give the desired product (307 mg ) as a colorless foam.
## Step C: 4-Chloro-7-(2-C-ethyl- $\beta$-D-ribofuramosyl)-7H-pyrrolo[2,3d] pyrimidine <br> To a solution of the compound from Step B ( $307 \mathrm{mg}, 0.45 \mathrm{mmol}$ ) in

 dichloromethane ( 8 mL ) was added boron trichloride ( 1 M in dichloromethane) (4.50 $\mathrm{mL}, 4.50 \mathrm{mmol}$ )'at $-78^{\circ} \mathrm{C}$. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 1 h , then at $-10^{\circ} \mathrm{C}$ for Sh. The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) ( 10 mL ), stirred at $-15^{\circ} \mathrm{C}$ for 30 min , and neutralized by addition of aqueous ammonium hydroxide. The mixture was evaporated under diminished pressure and the resulting oil purified on silica gel using methanol/dichloromethane (1:9) as eluent. Fractions containing the product were pooled. and evaporated in vacuo to give the desired product ( 112 mg ) as a colorless foam.
## Step D: $\quad 4$-Amino-7-(2-C-ethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-

## dlpyrimidine

To the compound from Step C ( $50 \mathrm{mg}, 0.16 \mathrm{mmol}$ ) was added saturated ammonia in methanol ( 4 mL ). The mixture was stirred at $75^{\circ} \mathrm{C}$ for 72 h in a closed container, cooled and evaporated in vacuo. The crude mixture was purified on silica gel using methanol/dichloromethane (1:9) as eluent. Fractions containing the
product were pooled and evaporated in vacuo to give the desired product ( 29 mg ) as a colorless powder.
${ }^{1} \mathrm{HNMR}\left(200 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right): ~ \delta 0.52(\mathrm{t}, 3 \mathrm{H}), 1.02(\mathrm{~m}, 2 \mathrm{H}), 4.01-3.24(\mathrm{~m}, 6 \mathrm{H}), 5.06$ $(\mathrm{m}, 1 \mathrm{H}), 6.01(\mathrm{~s}, 1 \mathrm{H}), 6.51(\mathrm{~d}, 1 \mathrm{H}), 6.95(\mathrm{~s}$ br, 2H), $6.70(\mathrm{~d}, 1 \mathrm{H}), 7.99(\mathrm{~s}, 1 \mathrm{H})$.
5 LC-MS: Found: $295.2\left(\mathrm{M}^{\prime}+\mathrm{H}^{+}\right)$; calc. for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 295.14$.

## EXAMPLE 4

2-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3- $d$ ]pyrimidin-4(3H)-one


Step A: 2-Amino-4-chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine To an ice-cold solution of the product from Step C of Example 2 ( 1.27 $\mathrm{g}, 2.57 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL})$ was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid; 3 mL )

2-Amino-4-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3dIpyrimidine
To a solution of the product from Step A ( $630 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ) $(10 \mathrm{~mL}, 10$
mmol ). The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2 h , then at $-20^{\circ} \mathrm{C}$ for 2.5 h . The reaction was quenched with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(1: 1)(10 \mathrm{~mL})$, stirred at $-20^{\circ} \mathrm{C}$ for 0.5 h , and neutralized at $0^{\circ} \mathrm{C}$ with aqueous ammonia. The solid was filtered, washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(1: 1)$ and the combined filtrate evaporated in vacuo. The residue was

2-Amino-4-cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine


A solution of 2-amino-4-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)- 7 H pyrrolo[ $2,3-d$ ]pyrimidine (Example 4, Step B) ( $21 \mathrm{mg}, 0.07 \mathrm{mmol}$ ) in cyclopropylamine ( 0.5 mL ) was heated at $70^{\circ} \mathrm{C}$ for two days, then evaporated to an oily residue and purified on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}, 20 / 1$, as eluent to give the title compound as a white solid ( 17 mg ).
${ }^{1} \mathrm{H}$ NMR ( $200 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}$ ): $\delta 0.61(\mathrm{~m}, 2 \mathrm{H}), 0.81(\mathrm{~m}, 2 \mathrm{H}), 0.85(\mathrm{~s}, 3 \mathrm{H}), 2.83(\mathrm{~m}$, $1 \mathrm{H}), 3.74-3.86(\mathrm{~m}, 1 \mathrm{H}), 3.93-4.03(\mathrm{~m}, 2 \mathrm{H}), 4.11(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.02(\mathrm{~s}, 1 \mathrm{H})$, $6.49(\mathrm{~d}, J=3.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.00(\mathrm{~d}, J=3.7 \mathrm{~Hz}, 1 \mathrm{H})$.

5

## EXAMPLE 6

4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5carbonitrile


10
This compound was prepared following procedures described by Y . Murai et al. in Heterocycles 33: 391-404 (1992).

## EXAMPLE 7

15. 4-Amino-7. (2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $2,3-d]$ pyrimidine-5carboxamide


This compound was prepared following procedures described by Y . Murai et al. in Heterocycles 33: 391-404 (1992).

## EXAMPLE 8

## General process to SATE prodrug moiety

S-Acyl-2-thioethyl (SATE) pronucleotides are discussed in C.R.

Wagner, V.V. Iyer, and E.J. McIntee, "Pronucleotides: Toward the In Vivo Delivery of Antiviral and Anticancer Nucleotides," Med. Res. Rev., 20: 1-35 (2000), which is. incorporated by reference herein in its entirety. SATTE derivatives of nucleosides are also disclosed U.S. Patent Nos. 5,770,725; 5,849,905; and 6,020,482, the contents of each of which are incorporated by reference herein in their entirety.

Bis(S-acetyl-2-thioethyl)- $N, N$-diisopropylphosphoramidite
2-Mercaptoethanol ( $5 \mathrm{~g}, 64 \mathrm{mmol}$ ) was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$. To this solution was added triethylamine ( $7.67 \mathrm{~mL}, 57.6 \mathrm{mmol}$ ), and the reaction mixture was cooled in an ice bath to $0^{\circ} \mathrm{C}$. Acetic anhydride ( $4.54 \mathrm{~mL}, 48 \mathrm{mmol}$ ) was added dropwise in 10 min ., and the reaction mixture was stirred for 1 h at $0^{\circ} \mathrm{C}$. The reaction mixture was then allowed to come to room temperature over a period of 2 h . The reaction mixture was diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$, washed with water ( 75 mL ), $5 \%$ aqueous $\mathrm{NaHCO}_{3}(75 \mathrm{~mL})$ and brine ( 75 mL ). The organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo to give an oil. The oil was then dissolved in anhydrous THF ( 40 mL ) and anhydrous triethylamine ( 7.76 mL ) was added. To this mixture was added activated molecular sieves ( $4 \AA$ ) and was kept at room temperature for 10 min . The reaction mixture was cooled in an ice bath to $0^{\circ} \mathrm{C}$ and diisopropylphosphoramidous dichloride ( $6.47 \mathrm{~g}, 32.03 \mathrm{mmol}$ ) was added. The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 2 h under inert atmosphere. Hexane ( 40 mL ) was added to the reaction mixture and the precipitate formed was filtered. The filtrate was concentrated to one fourth of the volume, purified by loaded silica gel column chromatography and eluted with hexane containing $3 \%$ triethylamine and incremental amount of ethyl acetate ( 0 to $7 \%$ ) to give the title compound as an oil ( 2.36 g ).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 1.17(\mathrm{~s}, 6 \mathrm{H}), 1.21(\mathrm{~s}, 6 \mathrm{H}), 2.36(\mathrm{~s}, 6 \mathrm{H}), 3.14(\mathrm{t}, J=6.44 \mathrm{~Hz})$, $3.51-3.84(\mathrm{~m}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 24.47,24.61,30.48,42.85,43.1,61.88$, $62.23,195.26 ;{ }^{13} \mathrm{P}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 146.96$.

## EXAMPLE 9

5'-Triphosphate Derivatives

The nucleoside 5 '-triphosphates of the present invention were prepared following general'procedures described in Chem. Rev. 100: 2047 (2000).

## EXAMPLE 10

## Purification and Purity Analysis of 5'-Triphosphate Derivatives

The triphosphate derivatives were purified by anion exchange (AX) chromatography using a $30 \times .100 \mathrm{~mm}$ Mono $Q$ column (Pharmacia) with a buffer system of 50 mM This, pH 8 . Elution gradients were typically from 40 mM NaCl to 0.8 M NaCl in two column volumes at $6.5 \mathrm{~mL} / \mathrm{min}$. Appropriate fractions from anion exchange chromatography were collected and desalted by reverse-phase (RP) chromatography using a Luna C18 $250 \times 21 \mathrm{~mm}$ column (Phenomenex) with a flow rate of $10 \mathrm{~mL} / \mathrm{min}$. Elution gradients were generally from $1 \%$ to $95 \%$ methanol in 14 min at a constant concentration of 5 mM triethylammonium acetate (TEAA).

Mass spectra of the purified triphosphates were determined using online HPLC mass spectrometry on a Hewlett-Packard (Pablo Alto, CA) MSD 1100. A Phenomenex Luna (C18(2)), $150 \times 2 \mathrm{~mm}$, plus $30 \times 2 \mathrm{~mm}$ guard column, $3-\mu \mathrm{m}$ particle size was used for RP HPLC. A 0 to $50 \%$ linear gradient ( 15 min ) of acetonitrile in 20 mM TEAA (triethylammonium acetate) pH 7 was performed in series with mass spectral detectionin the negative ionization mode. Nitrogen gas anda pneumatic nebulizer were used to generate the electrospray. The mass range of $150-$ 900 was sampled. Molecular masses were determined using the HP Chemstation analysis package.

The purity of the purified triphosphates-was determined by analytical RP and AX HPLC. RP HPLC with a Phenomonex Luna or Jupiter column ( $250 \times$. 4.6 mm ), $5-\mu \mathrm{m}$ particle size was typically run with a $2-70 \%$ acetonitrile gradient in 15 min in 100 mM TEAA, pH 7. AX HPLC was performed on a $1.6 \times 5 \mathrm{~mm}$ Mono Q column (Pharmacia). Triphosphates were eluted with a gradient of 0 to 0.4 M NaCl at constant concentration of 50 mM This, $\mathrm{pH} \dot{8}$. The purity of the triphosphates was generally $>80 \%$.

## EXAMPLE 11

5'-Monophosphate Derivatives

The nucleoside 5'-monophosphates of the present invention were prepared following the general procedures described in Tetrahedron Lett. 50: 5065 (1967).

EXAMPLE 12

## Mass Spectral Characterization of 5'-Triphosphate Derivatives

Mass spectra of 5'-triphosphates of the compounds of the present invention were determined as described in Example 10. Listed in the following table are the calculated and experimental masses for representative 5 '-triphosphates prepared according to the procedures of Example 9. The example numbers correspond to the parent compound of the 5 '-triphosphate.

| Example | Calculated | Found |
| :---: | :---: | :---: |
| 1 | 520.0 | 519.9 |
| 2 | 520.0 | 520.0 |
| 3 | 534.0 | 534.0 |
| 4 | 536.0 | 536.0 |

EXAMPLE 13
[4-Amino-7-(2-C-methyl- $\beta$-D-1ibofuranosyl)-7H-pyrrolo[2,3- $d$ ]-pyrimidine]-5'monophosphate


To the compound from Step F of Example 2 ( $14 \mathrm{mg}, 0.05 \mathrm{mmol}$ ) (dried by coevaporation with pyridine and several times with toluene) was added trimethyl phosphate ( 0.5 mL ). The mixture was stirred overnight in a sealed container. It was then cooled to $0^{\circ} \mathrm{C}$ and phosphorous oxychloride ( $0.0070 \mathrm{~mL}, 0.075$

- 38 -
mol) was added via a syringe. The mixture was stirred for 3 h at $0^{\circ} \mathrm{C}$, then the reaction was quenched by addition of tetraethylammonium bicarbonate (TEAB) (1M) $(0.5 \mathrm{~mL})$ and water ( 5 mL ). The reaction mixture was purified and analyzed according to the procedure described in Example 10.
5 Electron spray mass spectrum (ES-MS): Found: $359.2\left(\mathrm{M}-\mathrm{H}^{+}\right)$, calc. for $\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{~N}_{4} \mathrm{O}_{7} \mathrm{P}-\mathrm{H}^{+}: 359.1$.


## EXAMPLE $14^{\circ}$

[4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]-pyrimidine]-5!diphosphate


To the compound from Step F of Example $2(56 \mathrm{mg}, 0.20 \mathrm{mmol}$ ) (dried by coevaporation with pyridine and several times with toluene) was added trimethyl phosphate (stored over sieves) $(1.0 \mathrm{~mL})$. The mixture was stirred overnight in a sealed container. It was then cooled to $0^{\circ} \mathrm{C}$ and phosphorous oxychloride $(0.023$ $\mathrm{mL}, 0.25 \mathrm{mmol}$ ) was added via a syringe. The mixture was stirred for 2 h at $0^{\circ} \mathrm{C}$, then tributylamine ( $0.238 \mathrm{~mL}, 1.00 \mathrm{mmol}$ ) and tributylammonium phosphate (generated from phosphoric acid and tributylamine in pyridine, followed by repeated azeotropic evaporation with pyridine and acetonitrile) ( 1.0 mmol in 3.30 mL acetonitrile) was added. The mixture was stirred for an additional 30 min at $0^{\circ} \mathrm{C}$, the sealed vial was then opened and the reaction quenched by addition of TEAB (1M) ( 1.0 mL ) and water $(5 \mathrm{~mL})$. The reaction mixture was purified and analyzed according to the procedure described in Example 10.
ES-MS: Found: $439.0\left(\mathrm{M}_{-} \mathrm{H}^{+}\right)$, calc. for $\mathrm{C}_{12} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{10} \mathrm{P}_{2}-\mathrm{H}^{+}: 439.04$.

## EXAMPLE 15

[4-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]-pyrimidine]-5'triphosphate


To the compound from Step F of Example $2(20 \mathrm{mg}, 0.07 \mathrm{mmol})$ (dried by coevaporation with pyridine and several times with toluene) was added trimethyl phosphate (stored over sieves) ( 0.4 mL ). The mixture was stirred overnight in a sealed container. It was then cooled to $0^{\circ} \mathrm{C}$ and phosphorous oxychloride $(0.0070$ $\mathrm{mL}, 0.075 \mathrm{mmol}$ ) was added via syringe. The mixture was stirred for 3 h at $0^{\circ} \mathrm{C}$, then tributylamine ( $0.083 \mathrm{~mL}, 0.35 \mathrm{mmol}$ ), tributylammonium pyrophosphate ( 127 mg , $0.35 \mathrm{mmol})$ and acetonitrile (stored over sieves) $(0.25 \mathrm{~mL})$ were added. The mixture was stirred for an additional 30 min at $0^{\circ} \mathrm{C}$, the sealed vial was then opened and the reaction quenched by addition of TEAB ( 1 M ) ( 0.5 mL ) and water ( 5 mL ). The reaction mixture was purified and analyzed according to the procedure described in Example 10.
ES-MS: Found: $519.0\left(\mathrm{M}-\mathrm{H}^{+}\right)$, calc. for $\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{~N}_{4} \mathrm{O}_{13} \mathrm{P}_{3}-\mathrm{H}^{+}: 519.01$.

## EXAMPLE 16

7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4(3H)-one


- 40 -

To the compound from Step E of Example 2 ( $59 \mathrm{mg}, 0.18 \mathrm{mmol}$ ) was added aqueous sodium hydroxide ( 1 M ). The mixture was heated to reflux for 1 hr , cooled, neutralized with aqueous $\mathrm{HCl}(2 \mathrm{M})$ and evaporated in vacuo. The residue was purified on silica gel using dichloromethane/methanol (4:1) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 53 mg ) as a colorless oil.
$1_{\text {II NMR }}\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta 0.70(\mathrm{~s}, 3 \mathrm{H}), 3.34-4.15$ (overlapping m, 7 H ), $6.16(\mathrm{~s}, 1 \mathrm{H}), 6.57$ (d, $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{~d}, 3.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.83(\mathrm{~s}, 1 \mathrm{H})$.

## 4-Amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d $d$ ]pyrimidine



To a pre-cooled solution $\left(0^{\circ} \mathrm{C}\right)$ of the compound from Step F of

4-Amino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl) -7 H -pyrrolo[2,3- $\varnothing$ ]pyrimidine


To a pre-cooled solution ( $0^{\circ} \mathrm{C}$ ) of the compound from Step $F$ of Example $2(28 \mathrm{mg}, 0.10 \mathrm{mmol})$ in DMF $(0.5 \mathrm{~mL})$ was added $N$-bromosuccinimide ( $0.018 \mathrm{~g}, 0.10 \mathrm{mmol}$ ) in DMF ( 0.5 mL ) dropwise. The solution was stirred at $0^{\circ} \mathrm{C}$ for 20 min , then at it for 10 min . The reaction was quenched by addition of methanol ( mLL ) and evaporated in vacuo. The crude product was purified on silica gel using methanol/dichloromethane ( $1: 9$ ) as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 13.0 mg ) as a colorless solid.
$10 \quad 1 \mathrm{H} N \mathrm{NR}\left(\mathrm{CD}_{3} \mathrm{CN}\right): \delta 0.69(\mathrm{~s}, 3 \mathrm{H}), 3.46-4.00$ (overlapping m, 7 H ), $5.83(\mathrm{~s} \mathrm{br}, 2 \mathrm{H}$ ), $6.06(\mathrm{~s}, 1 \mathrm{H}), 7.45(\mathrm{~s}, 1 \mathrm{H}), 8.05(\mathrm{~s}, 1 \mathrm{H})$.
ES-MS: Found: $359.1\left(\mathrm{M}+\mathrm{H}^{+}\right)$, calc.for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{BrN}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 359.04$.

## EXAMPLE 19

2-Amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine


A mixture of 2-amino-4-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine (Example 4, Step B) ( $20 \mathrm{mg}, 0.07 \mathrm{mmol}$ ) in EtOH ( 1.0 mL ), pyridine ( 0.1 mL ) and $10 \% \mathrm{Pd} / \mathrm{C}(6 \mathrm{mg})$ under $\mathrm{H}_{2}$ (atmospheric pressure) was stirred overnight at room temperature. The mixture was filtered through a Celite pad which was thorougly washed with EtOH. The combined filtrate was evaporated and purified

$$
-42
$$

IPO DELHI 23-06-2015 15:59
on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}, 20 / 1$ and $10 / 1$, as eluent to give the title compound as a white solid ( 16 mg ).
$1^{1} \mathrm{H}$ NMR ( $200 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 0.86\left(\mathrm{~s}, 3 \mathrm{H}, 2^{\prime} \mathrm{C}-\mathrm{Me}\right), 3.82\left(\mathrm{dd}, J_{5^{\prime} 4^{\prime}}=3.6 \mathrm{~Hz} ., J_{5^{\prime}, 5^{\prime \prime}}=\right.$ $\left.12.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}\right), 3.94-4.03$ ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{H}-5^{\prime}, \mathrm{H}-4^{\prime}$ ), 4.10 (d, $J_{3^{\prime} 4^{\prime}}=8.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3^{\prime}$ ),

2-Amino-5-methyl-7-(2-C22-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4 ( $3 H$ )-one


Step A: 2-Amino-4-chloro-7-13,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyl]-5-methyl-7H-pyrrolo[2,3-d]pyrimidine
To an ice-cold solution of the product from Step C of Example 2 ( 1.57
g, 3.16 mmol ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(50^{\mathrm{mL}}\right)$ was added $\mathrm{HBr}(5.7 \mathrm{M}$ in acetic acid; 3.3 mL ) dropwise. The reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 1 h and then at room temperature for 2 h , concentrated in vacuo and co-evaporated with toluene ( $2 \times 20$ $\mathrm{mL})$. The resulting oil was dissolved in $\mathrm{MeCN}(20 \mathrm{~mL})$ and added dropwise to a solution of the sodium salt of 2-amino-4-chloro-5-methyl-1H-pyrrolo[2,3d] pyrimidine in acetonitrile [generated in situ from 2-amino-4-chloro-5-methyl-1H-pyrrolo[2,3-d]pyrimidine [for preparation, see Liebigs Ann. Chem. 1984: 708-721] $(1.13 \mathrm{~g}, 6.2 \mathrm{mmol})$ in anhydrous acetonitrile ( 150 mL ), and NaH ( $60 \%$ in mineral oil, $248 \mathrm{mg}, 6.2 \mathrm{mmol}$ ), after 2 h of vigorous stirring at rt$]$. The combined mixture was stirred at It for 24 h and then evaporated to dryness. The residue was suspended in water ( 100 mL ) and extracted with EtOAc $(300+150 \mathrm{~mL})$. The combined extracts were washed with brine ( 100 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude product was purified on a silica gel column $(5 \times 7 \mathrm{~cm})$ using ethyl
acetate/hexane ( 0 to $30 \%$ EtOAc in $5 \%$ step gradient) as the eluent: Fractions containing the product were combined and evaporated in vacuo to give the desired product ( 0.96 g ) as a colorless foam.

Step B: $\quad$ 2-Amino-4-chloro-7-[3,5-bis- $O$-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl]-5-methyl-7 H -pyrrolo[2,3-d]pyrimidine
To an ice-cold mixture of the product fiorin Step A ( $475 \mathrm{mg}, 0.7 \mathrm{mmol}$ ) in THF ( 7 mL ) was added $\mathrm{NaH}\left(60 \%\right.$ in mineral oil, 29 mg ) and stirred at $0^{\circ} \mathrm{C}$ for 0.5 h. Then Mel $(48 \mu \mathrm{~L})$ was added and reaction mixture stirred at it for 24 h . The reaction was quenched with MeOH and the mixture evaporated. The crude product was purified on a silica gel column $(5 \times 3.5 \mathrm{~cm})$ using hexane/ethyl acetate $(9 / 1,7 / 1$, $5 / 1$ and $3 / 1$ ) as eluent. Fractions containing the product were combined and evaporated to give the desired compound ( 200 mg ) as a colorless foam.

Step C: , 2-Amino-7- 3 3,5-bis- $O$-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl-ß-D-ribofuranosyl]-5-methyl-7H-pyrrolo [2,3-d]pyrimidine-4(3H)-one A mixture of the product from Step B ( $200 \mathrm{mg}, 0.3 \mathrm{mmol}$ ) in $1,4-$ dioxane ( 15 mL ) and aqueous $\mathrm{NaOH}(2 \mathrm{~N}, 15 \mathrm{~mL})$ in a pressure bottle was heated overnight at $135^{\circ} \mathrm{C}$. The mixture was then cooled to $0^{\circ} \mathrm{C}$, neutralized with 2 N aqueous HCl and evaporated to dryness. The crude product was suspended in MeOH , filtered, and the solid thoroughly washed with MeOH . The combined filtrate was concentrated, and the residue purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) using $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(40 / 1,30 / 1$ and $20 / 1$ ) as eluent to give the desired compound $(150-\mathrm{mg})$ as a colorless foam.

Step D: 2-Amino-5-methyl-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7Hpyrrolo 2,3 -d]pyrimidin-4(3H)-one
A mixture of the product from Step C ( $64 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) in MeOH ( 5 $\mathrm{mL})$ and $\mathrm{Et}_{3} \mathrm{~N}(0.2 \mathrm{~mL})$ and $10 \% \mathrm{Pd} / \mathrm{C}(24 \mathrm{mg})$ was hydrogenated on a Parr hydrogenator at 50 psi at rit. for 1.5 days, then filtered through a Celite pad which was. thoroughly washed with MeOH . The combined filtrate was evaporated and the residue purified on a silica gel column $(3 \times 4 \mathrm{~cm})$ with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(30 / 1,20 / 1)$ as eluent to yield 2-amino-5-methyl-7-(5-O-benzyl-2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4( $3 H$ )-one. The compound ( 37 mg ) was
further hydrogenated in $\mathrm{EtOH}(2 \mathrm{~mL})$ with $10 \% \mathrm{Pd} / \mathrm{C}$ and under atmospheric pressure of hydrogen. After stirring 2 days at rit., the reaction mixture was filtered through Celite, the filtrate evaporated and the crude product purified on a silica gel column ( 1 $\times 7 \mathrm{~cm})$ with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(30 / 1,20 / 1$ and $10 / 1)$ as eluent to yield the title compound ( 12 mg ) after freeze-drying.
$1 \mathrm{H} N \mathrm{NR}\left(200 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right): \delta 0.81\left(\mathrm{~s}, 3 \mathrm{H}, 2^{\prime} \mathrm{C}-\mathrm{Me}\right), 2.16\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{H}-6, \mathrm{C} 5-\mathrm{Me}}=1.3 \mathrm{~Hz}\right.$,
 3.81-3.91 (m, 3H, H-5', H-4', H-3'), 6.10 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}$ ); 6.66 (d, $1 \mathrm{H}, \mathrm{H}-6$ ).

ES MS: $323.3(\mathrm{M}-\mathrm{H})^{+}$.

EXAMPLE 21
4-Amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $2,3-\alpha]$ pyrimidine


Step A: 4.Chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-methyl- $\beta$-D-ribofuranosyl]-5-methyl-7H-pyrrolo[2,3-d]pyrimidine
To an ice-cold solution of the product from Step $C$ of Example 2 (1.06 $\mathrm{g}, 2.1 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL}$ ) was added HBr ( 5.7 M in acetic acid; 2.2 mL ) dropwise. The reaction mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 1 h and then at room temperature for 2 h , concentrated in vacuo and co-evaporated with toluene ( $2 \times 15$ $\mathrm{mL})$. The resulting oil was dissolved in $\mathrm{MeCN}(10 \mathrm{~mL})$ and added dropwise into a solution of the sodium salt of 4-chloro-5-methyl-1H-pyrrolo[2,3-d]pyrimidine in acetonitrile [generated in situ from 4-chloro-5-methyl- $1 H$-pyrrolo [2,3- $d$ ]pyrimidine [for preparation, see J. Med. Chem. 33: 1984 (1990)] ( $0.62 \mathrm{~g}, 3.7 \mathrm{mmol}$ ) in anhydrous acetonitrile ( 70 mL ), and NaH ( $60 \%$ in mineral oil, $148 \mathrm{mg}, 3.7 \mathrm{mmol}$ ), after 2 h of vigorous stirring at rt]. The combined mixture was stirred at rt for 24 h and then evaporated to dryness. The residue was suspended in water ( 100 mL ) and extracted with EtOAc $(250+100 \mathrm{~mL})$. The combined extracts were washed with brine ( 50
mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude product was purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) using hexane/ethyl acetate $(9 / 1,5 / 1,3 / 1)$ gradient as the eluent. Fractions containing the product were combined and evaporated in vacuo to give the desired product ( 0.87 g ) as a colorless foam.
5.

Step B: $\quad$ 4-Chloro-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidinc
To a solution of the compound from Step A ( $0.87 \mathrm{~g}, 0.9 \mathrm{mmol}$ ) in dichloromethane ( 30 mL ) at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in dichloromethane, $9.0 \mathrm{~mL}, 9.0 \mathrm{mmol}$ ) dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2.5 h , then at $-30^{\circ} \mathrm{C}$ to $-20^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched by addition of methanol/dichloromethane $(1: 1)(9 \mathrm{~mL})$ and the resulting mixture stirred at $-15^{\circ} \mathrm{C}$ for 30 min ., then neutralized with aqueous ammonia at $0^{\circ} \mathrm{C}$ and stirred at rt for 15 min . The solid was filtered and washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(1 / 1,50 \mathrm{~mL})$. The combined filtrate was evaporated, and the residue was purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(40 / 1$ and $30 / 1$ ) gradient as the eluent to furnish the desired compound $(0.22 \mathrm{~g})$ as a colorless foam.

Step C: 4-Amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $2,3-$ d]pyrimidine
To the compound from Step B ( $0.2 \mathrm{~g}, 0.64 \mathrm{mmol}$ ) was added methanolic ammonia (saturated at $0^{\circ} \mathrm{C} ; 40 \mathrm{~mL}$ ). The mixture was heated in a stainless steel autoclave at $100^{\circ} \mathrm{C}$ for 14 h , then cooled and evaporated in vacuo. The crude mixture was purified on a silica gel column ( $5 \times 5 \mathrm{~cm}$ ) with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ ( $50 / 1$, $30 / 1,20 / 1$ ) gradient as eluent to give the title compound as a white solid ( 0.12 g ). ${ }^{1} \mathrm{H}$ NMR (DMSSO- $d_{6}$ ): $\delta 0.60$ ( $\mathrm{s}, 3 \mathrm{H}, 2^{\prime} \mathrm{C}-\mathrm{Me}$ ), 2.26 (s, $3 \mathrm{H}, 5 \mathrm{C}-\mathrm{Me}$ ), 3.52-3.61 (m, 1H, H-5'), 3.70-3.88 (m, 3H, H-5', H-4', H-3'), 5.00 ( $\mathrm{s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}$ ), 4.91-4.99 (m, $3 \mathrm{H}, 2^{\prime}-\mathrm{OH}, 3^{\prime}-\mathrm{OH}, 5^{\prime}-\mathrm{OH}$ ), 6.04 ( $\mathrm{s}, \mathrm{IH}, \mathrm{H}-1^{\prime}$ ), 6.48 (br s, $2 \mathrm{H}, \mathrm{NH}_{2}$ ), 7.12 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-$ 6), $7.94(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-2)$. ES MS: $295.2\left(\mathrm{MH}^{+}\right)$.

## EXAMPLE 22

4-Amino-7-(2-C-methyl-1]-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5carboxylic acid


The compound of Example $6(0.035 \mathrm{~g}, 0.11 \mathrm{mmol})$ was dissolved in a mixture of aqueous ammonia ( $4 \mathrm{~mL}, 30 \mathrm{wt} \%$ ) and saturated methanolic ammonia (2 $\mathrm{mL})$, and a solution of $\mathrm{H}_{2} \mathrm{O}_{2}$ in water ( $2 \mathrm{~mL}, 35 \mathrm{wt} \dot{\%}$ ) was added. The reaction

## 4-Amino-7-(2-C-vinyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $2,3-d$ pyrimidine



Step A: 3,5-Bis-O-(2,4-dichlorophenylmethyl)-2-C-vinyl-1-O-methyl- $\alpha-\mathrm{D}$ ribofuranose

Cerium chloride heptahydrate ( $50 \mathrm{~g}, 134.2 \mathrm{mmol}$ ) was finely crushed in a pre-heated mortar and transferred to a round-bottom flask equipped with a mechanical stirrer. The flask was heated under high vacuum overnight at $160^{\circ} \mathrm{C}$. The vacuum was released under argon and the flask was cooled to room temperature.

Anhydrous THF ( 300 mL ) was cannulated into the flask. The resulting suspension was stirred at room temperature for 4 h and then cooled to $-78^{\circ} \mathrm{C}$. Vinylmagnesium bromide ( 1 M in THF, $120 \mathrm{~mL}, 120 \mathrm{mmol}$ ) was added and stirring continued at $-78^{\circ} \mathrm{C}$ for 2 h . To this suspension was added a solution of 3,5 -bis- O -( $2,4-$ dichlorophenylmethyl)-1-O-methyl- $\alpha$-D-erythro-pentofuranose-2-ulose ( $14 \mathrm{~g}, 30$ mol) [from Example 2, Step B] in anhydrous THF ( 100 mL ); dropwise with constant stirring. The reaction was stirred at $-78^{\circ} \mathrm{C}$ for 4 h . The reaction was quenched with saturated ammonium chloride solution and allowed to come to room temperature. The mixture was filtered through a celite pad and the residue washed with $\mathrm{Et}_{2} \mathrm{O}(2 \times 500 \mathrm{~mL})$. The organic layer was separated and the aqueous layer extracted with $\mathrm{Et}_{2} \mathrm{O}(2 \times 200 \mathrm{~mL})$. The combined organic layers were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to a viscous yellow oil. The oil was purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \%$ EtOAc in hexanes). The title compound ( 6.7 g , 13.2 mmol ) was obtained as a pale yellow oil.

Step B: $\quad$ 4-Chloro-7- 33,5 -bis- $O$-(2,4-dichlorophenylmethyl) $-2-C$-vinyl- $\beta$-Dribofuranos $\dot{1} 11-7 \mathrm{H}$-pyrrolo $[2,3-d]$ pyrimidine
' To a solution of the compound from Step A ( $6.4 \mathrm{~g}, 12.6 \mathrm{mmol}$ ) in anhydrous dichloromethane $(150 \mathrm{~mL})$ at $-20^{\circ} \mathrm{C}$ was added $\mathrm{HBr}(30 \%$ solution in $\mathrm{AcOH}, 20 \mathrm{~mL}, 75.6 \mathrm{mmol}$ ) dropwise. The resulting solution was stirred between $-10^{\circ} \mathrm{C}$ and $0^{\circ} \mathrm{C}$ for 4 h , evaporated in vacuo and co-evaporated with anhydrous toluene ( $3 \times 40 \mathrm{~mL}$ ). The oily. residue was dissolved in anhydrous acetonitrile ( 100 mL ) and added to a solution of the sodium salt of 4-chloro- 1 H -pyrrolo[2,3d] pyrimidine ( $5.8 \mathrm{~g}, 37.8 \mathrm{mmol}$ ) in acetonitrile (generated in situ as described in Example 2) at $-20^{\circ} \mathrm{C}$. The resulting mixture was allowed to come to room temperature and stirred at room temperature for 24 h . The mixture was then evaporated top dryness, taken up in water and extracted with EtOAc ( $2 \times 300 \mathrm{~mL}$ ). The combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The crude mixture was purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \% \mathrm{EtOAc}$ in hexanes) and the title compound ( 1.75 g ) isolated as a white foam ${ }_{i}$

> Step C: $\frac{4 \text {-Amino- } 7-[3,5-\text {-bis-O-(2,4-dichlorophenylmethyl)-2-C-vinyl- } \beta \text {-D- }}{\text { ribofuranosyll]- } 7 \mathrm{H} \text {-pyrrolo }[2,3-d] \text { pyrimidine }}$ The compound from Step B $(80, \mathrm{mg})$ was dissolved in the minimum
Step D: 4-Amino-7-(2-C-vinyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-
dlpyrimidine
To a solution of the compound from Step C. $(60 \mathrm{mg})$ in .
dichloromethane at $-78^{\circ} \mathrm{C}$ was added boron trichloride ( 1 M in dichloromethane)
dropwise. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2.5 h , then at $-30{ }^{\circ} \mathrm{C}$ to $-20^{\circ} \mathrm{C}$ for
3 h . The reaction was quenched by addition of methanol/dichloromethane ( $1: 1$ ) and
the resulting mixture stirred at $-15^{\circ} \mathrm{C}$ for 0.5 h , then neutralized with aqueous
ammonia at $\varphi^{\circ} \mathrm{C}$ and stirred at room temperature for 15 min . The solid was filtered
and washed with methanol/dichloromethane ( $1: 1$ ). The combined filtrate was
evaporated and the residue purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \%$ methanol in
EtOAc containing $0.1 \%$ triethylamine). The fractions containing the product were
evaporated to give the title compound as a white solid ( 10 mg ).
${ }^{1}{ }^{H}$ NMR (DMSO-d ${ }_{6}$ ): $\delta 3.6$ (m, 1H, H-5'), 3.8 (m, 1H; H-5"), 3.9 (m d, 1-H, H-4'),
4.3 (t, $\left.1 \mathrm{H}, \mathrm{H}-3^{\prime}\right), 4.8-5.3\left(\mathrm{~m}, 6 \mathrm{H}, \mathrm{CH}=\mathrm{CH}_{2}, 2^{\prime}-\mathrm{OH}, 3^{\prime}-\mathrm{OH}, 5^{\prime}-\mathrm{OH}\right) 6.12\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right)$,
6.59 (d, 1H, H-5), 7.1 (br s, 1H,-NH2), 7.43 (d, 1H, H-6), 8.01 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-2$ ).
ES-MS: Found: 291.1 (M-H); call. for $\mathrm{C}_{13} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{4}-\mathrm{H}^{-}$: 291.2.

## EXAMPLE 24.

4-Amino-7-(2-C-hydroxymethyl-B-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


Step A: 4-Chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-hydroxymethyl- $\beta$-D-ribofuranosyll-7H-pyrrolo [2,3-d]pyrimidine To a solution of the compound from Example 23, Step B ( 300 mg , 0.48 mmol ) in 1,4-dioxane ( 5 mL ) were added $N$-methylmorpholine- $N$-oxide ( 300 mg , 2.56 mmol ) and osmium tetroxide ( $4 \%$ solution in water, 0.3 mL ). The mixture was stirred in the dark for 14 h . The precipitate was removed by filtration through a celite plug, diluted with water ( $3 \dot{x}$ ), and extracted with EtOAc. The EtOAc layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The oily residue was taken up in dichloromethane ( 5 mL ) and stirred over $\mathrm{NaIO}_{4}$ on silica gel $\left(3 \mathrm{~g}, 10 \% \mathrm{NaIO}_{4}\right)$ for 12 $h$. The silica gel was removed by filtration and the residue was evaporated and taken up in absolute ethanol ( 5 mL ). The solution was cooled in an ice bath and sodium borohydride ( $300 \mathrm{mg}, 8 \mathrm{mmol}$ ) was added in small portions. The resulting mixture was stirred at room temperature for 4 h and then diluted with EtOAc. The organic layer was washed with water ( $2 \times 20 \mathrm{~mL}$ ), brine $(20 . \mathrm{mL})$ and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The solvent was evporated and the residue purified by flash chromatography ( $\mathrm{SiO}_{2}, 2: 1$ hoxanes/EiOAc) to give the title compound ( $160 \mathrm{mg}, 0.25 \mathrm{mmol}$ ) as white flakes.

Step B: 4-Amino-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C
hydroxymethyl- $\beta$-D-ribofuranosyll-7 H -pyrrolo $2,3-d]$ pyrimidine
The compound from Step A ( $150 \mathrm{mg}, 0.23 \mathrm{mmol}$ ) was dissolved in the minimum anount of 1,4 -dioxane ( 10 mL ) and placed in a stainless steel bomb. The bomb was cooled to $-78^{\circ} \mathrm{C}$ and liquid ammonia was added. The bomb was sealed and heated at $90^{\circ} \mathrm{C}$ for 24 h . The ammonia was allowed to evaporate and the residue concentrated to a white.solid which was used in the next step without further purification.

Step C: . 4-Amino-7-(2-C-hydroxymethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine
The compound from Step B ( $120 \mathrm{mg}, 0.2 \mathrm{mmol}$ ) was dissolved in $1: 1$ methanol/dichloromethane, $10 \%$ Pd-C was added, and the suspension stirred under an $\mathrm{H}_{2}$ atmosphere for 12 h . 'The catalyst was removed by filtration through a celite pad and washed with copious amounts of inethanol. The combined filtrate was evaporated in vicuo and the residue was purified by flash chromatography $\left(\mathrm{SiO}_{2}, 10 \%\right.$ methanol in EtOAc containing $0.1 \%$ triethylamine) to give the title compound (50 mg ) as a white powder.
${ }^{1}{ }^{1} \mathrm{NMR}\left(\mathrm{CD}_{3} \mathrm{OD}\right): \delta 3.12\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{CH}_{2}{ }^{\prime}\right), 3.33\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{CH}_{2}{ }^{\prime}{ }^{\prime}\right), 3.82\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}\right)$, 3.99-4.1(m, 2H, H-4', H-5'), 4.3 (d, 1H, H-3'), 6.2 (s, 1H, H-1'), 6.58 (d, 1H, H-5), 7.45 (d, 1HI, H-6), 8.05 (s, 1H, H-2).

LC-MS: Found: $297.2\left(\mathrm{M}+\mathrm{H}^{+}\right)$; calc. for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{5}+\mathrm{H}^{+}: 297.3$.

EXAMPLE 25.
4-Amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d]$ pyrimidine


Slep A: 4-Chloro-7-53,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-fluoromethyl-B-D-ribofuranosyll-7H-pyrrolo[2,3-d]pyrimidine T'o a solution of the compound from Example 24, Step A ( $63 \mathrm{mg}, 0.1$ mmol ) in anhydrous dichloromethane ( 5 mL ) under argon, were added 4dimethylaminopyridine (DMAP) ( $2 \mathrm{mg}, 0.015 \mathrm{mmol}$ ) and triethylamine ( $62 \mu \mathrm{~L}, 0.45$ mmol ). The solution was cooled in an ice bath and p-toluenesulfonyl chloride ( 30 $\mathrm{mg}, 0.15 \mathrm{mmol}$ ) was added. The reaction was stirred at room temperature overnight, washed with $\mathrm{NaHCO}_{3}(2 \times 10 \mathrm{~mL})$, water ( 10 mL ), brine ( 10 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to a pink solid in vacuo. The solid was dissolved in anhydrous THF ( 5 mL ) and cooled in ah icebath. Tetrabutylammonium fluoride ( 1 M solution in THF,
$1 \mathrm{~mL}, 1 \mathrm{mmol}$ ) was added and the mixture stirred at room temperature for 4 h . The solvent was removed in vacuo, the residue taken up in dichloromethane, and washed with $\mathrm{NaHCO}_{3}(2 \times 10 \mathrm{~mL})$, water $(10 \mathrm{~mL})$ and brine $(10 \mathrm{~mL})$. The dichloromethane layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, concentrated in vacuo, and purified by flash
 $\left.\mathrm{CH}_{2}\right) 5.12\left(\mathrm{t}, 1 \mathrm{H}, 5^{\prime}-\mathrm{OH}\right), 5.35\left(\mathrm{~d}, 1 \mathrm{H}, 3^{\prime}-\mathrm{OH}\right), 5.48\left(\mathrm{~s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}\right), 6.21(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-$ $1^{\prime}$ ), 6.52 (d, $1 \mathrm{H}, \mathrm{H}-5$ ), 6.98 ( $\mathrm{br} \mathrm{s}, 2 \mathrm{H}, \mathrm{NH} 2$ ), 7.44 (d, $1 \mathrm{H}, \mathrm{H}-6$ ), 8.02 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-2$ ). 19F NMR (DMSO-d $\mathrm{d}_{6}$ ): 8 -230.2 (t). ES-MS: Found: $299.1\left(\mathrm{M}+\mathrm{H}^{+}\right)$, calc.for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{FN}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 299.27$. chromatography $\left(\mathrm{SiO}_{2}, 2: 1\right.$ hexanes/ EtOAc ) to afford the title compound ( 20 mg ) as a white solid.

Step B: 4-Amino-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-fluoromethyl-
$\beta$-D-ribofuranosyll-7H-pyrrolo[2,3-d]pyrimidine
The compound from Step A ( $18 \mathrm{mg}, 0.03 \mathrm{mmol}$ ) was dissolved in the minimum amount of 1,4 -dioxane and placed in a stainless steel bomb. The bomb was cooled to $-78^{\circ} \mathrm{C}$ and liquid ammonia was added. The bomb was sealed and heated at $90^{\circ} \mathrm{C}$ for 24 h . The ammonia was allowed to evaporate and the residue concentrated to a white solid which was used in the next step without further purification.

Step C: 4-Amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine
The compound from Step B ( 16 mg ) was dissolved in I:1
methanol/dichloromethane, $10 \% \mathrm{Pd}-\mathrm{C}$ was added, and the suspension stirred under an $\mathrm{H}_{2}$ atmosphere for 12 h . The catalyst was removed by filtration through a celite pad and washed with copious amounts of methanol. The combined filtrate was evaporated in vaçuo and the residue was purified by flash chromatography ( $\mathrm{SiO}_{2}, 10 \%$ methanol in EtOAc containing $0.1 \%$ triethylamine) to give the title compound ( 8 mg ) as a white powder.

## EXAMPLES 26 and 27

4-Amino-7-(3-deoxy-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ] pyrimidine

- and 4-amino-7-(3-deoxy-2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d]$ pyrimidine



Step A: 7-[2,5-Bis- O-(tert-butyldimethylsilyl)- $\beta$-D-ribofuranosyl]-7Hpyrrolo [2,3- $\alpha$ ]pyrimidine and 7 - $[3,5$-Bis- $O$-(tert-butyldimethylsily $]$ ) $-\beta$ -D-ribofuranosyll- 7 H -pyrrolo $[2,3-d]$ pyrimidine
To a stirred solution of tubercidin ( $5.0 \mathrm{~g}, 18.7 \mathrm{mmol}$ ) in a mixture of pyridine ( 7.5 mL ) and DMF ( 18.5 mL ) was added silver nitrate ( $6.36 \mathrm{~g}, 38.8 \mathrm{mmol}$ ). This mixture was stirred at room temperature for 2 h . It was cooled in an ice bath and THF ( 37.4 mL ) and tert-butyldimethylsilyl chloride ( $5.6 \mathrm{~g}, 37 \mathrm{mmol}$ ) was added and the mixture was stirred at room temperature for 2 h : The mixture was then filtered through a pad of celite and washed with THF. The filtrate and washings were diluted with ether containing a small amount of chloroform. The organic layer was washed' successively with sodium bicarbonate and water ( $3 \times 50 \mathrm{~mL}$ ), dried over anhydrous sodium sulfate and concentrated. The pyridine was removed by coevaporation with toluene and the residue was purified by flash chromatography on silica gel using 5-7\% MeOH in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ as the eluent; yield 3.0 g .

Step B:

$$
00 \text {. }
$$ mmol ) in anhydrous pyridine ( 30 mL ) was added 4,4'-dimethoxytrityl chloride ( 2.8 g , 8.2 mmol ) and the reaction mixture was stirred at room temperature overnight. The

mixture was then triturate with aqueous pyridine and extracted with ether. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to a yellow foam ( 5.6 g ). The residue was purified by flash chromatography over silica gel using 20-25\% EtOAc in hexanes as the eluent. The appropriate fractions were collected and concentrated to furnish $2^{\prime}, 5^{\prime}$-bis-O-(tert-butyldimethylsilyl)- and $3^{\prime}, 5^{\prime}$-bis-O-(tert-butyldimethylsilyl) protected nucleosides as colorless foams ( 2.2 g and 10 g , respectively).

Step C: 7-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-O-tosyl- $\beta$-D-ribofuranosyl)]-
4-[di-(4-methoxyphenyl)phenylmethyl]amino-7 H -pyrrolo[2,3pyrimidine
To an ice-cooled solution of $2^{\prime}, 5^{\prime}$-bis-O-(tert-butyldimethylsilyl)protected nucleoside from Step B ( $2.0 \mathrm{~g}, 2.5 \mathrm{mmol}$ ) in pyridine ( 22 mL ) was added ptoluenesulfonyl chloride ( $1.9 \mathrm{~g}, 9.8 \mathrm{mmol}$ ). The reaction mixture was stirred at room temperature for four days. It was then triturate with aqueous pyridine ( $50 \%, 10 \mathrm{~mL}$ ) and extracted with ether ( $3 \times 50 \mathrm{~mL}$ ) containing a small amount of $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$. The organic layer was washed with sodium bicarbonate and water ( $3 \times 30 \mathrm{~mL}$ ). The organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated. Pyridine was removed by co-evaporation with toluene ( $3 \times 25 \mathrm{~mL}$ ). The residual oil was filtered through a pad of silica gel using hexane:ethyl acetate (70:30) as eluent; yield 1.4 g .

Step D: $\quad$| 4-[di-(4-methoxyphenyl)phenylmethyllamino-7-[3-O-tosyl- $\beta-\mathrm{D}$ - |
| :--- |
| ribofuranosyl-7H-pyrrolo[2,3-d]pyrimidine |

A solution of the compound from Step $\mathrm{C}(1.0 \mathrm{~g}, 1.1 \mathrm{mmol})$ and THF

Step E: 4-Amino-7-(3-deoxy-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]-pyrimidine and 4-amino-7-(3-deoxy-2-C-methyl- $\beta$-D-arabinofuranosyl)- 7 H -pyrrolo-[2,3-d]pvrimidine A solution of $\mathrm{CH}_{3} \mathrm{MgI}$ ( 3.0 M solution in ether, 3.0 mL ) in anhydrous toluene ( 3.75 mL ) was cooled in an ice bath. To this was added a solution of the
compound from Step D ( $500 \mathrm{mg}, 0.8 \mathrm{mmol}$ ) in anhydrous toluene ( 3.7 mL ). The resulting mixture was stirred at room temperature for $3: 5 \mathrm{~h}$. It was cooled and treated with aqueous $\mathrm{N}!\mathrm{L}_{4} \mathrm{Cl}$ solution and extracted with ether ( 50 mL containing 10 mL of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ). The organic layer was separated and washed with brine ( $2 \times 30 \mathrm{~mL}$ ) and water ( $2 \times 25 \mathrm{~mL}$ ), dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to an oil which was purified by flash chromatography on silica gel using $4 \% \mathrm{MeOH}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to furnish the 2-C-u-methyl compound ( 149 mg ) and the $2-\mathrm{C}-\bar{\beta}$-methyl compound ( 34 $\mathrm{mg})$. These derivatives were separately treated with $80 \%$ acetic acid and the reaction mixture stirred at room temperature for 2.5 h . The acetic acid was removed by
10 repeated co-evaporation with ethanol and toluene. The residue was partitioned between chloroform and water. The aqueous layer was washed with chloroform and concentrated. The evaporated residue was purified on silica gel using $5-10 \% \mathrm{MeOH}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ as the eluent to fumish the desired compounds as white solids.
4-Amino-7-(3-deoxy-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine
15 ( 9.0 mg ):
$1^{1} \mathrm{H}$ NMR (DMSO- $\mathrm{d}_{6}$ ): $\delta 0.74$ (s, $3 \mathrm{H}, \mathrm{CH}_{3}$ ), 1.77 (dd, $1 \mathrm{H}, \mathrm{H}-3^{\prime}$ ), 2.08 (t, $1 \mathrm{H}, \mathrm{H}-3^{\prime \prime}$ ), 3.59 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}-5^{\prime}$ ), 3.73 (m, 1H, H-5"), 4.15 (m, 1H, H-4'), 5.02 (t, 1H, OH-5'), 5.33 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{OH}-2^{\prime}$ ) , 6.00 (s, 1H, H-1'), 6.54 (d, 1H, H-7), 6.95 (br s, $2 \mathrm{H}, \mathrm{NH}_{2}$ ), 7.47 (d, 1H, H-8), 8.00 (s, 1H, H-2); ES-MS: 263.1 [M-H].
20 4-Amino-7-(3-deoxy-2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo [2,3-d]pyrimidine ( 15 mg ):
${ }^{1} \mathrm{H}$ NMR (DMSO- $\mathrm{d}_{6}$ ): $\delta 1.23$ ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ), 2.08 (ddd, $2 \mathrm{H}, \mathrm{H}-3$ 'and 3 "), 3.57 ( $\mathrm{m}, 2 \mathrm{H}$, H-5'and 5"), 4.06 (m, 1H, H-4), $5.10\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}-2^{\prime}\right), 5.24\left(\mathrm{t}, 1 \mathrm{H}, \mathrm{OH}-5^{\prime}\right), 6.01(\mathrm{~s}, 1 \mathrm{H}$, $\mathrm{H}-1^{\prime}$ ), 6.49 (d, 1H, H-7), 6.89 (br s, 2H, NH2 $), 7.35$ (d, 1H, H-8), 8.01 (s,1H,H-2).
ES-MS: $265.2[\mathrm{M}+\mathrm{H}]$.

## EXAMPLE 28.

4-Amino-7-(2,4-C-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyirolo [2,3-d]pyrimidine


Step A: S-Deoxy-1,2-O-isopropylidene-D-xylofuranose
$1,2-O$-Isopropylidene-D-xylofuranose ( $38.4 \mathrm{~g}, 0.2 \mathrm{~mol}$ ), 4 dimethylaminopyridine ( 5 g ), triethylamine ( $55.7 \mathrm{~mL}, 0.4 \mathrm{~mol}$ ) were dissolved in dichloromethane ( 300 mL ). p-Toluenesulfonyl chloride ( $38.13 \mathrm{~g}, 0.2 \mathrm{~mol}$ ) was added and the reaction mixture was stirred at room temperature for 2 h . The reaction mixture was then poured into saturated aqueous sodium bicarbonate ( 500 mL ) and the two layers were separated. The organic layer was washed with aqueous citric acid solution $(20 \%, 200 \mathrm{~mL})$, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and evaporated to give a solid ( 70.0 g ). The solid was dissolved in dry $\mathrm{THF}(300 \mathrm{~mL})$ and $\mathrm{LiAlH}_{4}(16.0 \mathrm{~g}, 0.42 \mathrm{~mol})$ was added in portions over 30 min . The mixture was stirred at room temperature for 15 . Ethyl acetate ( 100 mL ) was added dropwise over 30 min and the mixture was filtered through a silica gel bed. The filtrate was concentrated and the resulting oil was chromatographed on silica gel (EtOAc/hexane 1/4) to afford the product as a solid ( 32.5 g ).

Step B: : 3,5-Bis-O-(2,4-dichlorophenylmethyl)-1-O-methyl-4-methyl- $\alpha$-Dribofuranose
Chromium oxide ( $50 \mathrm{~g}, 0.5 \mathrm{~mol}$ ), acetic anhydride ( $50 \mathrm{~mL}, 0.53 \mathrm{~mol}$ ) and pyridine ( $100 \mathrm{~mL}, 1.24 \mathrm{~mol}$ ) were added to dichloromethane ( 1 L ) in an ice-water bath and the mixture was stirred for 15 min . 5 -Deoxy- $1,2-O$-isopropylidene-Dxylofuranose ( $32 \mathrm{~g}, 0.18 \mathrm{~mol}$ ) in dichloromethane ( 200 mL ) was added, and the mixture was stirred at the same temperature for 30 min . The reaction solution was diluted with ethyl acetate ( 1 L ) and filtered through a silica gel bed. The filtrate was concentrated to give a yellow oil. The oil was dissolved in 1,4-dioxane ( 1 L ) and formaldehyde $(37 \%, 200 \mathrm{~mL})$, The solution was cooled to $0^{\circ} \mathrm{C}$ and solid $\mathrm{KOH}(50 \mathrm{~g})$ was added. The mixture was stirred at room temperature overnight and was then extracted with ethyl acetate $(6 \times 200 \mathrm{~mL})$. After concentration, the residue was
chromatographed on silica gel (EtOAc) to afford the product as an oil ( 1.5 g ). The oil was dissolved in 1-methyl-2-pyrrolidinone ( 20 mL ) and 2,4-dichlorophenylmethyl chloride ( $4 \mathrm{~g}, 20.5 \mathrm{mmol}$ ) and $\mathrm{NaH}(60 \%, 0.8 \mathrm{~g})$ were added. The mixture was stirred overnight and diluted with toluene ( 100 mL ). The mixture was then washed with saturated aqueous sodium bicarbonate $(3 \times 50 \mathrm{~mL})$, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{1}\right)$ and evaporated. The residue was dissolved in methanol ( 50 mL ) and HCl in dioxane ( $4 \mathrm{M}, 2 \mathrm{~mL}$ ) was added. The solution was stirred overnight and evaporated. The residue was chromatographed on silica gel (EtOAc/hexane:1/4) to afford the desired product as an oil ( 2.01 g ).

Step C: $\quad$ 3,5-Bis- $O$-(2,4-dichlorophenylmethyl)-2,4-di- $C$-methyl-1- $O$-methyl- $\alpha$ -D-ribofuranose
The product ( $2.0 \mathrm{~g}, 4.0 \mathrm{mmol}$ ) from Step B and Dess-Martin periodinane ( 2.0 g ) in dichloromethane ( 30 mL ) were stirred overnight at room temperature and then concentrated under reduced pressure. The residue was triturated with ether ether ( 50 mL ) and filtered. The filtrate was washed with a solution of$\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} .5 \mathrm{H}_{2} \mathrm{O}(2.5 \mathrm{~g})$ in saturated aqueous sodium bicarbonate solution ( 50 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and evaporated. The residue was dissolved in anhydrous $\mathrm{Et}_{2} \mathrm{O}$ $(20 \mathrm{~mL})$ and was added dropwise to a solution of MeMgBr in $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{M}, 10 \mathrm{~mL})$ at $78^{\circ} \mathrm{C}$. The reaction mixture was allowed to warm to $-30^{\circ} \mathrm{C}$ and stirred at $-30^{\circ} \mathrm{C}$ to $15^{\circ} \mathrm{C}$ for 5 h , then poured into saturated aqueous ammonium chloride ( 50 mL ). The two layers were separated and the organic layer was dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentrated, The residue was chromatographed on silica gel (EtOAc/hexane: 1/9) to afford the title compound as a syrup ( 1.40 g ).

Step D: 4-Chloro-7-33,5-bis-O.(2,4-dichlorophenylmethyl)-2,4-di-C-methyl- $\beta$ -D-ribofuranosyll 7 H -pyrrolo $[2,3-d]$ pyrimidine
To the compound from Step C ( $0.70 . \mathrm{g}, 1.3 \mathrm{mmol}$ ) was added $\mathrm{HBr}(5.7$ M in acetic acid, 2 mL ). The resulting solution was stirred at room temperature for 1 $h$, evaporated in vacuo and co evaporated with anhydrous toluene ( $3 \times 10 \mathrm{~mL}$ ). 4-Chloro- $1 H$-pyrrolo $[2,3-c]$ pyrimidine ( $0.5 \mathrm{~g}, 3.3 \mathrm{mmol}$ ) and powdered $\mathrm{KOH}(85 \%$, $150 \mathrm{mg}, 2.3 \mathrm{mmol}$ ) were stirred in 1-methyl-2-pyrrolidinone ( 5 mL ) for 30 min and the mixture was co-evaporated with toluene ( 10 mL ). The resulting solution was poured into the above bromo sugar residue and the mixture was stirred overnight.

The mixture was diluted with toluene ( 50 mL ), washed with water ( $3 \times 50 \mathrm{~mL}$ ) and concentrated; under reduced pressure. The residue was chromatographed on silica gel eluting with EtOAc/ Hexane (15/85) to afford a solid ( 270 mg ).

Step E: $\quad 4$-Amino- 7 -(2,4-C-dimethyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo[2,3dy pyrimidine
The compound from Step D ( 270 mg ) was dissolved in diuxane ( 2 mL ) and liquid ammonia ( 20 g ) was added in a stainless steel autoclave. The mixture was heated at $100^{\circ} \mathrm{C}$ for 15 , then cooled and evaporated: The residue was chromatographed on silica gel (EtOAc) to afford a solid ( 200 mg ). The solid ( 150 $\mathrm{mg})$ and $\mathrm{Pd} / \mathrm{C}(10 \% 150 \mathrm{mg})$ in methanol ( 20 mL ) , were shaken under $\mathrm{H}_{2}(30 \mathrm{psi})$ for 3 h , filtered and evaporated. The residue was chromatographed on silica gel ( $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} ; 1 / 9$ ) to afford the desired product as a solid ( 35 mg ).
${ }^{1 H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.65(\mathrm{~s}, 3 \mathrm{H}), 1.18(\mathrm{~s}, 3 \mathrm{H}), 3.43(\mathrm{~m}, 2 \mathrm{H}), 4.06(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J} 6.3$
Hz ), 4.87 (s, 1H), 5.26 (br, 1H), $5.08(\mathrm{~d}, 1 \mathrm{H}, J 6.3 \mathrm{~Hz}) ; 5.25(\mathrm{t}, 1 \mathrm{H}, J 3.0 \mathrm{~Hz}), 6.17$ (s, $1 \mathrm{H}), 6.54(\mathrm{~d}, 1 \mathrm{H}, J 3.5 \mathrm{~Hz}), 6.97(\mathrm{~s}, \mathrm{br}, 2 \mathrm{H}), 7.54(\mathrm{~d}, 1 \mathrm{H}, J 3.4 \mathrm{~Hz}), 8.02(\mathrm{~s}, 1 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR (DMSO-d $d_{6}$ ): $\delta 18.19,21.32,65.38,73.00,79.33,84.80,90.66,99.09$, 102.41, 121.90, 149.58, 151.48, 157.38.

LC-MS: Found: $295.1\left(\mathrm{M}+\mathrm{H}^{+}\right)$; calculated for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 295.1$.

## EXAMPLE 29

4-Amino-7-(3-deoxy-3-fluoro-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d pyrimidine


Sep A: 3-Deoxy-3-fluoro-1-O-methyl-5-O-toluoyl- $\alpha$-D-ribofuranose

1,2-O-Isopropylidene-D-xylofuranose ( $9.0 \mathrm{~g}, 50 \mathrm{mmol}$ ) and $p$-toluoyl chloride ( $7.0 \mathrm{~mL}, 50 \mathrm{mmol}$ ) in pyridinc ( 50 mL ) were stirred for 30 min . Water ( 10 mL ) was added and the mixture was concentrated under reduced pressure. The residue was dissolved in toluene ( 500 mL ) and the solution was washed with water ( 200 mL ) and saturated aqueous sodium bicarbonate $(200 \mathrm{~mL}$ ). The two layers were separated and the organic layer was evaporated. The residue was dissolved in methanol ( 100 mL ) and HCl in dioxane ( $4 \mathrm{M}, 10 \mathrm{ml}$ ) was added. The mixture was stirred at room temperature overnight and was then evaporated under reduced pressure. The resulting oil was chromatographed on silica gel (EtOAc/hexane: $1 / 1$ ) to afford an oil $(10.1 \mathrm{~g})$. The oil was dissolved in dichloromethane ( 100 mL ) and. diethylaminosulfur trifluoride (DAST) ( 5.7 mL ) was added. The mixture was stirred overnight and was then poured into saturated aqueous sodium bicarbonate solution ( 100 mL ). The mixture was extracted with toluene ( $2 \times 50 \mathrm{~mL}$ ) and the combined organic layers were concentrated. The residue was chromatographed on silica gel (EtOAc/hexane: 15/85) to afford the title compound as an oil ( 1.50 g ).

## Step B: 3-Deoxy-3-fluoro-2-C-methyl-1-O-methyl-5-O-toluoyl- $\alpha$-Dribofuranose <br> The product from Step A ( $1.0 \mathrm{~g}, 3.5 \mathrm{mmol}$ ) and Dess-Martin

 periodinane $(2.5 \mathrm{~g})$ in dichloromethane $(20 \mathrm{~mL})$ were stirred overnight at room temperature and was then concentrated under reduced pressure. The residue was triturated with diethyl ether ( 50 mL ) and filtered. The filtrate was washed with a solution of $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} .5 \mathrm{H}_{2} \mathrm{O}$ ( 12.5 g ) in saturated aqueous sodium bicarbonate ( 100 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and evaporated. The residue was dissolved in anhydrous THF ( 50 mL ). $\mathrm{TiCl}_{4}(3 \mathrm{~mL})$ and methyl magnesium bromide in ethyl ether ( $3 \mathrm{M}, 10$ mL ) were added at $-78^{\circ} \mathrm{C}$ and the mixture was stirred at -50 to $-30^{\circ} \mathrm{C}$ for 2 h . The mixture was poured into saturated aqueous sodium bicarbonate solution ( 100 mL ) and filtered through Celite. The filtrate was extracted with toluene ( 100 mL ) and evaporated. The residue was chromatographed on silica gel (EtOAc/hexane: $15 / 85$ ) to afford the title compound as an oil ( 150 mg ).Step C: 4-Amino-7-(3-deoxy-3-fluoro-2-C-methyl- $\beta$-D-ribofuranosyl)-7Hpyrrolo $[2,3-d]$ pyrimidine

- The product from Step $B(150 \mathrm{mg}, 0.5 \mathrm{mmol})$ was dissolved in HBr $(30 \%)$ in acetic acid ( 2 mL ). After one hour, the mixture was evaporated under reduced pressure and co-evaporated with toluene ( 10 mL ). 4-Chloro- 1 H -pyrrolo[2,3d] pyrimidine ( $0.5 \mathrm{~g}, 3.3 \mathrm{mmol}$ ) and powdered $\mathrm{KOH}(85 \%, 150 \mathrm{mg}, 2.3 \mathrm{mmol})$ were stirred in DMF ( 3 mL ) for 30 min and the mixture was co-evaporated with toluene ( 2 mL ). The resulting solution was poured into the above bromo sugar and the mixture was stirred overnight. The mixture was diluted with toluene ( 50 mL ), washed with water ( $3 \times 50 \mathrm{~mL}$ ) and concentrated under reduced pressure. The residue was chromatographed on silica gel (EtOAc/hexane: 15/85) to afford an oil ( 60 mg ). The oil was dissolved in dioxane ( 2 mL ) and liquid ammonia ( 20 g ) was added in a stainless steel autoclave. The mixture was heated at $85^{\circ} \mathrm{C}$ for 18 h , then cooled and evaporated. The residue was chromatographed on silica gel (methanol/dichloromethane: $1 / 9$ ) to afford the title compound as a solid ( 29 mg ). $1_{\mathrm{H}}$ NMR (DMSO- $d_{6}$ ): $\delta 0.81 \cdot(\mathrm{~s}, 3 \mathrm{H}), 3.75(\mathrm{~m}, 2 \mathrm{H}), 4.16(\mathrm{~m}, 1 \mathrm{H}), 5.09(\mathrm{dd}, 1 \mathrm{H}, \mathrm{J}$ $53.2,7.8 \mathrm{~Hz}$ ), 5.26 (br, 1H), $5.77(\mathrm{~s}, 1 \mathrm{H}), 6.15(\mathrm{~d}, 1 \mathrm{H}, J 2.9 \mathrm{~Hz}), 6.59(\mathrm{~d}, 1 \mathrm{H}, J 3.4$ $\mathrm{Hz}), 7.02$ ( s b; 2 H ), 7.39 (d, 1H, J 3.4 Hz ), 8.06 ( $\mathrm{s}, 1 \mathrm{H}$ ).
${ }^{13}$ C NMR (DMSO- $d_{6}$ ): 19:40, 59.56, 77.24, 79.29, $90.15,91.92,99.88,102.39$, 121.17, 149.80, 151.77, 157.47.

19F NMR (DMSO $-d_{6}$ ): $\delta 14: 66(\mathrm{~m})$.
20 ES-MS: Found: $283.1\left(\mathrm{M}+\mathrm{H}^{+}\right)$; calculated for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{FN}_{4} \mathrm{O}_{3}+\mathrm{H}^{+}$: 283.1.

## EXAMPLE 30

4-Amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


Step A: 4-chloro-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl-$\beta$-D-ribofurariosyl]-7H-pyrrolo [2,3- d]pyrimidine

To a pre-cooled $\left(0^{\circ} \mathrm{C}\right)$ solution of the compound from Example 2, Step D ( $618 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) in THF ( 8 mL ) was added methyl iodide ( $709 \mathrm{mg}, 5.0 \mathrm{mmol}$ ) and NaH ( $60 \%$ in mineral oil) ( $44 \mathrm{mg}, 1.1 \mathrm{mmol}$ ). The resulting mixture was stirred overnight at It and then poured into a stirred mixture of saturated aqueous ammonium chloride $(50 \mathrm{~mL})$ and dichloromethane $(50 \mathrm{~mL})$. The organic layer was washed with water ( 50 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$ and evaporated in vacuo. The resulting crude product was purified on silica gel using ethyl acetate/hexane as the eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 735 mg ) as a colorless foam.

Step B: . 4-amino-7-[3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C,2-O-dimethyl-B-D-ribofuranosyl]-7H-pyrrolo[2,3-d] pyrimidine
To the compound from Step A ( $735 \mathrm{mg}, 1.16 \mathrm{mmol}$ ) was added methanolic ammonia (saturated at $\left.0^{\circ} \mathrm{C}\right)(20 \mathrm{~mL})$. The mixture was heated in a stainless steel autoclave at $80^{\circ} \mathrm{C}$ oveinight, then cooled and the content evaporated in vacuo. The crude mixture was punfied on silica gel using ethyl acetate/hexane as the eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 504 mg ) as colorless foam.

Step C: 4-amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3dapyrimidine
A mixture of the product from Step. C ( $64 \mathrm{mg}, 0.1 \mathrm{mmol}$ ), $\mathrm{MeOH}^{\prime}(5$ mL ), $\mathrm{Et}_{3} \mathrm{~N}(0.2 \mathrm{~mL})$ and $10 \% \mathrm{Pd} / \mathrm{C}(61 \mathrm{mg})$ was hydrogenated on a Parr hydrogenator at 50 psi at room temperature overnight. The mixture was filtered throught celite, evaporated in yacuo and filtered through a pad of silica gel using $2 \%$ methanol in dichloromethane as eluent. The desired product was collected and evaporated in vacuo. The compound was redissolved in methanol ( 10 mL ) and $10 \% \mathrm{Pd} / \mathrm{C}(61 \mathrm{mg})$ was added. The mixture was hydrogenated on a Parr hydrogenator at 55 psi at room temperature for two weeks. The mixture was filtered through celite, evaporated in vacuo and purified on silica gel using $10 \%$ methanol in dichloromethane as eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired product ( 110 mg ) as a colorless foam.
${ }^{1}{ }_{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.68(\mathrm{~s}, 3 \mathrm{H}$, ), $3.40(\mathrm{~s}, 3 \mathrm{H}), 3.52-3.99$ (overlapping m, 4 H ), $4.92(\mathrm{~d}, 1 \mathrm{H}), 5.07(\mathrm{t}, 1 \mathrm{H}), 6.26(\mathrm{~s}, 1 \mathrm{H}), 6.55(\mathrm{~d}, 1 \mathrm{H}), 7.00 \mathrm{~s} \mathrm{br}, 2 \mathrm{H}), 7.46(\mathrm{~d}, 1 \mathrm{H}), 8.05$ ( $\mathrm{s}, 1 \mathrm{H}$ ).
LC-MS: Found: $293.1\left(\mathrm{M}-\mathrm{H}^{+}\right)$; calc. for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{4} \mathrm{O}_{4}-\mathrm{H}^{+}$: 293.12 .

EXAMPLE 31

4-Methylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo [2,3-d]pyrimidine


The compound from Step E of Example $2(200 \mathrm{mg}, 0.67 \mathrm{mmol})$ was added to methylamine ( 5 mL condensed in a small stainless steel autoclave) and warmed at $85^{\circ} \mathrm{C}$ for 48 h , tlien cooled and evaporated in vacuo. The crude mixture was purified on a silica gel with ethanol as the eluent to give the title compound which separated as an amorphous solid after treatment with MeCN. The amorphous solid was dissolved in water and lyophilized to give a colorless powder ( 144 mg ). ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.63\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.32\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{NCH}_{3}\right), 3.58-3.67(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-$ '5'), 3.79-3.39 (m, 3H, H-5', H-4', H-3'), 5.03 ( $\mathrm{s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}$ ), $5.04-5.11$ ( $1 \mathrm{H}, 3^{\prime}-\mathrm{OH}$, $\left.1 \mathrm{H}, 5^{\prime}-\mathrm{OH}\right), 6.14\left(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-\mathrm{l}^{\prime}\right), 6.58\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{5,6}=3.6 \mathrm{~Hz}, \mathrm{H}-5\right), 7.46(\mathrm{~d}, 1 \mathrm{H}, \mathrm{H}-6)$, 7.70 (br s, 1H, NH), 8.14 (s, 1H, H-2).

LC-MS: Found: $295.1\left(\mathrm{M}-\mathrm{H}^{+}\right)$; calc. for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}$: 294.3 .

## EXAMPLE 32

4-Dimethylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine


The compound from Step E of Example 2 ( $200 \mathrm{mg}, 0.67 \mathrm{mmol}$ ) was added to dimethylamine ( 5 mL condensed in a small stainless steel autoclave) and warmed at $85^{\circ} \mathrm{C}$ for 48 h , then cooled and evaporated in vacuo. The crude mixture

4-Cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


The compound from Step E of Example 2 ( $200 \mathrm{mg}, 0.67 \mathrm{mmol}$ ) was added to cyclopropylamine ( 5 mL condensed in a small stainless steel autoclave) and warmed at $85^{\circ} \mathrm{C}$ for 48 h , then cooled and evaporated in vacuo. The crude mixture was purified on a silica gel with ethanol as the eluent to give the title compound

IPO DELHI 23-06-2015 15:59
which separated as an amorphous solid after treatment with MeCN . The amorphous solid was dissolved in water and lyophilized to give a colorless powder ( 148 mg ). ${ }^{1} \mathrm{H}$ NMR (DMSO- $d_{6}$ ): $\delta 0.51-0.58(\mathrm{~m}, 2 \mathrm{H}), 0.64\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 0.74-0.076(\mathrm{~m}, 2 \mathrm{H})$, 3.62-3.67 (m, 1H, H-5'), 3.79-3.82 (m, 3H, H-5"), 3.92-3.96 (m, H-4', H-3'), 5.03 ( s , $\left.1 \mathrm{H}, 2^{\prime}-\mathrm{OH}\right), 5.05-5.10\left(1 \dot{\mathrm{H}}, 3^{\prime}-\mathrm{OH}, 1 \mathrm{H}, 5^{\prime}-\mathrm{OH}\right), \dot{6}^{\circ} .15^{\prime}\left(\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 7.48\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{5.6}=\right.$ $3.6 \mathrm{~Hz}, \mathrm{H}-5)^{\prime}, 7.59$ (d, $1 \mathrm{H}, \mathrm{H}-6$ ), 8.13 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{H}-2$ ).
LC-MS: Found: $321.1\left(\mathrm{M}-\mathrm{H}^{+}\right)$; call. for $\mathrm{C}_{1} 5 \mathrm{H}_{20} \mathrm{~N}_{4} \mathrm{O}_{4}+\mathrm{H}^{+}: 320.3$.

## EXAMPLE 34

4-Amino-7-(3-C-methyl- $\beta$-D-xylofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


Step A: 7-[2,5-Bis-O-(tert-butyldimethylsilyl)- $\beta$-D-ribofuranosyl)]-4-[(4-methoxyphenyl)diphenylmethyllamino-7 H -pyrrolo $[2,3-d]$ pyrimidine and 7-[3,5-bis- $($ ( - (tert-butyldimethylsilyl) $)$ - -D-ribofuranosyl]-4-[(4-methoxyphenyl)diphenylmethyllamino- 7 H -pyrrolo $[2,3$ - $d$ ] pyrimidine-
To a solution of mixture of the compounds from Step A of Examples 26 and 27 ( $0.32 \mathrm{~g}, 0.65 \mathrm{mmol}$ ) in anhydrous pyridine ( 6 mL ) was added monomethoxytrityl chloride $(0.30 \mathrm{~g}, 0.98 \mathrm{mmol})$ and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated and the residue was partitioned between $\mathrm{CH}_{2} \mathrm{Cl}_{2}(70 \mathrm{~mL})$ and water $(20 \mathrm{~mL})$. The organic layer was washed with water and brine, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated. The residue was purified on silica gel column using $5-13 \%$ EtOAc in hexanes as the eluent. The appropriate fractions were collected and concentrated to furnish $2^{\prime}, 5^{\prime}$-bis-O-(tert-butyldimethylsilyl)- and 3',5'-bis-O-(rert-butyldimethylsilyl) protected nucleosides as: colorless foams ( 343 mg and 84 mg , respectively).

Step B: $\quad$ 7-12,5-Bis-O-(tert-butyldimethylsilyl)- $\beta$-D-erythro-pentofuranos-3ulosyll $]-4-[(4$-methoxyphenyl)diphenylmethyllamino- 7 H -pyrrolo $[2,3-$ d]pyrimidine
To a well-stirred suspension of chromium trioxide ( $91 \mathrm{mg}, 0.91 \mathrm{mmol}$ )
in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ were added pyridine ( $147 \mu \mathrm{~L}, 1.82 \mathrm{mmol}$ ) and then acetic anhydride ( $86 \mu \mathrm{~L}, 0.91 \mathrm{mmol}$ ). The mixture was stirred at room temperature for 0.5 h. Then the 2',5'-bis-O-(tert-butyldimethylsilyl) protected nuclenside from step.A ( 343 mg 0.45 mmol ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2.5 \mathrm{~mL}$ ) was added and the mixture stirred at room temperature 2 h . The mixture was then poured into ice-cold EtOAc ( 10 mL ) and filtered through a short silica gel column using EtOAc as the eluent. The filtrate was, evaporated and the residue purified on a silica gel column with hexanes and hexanes/EtOAc ( $7 / 1$ ) as the eluentito give the title compound ( 180 mg ).

Step C: $\quad 7-[2,5-\mathrm{Bis}-\mathrm{O}$-(tert-butyldimethylsilyl)-3-C-methyl- $\beta$-D-ribofuranosyl)-4-[(4-miethoxyphenyl)diphenylmethyllamino-7 $H$-pyrrolo[2,3d]pyrimidine and 7-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-C-methyl- $\beta$ -D-xylofuranosyl)-4-((4-methoxyphenyl)diphenylmethyllamino-7H-pyrrolo[2,3-d]pyrimidine
To a mixture of MeMgBr ( 3.0 M solution in ether; $0.17 \mathrm{~mL}, 0.5 \mathrm{mmol}$ ) in anhydrous hexanes $(1.5 \mathrm{~mL})$ at room temperature:was added dropwise a solution of the compound (rom Step B ( $78 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) in anhydrous hexanes ( 0.5 mL ). After. 2 h stirring at room temperature, the reaction mixture was poured into ice-cold water $(10 \mathrm{~mL})$ and diluted with EtOAc $(20 \mathrm{~mL})$, then filtered through Celite which was then thoroughly washed with EtOAc. The layers were separated and the organic layer was. washed with brine, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated. The residue was purified on a silica gel column using 8 to $25 \%$ EtOAc in hexanes as eluent to give the 3-C-methyl xylo- ( 60 mg ) and the 3-C-methyl ribo-isomer ( 20 mg ).

Step D: . 4-Amino-7-(3-C-methyl- $\beta$-D-xylofuranosyl)-7H-pyrrolo[2,3d dpyrimidine
To an ice-cold solution of 3-C-methyl-xylo isomer from Step C (60 $\mathrm{mg}, 0.08 \mathrm{mmol}$ ) in THF ( 2 mL ) was added TBAF ( 1 M in THF; $0.32 \mathrm{~mL}, 0.32 \mathrm{mmol}$ ). The reaction mixture was stirred at room temperature for 5 h , then diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$, washed with water ( $3 \times 15 \mathrm{~mL}$ ), dried, and evaporated. The residue was dissolved in dioxane ( 0.3 mL ) and $80 \%$ acetic acid ( 3 mL ) was added. The
reaction mixture was stirred at room temperature for $I \mathrm{~d}$ and then evaporated. The residue was co-evaporated with dioxane, taken up in water ( 50 mL ) and washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 10 \mathrm{~mL})$. The aqueous layer was concentrated and then freeze-dried.' The residue was purified on silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(20 / 1$ and $10 / 1$ ) as the eluent to give the title compound as a white fluffy compound after freeze drying ( 10 mg ).
1H NMR (CD $\mathrm{CD}_{3} \mathrm{CN}$ ): $\delta 1,28\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.5 \mathrm{~h}(\mathrm{hr} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 3.78\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{H} 4^{\prime}, \mathrm{H}\right.$ 5'. H-5"), 4.10 (br s, $1 \mathrm{H}, \mathrm{OH}$ ), 4.44 (d, $\left.1 \mathrm{H}, J_{2^{\prime} 1^{\prime}}=3.9 \mathrm{~Hz}, \mathrm{H}-2^{\prime}\right), 5.58\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right)$, 5.85 (br s, 2H, NH2), $6.15(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 6.48\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{5,6}=3.7 \mathrm{~Hz}, \mathrm{H}-5\right), 7.23(\mathrm{~d}$, 1H, H-6), 8.11 (s, 1H, H-2). ES-MS: $281[\mathrm{MH}]^{+}$.

## EXAMPLE 35

4-Amino-7-(3-C-methyl-B-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


The ribo-isomer ( 20 mg ) from Step C of Example 32 was deprotected using the procedure described in Step D of Example 32 to yield the title compound (4 mg ).
${ }_{1 H}$ NMR ( $\mathrm{CD}_{3} \mathrm{CN}$ ): 81.43 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ), 3.28 (br s, $1 \mathrm{H}, \mathrm{OH}$ ), $3.58\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5^{\prime}, \mathrm{H}-\right.$ $5^{\prime \prime}$ ), 3.99 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}-4^{\prime}$ ), 4.10 (br s, $11 \mathrm{H}, \mathrm{OH}$ ), 4.62 ( $\mathrm{d}, 1 \mathrm{H}, J_{2^{\prime} 1^{\prime}}=8.1 \mathrm{~Hz}, \mathrm{H}-2^{\prime}$ ), 5.69 (d, 1H, H-1'), 5.88 (br s, 3H, OH, NH2 $), 6.45(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{OH}), 6.51\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{5,6}=3.7\right.$ $\mathrm{Hz}, \mathrm{H}-5), 7.19$ (d, 1H, H-6), 8.12 (s, 1H, H-2). ES-MS: 281 [MH] ${ }^{+}$.

## EXAMPLE 36 .

2,4-Diamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-\alpha]$ pyrimidine


- A mixture of the product from Step B of Example 4 ( 24 mg ) in aqueous ammonia ( $30 \%, 10 \mathrm{~mL}$ ) was heated in a stainless steel autoclave at $100^{\circ} \mathrm{C}$ overnight, then cooled and evaporated. The residue was purified on a silica gel column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(10 / 1$ and $5 / 1)$ as the eluent to afford the title compound ( 15 mg ).
lH NMR (DMSO- $d_{6}$ ): $\delta 0.68$ ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ), 3.48-3:58 (m 1H, H-5'), 3.68-3.73 (m, 2H, $\mathrm{H}-5^{\prime \prime}, \mathrm{H}^{\prime} 4^{\prime}$ ), 3.84 ( $\mathrm{m}, 1 \mathrm{H}, \mathrm{H}-3^{\prime}$ ), 4.72 ( $\mathrm{s}, 1 \mathrm{H}, 2^{\prime}-\mathrm{OH}$ ), 4.97-5.03 (m, 2H, $3^{\prime}-\mathrm{OH}, 5^{\prime}-$ OH ), 5.45 (br s, $2 \mathrm{H}, \mathrm{NH}_{2}$ ), $6.00(\mathrm{~s}, 1 \mathrm{H}, \mathrm{H}-1$ '), 6.28 (d, $1 \mathrm{H}, J=3.7 \mathrm{~Hz}, \mathrm{H}-5$ ), 6.44 (br $\mathrm{s}, 2 \mathrm{H}, \mathrm{NH}_{2}$ ) $6.92(\mathrm{~d}, 1 \mathrm{HJ} \underset{\mathrm{x}}{ } 3.7 \mathrm{~Hz}, \mathrm{H} 6$ ).
ES MS: $294.1\left(\mathrm{M}-\mathrm{H}^{+}\right)$.


## EXAMPLE 37

4-Amino-2-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


To a solution of $\mathrm{HF} /$ pyridine $(70 \%, 2 \mathrm{~mL}$ ) diluted with pyridine ( 1 mL ) at $-30^{\circ} \mathrm{C}$ is added the compound of Example $36(60 \mathrm{mg}, 0.2 \mathrm{mmol})$ in 0.5 mL pyridine followed by tert-butyl nitrite ( $36 \mu \mathrm{~L}, 0.3 \mathrm{mmol}$ ). Stirring is continued for 5 $\min -25^{\circ} \mathrm{C}$. Then the solution is poured into ice-water ( 5 mL ), neutralized with 2 N aqueous NaOH , and evaporated to dryness. The residue is purified on a silica-gel
column with $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeO} \mathrm{H}$ (20/1 and $10 / 1$ ) as the eluent to afford the title compound.

## EXAMPLE 38

5
4-Amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine


Step A: 4-Acetylamino-7-(2,3,5-tri-O-acetyl-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d]$ pyrimidine
1.00 mmol ) in pyridine is added acetic anhydride ( $613 \mathrm{mg}, 6.0 \mathrm{mmol}$ ). The resulting solution is stirred overnight at ambient temperature evaporated in vacuo and the resulting crude mixture is purified on silica gel using ethyl acetate/hexane as the eluent. Fractions containing the desired product are pooled and evaporated in vacuo to give the desired product.

Step B: $\quad$ 4-Acetylamino-5-bromo-7-(2,3,5-tri- $O$-acetyl-2-C-methyl- $\beta$-D. ribofuranosyl)-7H-pyrrolo [2,3- $d$ ]pyrimidine
To a pre-cooled $\left(0^{\circ} \mathrm{C}\right)$ solution of the compound from Step A $(460 \mathrm{mg}$,
To a solution of the compound from step $F$ of Example 2 ( 280 mg ,

DMF is added $N$ bromusucciuimide ${ }^{\circ}(178 \mathrm{mg} 1.0 \mathrm{mmol}$ ) in DMF The 1.00 mmol ) in DMF is added $N$-bromosuccinimide ( $178 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) in DMF. The resulting solution is stirred at $0^{\circ} \mathrm{C}$ for 30 min then at room temperature for another 30 min . The reaction is quenched by addition of methanol and evaporated in vacuo. The resulting crude mixture is purified on silica gel using ethyl acetate/hexane as the eluent. Fractions containing the desired product are pooled and evaporated in vacuo to give the desired product.

Step C: 4-Amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d]pyrimidine

To a pre-cooled $\left(-78^{\circ} \mathrm{C}\right)$ solution of the compound from Step B (529 $\mathrm{mg}, 1.00 \mathrm{mmol}$ ) in THF is added butyl lithium ( 2 M in hexanes) ( $0.5 \mathrm{~mL}, 1.00 \mathrm{mmol}$ ). The resulting solution is stirred at $-78^{\circ} \mathrm{C}$ for 30 min and then quenched with N fluorobenzensulfonimide ( $315 \mathrm{mg}, 1.00 \mathrm{mmol}$ ) in THF. The resulting solution is very slowly allowed to come to ambient temperature and then poured into a stirred mixture of saturated aqueous ammonium chloride and dichloromethane. The organic phase is evaporated in vacuo and trcated with ammunium hydroxide at $55^{\circ} \mathrm{C}$ in a closed container overnight. The resulting crude mixture is purified on silica gel using dichloromethane/methanol as the eluent. Fractions containing the desired product are pooled and evaporated in vacuo to give the desired product.

## BIOLOGICAL ASSAYS

The assays employed to measure the inhibition of HCV NS5B polymerase and HCV replication are described below.

The effectiveness of the compounds of the present invention as inhibitors of HEV NS5B RNA-dependent RNA polymerase (RdRp) was measured in the following assay.

## A. Assay for Inhibition of HCV NS5B Polymerase:

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

Procedure:
Assay Buffer Conditions: ( $50 \mu \mathrm{~L}$-total/reaction)
20 mM Tris, pH 7.5
$50 \mu \mathrm{M}$ EDTA
5 mM DTT
$2 \mathrm{mM} \mathrm{MgCl}_{2}$
80 mM KCl
$0.4 \mathrm{U} / \mu \mathrm{L}$ RNAsin (Promega, stock is 40 units $/ \mu \mathrm{L}$ ).
$0.75 \mu \mathrm{~g}$ t500 (a 500 -nt RNA made using T7 runoff transcription with a sequence from the NS2/3 region of the hepatitis C genome)

WO 02/057287
PCT/US02/03086
$1.6 \mu \mathrm{~g}$ purifled hepatitis C NS5B (form with 21 amino acids C-terminally truncated)
$1 \mu \mathrm{MA}, \mathrm{C}, \mathrm{U}, \mathrm{GTP}$ (Nucleoside triphosphate mix)
[alpha- ${ }^{32}$ P]-GTP or [alpha- ${ }^{33}$ P]-GTP

The compounds were tested at various concentrations up to $100 \mu \mathrm{M}$ final concentration.

An appropriate volume of reaction buffer was made including enzyme and template t500. Nucleoside derivatives 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 $1-2 \mathrm{~h}$.

The reaction was quenched by addition of $20 \mu \mathrm{~L} 0.5 \mathrm{M}$ 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.
$50 \mu \mathrm{~L}$ 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 $5-\mathrm{mL}$ scintillation fluid in a scintillation counter.

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

Representative compounds tested in the HCV NS5B polymerase assay exhibited $\mathrm{IC}_{50}$ 's less than 100 micromolar.

## 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 (HuH7) 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 . Lohmann, F. Korner, J-O. Koch, U. Herian, L. Theilmann, and R. Bartenschlager, "Replication of a Sub-genomic Hepatitis C Virus RNAs in a Hepatoma Cell Line," Science 285:110 (1999).

## Protocol:

The assay was an in situ Ribonuclease protection, Scintillation Proximity based-plate assay (SPA). $10,000-40,000$ cells were plated in $100-200 \mu \mathrm{~L}$ of media containing $0.8 \mathrm{mg} / \mathrm{mL}$ G418 in 96 -well cytostar plates (Amersham).
Compounds were added to cells at various concentrations up to $100 \mu \mathrm{M}$ in $1 \%$ DMSO at time 0 to 18 h and then cultured for $24-96 \mathrm{~h}$. Cells were fixed ( $20 \mathrm{~min}, 10 \%$ for malin), permeabilized ( $20 \mathrm{~min}, 0.25 \%$ Triton X-100/PBS) and hybridized. (overnight, $50^{\circ} \mathrm{C}$ ) with a single-stranded ${ }^{33} \mathrm{P}$ RNA probe complementary to the $(+$ ) strund NS5B (or other genes) contained in the RNA viral genome. Cells were washed, treated with RNAse, washed, heated to $65^{\circ} \mathrm{C}$ and counted in a Top-Count. Inhibition of replication was read as a decrease in counts per minute (cpm).

Human Hu $\dot{H}-7$ hepatoma cells, which were selected to contain a subgenomic 'replicon, carry a cytoplasmic RNA consisting of an HCV 5' nontranslated region (NTR), a neomycin selectable marker, an EMCV IRES (internal ribosome entry site), and $\dot{H} C V$ non-structural proteins NS3 through NS5B, followed by the 3 ' NTR.

Representative compounds tested in the replication assay exhibited $\mathrm{EC}_{50}$ 's less than 100 micromolar. for cellular toxicity and anti-viral specificity in the counterscreens described below.

## C. COUNTERSCREENS:

The ability of the nucleoside derivatives of the present invention to inhibit human DNA polymerases was measured in the following assays.

## a. Inhibition of Human DNA Polymerases alpha and beta:

## Reaction Conditions:

$50 \mu \mathrm{~L}$ reaction volume

## Reaction buffer components:

20 mM Tris- $\mathrm{HCl}, \mathrm{pH} 7.5$
$200 \mu \mathrm{~g} / \mathrm{mL}$ bovine serum albumin
100 mM KCl

```
\(2 \mathrm{mM} \beta\)-mercaptoethanol \(10 \mathrm{mM} \mathrm{MgCl}_{2}\)
\(1.6 \mu \mathrm{M} \mathrm{dA}, \mathrm{dG}, \mathrm{dC}, \mathrm{dTTP}\) \(\alpha-{ }^{33}\) P-dATP
```


## Enzyme and template:

$0.05 \mathrm{mg} / \mathrm{mL}$ gaped fish sperm DNA template $0.01 \mathrm{U} / \mu \mathrm{L}$ DNA polymerase $\alpha$ or $\beta$

10 Preparation of gapped fish sperm DNA template:
Add $5 \mu \mathrm{~L} 1 \mathrm{M} \mathrm{MgCl}_{2}$ to $500 \mu \mathrm{~L}$ activated fish sperm DNA (USB 70076);
Warm to $37^{\circ} \mathrm{C}$ and add $30 \mu \mathrm{~L}$ of $65 \mathrm{U} / \mu \mathrm{L}$ of exonuclease III (GibcoBRL 18013-011); Incubate 5 min at $37^{\circ} \mathrm{C}$;
Terminate reaction by heating $5 \bar{\sigma} .65^{\circ} \mathrm{C}$ for 10 min ;
15 Load 50-100 $\mu \mathrm{L}$ aliquots onto Bio-spin 6 chromatography columns (Bio-Rad 7326002) equilibrated with 20 mM Iris- $\mathrm{HCl}, \mathrm{pH} 7.5$;

Elute by centrifugation at $1,000 \mathrm{Xg}$ 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 $-\mathrm{HCl}, \mathrm{pH} 7.5$ and the enzyme was diluted into an appropriate volume of 20 mM Tris- HCl , containing $2 \mathrm{mM} \beta$-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 $37^{\circ} \mathrm{C}$. The reaction was quenched by the addition of $20 \mu \mathrm{~L}$.
1 0.5M EDTA. $50 \mu \mathrm{~L}$ of the quenched reaction was spotted onto Whatman DE81 filter disks and air dried. The filter disks were repeatedly washed with 150 mL 0.3 M ammonium formate, pH 8 until 1 mL of wash is $<100 \mathrm{cpm}$. 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 $=[1-(\mathrm{cpm}$ in test reaction $-\mathrm{c} p m$ in blank $) /(\mathrm{cpm}$ in control reaction - cpm in blank)] x 100.
b. Inhibition of Human DNA Polymerase gamma :

The potential for inhibition of human DNA polymerase gamma was measured in reactions that included $0.5 \mathrm{ng} / \mu \mathrm{L}$ enzyme; $10 \mu \mathrm{M} \mathrm{dATP}, \mathrm{dGTP}, \mathrm{dCTP}$, and TTP; $2 \mu \mathrm{Ci} /$ reaction [ $\left(L^{33} \mathrm{P}\right.$ ]-dATP, and $0.4 \mu \mathrm{~g} / \mu \mathrm{L}$ activated fish sperm DNA (purchased from.US Biochemical) in a buffer containing 20 mM Tris $\mathrm{pH} 8,2 \mathrm{mM} \beta$ mercaptoethanol, $50 \mathrm{mM} \mathrm{KCl}, 10 \mathrm{mM} \mathrm{MgCl} 2$, and. $0.1 \mu \mathrm{~g} / \mu \mathrm{L}$ BSA. Reactions were allowed to proceed for 1 h at $37^{\circ} \mathrm{C}$ and were quenched by addition of 0.5 MEDTA to a final concentration of 142 mM . Product formation was quantified by anion exchange filter binding and scintillation counting. Compounds were tested at up to 50 $\mu \mathrm{M}$. equation: $\%$ inhibition $=[1-(\mathrm{cpm}$ in test reaction -cpm in blank $) /(\mathrm{cpm}$ in control reaction - cpm in blank)] x 100 .

The ability of the nucleoside derivatives 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 $\beta$-galactosidase ( $\beta$-gal) expression. Cells were infected for 48 h , and $\beta$-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 $100 \mu \mathrm{M}$; 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 immunedeficiency 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 nucleoside derivatives 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. Nalkabayashi, et al., Cancor Res., 42: 3858 (1982).

## e. Cytotoxicity assay:

Cell cultures were prepared in appropriate media at concentrations of approximately $1.5 \times 10^{5}$ cells $/ \mathrm{mL}$ for suspension cultures in 3 day incubations and 5.0 x $10^{4}$ cells $/ \mathrm{mL}$ for adherent cultures in 3 day incubations. $99 \mu \mathrm{~L}$ of cell culture was transferred to wells of a 96 -well tissue culture treated plate, and $1 \mu \mathrm{~L}$ of 100 -times final concentration of the test compound in DMSO was added. The plates were incubated at $37^{\circ} \mathrm{C}$ and $5 \% \mathrm{CO}_{2}$ for a specified period of time. After the incubation poriod, $20 \mu \mathrm{~L}$ of CellTiter 96 Aqueous One Solution Cell Proliferation Assay reagent (MTS) (Promega) was added to each well and the plates were incubated at $37^{\circ} \mathrm{C}$ and $5 \% \mathrm{CO}_{2}$ for an additional period of time up to 3 h . 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 49.0 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 inviention against other RNA-dependent RNA viruses:
a. Determination of In Vitro Antiviral Activity of Compounds Against Rhinovirus (Cytopathic Effect Inhibition Assay): . Assay conditions are described in the article by Sidwell and Huffman, "Use of disposable' microtissue culture plates for antiviral and interferon induction studies," Appl. Microbiol. 22: 797-801 (1971).

## Viruses:

Rhinovirus type 2 (RV-2), strain HGP, was used with KB cells and media ( $0.1 \%$ $\mathrm{NaHCO}_{3}$, 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 $0.1 \% \mathrm{NaHCO}_{3}$ was used as the growth medium.
Antiviral test medium for all three virus types was MEM with $5 \%$ FBS, $0.1 \%$ $\mathrm{NaHCO}_{3}, 50 \mu \mathrm{~g}$ gentamicin $/ \mathrm{mL}$, and 10 mM MgCl 2 .
$2000 \mu \mathrm{~g} / \mathrm{mL}$ 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 $5 \% \mathrm{CO}_{2}$ at $37^{\circ} \mathrm{C}$. 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 $=$ CC 50 $\div$ ED 50.
b. Determination of In Vitro Antiviral Activity' of Compounds Against Dengue, Banzi, and Yellow Fever (CPE mhibition 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 l 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 $5 \% \mathrm{FBS}$ and $0.1 \% \mathrm{NaHCO}_{3}$ and without antibiotics. Assay medium for dengue, yellow fever, and Banzi viruses was MEM, $2 \%$ FBS, $0.18 \% \mathrm{NaHCO}_{3}$ and $50 \mu \mathrm{~g}$ gentamicin $/ \mathrm{mL}$.

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, $1 \% \mathrm{FBS}, 0.1 \% \mathrm{NaHCO} 3$ and $50 \mu \mathrm{~g}$ gentamicin $/ \mathrm{mL}$ :

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 Wesı 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 the compound of Example 1 or Example 2 is formulated

WO 02/057287
with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O 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 heeinabove may be appliéable as a consequence of 1 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 compound of the structural formula I:

(I)

5
or $u$ pharmaceutically acceptable salt thereof;
wherein $R 1$ is $\mathrm{C}_{2-4}$ alkenyl, $\mathrm{C}_{2-4}$ alkynyl, or $\mathrm{C}_{1-4}$ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{1-4}$ alkylthio, or one to three fluorine atoms;
$\mathrm{R}^{2}$ is hydrogen, fluorine, hydroxy, mercapto, $\mathrm{C}_{1-4}$ alkoxy, or $\mathrm{C}_{1-4}$ alkyl; or $\mathrm{RI}^{1}$ and
R2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated monocyclic ring system optionally containing a heteroatom selected from O , S , and $\mathrm{NC}_{0}-4$ alkyl;
$R^{3}$ and $R^{4}$ are each independently selected from the group consisting of hydrogen, cyano, azide, halogen, hydroxy, mercapto, amino, $\mathrm{C}_{1-4}$ alkoxy, $\mathrm{C}_{2}-4$ alkenyl, $\mathrm{C}_{2-4}$
alkyloxycarbonyl, azido, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, hydroxy, $\mathrm{C}_{1-6}$ alkoxy, $\mathrm{C}_{1-6}$ alkylthio, $\mathrm{C}_{1-6}$ alkylsulfonyl, ( $\mathrm{C}_{1-4}$ alkyl )0-2 aminomethyl, or $\mathrm{C}_{4}-6$ cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, $C_{1-4}$ alkyl, and $C_{1-4}$ alkoxy; R 9 is hydrogen, cyano, nitro, $\mathrm{C}_{1-3}$ alkyl, $\mathrm{NHCONH}_{2}$, COR ${ }^{12 R} 12, \mathrm{CSNR}{ }^{12 R} 12$,
25 . TOR ${ }^{12}, \mathrm{C}(=\mathrm{NH}) \mathrm{NH}_{2}$, hydroxy, $\mathrm{C}_{1-3}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl)amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazol-2-yl), or (imidazol-2-yl); wherein

- 78 -

IPO DELHI 23-06-2015:15:59
alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboy, and $\mathrm{C}_{1}-3$ alkoxy; $\mathrm{R}^{10}$ and $\mathrm{R}^{11}$ are each independently hydrogen, hydroxy, halogen, $\mathrm{C}_{1-4}$ alkoxy, amino, $\mathrm{C}_{1-4}$ alkylamino, di( $\mathrm{C}_{1-4}$ alkyl) amino, $\mathrm{C}_{3}-6$ cycloalkylamino, di(C3-6 cycloalkyl)anino, or C4-6 cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, C1-4 alkyl, and Cl-4 alkoxy:
each R12 is independently hydrogen or $\mathrm{C}_{1-6}$ alkyl; and R13 and $\mathrm{R}^{14}$ are each independently hydroxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{SC}(=\mathrm{O}) \mathrm{C}_{1-4}$ alkyl, $\mathrm{OCH}_{2} \mathrm{O}(\mathrm{C}=\mathrm{O}) \mathrm{OC}_{1-4}$ alkyl, $\mathrm{NHCHMeCO}_{2} \mathrm{Me}, \mathrm{OCH}\left(\mathrm{C}_{1-4}\right.$ alkyl) $\mathrm{O}(\mathrm{C}=0) \mathrm{C}_{1-4}$ alkyl,

with the proviso that when $R^{1}$ is $\beta$-methyl and $R^{4}$ is hydrogen or $R^{4}$ is $\beta$-methyl and $R^{1}$ is hydrogen, $R^{2}$ and $R^{3}$ are $\alpha$-hydroxy, $R^{10}$ is amino, and $R^{5}, R^{6}, R^{7}, R^{8}$, and $\mathrm{Rll}^{11}$ are hydrogen, then $\mathrm{R}^{9}$ is not cyan or $\mathrm{CONH}_{2}$.
2. The compound of Claim 1 of the structural formula II:

(II)
or a pharmaceutically acceptable salt thereof;
wherein
$\mathrm{Rl}^{1}$ is $\mathrm{C}_{1-3}$ alkyl, wherein alkyl is optionally substituted with hydroxy, amino, $\mathrm{C}_{1-3}$ alkoxy, $\mathrm{C}_{1-3}$ alkylthio, or one to three fluorine atoms;
R 2 is hydroxy, fluoro, or $\mathrm{C}_{1-4}$ alkoxy;
$\mathrm{R}^{3}$ is hydrogen, halogen, hydroxy, amino, or $\mathrm{C}_{1-4}$ alkoxy;
$\mathrm{R}^{5}$ is hydrogen, $\mathrm{P}_{3} \mathrm{O}_{9} \dot{\mathrm{H}}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$, or $\mathrm{PO}_{3} \mathrm{H}_{2}$;
$\mathrm{R}^{8}$ is hydrogen , amino, or $\mathrm{C}_{1-4}$ alkylamino;
R 9 is hydrogen, cyano, methyl, halogen, or $\mathrm{CONH}_{2}$; and
R10 and R ${ }^{11}$ are each independently hydrogen, halogen, hydroxy, amino,
$5 \quad \mathrm{C}_{1-4}$ alkylamino, di(C1-4 alkyl)amino, or C3-6 cycloalkylamino;
with the proviso that when $R^{1}$ is $\beta$-methyl, $R^{2}$ and $R^{3}$ are $\alpha$-hydroxy, $R 10$ is amino, and $R^{5}, R^{8}$, and $R^{11}$ are hydrogen, then $R^{9}$ is not cyano or $\mathrm{CONH}_{2}$.
3. The compound of Claim 2 wherein
$10 R^{1}$ is methyl, fluoromethyl, hydroxymethyl, difluoromethyl, trifluoromethyl, or aminomethyl;
$\mathrm{R}^{2}$ is hydroxy, fluoro, or methoxy;
$R^{3}$ is hydrogen, fluoro, hydroxy, amino, or methoxy; $\mathrm{R}^{5}$ is hydrogen or $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}$;
$15 \quad \mathrm{R} 8$ is hydrogen or amino;
R 9 is hydrogen, cyano, methyl, halogen, or $\mathrm{CONH}_{2}$; and
R10 and R11 are each independently hydrogen, fluoro, hydroxy, or amino; with the proviso that when $\mathrm{R}^{1}$ is $\beta$-methyl, $\mathrm{R}^{2}$ and $\mathrm{R}^{3}$ are $\alpha$-hydroxy, R 10 is amino, and $R^{5}, R^{8}$, and $R^{11}$ are hydrogen, then $\mathrm{R}^{9}$ is not cyano or $\mathrm{CONH}_{2}$.
4. The compound of Claim I selected from the group consisting
of:
4-amino-7-(2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,
25 4-methylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-dimethylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-vinyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3-c]pyrimidine, 4-amino-7-(2-C-hydrox ẏmethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine-5carboxylic acid,
4-amino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,

4-amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo $[2,3-d$ ]pyrimidine, 4-amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 2,4-diamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo [2,3- $d$ ]pyrimidine, 2-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine,

2-amino-4-cyclopropylamino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidine,
2-amino-7-(2-C-mcthyl- $\beta$-D-ribofuranosyl)-7H-pyrrulo[2,3- $d$ ]pyrimidin-4(3H)-one, 4-amino-7-(2-C-ethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 7 -(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidin-4( $3 H$ )-one, 2-amino-5-methyl-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3d] pyrimidin-4( $3 H$ )-one,
4-amino-7-(3-deoxy-2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ] pyrimidine, 4-amino-7-(3-deoxy-2-G-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine,
4-amino-2-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine, 4-amino-7-(3-C-mëthyl- $\beta$-D-ribofuranosyl)- $7 H$-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(3-C-methyl- $\beta$-D-xylofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2,4-di-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, and 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3d] pyrimidine;
and the corresponding 5'-triphosphates;
or a pharmaceutically acceptable salt thereof. :
5. The compound of Claim 4 selected from the group consisting of:
4-amino-7-(2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7 H -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl):7 7 -pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-methyl-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, 4-amino-5-bromo-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosyl). 7 H -pyrrolo[2,3- $\alpha$ ]pyrimidine, 4-amino-5-fluoro-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, and
4-amino-7-(2-C,2-O-dimethyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine, -81.
and the corresponding $5^{\prime}$-triphosphates;
or a pharmaceutically acceptable salt thereof.
6. The compound of Claim 5 which is

4-amino-7-(2-C-methyl- $\beta$-D-arabinofuranosyl)-7H-pyirolo[2,3- $d$ ]pyrimidine; or a pharmaceutically acceptable salt thereof.
7. The compound of Claim 5 which is 4-arnino-7-(2-C-methyl- $\beta$-D-ribofuranosyl)-7H-pyrrolo[2,3- $\alpha$ ]pyrimidine; or a pharmaceutically acceptable salt thereof.
8. The compound of Claim 5 which is 4-amino-7-(2-C-fluoromethyl- $\beta$-D-ribofuranosyl)- 7 H -pyrrolo[2,3- $d$ ]pyrimidine; or a pharmaceutically acceptable salt thereof.
9. The compound of Claim 5 which is 4 -amino-5-chloro-7-(2-C-methyl- $\beta$-D-ribofuranosy!)-7H-pyrrolo[2,3- $d$ ]pyrimidine; or a pharmaceutically acceptable salt thereof.
10. The compound of Claim 5 which is 4 -amino-5-bromo-7-(2-C-methyl- $\beta$-1)-ribofuranosyl)-7H-pyrrolo[2,3- $d$ ]pyrimidine; or a pharmaceitically acceptable salt thereof.
11. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.
12. The pharmaceutical composition of Claim 11 useful for inhibiting RNA-dependent RNA viral polymerase, inhibiting RNA-dependent RNA replication, and/or treating RNA-dependent RNA viral infection.
13. The pharmaceutical composition of Claim 12 wherein said RNA-dependent RNA viral polymerase is HCV NS5B polymerase, said RNAdependent RNA viral replication is HCV replication, and said RNA-dependent RNA viral infection is HCV infection.


IPO DELHI 23-06-2015.15:59
14. A method of inhibiting RNA-dependent RNA viral polymerase and/or inhibiting RNA-dẹpendent RNA viral replicaţion comprising administering to a mammal in need of such inhibition an effective amnount of a compound according to Claim 1.
15. The method of Claim 14 wherein said RNA-dependent RNA viral polymerase is HCV NS5B polymerase and said RNA-dependent RNA viral replication is HCV viral replication.
16. A method of treating RNA-dependent RNA viral infection comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1 .
17. The method of Claim 16 wherein said RNA-dependent RNA viral infection is HCV infection.
18. The method of Claim 17 in combination with a therapeutically effective amount of another agent active against HCV.
19. The method of Claim 18 wherein said agent active against HCV is ribavirin; levovirin; thymosin alpha-1; an inhibitor of NS3 serine protease; an inhibitor of inosine monophosphate dehydrogenase; interferon- $\alpha$ or pegylated interferon- $\alpha$, alone or in combination with ribavirin or levovirin.
20. The method of Claim 19 wherein said agent active against HCV is interferon- $\alpha$ or pegylated interferon- $\alpha$, alone or in combination with ribavirin.
21. Use of a compound of Claim 1 for the inhibition of RNAdependent RNA viral polymerase or inhibition of RNA-dependent RNA viral replication in a mammal.
22. Use of a compound of Claim 1 for treatment of RNAdependent RNA viral infection in a mammal.

PCT/US02/03086
23. The use of Claim 22 wherein said RNA-dependent RNA viral infection is hepatitis $C$ infection.
24. Use of a compound of Claim 1 in the manufacture of a medicament for the inhibition of RNA-dependent RNA viral polymerase or the inhibition of RNA-dependent RNA viral replication in a mammal.
25. Use of a compound of Claim 1 in the manufacture of a medicament for treatment of RNA-dependent RNA viral infection in a mammal.
26. The use of Claim 25 wherein said RNA-dependent RNA viral infection is hepatitis $C$ infection.

- INTERNATIONAL APPLICATION PUBLISHED UNDER THE PA ́TENT COOPERATION TREATY (PCT)
(51) International Jratent Classification 6 :

C07H 19/06, 19/10, 19/16, 19/20, 19/207, C07D 473/00, 405/04, C07F 9/547, A61K 31/70
(21) International Application Number:

PCT/US99/04051
(22) International Filing Date:

25 February 1999 (25.02.99)
(30) Priority Data:

60/075,893
60/080,569
25 February 1998 (25.02.98)
3 April 1998 (03.04.98)
(71) Applicants (for all designated States except US): EMORY UNIVERSITY [US/US]; 2009 Ridgewood Drive, Atlanta, GA 30322 (US). THE UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC. [US /US]; Boyd Graduate Studies Research Center, Athens, GA 30602-7411 (US).
(71)(72) Applicants and Inventors:. SCHINAZI, Raymond, F. [US/US]; 1524 Regency Walk Drive, Decatur, GA 30033 (US). LIOTTA, Dennis, C. [US/US]; 251 Montrose Drive, McDonough, GA 30253 (US). CHU, Chung, K. [US/US]; 115 Ceder Springs Place, Athens, GA 30605 (US). McATEE, J., Jeffrey [US/US]; 1457 Willow Lake Drive, Atlanta, GA 30329 (US). SHI, Junxing [CN/US]; Apartment D3, 1031 Scott Boulevard, Decatur, GA 30030 (US). CHOI, Yongseok [KR/US]; Apartment A-211, 101 College Station Road, Athens, GA 30605 (US). LEE, Kyeong (KR/US]; Apartment A-211, 101 College Station
(11) International Publication Number:
(43) International Publication Date: 2 September 1999 (02.09.99)
(54) Title: 2'-l'LUORONUCLEOSIDES

10




## (57) Abstract

2'-Fluoronucleoside compounds are disclosed which are useful in the treatment of hepatitis B infection, hepatitis C infection, HIV and abnormal cellular proliferation, including tumors and cancer. The compounds have general formulae (I), (II), (III), (IV) wherein Base is a purine or pyrimidine base; $\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy, and base refers to a purine or pyrimidine base; $\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $R^{2}$ is $H$ or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and $\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof.

## FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.


IPO DELHI 23-06-2015 15:59

## 2'-FLUORONUCLEOSIDES

The invention described herein was made with Government support under grant number AI 32351 awarded by the National Institutes of Health. The United States Government has certain rights to this invention.

This invention is in the area of pharmaceutical chemistry, and in particular, Includes 2'-fluoronucleosides and methods for their preparation and use.

## BACKGROUND OF THE INVENTION

Synthetic nucleosides such as 5 -iodo-2'-deoxyuridine and 5 -fluoro-2'-deoxyuridine have been used for the treatment of cancer and herpes viruses for a number of years. Since the 1980's, synthetic nucleosides have also been a focus of interest for the treatment of HIV, hepatitis, and Epstein-Barr viruses.

In 1981, acquired immune deficiency syndrome (AIDS) was identified as a disease that severely compromises the human immune system, and that almost without exception leads to death. In 1983, the etiological cause of AIDS was determined to be the human immunodeficiency virus (HIV): In 1985, it was reported that the synthetic nucleoside $3^{\prime}$ -azido-3'-deoxythymidine (AZT) inhibits the replication of human immunodeficiency virus. Since then, a number of other synthetic nucleosides, including $2^{\prime}, 3^{\prime}$-dideoxyinosine (DDI), $2^{\prime}, 3^{\prime}$-dideoxycytidine (DDC), and $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}, 3^{\prime}$-didehydrothymidine (D4T), have been: proven to be effective against HIV. After cellular phosphorylation to the 5 -triphosphate by cellular kinases, these synthetic nucleosides are incorporated into a growing strand of viral DNA, causing chain termination due to the absence of the 3 '-hydroxyl group. They can also inhibit the viral enzyme reverse transcriptase.

The success of various synthetic nucleosides in inhibiting the replication of HIV in vive or in vitro has led a number of researchers to design and test nucleosides that substitute a heteroatom for the carbon atom at the 3'-position of the nucleoside. European Patent Application Publication No. 0337713 and U.S. Patent No. 5,041,449, assigned to BioChem Pharma, Inc., disclose racemic 2 -substituted-4-substituted-1,3-dioxolanes that exhibit antiviral activity. U.S. Patent No. 5,047,407 and European Patent Application No. 0382 526, also assigned top BioChem Pharma, Inc., disclose that a number of racemic 2-substituted-5-
substituted-1,3-pxathiolane nucleosides have antiviral activity, and specifically report that the racemic mixture of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (referred to below as BCH-189) has approximately the same activity against HIV as AZT, with little toxicity. The $(-)$-enantiomer of the racemate $\mathrm{BCH}-189$, known as 3 TC , which is covered by U.S. Patent No. $5,539,116$ to Liotta et al., is currently sold for the treatment of HIV in combination with AZT in humans in the U.S.

It has also been disclosed that cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3oxathiolane ("FTC") has potent HIV activity. Schinazi, et al., "Selective Inhibition of Human Immunodeficiency viruses by Racemates und Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolane-5-yl]Cytosine" Antimicrobial Agents and Chemotherapy, November 1992, pp. 2423-2431. See also U.S. Patent No. 5,210,085; WO 91/11186, and WO 92/14743.

Another virus that causes a serious human health problem is the hepatitis $B$ virus (referred to below as "HBV"). HBV is second only to tobacco as a cause of human cancer: The mechanism by which HBV induces cancer is unknown. It is postulated that it may directly trigger tumor development, or indirectly triggèr tumor development through chronic inflammation, cirhosis, and.cell regeneration associated with the infection.

After a two to six month incubation period in which the host is unaware of the infection, HBV infection can lead to acute hepatitis and liver damage, that causes abdominal pain, jaundice, and elevated blood levels of certain enzymes. HBV. can cause fulminant hepatitis, a rapidly progressive, often fatal form of the disease in which massive sections of the liver are destroyed.

Patients typically recover from acute hepatitis. In some patients, however, high levels of viral antigen persist in the blood for an extended, or indefinite, period, causing a chronic infection. Chronic infections can lead to chronic persistent hepatitis. Patients infected with chronic persistent HBV are most common in developing countries. By mid-1991, there were approximately 225 million chronic carriers of HBV in Asia alone, and worldwide, almost 300 million carriers. Chronic persistent hepatitis can cause fatigue, cirrhosis of the liver, and hepatocellular carcinoma, a primary liver cancer.

In western industrialized countries, high risk groups for HBV infection include those in contact with HBV carriers or their blood samples. The epidemiology of HBV is very
2

IPO DELHI 23-06-201.5 15:59
similar to that of acquired immune deficiency syndrome, which accounts for why HBV infection is common among patients infected with HIV or AIDS. However, HBV is more contagious than HIV.

Both FTC and 3TC exhibit activity against HBV. Furman, et al., "The Anti-Hepatitis $B$ Virus Activities, Cytotoxicities, and Anabolic Profiles of the ( - ) and ( + ) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-oxathiolane-5-yil]-Cytosine" Antimicrobial Agents and Chemotherapy, December 1992, pp. 2686-2692; and Cheng, et al., Journal of Biological Chemistry, Volume 267(20), pp.13938-13942 (1992).

A human serum-derived vaccine has been developed to immunize patients against HBV. While it has been found effective, production of the vaccine is troublesome because the supply of human serum from chronic carriers is limited, and the purification procedure is long and expensive. Further, each batch of vaccine prepared from different serum must be tested in chimpanzees to ensure safety. Vaccines have also been produced through genetic engineering. Daily treatments with a- interferon, a genetically engineered protein, has also shown promise.

Hepatitis C virus (" HCV ") is the major causative agent for post-transfusion and for sporadic non A, non B hepatitis (Alter, H. J. (1990) J. Gastro. Hepatol. 1:78-94; Dienstag, J. L. (1983) Gastro 85:439-462). Despite improved screening, HCV still accounts for at least $25 \%$ of the acute viral hepatitis in many countries (Alter, H. J. (1990) supra; Dienstag, J. L. (1983) supra; Alter M. J. et al, (1990a) J.A.M.A. 264:223i-2235; Alter M.J. et al (1992) N. Engl. J. Med. 32́7:1899-1905; Alter, M.J. et al. (1990b) N. Angl. J. Med. 321:1494-1500). Infection by HCV is insidious in a high proportion of chronically infected (and infectious) carriers who may not experience clinical symptoms for many years. The high rate of progression of acute infection to chronic infection (70-100\%) and liver disease ( $>50 \%$ ), its world-wide distribution and lack of a vaccine make HCV a significant cause of morbidity and mortality.

A tumor is an unregulated, disorganized proliferation of cell growth. A tumor is malignant, or cancerous, if it has the properties of invasiveness and metastasis. Invasiveness ${ }^{\boldsymbol{}}$ refers to the tendency of a tumor to enter surrounding tissue, breaking through the basal laminas that define the boundaries of the tissues, thereby often entering the body's circulatory
system. Metastasis refers to the tendency of a tumor to migrate to other areas of the body and establish areas of proliferation away from the site of initial appearance.

Cancer is now the second leading cause of death in the United States. Over $8,000,000$ persons in the United States have been diagnosed with cancer, with 1,208,000 new diagnoses expected in 1994. Over 500,000 people die annually from the disease in this country.

Cancer is not fully understood on the molecular level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or radiation, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene". Suppressive genes are growth regulatory genes, which upon mutation, can no longer control cell growth. Oncogenes are initially normal genes (called prooncongenes) that by mutation or altered context of expression become transforming genes. The products of transforming genes cause inappropriate cell growth. More than twenty different normal cellular genes can become oncogenes by genetic alteration. Transformed cells differ from normal cells in many ways, including cell morphology, cell-to-cell interactions, membrane content, cytoskeletal structure, protein secretion, gene expression and mortality (transformed cells can grow indefinitely).

All of the various cell types of the body can be transformed into benign or malignant tumor cells. The most frequent tumor site is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary. Other prevalent types of cancer include leukemia, central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer.

Cancer is now primarily treated with one or a combination of three years of therapies: surgery, radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon, and skin, it cannot be used in the treatment of tumors located in other areas, such as the backbone, nor in the treatment of disseminated neoplastic conditions such as leukemia.

Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of leukemia, as well as breast, lung, and testicular cancer.

There are five major classes of chemotherapeutic agents currently in use for the treatment of cancer: natural products and their derivatives; anthacyclines; alkylating agents;
antiproliferatives (also called antimetabolites); and hormonal agents. Chemotherapeutic agents are often referred to as antineoplastic agents.

The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A disadvantage with these compounds is that they not only attach malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue.

Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription-of-nueleic acids.

Several synthetic nucleosides have been identified that exhibit anticancer activity., A well known nucleoside derivative with strong anticancer activity is 5-fluorouracil. 5Fluorouracil has been used clinically in the treatment of malignant tumors, including, for example, carcinomas, sarcomas, skin cancer, cancer of the digestive organs, and breast cancer. 5-Fluorouracil, however, causes serious adverse reactions such as nausea, alopecia, diarrhea, stomatitis, leukocytic thrombocylopenia, anorexia, pigmentation, and edema. Derivatives of 5 -fluorouracil with anti-cancer activity have been described in U.S. Patent No 4,336,381, and in Japanese patent publication Nos. 50-50383, 50-50384, 50-64281, 51146482, and 53-84981.
U.S. Paten! No. 4,000,137 discloses that the peroxidate oxidation product of inosine, adenosine, or cytidine with methanol or ethanol has activity against lymphocytic leukemia.

Cytosine arabinoside (also referred to as Cytarabin, araC, and Cytosar) is a nucleoside analog of deoxycytidine that was first synthesized in 1950 and introduced into clinical medicine in 1963. It is currently an important drug in the treatment of acute myeloid leukemia. It is also active against acute lymphocytic leukemia, and to a lesser extent, is useful in chronic myelocytic leukemia and non-Hodgkin's lymphoma. The primary action of araC is inhibition of nuclear DNA synthesis. Handschumacher, R. and Cheng, Y., "Purine and Pyrimidine Antimetabolites", Cancer Medicine, Chapter XV-1, 3rd Edition, Edited by J. Holland, et al., Lea and Febigol, publishers.

5-Azacytidine is a cytidine analog that is primarily used in the treatment of acute myelocytic leukemia and myelodysplastic syndrome.

2-Fluoroadenosine-5'-phosphate (Fludara, also referred to as FaraA)) is one of the most active agents in the treatment of chronic lymphocytic leukemia. The compound acts by inhibiting DNA synthesis. Treatment of cells with F -araA is associated with the accumulation of cells at the G1/S phase boundary and in $S$ phase; thus, it is a cell cycle $S$ phase-specific drug. Incorporation of the active metabolite, F-araATP, retards DNA chain elongation. F-araA is also a potent inhibitor of ribonucleotide reductase, the key enzyme responsible for the formation of $\mathrm{d} A T P$.

2-Chlorodeoxyadenosine is useful in the treatment of low grade B-cell neoplasms such as chronic lymphocytic leukemia, non-Hodgkins' lymphoma, and hairy-cell leukemia.

In designing new biologically active nucleosides, there have been a number of attempts to incorporate a fluoro substituent into the carbohydrate ring of the nucleoside. Fluorine has been suggested as a substituent because it might serve as an isopolar and isosteric mimic of a hydroxyl group as the C-F bond length ( $1.35 \AA$ ) is so similar to the C-O bond length ( $1.43 \AA$ ) and because fluorine is a hydrogen bond acceptor. Fluorine is capable of producing significant electronic changes in a molecule with minimal steric perturbation. The substitution of fluorine for another group in a molecule can cause changes in substrate metabolism because of the high strength of the C-F bond ( $116 \mathrm{kcal} / \mathrm{mol}$ vs. $\mathrm{C}-\mathrm{H}=100$ $\mathrm{kcal} / \mathrm{mol})$.

A number of references have reported the synthesis and use of $2^{\prime}$-arabinofluoronucleosides (i.e., nucleosides in which a 2 'fluoro group is in the "up"-configuration). There have been several reports of 2-fluoro- $\beta$-D-arabinofuranosyl nucleosides that exhibit activity against hepatitis B and herpes. See, for example, U.S. Patent No. 4,666,892 to Fox, et al.; U.S. Patent No. 4,211,773 to Lopez, et al; Su, et al., Nucleosides. 136, "Synthesis and Antiviral Effects of Several 1-(2-Deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-5-alkyluracils." "Some Structure-Activity Relationships," J. Med. Chem., 1986, 29, 151-154; Borthwick, et al., "Synthesis and Enzymatic Resolution of Carbocyclic 2'-Ara-fluoro-Guanosine: A Potent New Anti-Herpetic Agent," J. Chem. Soc., Chem. Commun, 1988; Wantanabe, et al., "Synthesis and Anti-HIV Activity of 2'-"Up"-Fluoro Analogues of Active Anti-Aids Nucleosides 3'-Azido-3'-deoxythymidine (AZT) and 2',3'-dideoxycytidine (DDC)," J. Med.

Chem 1990, 33, 2145-2150; Martin, et al.. "Synthesis and Antiviral Activity of Monofluoro and Difluoro Analogues of Pyrimidine Deoxyribonucleosides against Human Immunodeficiency Virus (HIV-1)," J. Med., Chem. 1990, 33, 2137-2145; Sterzycki, et al., "Synthesis and Anti-HIV Activity of Several 2'-Fluoro-Containing Pyrimidine Nucleosides," J. Med. Chem. 1990, as well as EPA 0316017 also filed by Sterzycki, et al.; and Montgomery, et al., "9-(2-Deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)guanine: A Metabolically Stable Cytotoxic Analogue of 2'-Deoxyguanosine." U.S. Patent No. 5,246,924 discloses a method for treating a hepatitis infection that includes the administration of 1-( $2^{\prime}$-deoxy-2'-fluoro- $\beta$-D-arabinofuranosyl)-3-ethyluracil), also referred to as "FEAU." U.S. Patent No. 5,034,518 discloses 2 -fluoro-9-(2-deoxy-2-fluoro- $\beta$-D-arabino-furanosyl)adenine nucleosides which exhibit anticancer activity by altering the metabolism of adenine nucleosides by reducing the ability of the compound to serve as a substrate for adenosine. EPA 0292023 discloses that certain $\beta$-D-2'-fluoroarabinonucleosides are active against viral infections.
U.S. Patent No. 5,128,458 discloses $\beta$-D-2', $3^{\prime}$-dideoxy-4'-thioribonucleosides as antiviral agents. U.S. Patent No. 5,446,029 discloses that $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-fluoronucleosides have antihepatitis activity.

European Patent Application No. 0409227 A2 discloses certain 3'-substituted $\beta$-Dpyrimidine and purine nucleosides for the treatment of hepatitis $B$.

It has also been disclosed that L-FMAU (2'-fluoro-5-methyl-
$\beta$-L-arabinofuranosyluracil) is a potent anti-HBV and anti-EBV agent. See Chu, et al., "Use of 2'-Fluoro-5-methyl- $\beta$-L-arabinofuranosyluracil as a Novel Antiviral Agent for Hepatitis B Virus and Epstein-Barr Virus" Antimicrobial Agents and.Chemotherapy, April 1995 pages. 979-981; Balakrishna, et al., "!nhibition of Hepatitis B Virus by a Novel L-Nucleoside, 2'-Fluoro-5-Methyl- $\beta$-L-arabinofuranosyl Uracil," Antimicrobial Agents and Chemotherapy, Feb 1996, pages 380-356; U.S. Patent Nos. 5,587,362; 5,567,688; and 5,565,438.
U.S. Patent Nos. 5,426,183 and 5,424,416 disclose processes for preparing 2'-deoxy2', 2'-difluoronucleosides and 2'-deoxy-2'-fluoro nucleosideș. See also "Kinetic Studies of 2',2'-difluorodeoxycytidine (Gemcitabine) with Purified Human Deoxycytidine Kinase and Cytidine Deaminase,". BioChemical Pharmacology, Vol. 45 (No. 9) pages 4857-1861, 1993.
U.S. Patent No. 5,446,029 to Eriksson, et al., discloses that certain 2', $3^{\prime}$-dideoxy-3'. fluoronucleosides have hepatitis B activity. U.S. Patent No. 5,128,458 discloses certain 2',3'-
dideoxy-4'-thioribonucleosides wherein the 3 '-substituent is H , azide or fluoro. WO 94/14831 discloses certain 3'-fluoro-dihydropyrimidine nucleosides. WO 92/08727 discloses $\beta-L-2 '$-deoxy-3'-fluoro-5-substituted uridine nucleosides for the treatment of herpes simplex 1 and 2.

EPA Publication No. 0352248 discloses a broad genus of L-ribofuranosyl purine nucleosides for the reatment of HIV, herpes, and hepatitis. While certain 2'-fluorinated purine nucleosides fall within the broad genus, there is no information given in the specification on how to make these compounds in the specification, and they are not among specifically disclosed or the preferred list of nucleosides in the specification. The specification does disclose how to make 3 "-ribofuranosyl fluorinated nucleosides. A similar specification is found in WO 88/09001, filed by Aktiebolaget Astra.

European Patent Application 0357571 discloses a broad group of $\beta-D$ and $\alpha-D$ pyrimidine nucleosides for the treatment of AIDS which among the broad class generically includes nucleosides that can be substituted in the 2' or 3'-position with a fluorine group. Among this broad class, however, there is no specific disclosure of $2^{\prime}$-fluorinated nucleosides or a method for their production.

EPA 0463470 discloses a process for the preparation of (5S)-3-fluoro-tetrahydro-5-[(hydroxy)methyl]-2-(3H)-furanone, a known intermediate in the manufacture of $2^{\prime}$-fluoro$2^{\prime}, 3^{\prime}$-dideoxynucleosides such as $2^{\prime}$-fluoro- $2^{\prime}, 3^{\prime}$-dideoxycytidine.
U.S.S.N. 07/556,713 discloses $\beta$-D-2'-fluoroarabinofuranosyl nucleosides, and a method for their production, which are intermediates in the synthesis of $2^{\prime}, 3^{\prime}$-dideoxy- $\mathbf{2}^{\prime}$ fluoroarabinosyl nucleosides.
U.S. Patent No. 4,625,020 discloses a method of producing 1-halo-2-deoxy-2fluoroarabinofuranosyl derivatives bearing protective ester groups from 1,3,5-tri-O-acylribofuranose.

There appears to be a lack of disclosure of $\beta$-L-2'-fluoro-ribofuranosyl nucleosides for medicinal uses, including for HIV , hepatitis ( B or C ), or proliferative c̣onditions. At least with respect to 2 '-ribofuranosyl nucleosides, this may be because of the prior perceived difficulty in placing a fluoro group in the 2 'ribofuranosyl configuration. With respect to L -$2^{\prime}$-fluoro- $2^{\prime}, 3^{\prime}$-unsaturated purine nucleosides, it may be because the purine nucleösides are. unstable in acidic media, resulting in glycosyl bond cleavage.

In light of the fact that HIV acquired immune deficiency syndrome. AIDS-related complex, and hepatitis $B$ and $C$ viruses have reached epidemic levels worldwide, and have tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat these diseases that have low toxicity to the host. Further, there is a need to provide new antiproliferative agents.

Therefore, it is an object of the present invention to provide a method and composition for the treatment of human patients infected with hepatitis B or C .

It is another object of the present invention to provide a method and composition for the treatment of human patients infected with HIV.

It is a further object of the present invention to provide new antiproliferative agents.
It is still another object of the present invention to provide a new process for the preparation of 2 '-fluoro-ribofuranosȳ] nucleosides.

It is yet another object of the present invention to provide a new process for the preparation of $2^{\prime \prime}, 3^{\prime}$-dideoxy- $2^{\prime}, 3^{\prime}$-didehydro-2'-fluoro-L-glycero-pent-2-eno-furanosyl nucleosides.

## SUMMARY OF THE INVENTION

In one embodiment of the invention, a 2 '- $\alpha$-fluoro-nucleoside is provided of the structure:
wherein
Base is a purine or pyrimidine base as defined further herein;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy, and base refers to a purine or pyrimidine base;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vico, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, including a phospholipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound.

In a second embodiment, a $2^{\prime}$-fluoronucleoside is provided of the formula:
wherein the substituent are as defined above.
In a third embodiment, a 2'-fluoronucleoside is provided of the formula:

wherein the substituent are as defined above.
In a fourth embodiment, a 2 '-fluoronucleoside is provided of the structure:

whercin the substituents are as defined above.
These 2 '-fluoronucleosides can be either in the $\beta$-L or $\beta$ - D configuration. The $\beta-\mathrm{L}$ configuration is preferred.

The 2'-fluoronucleosides are biologically active molecules which are useful in the treatment of hepatitis B , hepatitis C or HIV. The compounds are also useful for the treatment of abnormal cellular proliferation, including tumors and cancer. One can easily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.

In another embodiment, for the treatment of hepatitis or HIV, the active compound or its derivative or salt can be administered in combination or alternation with another antiviral agent, such as an anti-HIV agent or anti-hepatitis agent, including those of the formula above. In general, in combination therapy, an effective dosage of two or more agents are administered together, whereas during alternation therapy, an effective dosage of each agent is administered serially, The dosages will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supcrvising the administration of the compositions.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include 2-hydroxymethyl-jं-(5-fluorocytosin-1-yl)-1,3oxathiolane (FTC); the ( - -enantiomer of 2-hydroxymethyl-5(cytosin-1-yl)-1,3-oxathiolane (3TC); carbovir, acyclovir, interferon, famciclovir, penciclovir, AZT, DDI, DDC, D4T, abacavir, L-(-).FMAU, L-DDA phosphate prodrugs, and $\beta$-D-dioxolane nucleosides such as $\beta$-D-dioxolanyl-guanine (DG), $\beta$-D-dioxolanyl-2,6-diaminopurine (DAPD), and $\beta$-D-dioxolanyl-6-chioropurine (ACP), non-nucleoside RT inhibitors such as nevirapine, MKC-
442. DMP-266 (sustiva) and also protease inhibitors such as indinavir, saquinavir, AZT, DMP-450 and others

The compounds can also be used to treat equine infectious anemia virus (EIAV), feline immunodeficiency virus; and simian immunodeficiency virus. (Wang, S., Montelaro, R., Schinazi, R.F., Jagerski, B., and Mellors, J.W.: "Activity of nucleoside and nonnucleoside reverse transcriptase inhibitors (NNRTI) against equine infectious anemia virus (EIAV)." First National Conference on Human Retro-viruses and Related Infections, Washington, DC, Dec. 12-16, 1993; Sellon D.C., "Equine Infectious Anemia," Vet. Clin. North Am. Equine Pract. UnitedStates, 9: 321-336, 1993; Philpott, M.S., Ebner, J.P., Hoover, E.A., "Evaluation of 9-(2-phosphonylmethoxyethyl) adenine therapy for feline immunodeficiency virus using a quantitative polymerase chain reaction," Vet. Immunol. Immunopathol. $35: 155166,1992$ :)

A new and completely diastereoselective method for the introduction of fluorine into a non-carbohydrate sugar ring precursor is also provided. The method includes reacting a chiral, non-carbohydrate sugar ring precursor (4S)-5-(protected oxy)-pentan-4-olide, which can be prepared from L-glutamic acid, with an electrophilic source of fluorine, including but not limited to $N$-fluoro-(bis)benzenesulfonimide, to yield key intermediate fluorolactone 6. The fluorolactone is reduced to the lactol and acetylated to give the anomeric acetate and then used for the synthesis of a number of novel $\beta-\mathrm{L}-\alpha-2$ '-fluoronucleosides. The corresponding $D$-enantiomer can also be synthesized using $D$-glutamic acid as a starting material.

In an-alternative embodiment, a fluorinated glycal is prepared which is dehydrogenated and then converted to ${ }^{\prime}{ }^{2} 2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}, 3^{\prime}$-didehydro- $2^{\prime}$-fluoronucleoside or a $\beta$-L or $\beta$-D-arabinosyl-2'-fluoronucleoside, as discussed further below.

A method for the facile prcparation of $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}, 3^{\prime}$-didehydro- $2^{\prime}$ fluoronucleosides is also presented that includes the direct condensation of silylated 6chloropurine with key immediate, which is prepared from $\dot{\text { L }}$-2,3-0-isopropylidene -glyceraldenhyde.

## DETAILED DESCRIPTION OF THE INVENTION

The invention as disclosed herein is a compound, method and composition for the treatment of HIV, hepatitis ( B or C ), or abnormal cellular proliferation, in humans or other
host animals, that includes administering an effective.amount of a 2'-fluoro-nucleoside, a pharmaceutically acceptable derivative, including a compound which has been alkylated or acylated at the 5'-position or on the purine or pyrimidine, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. The compounds of this invention either possess antiviral (i.e., anti-HIV-1, anti-HIV-2, or anti-hepatitis ( B or C)) activity, or antiproliferative activity, or are metabolized to a compound that exhibits such activity.

In summary, the present invention includes the following features:
(a) $\quad \beta$-L and $\beta$-D-2'-fluoronucleosides, as described herein, and pharmaceutically acceptable derivatives and salts thereof;
(b) $\quad \beta-L$ and $\beta$-D-2'-fluoronucleosides as described herein, and pharmaceutically acceptable derivatives and salts thereof for use in medical therapy, for example for the treatment or prophylaxis of an HIV or hepatitis ( B or C ) infection or for the treatment of abnormal cellular proliferation;
(c) 2',3':Dideoxy-2',3'-didehydro-2'-fluoro-L-glycero-pen-2-eno-furanosyl nucleosides, and pharmaceutically acceptable derivatives and salts thereof for use in medical therapy, for example for the treatment or prophylaxis of an HIV or hepatitis (B or C) infection or for the treatment of abnormal cellular proliferation
(d) use of these $2^{2}$-fluoronucleosides, and pharmaceutically acceptable derivatives and salts thereof in the manufacture of a medicament for treatment of an HIV or hepatitis infection orfor the treatment of abnormal cellular proliferation;
(e) pharmaceutical formulations comprising.thè 2'-fluoronucleosides or a pharmaceutically acceptable derivative or salt thereof together with a pharmaceutically acceptable carrier or diluent;
(f) processes for the preparation of $\beta-\mathrm{L}$ and $\beta-\mathrm{D}-2^{\prime}-\alpha$-fluoronucleosides, as described in more detail below, and
(g) proceseses for the preparation of $2^{\prime}, 3^{\prime}$-dideoxy-2',3'-didehydro-2'-fluoro-L-glycero-pent-2-eno-furanosyl nucleosides.

## 1. Active Compound, and Physiologically Acceptable Derivatives and Salts Thereof

A $2^{\prime}-\alpha$-fluoro-nucleoside is provided of the structure:

wherein $\mathrm{R}^{1}$ is $\mathrm{H}, \mathrm{OH}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy, and base refers to a purine or pyrimidine base. • $\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate, sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterc!; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound.

In a second embodiment, a 2 -fluoronucleoside is provided of the formula:

$\mathrm{Y}=\mathrm{O}, \mathrm{S}, \mathrm{CH}_{2}, \mathrm{CHF}$

In a third embodiment, a 2 -fluoronucleoside is provided of the formula:

$\mathrm{X}=\mathrm{S}, \mathrm{CH}_{2}$

In a fourth embodiment, a 2-fluoronucleoside is provided of the structure:


$$
\mathrm{X}=\mathrm{S}, \mathrm{CH}_{2}
$$

The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of $\mathrm{C}_{1}$ to $\mathrm{C}_{10}$, and specifically includes methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, $t$-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl,2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons; Second Edition, 1991, hereby incorporated by reference.

The term lower alkyl, as used herein, and unless otherwise specified, refers to a $C_{1}$ to $\mathrm{C}_{4}$ saturated straight, branched, or if appropriate, a cyclic (for example, cyclopropyl) alkyl group.

The term alkylamino or arylamino refers to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "protected" as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis. The term aryl, as used herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl, and preferably phenyl. The aryl group can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphoric acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as
known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons. Second Edition, 1991.

The term alkaryl or alkylaryl refers to an alkyl group with an aryl substituent. The term aralkyl or arylalkyl refers to an aryl group with an alkyl substituent.

The term halo, as used herein, includes chloro, bromo, jodo, and fluors.
The term purine or pyrimidine base includes, but is not limited to, adenine, $\mathrm{N}^{6}$ alkylpurines, $\mathrm{N}^{6}$-acylpurines (wherein acyl is $\mathrm{C}(\mathrm{O})$ (alkyl, aryl, alkylaryl, or arylalkyl), $\mathrm{N}^{6}$ benzylpurine, $\mathrm{N}^{6}$-halopurine, $\mathrm{N}^{6}$-vinylpurine, $\mathrm{N}^{6}$-acetylenic purine, $\mathrm{N}^{6}$-acyl purine, $\mathrm{N}^{6}$-hydroxyalkyl purine, $\mathrm{N}^{6}$-thioalkyl purine, $\mathrm{N}^{2}$-alkylpurines, $\mathrm{N}^{2}$-alkyl-6-thiopurines, thymine, cytosine, 5 -fluorocytosine, 5 -methylcytosine, 6 -azapyrimidine, including 6 -azacytosine, $2<$ and/or 4 -mercaptopyrmidine, uracil, 5 -halouracil, including 5 -fluorouracil, $C^{s}$-alkylpyrimidines, $C^{s}$-benzylpyrimidines, $C^{s}$-halopyrimidines, $C^{s}$-vinylpyrimidine, $C^{s}$ acetylenic pyrimidine, $\mathrm{C}^{5}$-acyl pyrimidine, $\mathrm{C}^{5}$-hydroxyalkyl purine, $\mathrm{C}^{5}$-amidopyrimidine, $\mathrm{C}^{5}$ cyanopyrimidine, $\mathrm{C}^{5}$-nitropyrimidine, $\mathrm{C}^{5}$-aminopyrimídine, $\mathrm{N}^{2}$-alkylpurines, $\mathrm{N}^{2}$-alkyl-6thiopurines; 5 -azacytidinyl, 5-azauracilyl, triazolopyridinyl; imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6 -diaminopurine, and 6 -chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, $t$-butyldimethylsilyl, and $t$-butyldiphenylsilyl, trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The active compound can be administered as any derivative that upon administration to the recipient, is capable of providing directly or indirectly, the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiotogically acceptable salts"), and a compound which has been alkylated or acylated at the 5 '-position or on the purine or pyrimidine base (alternatively referred to as "pharmaceutically acceptable derivatives"). Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the derivative and testing its antiviral activity according to the methods described herein, or other method known to those skilled in the art.

The term acyl refers to a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from straight, branched, or cyclic alkyl or lower alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, $C_{1}$ to $C_{4}$ alkyl or $C_{1}$ to $C_{4}$ alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group.

As used herein, the term "substantially free of" or "substantially in the absence of" refers to a nucleoside composition that includes' at least $95 \%$ to $98 \%$, or more preferably, $99 \%$ to $100 \%$, of the designated enantiomer of that nucleoside.

## Nucleotide Prodrug Formulations

Any of the nucleosides described herein can be administrated as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotidẽ prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol anịd alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

The active nucleoside can also be provided as a 5'-phosphoether lipid or a 5'-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L.S., N. lyer, E. Leake, A. Raben, Modest E.K., D.L.W., and C. Piantadosi. 1990. "Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation." AIDS Res. Hum. Retro Viruses. 6:491-501; Piantadosi, I C., J. Marasco C.J.; S.L. Morris-Natschke, K.L. Meyer, F. Gumus, J.R. Surles, K.S. Ishaq, L.S. Kucera, N. lyer, C.A. Wallen, S. Piantadosi, and E.J. Modest. 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity." J. Med. Chem. 34:1408.1414; Hosteller, K.Y., D.D. Richman, D.A. Carson, L.M. Stuhmiller, G.M. T. van Wijk, and H. van den Bosch. 1992. "Greatly enhanced inhibition of human
immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 31 -deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3,-deoxythymidine." Antimicrob. Agents Chemother. 36:2025.2029; Hosetler, K.Y., L.M. Stuhmiller, H.B. Lenting, H. van den Bosch, and D.D. Richman, 1990. "Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." J. Biol. Chem. 265:61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituents that can be covalently incorporated into the nucleoside, preferably at the 5 ' -OH position of the nucleoside or lipophilic preparations, include U.S. Patent Nos. 5,149,794 (Sep. 22, 1992, Yatvin et al.); 5,194,654 (Mar. 16, 1993, Hostetler et al., 5,223,263 (June 29, 1993, Hostetler et al.); 5,256,641 (Oct. 26, 1993, Yatvin et al.); 5,411,947 (May 2, 1995, Hostetler et al.); 5,463,092 (Oct. 31, 1995, Hostetler et al.); 5,543,389 (Aug. 6, 1996, Yatvin et al.); 5,543,390 (Aug. 6, 1996, Yatvin et al.); 5,543,391 (Aug. 6, 1996, Yatvin et al.); and 5,554,728 (Sep. 10, 1996; Basava et al.), all of which arc incorporated herein by reference. Foreign patent applications that disclose lipophilic substituents that can be attached to the nucleosides of the present invention, or lipophilic preparations, include WO 89/02733, W0 90/00555, w0 91/16920, W0 91/18914, W0 93/00910, W0 94/26273, W0 96/15132, EP 0350 287, EP 93917054.4, and W0 91/19721.

Nonlimiting examples of nucleotide prodrugs are described in the following references: Ho, D.H.W. (1973) "Distribution of Kinase and deaminase of $1 \beta-D$ arabinofuranosylcytosine in tissues of man and muse." Cancer Res. 33, 2816-2820; Holy, A. (1993) Isopolar phosphorous-modified nucleotide analogues," In: De Clercq (Ed.), Advances in Antiviral Drug Design, Vol. I, JAI Press, pp. 179-231; Hong, C.I., Nechaev, A:, and West, C.R. (1979a) "Synthesis and antitumor activity of 1- $\beta$-D-arabino-furanosylcytosine conjugates of cortisol and cortisone:" Bicohem. Biophys. Rs. Commun. 88, 1223-1229; Hong, C.I., Nechaev, A., Kirisits, A.J. Buchheit, D.J. and West, C.R. (1980) "Nucleoside conjugates as potential antitumor agents. 3. Synthesis and antitumor activity of 1-( $\beta$-Darabinofuranosyl) cyiosine conjugates of corticosteriods and selected lipophilic alcohols." J . Med. Chem. 28, 171-177; Hosteller, K.Y., Stuhmiller, L.M., Lenting, H.B.M. van den Bosch, H. and Richman J. Biol. Chem. 265, 6112-6117; Hosteller, K.Y., Carson, D.A. and Richman, D.D. (1991); "Phosphatidylazidothymidine: mechanism of antiretróviral action in-CEM cells." J. Biol Chem. 266, 11714-11717; Hosteller, K.Y., Korba, B. Sridhar, C., Gardener, M.
(1994a) "Antiviral activity of phosphatidyl-dideoxycytidine in hepatitis B-infected cells and enhanced hepatic uptake in mice." Antiviral Res. 24,59-67; Hosteller, K.Y., Richman, D.D., Sridhar. C.N. Felgner, P.L. Felgner, J., Ricci, J., Gardener, M.F. Selleseth, D.W. and Ellis, M.N. (1994b) "Phosphatidylazidothymidine and phosphatidyl-ddC: Assessment of uptake in mouse lymphoid tissues and antiviral activities in human immunodeficiency virus-infected cells and in rauscher leukemia virus-infected mice." Antimicrobial Agents Chemother. 38, 2792-2797; Hunston, R,N., Jones, A.A. McGuigan, C., Walker, R.T., Balzarini, J., and DeClercq, E. (1984) "Synthesis and biological properties of some cyclic phosphotriesters derived from 2'-deoxy-5-flourouridine." J. Med. Chem. 27, 440-444; Ji, Y.H., Moog, C., Schmitt, G., Bischoff, P. and Luu, B. (1990); "Monophosphoric acid esters of 7- $\beta$ hydroxycholesterol and of pyrimidine nucleoside as potential antitumor agents: synthesis and preliminary evaluation of antitumor activity." J. Med. Chem. 33 2264-2270; Jones, A.S., McGuigan, C., Walker, R.T., Balzarini, J. and DeClercq, E. (1984) "Syntheșis, properties, and biological activity of some nucleoside cyclic phosphoramidates." J. Chem. Soc. Perkin Trans. I, 1471-1474; Juodka, B.A. and Smrt, J. (1974) "Synthesis of diribonucleoside phosph (P-N) amino acid derivatives." Coll. Czech. Chem. Comm. 39, 363-968; Kataoka, S., Imai, J., Yamaji, N., Kato, M., Saito, M., Kawada, T. and Imai, S. (1989) "Alkylated cAMP derivatives; selective synthesis and biological activities." Nucleic Acids Res. Sym. Ser. 21, 12; Kataoka, S., Uchida, "(cAMP) benzyl and methyl triesters." Heterocycles 32, 1351-1356; Kinchington, D., Harvey, J.J., O'Connor, T.J., Jones, B.C.N.M., Devine, K.G., TaylorRobinson D., Jeffries, D.J. and McGuigan, C. (1992) "Comparison of antiviral effects of zidovudine phosphoramidate an dphosphorodiamidate derivates against HIV and ULV in vitro." Antiviral Chem. Chemöther ${ }^{\text {3 }}$, 107-112; Kodama, K", Morozumi, M., Saithoh, K:I., Kuninaka, H.,'Yosino, H. and Saneyoshi, M. (1989) "Antitumor activity and pharmacology of 1- $\beta$ - $D$-arabinofuranosylcytosine - 5 '-stearylphosphate; an orally active derivative of 1- $\beta$-Darabinofuranosylcytosine." Jpn. J. Cancer Res. 80, 679-685; Korty, M. and Engels, J. (1979) "The effects of adenosine- and guanosine 3 ',5' phosphoric and acid benzyl esters on guineapig ventricular myocardium." Naunyn-Schmiedeberg's Arch. Pharmacol. 310, 103-111; Kumar, A., Goe, P.L., Jones, A.S. Walker, R.T. Balzarini, J. and DeClercq, E. (1990) "Synthesis and biological evaluation of some cyclic phosphoramidate nucleoside derivatives." - J. Med. Chem, 33, 2368-2375; LeBec, C., and Huynh-Dinh, T. (1991). "Synthesis of lipophilic
phosphate triester derivatives of 5 -fluorouridine an arabinocytidine as anticancer prodrugs." Tetrahedron Lett. 32, 6553-6556; Lichtenstein, J., Bamer, H.D. and Cohen, S.S: (1960) "The metabolism of exogenously supplied nucleotides by Escherichia coli.," J. Biol. Chem. 235, 457-465; Lucthy, J., Von Daeniken, A., Friederich, J. Manthey, B., Zweifel, J., Schlatter, C. and Benn, M.H. (1981) "Synthesis and toxicological properties of three naturally occurring cyanoepithioalkanes.". Mitt. Geg. Lebensmittelunters. Hyg. 72, 131-133 (Chem. Abstr. 95, 127093); McGigan, C. Tollerfield, S.M. and Riley, P.a. (1989) "Synthesis and biological evaluation of some phosphate triester derivatives of the anti-viral drug Ara." Nucleic Acids Res. 17, 6065-6075; McGuigan, C., Devine, K.G., O'Connor, T.J., Galpin, S.A., Jeffries, D.J. and Kinchington, D. (1990a) "Synthesis and evaluation of some novel phosphoramidate derivatives of $3^{\prime}$-azido-3'-deoxythymidine (AZT) as anti-HIV compounds." Antiviral Chem. Chemother. 1 107-113; McGuigan, C., O'Connor, T.J., Nicholls, S.R. Nickson, C. and Kinchington, D. (1990b) "Synthesis and anti-HIV activity' of some novel substituted dialkyl phosphate derivatives of AZT and ddCyd." Antiviral Chem. 'Chemother. 1, 355-360;
McGuigan, C., Nicholls, S.R.; O'Connor, T.J., and Kinchington, D. (1990c) "Synthesis of some novel dialkyl phosphate derivative of 3 '-modified nucleosides as potential anti-AIDS drugs." Antiviral Chem. Chemother. 1, 25-33; McGuigan, C., Devin, K.G., O'Connor, T.J., and Kinchington, D. '(1991) "Synthesis and anti-HIV activity of some haloalkyl phosphoramidate derivatives of $3^{\prime}$-azido-3'-deoxythylmidine (AZT); potent activity of the trichloroethyl methoxyalaninyl compound." Antiviral Res. 15, 255-263; McGuigan, C., Pathirana, R.N., Balzarini, J. and DeClercq, E. (1993b) "Intracellular delivery of bioactive AZT nucleotides by aryil phosphate derivatives of AZT." J. Med. Chem. 36, 1048-1052.

Alkyl hydrogen phosphate derivatives of the anti-HIV agent AZT may be less toxic than the parent nucleoside analogue. Antiviral Chem. Chemother. 5, 271-277; Meyer, R. B., Jr., Shuman, D.A. and Robins, R.K. (1973) "Synthesis of purine nucleoside 3', 5'-cyclic phosphoramidates." Tetrahedron Lett. 269-272; Nagyvary, J. Gohil, R.N., Kirchner, C.R. and Stevens, J.D. (1973) "Studies on neutral esters of cyclic AMP," Biochem. Biophys. Res. Commun. 55, 1072-1077; Namane, A. Gouyette, C., Fillion, M.P., Fillion, G. and HuynhDinh, T. (1992) "Improved brain delivery of AZT using a glycosyl phosphotriester prodrug." J. Med. Chem. 35, 3039-3044; Nargeot, J. Nerbonne, J.M. Engels, J. and Leser, H-A. (1983) Natl. Acad. Sci. U.S.A. 80, 2395-2399; Nelson, K.A., Bentrude, W.G. Stser, W.N. and

Hutchinson, J.P. (1987) "The question of chair-twist equilibria for the phosphate rings of nucleoside cyclic 3', 5' monophosphates. 'HNMR and x-ray crystallographic study of the diastereomers of thymidine phenyl cyclic 3 ', 5'-monophosphate." J. Am. Chem. Soc. 109, 4058-4064; Nerbonne, J.M., Richard, S., Nargeot, J. and Lester, H.A. (1984) "New photoactivatable cyclic nucleotides produce intracellular jumps in cyclic AMP and cyclic GMP concentrations." Nature 301, 74-76; Neumann, J.M., Hervé, M., Debouzy, J.C., Guerra, F.I., Gouyette, C., Dupraz, B. and Huyny-Dinh, T. (1989) "Synthesis and transmembrane transport studies by NMR of a glucosy! phospholipid of thymidine." J. Am. Chem. Soc. 111, 4270-4277; Ohno, R., Tatsumi, N., Hirano, M., Imai, K. Mizoguchi, H., Nakamura, T., Kosaka, M., Takatuski, K., Yamaya, T., Toyama K., Yoshida, T., Masaoka, T., Hashimoto, S., Ohshima, T., Kimura, I., Yamada, K. and Kimura, J. (1991) "Treatment of myelodysplastic syndromes with orally administered 1- $\beta$-D-arabinouranosylcytosine -5' stearylphosphate." Oncology 48, 451-455. Palomino, E., Kessle, D. and Horwitz, J.P. (1989) "A dihydropyridine carrier system for sustained delivery of 2 ', 3 ' dideoxynucleosides to the brain." J. Med. Chem. 32, 22-625; Perkins, R.M., Barney, S. Wittrock, R., Clark, P.H., Levin, R. Lambert, D.M., Petteway, S.R., Serafinowska, H.T., Bailey, S.M., Jackson, S., Harnden, M.R. Ashton, R., Sutton, D., Harvey, J.J. and Brown, A.G. (1993) "Activity of BRL47923 and its oral prodrug, SB203657A against a rauscher murine leukemia virus infection in mice." Antiviral Res. 20 (Suppl. I). 84; Piantadosi, C.; Marasco, C.J., Jr., NorrisNatschke, S.L.; Meyer, K.L., Gumus, F., Suries, J.R., Ishaq, K.S., Kucera, L.S. Iyer, N., Wallen, C.A., Piantadosi, S. and Modest $\boldsymbol{t}_{j}$ E.J. (1991) "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HiV-1 activity." J. Med. Chem. 34, 1408-1414; Pompon, A., Lefebvre, I., Imbach, J.L., Kahn, S. and Farquhar, D. (1994). "Decomposition pathways of the mono- and bis(pivaloyloxymethyl) esters of azidothymidine-5'-monophosphate in cell extract and in tissue culture medium; an application of the 'on-line ISRP-cleaning HPLC technique." Antiviral Chem Chemother. 5, 91-98; Postemark, T. (1974) "Cyclic AMP and cyclic GMP." Annu. Rev. Pharmacol. 14, 23-33; Prisbee, E.J., Martin, J.C.M., McGhée, D.P.C., Barker, M.F., Smee, D.F. Duke, A.E., Matthews, T.R. and Verheyden, J.P.J. (1986) "Synthesis and aniherpes virus activity of phosphate an phosphonate derivatives of 9-[(1,3-dihydroxy-2-propoxy)methyl] guanine." J. Med. Chem. 29, 671-675; Pucch, F., Gosselin, G., Lefebvre, I., Pompon, a., Aubertin, A.M. Dirn, and Imbach, J.L. (1993) "Intracellular delivery
of nucleoside monophosphate through a reductase-mediated activation process." Antivral Res. 22, 155-174; Pugaeva, V.P.. Klochkeva, S.I., Mashbits, F.D. and Eizengart, R.S. (1969). "Toxicological assessment and health standard ratings for ethylene sulfide in the industrial atmosphere." Gig. Trf. Prof. Zabol. 14, 47-48 (Chem. Abstr. 72, 212); Robins, R.K. (1984) "The potential of nucleotide analogs.as inhibitors of Retro viruses and tumors." Pharm. Res. 11-18; Rosowsky, A., Kim. S.H., Ross and J. Wick, M.M. (1982) "Lipophilic 5'(alkylphosphate) esters of $1-\beta$ - D -arabinofuranosylcytosine and its $\mathrm{N}^{4}$-acyl and $2.2^{1}$-anhydro$3^{\prime} 0$-acyl derivatives as potential prodrugs." J. Med. Chem. 25, 171-178; Ross, W. (1961) "Increased sensitivity of the walker turnout towards aromatic nitrogen mustards carrying basic side chains following glucose pretreatment." Biochem. Pharm. 8, 235-240; Ryu, E.K., Ross, R.J. Matsushita, T., MacCoss, M., Hong, C.l. and West, C.R. (1982). "Phospholipidnucleoside conjugates. 3. Synthesis and preliminary biological evaluation of 1- $\beta$-Darabinofuranosylcytosine 5 ' diphosphate [-], 2-diacylglycerols." J. Med. Chem. 25, 13221329; Saffhill, R. and Hume, W.J. (1986) "The degradation of 5-iododeoxyuridine and 5bromoethoxyuridine by serum from different sources and its consequences for the use of these compounds for incorporation into DNA." Chem. Biol. Interact. 57, 347-355; Saneyoshi, M., Morozumi, M., Kodama, K., Machida, J., Kuninaka, A. and Yoshino, H. (1980) "Synthetic nucleosides and nucleotides. XVI. Synthesis and biological evaluations of a series of 1- $\beta$-D-arabinofuranosylcytosine 5 '-alky or arỵlphosphates." Chem Pharm. Bull. 28, 2915-2923; Sastry, J.K., Nehete, P.N., Khan, S., Nowak, B.J., Plunkett, W., Arlinghaus, R.B. and Farquhar, D. (1992) "Membrane-permeable dideoxyuridine 5'-monophosphate analogue inhibits human immunodeficiency virus infection.". Mol. Pharmacol. 41, 441-445; Shaw, J.P., Jones, R.J. Arimilli, M.N., Louie, M.S., Lee, W.A. and Cundy, K.C. (1994) "Oral bioavailability of PMEA from PMEA prodrugs in male Sprague-Dawley rats." 9th Anniual AAPS Meeting. San Diego, CA (Abstract). Shuto, S., Ueda, S., Imamura, S., Fukukawa, K. Matsuda, A. and U'eda, T. (1987) " A facile one-step synthesis of 5' phosphatidylnucleosides by an enzymatic two-phase reaction." Teirahedron Lett. 28, 199-202; Shuto, S. Itoh, H., Ueda, S., Imamura, S., Kukukawa, K., Tsujino, M., Matsuda, A. and Ueda, T. (1988) Pharm. Bull. 36, 209-217. An example of a useful phosphate prodrug group is the S-acyl-2-thioethyl group, also referred to as "SATE".

## II. Combination and Alternation Therapy

It has been recognized that drug-resistant variants of HIV and HBV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication, and most typically in the case of HIV, reverse transcriptase, protease, or DNA polymerase, and in the case of HBV, DNA polymerase. Recently, it has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively; the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

The second antiviral agent for the treatment of HIV, in one embodiment, can be a reverse transcriptase inhibitor (a "RTI"), which can be either a synthetic nucleoside (a "NRTI") or a non-nucleoside compound (a "NNRTI"). In an alternative embodiment, in the case of HIV, the second (or third) antiviral agent can be a protease inhibitor. In other embodiments, the second (or third) compound can be a pyrophosphate analog, or a fusion binding inhibitor A list compiling resistance data collected in vitro and in vive for a number of antiviral compounds is found in Schinazi, et al, Mutations in retroviral genes associated with drug resistance, International Antiviral News, 1997.

Preferred compounds for combination or alternation therapy for the treatment of HBV include 3TC, FTC, L-FMAU, interferon, $\beta$-D-dioxolanyl-guanine (DXG), $\beta$-D-dioxolanyl-2,6-diaminopurine (DAPD), and $\beta$-D-dioxolanyl-6-chloropurine (ACP), famciclovir, penciclovir, BM'S-200475, bis pom PMEA (adefovir, dipivoxil); lobucavir, ganciclovir, and ribavarin.

Preferred examples of antiviral agents that can be used in combination or alteration with the compounds disclosed herein for HIV therapy include cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC); carbovir, acyclovir, foscarnet, interferon, AZT, DDI, DDC, D4T, CS-87 (3'-azido-2', $3^{\prime}$-dideoxy-uridine), and $\beta$-D-dioxolane nucleosides such as
$\beta$-D-dioxolanyl-guanine (DXG), $\beta$-D-dioxolanyl-2,6-diaminopurine (DAPD), and $\beta$-D-dioxolanyl-6-chloropurine (ACP), MKC-442 (6-benzyl-1-(ethoxymethyl)-5-isopropyl uracil.

Preferred protease inhibitors include crixivan (Merck), nelfinavir (Agouron), ritonavir (Abbott), saquinavir (Roche), DMP-266 (Sustiva) and DMP-450 (DuPont Merck).

A more comprehensive list of compounds that can be administered in combination or alternation with any of the disclosed nucleosides include. (1K,4R)-4-[2-amino-6-cyclopropyl. amino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate ("1592", a carbovir analog; GlaxoWellcome); 3TCC: (-)- $\beta$-L-2', $3^{\prime}$-dideoxy- $3^{\prime}$-thiacytidine (GlaxoWellcome); a-APA R18893: a-nitro-anilino-phenylacetamide; A-77003; C2 symmetry-based protease inhibitor (Abbott); A-75925: C2 symmetry-based protease inhibitor (Abbott); AAP-BHAP: bishetcroarylpiperazine analog (Upjohn); ABT-538: C2 symmetry-based protease inhibitor (Abbott); AzddU:3'-azido-2',3'-dideoxyuridine; AZT: 3'-azido-3'-deoxythymidine (GlaxoWellcome); AZT-p-ddI: $3^{\prime}$-azido- $3^{\prime}$-deoxythymidilyl-( $5^{\prime}, 5^{\prime}$ )-2', $3^{\prime}$-dideoxyinosinic acid (lvax); BHAP: bisheteroarylpiperazine; BILA 1906: $\mathrm{N}-\{1 \mathrm{~S}-[[[3-[2 \mathrm{~S}-\{(1,1-$ dimethylethyl)amino carbonyl\}-4R-]3-pyridinylmethyl)thio]-1 -piperidinyl]-2R-hydroxy-1S-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl \}-2-quinolinecarboxamide (Bio Mega/Boehringer-Ingelheim); BILA 2185: N -(1,1-dimethylethyl)-1-[2S-[[2-2,6-dimethyphenoxy)-1-oxoethyl]amino]-2R-hydroxy-4-phenylbutyll 4 R -pyridinylthio)-2piperidinecarboxamide (BioMega/Boehringer-Ingelheim); BM +51.0836 : thiazoloisoindolinone derivative; BMS-186,318: aminodiol derivative HIV-1 protease inhibitor (Bristol-Myers-Squibb); d4API: 9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanel]adenine (Gilead); d4C: 2', 3'-didehydrọ-2', $3^{\prime}$-dideoxycytidine; d4T: 2', $3^{\prime}$-didehydro- $3^{\prime}$-deoxythymidine (Bristol-Myers-Squibb); ddC; 2', 3'-dideoxycytidine (Roche); ddI: 2',3'-dideoxyinosine (Bristol-Myers-Squibb); DMP-266: a 1,4-dihydro-2H-3, 1-benzoxazin-2-one; DMP-450: \{[4R-(4-a,5-a,6-b,7-b)]-hexahydro-5,6-bis(hydroxy)-1,3-bis(3-amino)phenyl]methyl)-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one\}-bismesylate (Avid); DXG:(-)-ß-D-dioxolaneguanosine (Triangle); EBU-dM:5-ethyl-1-ethoxymethyl-6-(3,5-dimethylbenzyl)uracil; EEBU: 5-ethyl-1-ethoxymethyl-6-benżyluracil; DS: dextran sulfate; E-EPSeU:1-(ethoxymethyl)-(6-phenylselenyl)-5-ethyluracil; E-EPU: 1-(ethoxymethyl)-(6-phenyl-thio)-5ethyluracil; FTC: 3 -2', 3 '-dideoxy-5-fluoro-3'-thiacytidine (Triangle); H.BY097:S-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxalin-2(1H)-thione;

HEPT: 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine; HIV-1:human immunodeficiency virus type 1; JM2763: 1, 1'-(1,3-propanediyl)-bis-1,4,8,11tetraazacyclotetradecane (Johnson Matthey); JM3100:1, $1^{1}:[1,4$-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane(Johnson Matthey); KNI-272: (2S.3S)-3-amino-2- hydroxy-4-phenylbutyric acid-containing tripeptide; L-697,593;5-ethyl-6-methyl-3-(2-phthalimido-ethyl)pyridin-2(1H)-one; L-735,524:hydroxy-aminopentanc amide HIV-1 protease inhibitor (Merck); L-697,661: 3-\{[(-4,7-dichloro-1,3-benzoxazol-2yl)methyl]amino $\}$-5-ethyl-6-methylpyridin -2(1 H)-one; L-FDDC: (-)- $\beta$-L-5-fluoro-2',3'dideoxycytidine; L-FDOC:(-)- $\beta$-L-5-fluoro-dioxolane cytosine; MKC442:6-benzyl-1-ethoxymethyl-5-isopropyluracil (I-EBU; Triangle/Mitsubishi); Nevirapine:11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyridol[3,2-b:2', $3^{\prime}$-e]diazepin-6-one (Boehringer-Ingelheim); NSC648400:1-benzyloxymethyl-5-ethyl-6-(alpha-pyridylthio)uracil (E-BPTU); P9941: [2-pyridylacetyl-IlePheAla-y(CHOH)]2 (Dupont Merck); PFA: phosphonoformate (foscarnet; Astra); PMEA: 9-(2-phosphonylmethoxyethyl)adenine (Gilead); PMPA: (R)-9-(2phosphonylmethoxypropyl)adenine (Gilead); Ro 31-8959:' hydroxyethylamine derivative HIV-1 protease inhibitor (Roche); RPI-312: peptidyl protease inhibitor, 1-[(3s)-3-(n-alpha-benzyloxycarbonyl)-1-asparginyl)-amino-2-hydroxy-4-phenylbutyryl]-n-tert-butyl-1-proline amide; 2720: 6-chloro-3,3-dimethyl-4-(isopropenyloxycarbonyl)-3,4-dihydro-quinoxalin2(1H)thione; SC-52151: hydroxyethylurea isostere protease inhibitor (Searle); SC-55389A: hydroxyethyl-urea isostere protease inhibitor (Searie); TIBO R82150: (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)thione (Janssen); TIBO 82913: (+)-(5S)-4,5,6,7,-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1jk]-[1,4]benzo-diazepin-2(1H)-thione (Janssen); TSAO-m3T:[2',5'-bis-O-(tert-butyldimethylsilyl)-3'-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide)]-b-D-pentofuranosyl-N3-methylthymine;-U90152:1-[3-[(1-methylethyl)-amino]-2-pyridinyl]-4-[[5-[(methylsulphonyl)-amino]-1H -indol-2yl]carbonyl]piperazine; UC: thiocarboxanilide derivatives (Uniroyal); UC-781 $=\mathrm{N}$-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3furancarbothioamide; UC -82 $=\mathrm{N}$-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3thiophenecarbothioamide; VB 11,328: hydroxyethyl-sulphonamide protease inhibitor (Vertex); VX-478:hydroxyethylsulphonamide protease inhibitor (Vertex); XM 323: cyclic urea protease inhibitor (Dupont Merck).

## Combination Therapy for the Treatment of Proliferative Conditions

In another embodiment, the compounds, when used as an antiproliferative, can be administered in combination with another compound that increases the effectiveness of the therapy, including but not limited to an antifolate, a 5 -fluoropyrimidine (including 5 - fluorouracil), a cytidine analogue such as $\beta$-L-1,3-dioxolanyl cytidine or $\beta$-L-1,3-dioxolanyl 5-fluorocytidine, antimctabolites (including purine antinitetabolites, cytarabine, fudarabine, floxuridine, 6 -mercaptopurine, methotrexate, and 6-thioguanine), hydroxyurea, mitotic inhibitors (including CPT-11, Etopoṣide (VP-21), taxol, and vinca alkaloids such as vincristine and vinblastine, an alkylating agent (including but not limited to busulfan, chlorambucil, cyclophosphamide, ifofamide, mechlorethamine, melphalan, and thiotepa), nonclassical alkylating agents, platinum containing compounds, bleomycin, an anti-tumor antibiotic, an anthracycline such as doxorubicin and dannomycin, an anthracenedione, topoisomerase II inhibitors, hormonal agents (including but not limited to corticosteroids (dexamethasone, prednisone, and methylprednisone), androgens such as fluoxymesterone and methyltestosterone, estrogens such às diethylstilbesterol, antiestrogens such as tamoxifen, LHRH analogues such as leuprolide, antiandrogens such as flutamide, aminoglutethimide, megestrol acetate, and medroxyprogesterone), asparaginase, carmustine, lomustine, hexamethyl-melamine, dacarbaziné, mitotane, streptozoc̣in, cisplatin, carboplatin, levamasole, and leucovorin. The compounds of the present invention can also be used in combination with enzyme therapy agents and immune system modulators such as an interferon, interleukin, tumor necrosis factor, macrophage colony-stimulating factor and colony stimulating factor.

## III. Process for the Preparation of Active Compounds

In one embodiment of the invention, a diastereoselective reaction for effecting the introduction of fluorine into the sugar portion of novel nucleoside analogs is provided. This synthesis can be used to make both purine and pyrimidine derivatives. The key step in the synthetic route is the fluorination of a chiral, non-carbohydrate sugar ring precursor (4S)-5-(protected-oxy)-pentan-4-olide, for example, . (4S)-5-(t-butyldiphenylsiloxy)-pentan-4-olide 4 using an electrophilic fluorine source, including, but not limited to, $N$-fluoro-(bis)benzenesulfonimide 5. This relatively new class of $N$-fluorosulfonimide reagents was originally developed by Barnette in 1984 and since then has seen much
refinement and use as a convenient and highly reactive source of electrophilic fluorine
(Barnette, W. E. J. Am. Chem. Soc. 1984, 106, 452.; Davis, F. A.; Han; W., Murphy, C. K. J. Org. Chem. 1995, 60, 4730; Snieckus, V.; Beaulieu, F.; Mohri, K.; Han, W.; Murphy, C. K.; Davis, F. A. Tetrahedron Lett. 1994, 35(21), 3465). Most often, these reagents are used to deliver fluorine to nucleophiles such as enolates and metalated aromatics (Davis, F. A.; Han; W., Murphy, C. K. J. Org. Chem. 1995, 60, 4730). Specifically, $N$-fluoro-(bis)benzenesulfonimide (NFSi) is an air stable, easily handled solid with sufficient steric bulk to stereoselectively fluorinate the enolate of silyl-protected lactone 4. As a nonlimiting example of this process, the synthesis of fluorolactone 6 and its use a common intermediate in the synthesis of a number of novel $\alpha$ - 2 '-fluoro nucleosides is described in detail below. Given this description, one of ordinary skill can routinely modify the process as desired to accomplish a desired objective and to prepare a compound of interest.

Any source of electrophilic fluorine can be used that fluorinates the precursor (4S)-5-(protected-oxy)-pentan-4-olide, for example, (4S)-5-( $t$-butyl-diphenylsiloxy)-pentan-4-olide. Alternative sources of electrophilic fluorine include N fluorosulfams (Differding, et al, Tet. Letl. Vol. 29, No. 47 pp 6087-6090 (1988); Chemical Reviews, 1992, Vol 92, No. 4 (517)), N-fluoro-O-benzenedisulfonimide (Tet. Lett. Vol. B5, pages 3456-3468 (1994), Tet. Lett. Vol 35. No. 20, pages 3263-3266 (1994)); J. Org. Chem. 1995, 60, 4730-4737), 1-fluoroethene and synthetic equivalents (Matthews, Tet. Lett. Vol. 35, No. 7, pages 1027-1030 (1994); Accufluor fluorinating agents sold by Allied Signal, Inc., Buffalo Research Laboratory, Buffalo, New York (NFTh (1-fluoro-4-hydroxy-1,4-diazoabicycto[2.2.2]octane bis(tetrafluoroborate)), NFPy (N-fluoropyridinium pyridine heptafluorodiborate), and NFSi (N-fluorobenzenesulfonimide); electrophilic fluorinating reagents sold by Aldrich Chemical Company, Inc., including $N$-fluoropyridinium salts ( $(1-$ fluoro-2,4,6-trimethylpyridinium triflate, 3,5-dichloro-1-fluoropyridinium triflate, 1fluoropyridinium triflate, 1-fluoropyridinium tetrafluoroborate, and 1 -fluoropyridinium pyridine heptafluorodiborate)'see also J. Am. Chem. Sóc., Vol 112, No. 23 1990); Nfluorosulfonimides and-amides ( N -fluoro- N -methyl-p-toluenesulfonamide, N -fluoro- N -propyl-p-toluenesulfonamide, and N -fluorobenzenesulfonimide) ; N -fluoro-quinuclidinium fluoride (J. Chem. Soc. Perkin Trans I 1988, 2805-2811); perfluoro-2,3,4,5tetrahydropyridine and perfluoro-(1-methylpyrrolidine), Banks, Cheng, and Haszeldine,

Heterocyclic Polyfluoro-Compounds Pan II (1964); 1-fluoro-2-pyridone, J. Org. Chem., 1983 48, 761-762; quaternary stereogenic centers possessing a fluorine atom (J. Chem. Soc. Perkin Trans. pages 221-227 (1992)); N-fluoro-2,4,6-pyridinium triflate, Shimizu, Tetrahedron Vol 50(2), pages 487-495 (1994); N-fluoropyridinium pyridine heptafluorodiborate, J. Org. Chem. 1991, 56, 5962-5964; Umemoto, et al., Bull. Chem. Soc. Jpn., 64 1081-1092 (1991); N-fluuroperfluoroalkylsulfonimides, J. Am. Chem. Soc., 1987, 109, 7194-7196; Purrington, et al., Lewis Acid Mediated Fluorinations of Aromatic Substrates, J. Org. Chem. 1991, 56, 142-145.

A significant advantage of this methodology is the ability to access separately either the "natural" (la) D or the "unnatural" (1b) L enantiomer of the nucleosides by appropriate choice of L-or D - glutamic acid starting material; respectively.

$1 a$

$\mathrm{F}_{1}=\mathrm{H}, \mathrm{CH}_{3} ; \mathrm{F}$
$\mathrm{R}_{2}=\mathrm{OH}, \mathrm{NH}_{2}$, NHAC

Lactone 4 was synthesized by the route shown in Scheme 1 from L-glutamic acid as described by Ravid et al. (Tetrahedron 1978, 34, 1449) and Taniguchi et al. (Tetrahedron 1974, 30, 3547).

Scheme 1


The enolate of lactone 4 , prepared at $-78^{\circ} \mathrm{C}$ with LiHMDS in THF, is known to be stable. Several syntheses using this enolate have been performed, including addition of electrophiles such as diphenyldiselenide, diphenyldisulfide, and alkyl halides in high yield (Liotta, D. C.; Wilson, L. J. Tetrahedron Lett. 1990, 3̇1(13), 1815; Chu, C: K.; Babu, J. R.;

Beach, J. W.; Ahn. S. K.; Huang, H.; Jeong, L. S.; Lee, S. J. J. Org. Chem., 1990, 55, 1418; Kawakami, H.; Ebata, T.; Koseki, K.; Matsushita, H.; Naoi, Y.; Itoh, K. Chem. Lett. 1990, 1459). However, addition of a THF solution of 5 to the enolate of 4 gave poor yields of the desired monofluorinated product 6. Numerous by-products were formed including what was
$25^{\circ}$. detectable $\alpha$ anomer by NMR, as reported by Niihata et al. (Bull. Chem. Soc. Jpn. 1995, 68, 1509).

Scheme 2

5


Coupling of 8 with silylated pyrimidine bases was performed by standard Vorbruggen methodology (Tetrahedron Lett. 1978, 15, 1339) using TMS triflate as the Lewis acid.

Alternatively, any other Lewis acid known to be useful to condense a base with a carbohydrate to form a nucleoside can be used, including tin chloride, titanium chloride, and other tin or titanium compounds. A number of bases were successfully coupled in high yields ranging from $72 \%=100 \%$ after column chromatography (eq 2, Table 1).

## Equation 2



Table 1. Glycosylation of Substituted Pyrimidines with 8


Proton NMR indicated that the ratio of $\beta$ to $\alpha$ nucleoside anomers was approximately 2:1 in all cases. The silyl protected nucleosides could not be resolved by column chromatography into the separate anomers. However, after deprotection of the 5 '-oxygen with $\mathrm{NH}_{4} \mathrm{~F}$ in methanol (eq 3 ), the $\alpha$ and $\beta$ anomers could be readily separated and the results are summarized in Table 2.

Fquatinn 3

$9,10,11,12,13$
Table 2. Deprotection of Nucleosides

| $\mathbf{R}_{\mathbf{1}}$ | $\mathbf{R}_{2}$ | $\mathbf{a}$ | yield | $\mathbf{b}$ | yield |
| :---: | :---: | :---: | :---: | :---: | :---: |
| F | OH | $\mathbf{1 4 a}$ | $19 \%$ | $\mathbf{1 4 b}$ | $48 \%$ |
| F | $\mathrm{NH}_{2}$ |  | $\mathbf{1 5 a}$ | $27 \%$ | $\mathbf{1 5 b}$ |
| H | NHAc | $\cdot$ | $\mathbf{1 6 a}$ | $17 \%$ | $51 \%$ |
| H | $\mathrm{NH}_{2}$ | $\mathbf{1 7 a}$ | $\mathbf{1 6 b}$ | $31 \%$ |  |
| $\mathrm{CH}_{3}$ | OH | $\mathbf{1 8 a}$ | $12 \%$ | $\mathbf{1 7 b}$ | $\cdots$ |

The classification of the frec nucleosides as $\alpha$ or $\beta$ was based on the chemical shift of the anomeric proton (Table 3) and on the polarity of the nucleosides as observed by thin layer chromatography. $A$ trend for all of the $\alpha / \beta$ pairs of free nucleosides was observed in that the less polar compound of the two had an anomeric proton chemical shift that was notably upfield from that of the more polar compound.

Table 3. Anomeric Proton Chemical Shift (ppm)


The correlation between anomeric proton chemical shift and absolute structure was verified by comparison of 18a (Niihata, S.; Ebata, T.; Kawakami, H.; Matsushida, H. Bull. Chem. Soc. Jpn. 1995, 68, 1509) and 18b (Aerschot, A. V.; Herdewijn, P.; Balzarini, J.; 'Pauwels, R.; De Clercq, E. J. Med. Chem. 1989, 32, 1743) with previously published spectral data and through X -ray crystal structure determination of $\mathbf{1 4 b}$ and $\mathbf{1 5 b}$. This finding is the opposite of the usual trend for nucleosides in which the $\alpha$ anomer is normally the less polar of the two. Presumably, in the "down" 2' : fluorinate nucleosides, the strong dipole of the C-F bond opposes the $\mathrm{C}-\mathrm{N}$ anomeric bond dipole in the $\beta$ isomer and reduces the overall molecular dipole. Conversely, the $\alpha$ anomer has a geometry that allows reinforcement of the molecular dipole through the addition of the C-F and C-N bond dipoles. Thus, the $\alpha$ anomer is more polar than the $\beta$ anomer in the case of $\alpha-2$ '-fluor nucleosides.

The $\alpha$ and $\beta$ anomers 17a and 17b could not be separated by column chromatography because the free amino group caused the nucleosides to streak on silica gel. Therefore, it was necessary to use $N^{4}$-acetylcytosine to prepare 11 and then resolve 16 a and 16 b . The $N^{4}$ acetyl group was removed quantitatively with a saturated solution of ammonia in methanol in order to obtain separated 17 a and 17 b . When 5 -fluorocytosine was used as the base (compound 10), the anomers 15a and 15b were easily separated and no streaking on silica gel was observed.

Of the ten nucleosides. listed in Table 2, it appears that only 17b (Martin, J. A.; Bushnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parks, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A.; Kinchington, D. J. Med. Chem. 1990, 33(8), 2137; Zenchoff, G. B.; Sun, R.; Okabe, M. J. Org. Chem. 1991, 56,
4392), 18u (Niihata, S.; Ebata, T.; Kawakami, H.; Matsushida, H. Bull. Chem. Soc. Jpn. 1995, 68, 1509), and 18b (Aerschot, A. V.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De ;Clergy, E. J. Med. (hem. 1989, 32, 1743) have been synthesized previously. They, like the numerous known $2^{\prime} \cdot \beta$ or "up" fluor nucleoside analogs ${ }^{14}$ have been synthesized from natural precursors (ie., they are in the $\beta$-D configuration). It appears that no $\beta$-L-2'-fluororibofuranosyl nucleosides have been identified in the literature prior to this invention.

Fluorine is usually introduced into these molecules through nucleophilic attack on an anhydro-nucleoside (Mengel, R.; Guschlbauer, W. Angew. Chem., Int. Ed. Engl. 1978, 17, 525) or through replacement and inversion of a stereochemically fixed hydroxyl group with diethylaminosulfur trifluoride (DAST) (Herdewijn, P.; Aerschot, A. V.; Kerremans, L. Nucleosides Nucleotides $1989,8(1), 65)$. One advantage of the present methodology is that no hydroxyl group is needed for fluorine introduction. Thus, the process is not limited to natural nucleosides or sugars as starting materials, and provides an easy to access the unnatural enantiomers of the 2'-fluoro nucleosides.

Accordingly, several unnatural nucleosides were synthesized using this synthetic route with D-glutamic acid 19 as the starting material (Scheme 3). The sugar ring precursor 20 was fluorinate in the manner described above and coupled with various silylated bases (Table 4).

Scheme 3

5




23, 24, 25
10

$$
\xrightarrow{\mathrm{NH}_{4} \mathrm{~F}}
$$



26a, 27a, 28a


26b, 27b, 28b

15

Table 4. Yields of Unnatural Nucleoside Analogs


Scheme 4


Successful synthesis of 29, as shown in Scheme 4, allows access to two categories of nucleosides. The first is the class of compounds known as $2^{\prime}, 3^{\prime}$-dideoxy- $\mathbf{2}^{\prime}, 3^{\prime}$ 'didehydro-2-2'-fluoro-nucleosides, $\mathbf{3 0}$, and the second is the "up"-fluoro or arabino analogs, $\mathbf{3 1}$, of the nucleosides described in Scheme 5 below.

## Scheme 5



30
-


31
$i$

Compounds 30 and 31 may be synthesized from a common intermediate 32 , which may be accessed through selenylation of fluoroglycal 29.
-

Selenylated compound 32 may be transformed into the "up" fluor analog 31 through reduction with Raney nickel. Alternatively, oxidation of the selenide 32 with $\mathrm{NaIO}_{4}$ or hydrogen peroxide followed by thermal elimination of the selenoxide intermediate lead to 30 . Both of these transformations on the unfluorinated systems are well documented and have been reported (Wurster, J: A.; Phi.D. Thesis, Emory University, 1995; Wilson, L. J.; Ph.D. Thesis, Emory University, 1992).

In addition, the synthesis of the enantiomers of nucleosides $\mathbf{3 0}$ and $\mathbf{3 1}$ is also possible since they arise from the enantiomer of 29.

An alternative route for the preparation of compounds of the type represented by $\mathbf{3 0}$, the 2', $3^{\prime}$-dideoxy-2', 3'-didehydro-2'-flouro-nucleosides, is shown in Scheme 7. This route provides simple, direct access to this class of compounds utilizing a wide range of silylated bases and has been successfully completed.

Scheme 7



Formation of silyl ketene acetal from 6 allows for the stereoselective addition of phenyl selenium bromide to generate compound 36 as a single isomer. Reduction and acetylation of this compound proceeds smoothly and in high yield over the two steps to 37. The $\alpha$ orientation of the phenyl selenyl group allows for stereoselection in the subsequent glycosylation step, and synthesis of the $\beta$ isomer of the nucleoside 38 is accomplished in good yield. Compound 38 may be oxidized with hydrogen peroxide in dichloromethane to yield the elimination product 39 , but in our experience, it was merely necessary to adsorb 38 onto silica gel and allow to stand for several hours, after which time 39 could be eluted from a plug column in nearly quantitative yield. Removal of the protected group from 39 to obtain the final compound $\mathbf{3 0}$ was performed as before and resulted in a good yield ( $81 \%$ ) of product nucleoside.

Scheme 8


The same series of chemical transformations that were used for the synthesis of 30 and 31 may also be used for the synthesis of 34 and 35 .

## Experimental Section

## General Procedures:

$N$ - Fluoro - (bis)benzenesulfonimide 5 was obtained from Allied Signal, and was used without further purification. All other reagents were obtained from Aldrich Chemical Company and were used without further purification: Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet Impact 400 FT-IR spectrometer. 'H NMR and ${ }^{13} \mathrm{C}$ NMR spectra were recorded on either NT - 360 or Varian 400 MHz spectrometer. TLC plates were silica gel 60 $\mathrm{F}_{254}$ ( 0.25 mm thickness) pürchased from EM Science. Flash chromatography was carried out with silica gel 60 ( $230-400$ mesh ASTM) from EM Science. All reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solvents were removed by rotary evaporation: Elemental analyses were performed by Atlantic Microlab, Inc, Atlanta, GA. (2S,4R)-5-(t-butyldiphenylsiloxy) - 2 - fluoropentan - 4- olide (20). To a flask was added (4R) - 5 - ( $t$-butyldiphenylsiloxy) - pentan - 4 - olide ( $20.0 \mathrm{~g}, 0.0564 \mathrm{~mol}, 1.0$ eq.) and $N$ - fluoro - (bis)benzenesulfonimide (NFSi) $5(17.80 \mathrm{~g}, 0.0564 \mathrm{~mol}, 1.0 \mathrm{eq}$.) in 250 mL of anhydrous THF. The solution was cooled to $-78^{\circ} \mathrm{C}$ and 68.0 mL ( $0.0680 \mathrm{~mol}, 1.2 \mathrm{eq}$.) of a 1.0 M solution of LiHMDS in THF was added dropwise over a period of 1 hr . This was allowed to stir at $-78^{\circ} \mathrm{C}$ for an additional 2 hrs. and was then warmed to room temperature to stir for one hour. After completion, the reaction was quenched with 10 mL of saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution. The mixture was diluted with three volumes of diethyl ether and was poured onto an equal volume of saturated $\mathrm{NaHCO}_{3}$. The organic layer was washed a second time with saturated $\mathrm{NaHCO}_{3}$ and once with saturated NaCl . The organic layer was dried over $\mathrm{MgSO}_{4}$, filtered, and concentrated to a light yellow oil. The oil was purified by silica gel column chromatograpy using a $30 \%$ diethyl ether / $70 \%$ hexanes solvent system. The resultant white solid was then crystallized from hot hexanes to yield 13.04 g ( $62 \%$ yield) of a transparent crystalline solid: $\mathrm{R}_{\mathrm{r}}\left(30 \%\right.$ diethyl ether $/ 70^{\circ} \%$ hexanes $)=0.26 ; \mathrm{mp} 115-116^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR $\left(360 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 7.63-7.60(\mathrm{~m}, 4 \mathrm{H}), 7.45-7.35(\mathrm{~m}, 6 \mathrm{H}), 5.49(\mathrm{dt}, \mathrm{J}=52.9$ and $7.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.69(\mathrm{~d}, \mathrm{~J}=9.36 \mathrm{~Hz}, 1 \mathrm{H}), 3.91(\mathrm{~d}, \mathrm{~J}=11.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.60(\mathrm{~d}, \mathrm{~J}=11.5 \mathrm{~Hz}, 1 \mathrm{H})$,
2.72-2.40(m,2H), $1.05(\mathrm{~s}, 9 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $172.1(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz})$, $135.5,135.4,132.3,131.7,130.1,128.0,127.9,85.6(\mathrm{~d}, \mathrm{~J}=186.6 \mathrm{~Hz}), 77.3(\mathrm{~d}, \mathrm{~J}=5.3 \mathrm{~Hz})$, $65.0,31.8(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 26.7,19.1$; $\mathrm{IR}($ thin film $) 2958,1796,1252,1192,1111,1016$ $\mathrm{cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{21} \mathrm{H}_{29} \mathrm{O}_{3} \mathrm{FSiLi}: 379.1717$. Found: 379.1713. Anal. Call. CHAFFS : C, 67.71; H; 6.76. Found: C, 67.72; H, 6.78.

5-0-(t -butyldiphenylsilyl) - 2,3-didéoxy - 2 - fluoro-(L) - erythron - pentofuranose (21). To a flask was added lactone $20(12.12 \mathrm{~g}, 0.0325 \mathrm{~mol}, 1.0 \mathrm{eq}$.) and 240 mL of anhydrous THF. The solution was cooled to $-78^{\circ} \mathrm{C}$ and $65 \mathrm{~mL}(0.065 \mathrm{~mol}, 2.0 \mathrm{eq}$.) of a $1: 0$ $M$ solution of DIBALH in hexanes was added dropwise over a period of 30 min . This was allowed to stir at
$-78^{\circ} \mathrm{C}$ for 3 hrs ., after which time the reaction was quenched by the slow addition of 2.93 $\mathrm{mL}(0.163 \mathrm{~mol}, 5.0 \mathrm{eq}$.) of water. The reaction was allowed to warm to room temperature and stir for 1 hr ., after which time a clear gelatinous solid formed throughout the entire flask. The reaction mixture was diluted with two volumes of diethyl ether and was poured onto an equal volume of saturated aqueous sodium potassium tartrate solution in an Erlenmeyer flask. This was stirred for 20 min . until the emulsion had broken. The organic layer was separated and the aqueous layer was extracted three times with 250 mL of diethyl ether. The combined organic layers were dried over $\mathrm{MgSO}_{4}$, filtered, and concentrated to a light yellow oil. The product was purified by silica gel column chromatography using a $6: 1$ hexanes / ethyl acetate solvent system. The resulting clear oil was crystallized from boiling hexanes to give 11.98 g ( $98 \%$ yield) of a white crystalline solid: $\mathrm{R}_{\mathrm{f}}(30 \%$ diethyl ether $/ 70 \%$ hexanes $)=0.33$; mp $66-67^{\circ} \mathrm{C}$. ${ }^{\text {'H NMR }}\left(360 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 7.68-7.66(\mathrm{~m}, 4 \mathrm{H}), 7.55-7.38(\mathrm{~m}, 6 \mathrm{H}), 5.39(\mathrm{t}, \mathrm{J}$ $=7.6 \mathrm{~Hz}, 1 \mathrm{H}) ; 4.99(\mathrm{dd}, \mathrm{J}=52.2$ and $4.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.52(\mathrm{~m}, 1 \mathrm{H}), 3.88(\mathrm{dd}, \mathrm{J}=10.8$ and 2.5 $\mathrm{Hz}, 1 \mathrm{H}), 3.65(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 349(\mathrm{dd}, \mathrm{J}=7.9$ and $1.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.44-2.07(\mathrm{~m}, 2 \mathrm{H}), 1.07$ (s, 9 H ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $135.7,135.5,132.2,132.1,130.2,130.0,129.8$, 127.9, 127.7, $99.8(\mathrm{~d}, \mathrm{~J}=31.1 \mathrm{~Hz}), 96.6(\mathrm{~d}, \mathrm{~J}=178.3 \mathrm{~Hz}), 79.4,64.8,29.9(\mathrm{~d}, \mathrm{~J}=21.2 \mathrm{~Hz})$, 26.8, 19.2; IR (thin film) $3423,2932,1474,1362,1113 \mathrm{~cm}^{-1}$; HRMS calculated for [M + Li] $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{O}_{3} \mathrm{FSiLi}: 381.1874$. Found: 381.1877. Anal. Calc.. $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{O}_{3} \mathrm{FSi}: \mathrm{C}, 67.35 ; \mathrm{H}, 7.27$. Found: C, 67.42; H, 7.31 .
1-O-Acetyl-5-0-(t -butyldiphenylsilyl)-2,3-dideoxy:-2-fluoro-(L) - erythron pentofuranose (22). To a flask was added lactol $21(8.50 \mathrm{~g}, 0.0227 \mathrm{~mol}, 1.0 \mathrm{eq}$.) and 170
mL of anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. Then. DMAP ( $0.277 \mathrm{~g}, 0.00277 \mathrm{~mol}, 0.1 \mathrm{eq}$.) and acetic anhydride ( $13.5 \mathrm{~mL}, 0.143 \mathrm{~mol}, 6.3 \mathrm{eq}$.) wẹre added and stirred at room temperature overnight. Upon completion, the reaction was poured onto saturated $\mathrm{NaHCO}_{3}$ solution. The organic layer was separated, and the aqueous layer was extracted three times with chloroform. The combined organic layers were dried over $\mathrm{MgSO}_{4}$, filtered, and the solvent removed to yield a light yellow oil. The oil was purified by silica gel column chromatography using an $8: 1$ hexanes / ethyl acetate solvent system to give 9.85 g ( $99 \%$ yield) of a clear colorless oil: $\mathrm{R}_{\mathrm{f}}$ ( $30 \%$ diethyl ether $/ 70 \%$ hexanes $)=0.44 ;{ }^{\prime} \mathrm{H}$ NMR $\left(360 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 7.69-7.67(\mathrm{~m}, 4 \mathrm{H})$, $7.43 \cdot 7.38(\mathrm{~m}, 6 \mathrm{H}), 6.30(\mathrm{~d}, \mathrm{~J}=10.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.06(\mathrm{~d}, \mathrm{~J}=54.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.53(\mathrm{~m}, 1 \mathrm{H}), 3.81$ (dd, J = 10.8 and $4.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.72(\mathrm{dd}, \mathrm{J}=10.8$ and $4.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.38-2.12(\mathrm{~m}, 2 \mathrm{H}), 1.89$ ( s , 3 H ), 1.07 ( $\mathrm{s}, 9 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d 169.4, 135.6, 135.5, 133.2, 133.1, 129.8, $129.7,127.8,127.7,99.3(\mathrm{~d}, \mathrm{~J}=34.1 \mathrm{~Hz}), 95.5(\mathrm{~d}, \mathrm{~J}=178.2 \mathrm{~Hz}), 81.4,65.3,31.6(\mathrm{~d}, \mathrm{~J}=20.5$ Hz ), 26.8, 21.1, 19.3; IR (thin film) $3074,2860,1750,1589,1229,1113 \mathrm{~cm}^{-1}$; HRMS calculated for $\left[\mathrm{M}-\mathrm{OCOCH}_{3}\right] \mathrm{C}_{21} \mathrm{H}_{26} \mathrm{O}_{2} \mathrm{FSi}: 357.1686$. Found: 357.1695. Anal. Talc.. $\mathrm{C}_{23} \mathrm{H}_{29} \mathrm{O}_{4} \mathrm{FSi}: \mathrm{C}, 66.32 ; \mathrm{H}, 7.02$. Found: $\mathrm{C}, 66.30 ; \mathrm{H}, 7.04$.
Representative procedure for the coupling of a silylated base with 22: (L) - 5' - O( $t$-butyldiphenylsilyl)-2',3-dideoxy-2'-fluoro-5-fluorocytidine (25). To a flask equipped with a short-path distillation head was added 5 - fluoroçytosine ( $2.01 \mathrm{~g}, 15.6 \mathrm{mmol}, 5.0 \mathrm{e}^{\prime} \mathrm{q}$ ), 35 mL of $1,1,1,3,3,3$ - hexamethyldisilazane, and a catalytic amount $(\sim 1 \mathrm{mg})$ of $\left(\mathrm{NH}_{4}\right)_{2} \mathrm{SO}_{4}$. The white suspension was heated to boiling for 1 hr . until the base was silylated and reaction was a clear solution. The excess HMDS was distilled off and the oily residue that remained was placed under vacuum for 1 hr . to remove the last traces of HMDS. A white solid resulted which was dissolved, under argon, in 5 mL of anhydrous 1,2 - dichloroethane. To this clear: solution was added a solution of acetate $22(1.30 \mathrm{~g}, 3.12 \mathrm{mmol}, 1.0 \mathrm{eq}$.) in 5 mL of anhydrous 1,2 - dichloroethane. To this was added, at room temperature, trimethylsilyl trifluoromethanesulfonate ( $3.32 \mathrm{~mL}, 17.2 \mathrm{mmol}, 5.5 \mathrm{eq}$ ); The reaction was monitored by TLC ( $10 \%$ methanol / $90 \% \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ) and was observed to be complete in 4 hrs. The reaction mixture was poured onto saturated $\mathrm{NaHCO}_{3}$. The organic layer was then separated, and the aqueous layer was extracted three times with chloroform. The combined organic layers were dried over $\mathrm{MgSO}_{4}$, filtered, and the solvent removed to yield a white foam. The compound was purified by silica gel column chromatography using a gradient solvent system from 100
\% $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to $10 \%$ methanol in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The compound was isolated as 1.51 g ( $99 \%$ yield) of a white foam: mixture of anomers $\mathrm{R}_{\mathrm{f}}(100 \% \dot{\mathrm{Et}} \mathrm{OAc})=0.36 ; \mathrm{mp} 74-80^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR ( 400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d} 8.84(\mathrm{bs}, \mathrm{l} \mathrm{H}), 8.04(\mathrm{~d}, \mathrm{~J}=6.4 \mathrm{~Hz}, 0.67 \mathrm{H}), 7.67-7.63(\mathrm{~m}, 4 \mathrm{H}), 7.51-7.39$ $(\mathrm{m}, 6.33 \mathrm{H}), 6.11(\mathrm{~d}, \mathrm{~J}=20 \mathrm{~Hz}, 0.33 \mathrm{H}), 5.98(\mathrm{~d}, \mathrm{~J}=16.4 \mathrm{~Hz}, 0.67 \mathrm{H}), 5.88(\mathrm{bs}, 1 \mathrm{H}), 5.41(\mathrm{~d}, \mathrm{~J}$ $=52.4 \mathrm{~Hz}, 0.33 \mathrm{H}), 5.23(\mathrm{dd}, \mathrm{J}=50.4$ and $4 \mathrm{~Hz}, 0.67 \mathrm{H}), 4.56(\mathrm{~m}, 0.33 \mathrm{H}), 4.45(\mathrm{~m}, 0.67 \mathrm{H})$, 4.23 (dd, $\mathrm{J}=12.0$ and $1.6 \mathrm{~Hz}, 0.67 \mathrm{H}$ ), $3.89(\mathrm{dd}, \mathrm{J}=11.2$ and $3.2 \mathrm{~Hz}, 0.33 \mathrm{H}$ ), $3.74-3.66(\mathrm{~m}$, $1 \mathrm{H}), 2.45-1.96(\mathrm{~m}, 2 \mathrm{H}), 1.09(\mathrm{~s}, 6 \mathrm{H}), 1.06(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $158.6(\mathrm{~d}$, $\mathrm{J}=14.4 \mathrm{~Hz}), 158.4(\mathrm{~d}, \mathrm{~J}=14.4 \mathrm{~Hz}), 153.9,153.8,136.6(\mathrm{~d}, \mathrm{~J}=240.5 \mathrm{~Hz}),{ }^{1} 136.3(\mathrm{~d}, \mathrm{~J}=-239.7$ $\mathrm{Hz}), 135.6,135.56,135.5,135.4,133.1,132.9,132.5,132.4,130.1,130.0,129.9,127.9$, 127.8, $125.8(\mathrm{~d}, \mathrm{~J}=33.4 \mathrm{~Hz}$ ), $124.6(\mathrm{~d}, \mathrm{~J}=32.6 \mathrm{~Hz}), 96.5(\mathrm{~d}, \mathrm{~J}=182.0 \mathrm{~Hz}), 91.7(\mathrm{~d}, \mathrm{~J}=$ $185.1), 90.7(\mathrm{~d}, \mathrm{~J}=35.6 \mathrm{~Hz}), 87.7\left(\mathrm{~d}, \mathrm{~J}=\frac{1}{1} 5.2 \mathrm{~Hz}\right), 81.5,79.5,64.9,63.0,33.5(\mathrm{~d}, \mathrm{~J}=20.5$ Hz ), 30.6 (d, J = 20.4 Hz), 26.9, 26.8, 19.22, 19.18; IR (thin film) 3300 , 2960, 1682, 1608, $1513,1109 \mathrm{~cm}^{-1} ;$ HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2} \mathrm{Li}: 492.21 .06$.
Found:492.2085. Anal. Callc. $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2} \cdot 1 / 2 \mathrm{H}_{2} \mathrm{O} . \mathrm{C}, 60.71 ; \mathrm{H}, 6.11 ; \mathrm{N}, 8.50$. Found: C, 60.67; H, 6.03 ; N, 8.44.

Representative Procedure for the deprotection of silyl-protected nucleosides: $\alpha$ - and $\beta$ (L) - 2',3' - dideoxy - 2' - fluoro - 5-fluoro cytidine (28a and 28b): Nucleoside 25 (1.098 g, $2.26 \mathrm{mmol}, 1.0 \mathrm{eq}$.) was dissolved in 15 mL of methanol to which was added ammonium fluoride ( $0.838 \mathrm{~g}, 22.6 \mathrm{mmol}, 10.0 \mathrm{eq}$.). This was stirred vigorously for 24 hrs ., after which time TLC ( $15 \%$ ethanol / $85 \%$ ethyl acetate) revealed that the reaction was complete. The reaction mixture was diluted with three volumes of ethyl acetate and was filtered through a small ( 1 cm ) silica gel plug. The plug was rinsed with 200 mL of $15 \%$ ethanol $/ 85 \%$ ethyl acetate solution and the solvent was removed to yield a white foam. The compound was purified by silica gel column chromatography using a $15 \%$ ethanol / $85 \%$ ethyl acetate solvent system which also effected the separation of the $\alpha$ and $\beta$ anomers. The yield of a as a white foam was $0.190 \mathrm{~g}(0.768 \mathrm{mmol}, 34 \%$ yield $)$ and the.yield of $\beta$ as a white foam was .$0.290 \mathrm{~g}(1.17 \mathrm{mmol}, 52 \%$ yjeld $):(28 \mathrm{a}) \mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \% \mathrm{EtOAc})=0.22 ; \mathrm{mp} 199-203$ ${ }^{\circ} \mathrm{C}($ dec. $) .{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $7.78(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.07(\mathrm{~d}, \mathrm{~J}=19.2 \mathrm{~Hz}$, $1 \mathrm{H}), \dot{5} .37(\mathrm{~d}, \mathrm{~J}=54.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.60(\mathrm{~m}, 1 \mathrm{H}), 3.80(\mathrm{dd}, \mathrm{J}=12.0$ and $3.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.56(\mathrm{dd}, \mathrm{J}=$ 12.4 and $4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.40-\dot{2} .00(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}$ ) 157.7 ( $\mathrm{d}, \mathrm{J}=$ $13.6 \mathrm{~Hz}), 153.2,135.9(\mathrm{~d}, \mathrm{~J}=239.0 \mathrm{~Hz}), 126.2(\mathrm{~d}, \mathrm{~J}=31.1 \mathrm{~Hz}), 92.4(\mathrm{~d}, \mathrm{~J}=183.6 \mathrm{~Hz}), 86.7$
( $\mathrm{d}, \mathrm{J}=15.2 \mathrm{~Hz}$ ), 79.6, 62.7, $33.3(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}$ ); $\operatorname{IR}(\mathrm{KBr}) 3343,3100,1683,1517,1104$ $\mathrm{cm}^{-1}$; HRMS calculated for [M+Li] $\mathrm{C}_{9} \mathrm{H}_{1} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \mathrm{Li}: 254.0929$. Found: 254.0919. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \cdot 1 / 2 \mathrm{H}_{2} \mathrm{O}: \mathrm{C}, 42.19 ; \mathrm{H}, 4.72 ; \mathrm{N}, 16.40$. Found: $\mathrm{C}, 42.44 ; \mathrm{H}, 4.56 ; \mathrm{N}$, 16.56. (28b) $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \% \mathrm{EtOAc})=0.37$; mp $182-186^{\circ} \mathrm{C}$ (dec.). ${ }^{\mathrm{h}} \mathrm{H} \operatorname{NMR}(400$ $\left.\mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}\right) \mathrm{d} 8.32(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.79(\mathrm{bs}, 1 \mathrm{H}), 7.53(\mathrm{bs}, 1 \mathrm{H}), 5.81(\mathrm{~d}, \mathrm{~J}=16.8$ $\mathrm{Hz}, 1 \mathrm{H}), 5.37(\mathrm{t}, \mathrm{J}=4.8 \mathrm{~Hz}$ ), $5.18(\mathrm{dd}, \mathrm{J}=51.6$ and $3.2 \mathrm{~Hz}, \mathrm{lH}), 4.32(\mathrm{~m}, 1 \mathrm{H}), 3.88(\mathrm{dd}, \mathrm{J}=$ 12.0 and $2.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.59(\mathrm{dd}, \mathrm{J}=12.4$ and $2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.20-1.99(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}(100$ MHz , DMSO - $\mathrm{d}_{6}$ ) $\mathrm{d} 157.7(\mathrm{~d}, \mathrm{~J}=13.7 \mathrm{~Hz}), 153.2,136.1(\mathrm{~d}, \mathrm{~J}=237.4 \mathrm{~Hz}), 125.3(\mathrm{~d}, \mathrm{~J}=33.4$ $\mathrm{Hz}), 97.3(\mathrm{~d}, \mathrm{~J}=176.8 \mathrm{~Hz}), 89.9(\mathrm{~d}, \mathrm{~J}=35.7 \mathrm{~Hz}), 81.6,60.2,30.3(\mathrm{~d}, \mathrm{~J}=19.7 \mathrm{~Hz}) ;$ IR ( KBr ) 3487, 2948, 1678, 1509, $1122 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\mathrm{M}+\mathrm{Li}$ ] $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \mathrm{Li}$ : 254.0929. Found: 254.0935. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2}: \mathrm{C}, 43.73 ; \mathrm{H}, 4.49 ; \mathrm{N}, 17.00$. Found: C, 43.69; H, 4.53; N, 16.92.
(D) - 5' - O - ( 1 -butyldiphenylsilyl) - 2',3'-dideoxy-2'-fluoro-5-fluorouridine (9). mixture of anomers $\mathrm{R}_{\mathrm{f}}(1: 1$ hexanes $/ \mathrm{EtOAc})=0.48 ; \mathrm{mp} 65-70^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d}$ $10.0(\mathrm{bm}, 1 \mathrm{H}), 7.99(\mathrm{~d}, \mathrm{~J}=5.6 \mathrm{~Hz}, 0.63 \mathrm{H}), 7.65(\mathrm{~m}, 4 \mathrm{H}), 7.42(\mathrm{~m}, 6.37 \mathrm{H}), 6.12(\mathrm{dd}, \mathrm{J}=18.0$ and $1.6 \mathrm{~Hz}, 0.37 \mathrm{H}), 6.00(\mathrm{~d}, \mathrm{~J}=16 \mathrm{~Hz}, 0.63 \mathrm{H}), 5.37(\mathrm{dd}, \mathrm{J}=54.6$ and $2.4 \mathrm{~Hz}, 0.37 \mathrm{H}), 5.22$ $(\mathrm{dd}, \mathrm{J}=50.4$ and $4 \mathrm{~Hz}, 0.63 \mathrm{H}), 4.57(\mathrm{~m}, 0.37 \mathrm{H}), 4.44(\mathrm{~m}, 0.63 \mathrm{H}), 4.22(\mathrm{dd}, \mathrm{J}=12.2$ and 2.0 $\mathrm{Hz}, 0.63 \mathrm{H}$ ), 3.92 (dd, J = 11.2 and $3.2 \mathrm{~Hz}, 0.37 \mathrm{H}$ ), $3.70(\mathrm{~m}, 1 \mathrm{H}), 2.22(\mathrm{~m}, 2 \mathrm{H}), 1.09(\mathrm{~s}$, $5.67 \mathrm{H}), 1.074(\mathrm{~s}, 3.33 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $157.2(\mathrm{~d}, \mathrm{~J}=31.7 \mathrm{~Hz}$ ), $157.1(\mathrm{~d}, \mathrm{~J}=$ $25.8 \mathrm{~Hz}), 149.1,148.8,140.4(\mathrm{~d}, \mathrm{~J}=236.6 \mathrm{~Hz}), 140.1(\mathrm{~d}, \mathrm{~J}=235.2 \mathrm{~Hz}), 135.6,135.5,135.4$, 132.9, 132.7. $132.4,132.3,130.1,130.0,129.9,127.9,127.8,125.1(\mathrm{~d}, \mathrm{~J}=34.9 \mathrm{~Hz}), 123.6$ (d, $\mathrm{J}=34.1 \mathrm{~Hz}$ ), $96.4(\mathrm{~d}, \mathrm{~J}=182.0 \mathrm{~Hz}$ ), $92.0(\mathrm{~d}, \mathrm{~J}=185.9 \mathrm{~Hz}), 90.2(\mathrm{~d}, \mathrm{~J}=37.2 \mathrm{~Hz}), 87.0(\mathrm{~d}, \mathrm{~J}=$ 15.2 Hz ), 81.7, 79.8, 64.8, 63.0, 33.3 ( $\mathrm{d}, \mathrm{J}=21.2 \mathrm{~Hz}$ ), $31.0(\mathrm{~d}, \mathrm{~J}=21.2 \mathrm{~Hz}$ ), 26.9, 26.8, 19.2; IR (thin film) $3185,1722,1117 \mathrm{~cm}^{-1} ;$ HRMS calculated for $[\mathrm{M}+1] \mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}_{2}$ : 487.1866. Found: 487.1853. Anal. Calc. $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}_{2}$ : C, 61.71; H, 5.80; $\mathrm{N}, 5.76$. Found: C, 61.72; H, 5.86; N, 5.72 .
(D) - 5' - O-(1-butyldiphenylsilyl) - 2', 3' - dideoxy - $\mathbf{2}^{\prime}$ - fluoro - 5 - fluorocytidine (10). mixture of anomers $\mathrm{R}_{\mathrm{f}}(100 \% \mathrm{EtOAc})=0.36$; mp $75-81^{\circ} \mathrm{C} .{ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \mathrm{d}$ $8.50(\mathrm{bm}, 1 \mathrm{H}), 8.05(\mathrm{~d}, \mathrm{~J}=6.0 \mathrm{~Hz}, 0.67 \mathrm{H}), 7.67-7.63(\mathrm{~m}, 4 \mathrm{H}), 7.51-7.39(\mathrm{~m}, 6.33 \mathrm{H}), 6.10$ $(\mathrm{d}, \mathrm{J}=20 \mathrm{~Hz}, 0.33 \mathrm{H}), 5.98(\mathrm{~d}, \mathrm{~J}=16.4 \mathrm{~Hz}, 0.67 \mathrm{H}), 5.62(\mathrm{bm}, 1 \mathrm{H}), 5.4 \mathrm{l}(\mathrm{d}, \mathrm{J}=52.4 \mathrm{~Hz}$, $0.33 \mathrm{H}), 5.23(\mathrm{dd}, \mathrm{J}=51.6$ and $.4 \mathrm{~Hz}, 0.67 \mathrm{H}), 4.57(\mathrm{~m}, 0.33 \mathrm{H}), 4.48(\mathrm{~m}, 0.67 \mathrm{H}), 4.24(\mathrm{dd}, \mathrm{J}=$
12.4 and $2.0 \mathrm{~Hz}, 0.67 \mathrm{H}), 3.89(\mathrm{dd}, \mathrm{J}=11.2$ and $3.2 \mathrm{~Hz}, 0.33 \mathrm{H}), 3.74-3.66(\mathrm{~m}, 1 \mathrm{H}), 2.39$ $1.95(\mathrm{~m}, 2 \mathrm{H}), 1.09(\mathrm{~s}, 6 \mathrm{H}), 1.06(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $158.4(\mathrm{~d}, \mathrm{~J}=14.4$ $\mathrm{Hz}), 158.3(\mathrm{~d}, \mathrm{~J}=15.2 \mathrm{~Hz}), 153.8,153.7,136.5(\mathrm{~d}, \mathrm{~J}=240.5 \mathrm{~Hz}), 136.2(\mathrm{~d}, \mathrm{~J}=241.8 \mathrm{~Hz})$, $135.59,135.56,135.4,133.0,132.9,132.5,132.4,130.1,130.0,129.9,127.9,127.8,124.8$ $(\mathrm{d}, \mathrm{J}=31.9 \mathrm{~Hz}), 96.5(\mathrm{~d}, \mathrm{~J}=181.3 \mathrm{~Hz}), 91.8(\mathrm{~d}, \mathrm{~J}=175.2 \mathrm{~Hz}), 90.7(\mathrm{~d}, \mathrm{~J}=24.9 \mathrm{~Hz}), 87.8(\mathrm{~d}$, $J=21.2 \mathrm{~Hz}), 81.6,79.6,64: 9,63.0,33.5(\mathrm{~d}, \mathrm{~J}=19.7 \mathrm{~Hz}), 30.6(\mathrm{~d}, \mathrm{~J}=21.3 \mathrm{~Hz}), 26.9,26.8$, 19.2, 14.2; IR (thin film) $3304,2959,1680,1621,1508,1105 \mathrm{~cm}^{-1}$; $\mathrm{HRMS}^{2}$ calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2} \mathrm{Li}: 492.2106$. Found:492.2110. Anal. Calc. $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{SiF}_{2}: \mathrm{C}$, $61.84 ; \mathrm{H}, 6.02$; N, 8.65 . Found: C, 61.86; H, $6.09 ; \mathrm{N}, 8.55$.
(D) - $N^{4}$-acetyl-5'-0'( $t$-butyldiphenylsilyl)-2', $3^{\prime}$-dideoxy-2'-fluoro-cytidine (11). mixture of anomers $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \% \mathrm{EtOAc})=0.75 ; \mathrm{mp} 81-86^{\circ} \mathrm{C} .{ }^{1} \mathrm{H} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ d $10.58(\mathrm{bs}, 1 \mathrm{H}), 8.40(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 0.61 \mathrm{H}), 7.86(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 0.38 \mathrm{H}), 7.67-7.65(\mathrm{~m}, 4 \mathrm{H})$, $7.51 \cdot 7.41(\mathrm{~m}, 6 \mathrm{H}), 7.27(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.12(\mathrm{t}, \mathrm{J}=15.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.51(\mathrm{~d}, \mathrm{~J}=52.6 \mathrm{~Hz}$, $0.38 \mathrm{H}), 5.21(\mathrm{dd}, \mathrm{J}=50.8$ and $2.9 \mathrm{~Hz}, 0.61 \mathrm{H}), 4.62(\mathrm{~m}, 0.38 \mathrm{H}), 4.54(\mathrm{~m}, 0.61 \mathrm{H}), 4.28(\mathrm{~d}, \mathrm{~J}=$ $11.5 \mathrm{~Hz}, 0.61 \mathrm{H}), 3.95(\mathrm{dd}, \mathrm{J}=11.9$ and $3.2 \mathrm{~Hz}, 0.38 \mathrm{H}), 3.79-3.70(\mathrm{~m}, 1 \mathrm{H}), 2.46-2.04(\mathrm{~m}$, $5 \mathrm{H}), 1.12(\mathrm{~s}, 5.49 \mathrm{H}), 1.07(\mathrm{~s}, 3.42 \mathrm{H}) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ d $171.5,171.3,163.4$, 154.9, 144.9, 144.1, 135.5, 135.4, 133.0, 132.8, 132.5, 132.2, 130.2, 130.1, 129.9, 128.0, 127.8, $96.8(\mathrm{~d}, \mathrm{~J}=91.1 \mathrm{~Hz}), 96.2(\mathrm{~d}, \mathrm{~J}=147.9 \mathrm{~Hz}), 92.3,91.2(\mathrm{~d}, \mathrm{~J}=35.7 \mathrm{~Hz}), 90.5,88.5(\mathrm{~d}$, $\mathrm{J}=15.9 \mathrm{~Hz}), 81.9,80.1,64: 7,62.9,33.5(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 30.5(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 26.9,26.8$, 24.9, 24.8, 19.3, 19.2; IR (thin film) $3237,2932,1722,1671,1559,1493,1107 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{27} \mathrm{H}_{32} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{FSiLi}: 516.2306$. Found: 516.2310. Anal. Calc.. $\mathrm{C}_{27} \mathrm{H}_{32} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{FSi}: \mathrm{C}, 63.63 ; \mathrm{H}, 6.33 ; \mathrm{N}, 8.24$. Found: C, $63.45 ; \mathrm{H}, 6.42 ; \mathrm{N}, 8.09$. (D) - 5' - O - ( $t$-butyldiphenylsilyl)-2',3'-dideoxy-2'-fluoro-cytidine (12). mixture of anomers $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \% \mathrm{EtOAc})=0.50 ; \mathrm{mp} 98-104^{\circ} \mathrm{C} \cdot{ }^{1} \mathrm{H} \mathrm{NMR}\left(360 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ d $7.97(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 0.64 \mathrm{H}, \mathrm{H}-6), 7.65(\mathrm{~m}, 4 \mathrm{H}), 7.47-7.38(\mathrm{~m}, 6.36 \mathrm{H}), 6.15(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}$, $0.36 \mathrm{H}), 6.05(\mathrm{~d}, \mathrm{~J}=16.6 \mathrm{~Hz}, 0.64 \mathrm{H}), 5.83(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 0.36 \mathrm{H}), 5.46(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 0.64 \mathrm{H})$, $5.30-5.10(\mathrm{~m}, \mathrm{lH}), 4.55(\mathrm{~m}, 0.36 \mathrm{H}), 4.44(\mathrm{~m}, 0.64 \mathrm{H}), 4.22(\mathrm{~d}, \mathrm{~J}=9.7 \mathrm{~Hz}, 0.64 \mathrm{H}), 3.88-$ $3.63(\mathrm{~m}, 1.36 \mathrm{H}), 2.38-1.95(\mathrm{~m}, 2 \mathrm{H}), 1.09(\mathrm{~s}, 5.76 \mathrm{H}), 1.06(\mathrm{~s}, 3.24 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 100 MHz , $\mathrm{CDCl}_{3}$ ) d $166.1,155.8,141.5,140.5,135.6,135.4,133.1,132.9,132.8,132.4,130.1,130.0$, 129.8, 128.0, 127.9, 127.8, $96.7(\mathrm{~d}, \mathrm{~J}=181.3 \mathrm{~Hz}$ ), $93.4(\mathrm{~d}, \mathrm{~J}=140.3 \mathrm{~Hz}$ ), $94.5,90.8(\mathrm{~d}, \mathrm{~J}=$ $35.6 \mathrm{~Hz}), 90.8,87.8(\mathrm{~d}, \mathrm{~J}=15.9 \mathrm{~Hz}), 8 \mathrm{t} .2,79.4,65.0,63.2,33.7(\mathrm{~d}, \mathrm{~J}=21.2 \mathrm{~Hz}), 30.8(\mathrm{~d}, \mathrm{~J}=$
20.4 Hz ), 26.9, 26.8, 19.3, 19.2: IR (thin film) $3470,3339,1644,1487,1113 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{25} \mathrm{H}_{30} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{FSiLi}: 474.2201$. Found: 474.2198. Anal. Calc. $\mathrm{C}_{25} \mathrm{H}_{30} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{FSi}: \mathrm{C}, 64.21 ; \mathrm{H}, 6.47 ; \mathrm{N}, 8.99$. Found: C, $64.04 ; \mathrm{H}, 6.58 ; \mathrm{N}, 8.76$. $\alpha$ - (D) - 2', 3' - Dideoxy - 2' - fluoro - 5-fluorouridine (14a). $\mathrm{R}_{\mathrm{f}}(100 \% \mathrm{EtOAc})=0.38$; $\operatorname{mp} 153-155^{\circ} \mathrm{C} .{ }^{\text {' }} \mathrm{H}$ NMR ( $\left.360 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 7.80(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.11(\mathrm{~d}, \mathrm{~J}=18.7$ $\mathrm{Hz}, 1 \mathrm{H}), 5.35(\mathrm{~d}, \mathrm{~J}=52.9,1 \mathrm{H}), 4.59(\mathrm{~m}, 1 \mathrm{H}), 3.81(\mathrm{~d}, \mathrm{~J} \doteq 11.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.57 .(\mathrm{dd}, \mathrm{J}=12.6$ and $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.36-2.15(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 159.6(\mathrm{~d}, \mathrm{~J}=25.8 \mathrm{~Hz})$, $150.7,141.5(\mathrm{~d}, \mathrm{~J}=230.6 \mathrm{~Hz}), 127.0(\mathrm{~d}, \mathrm{~J}=34.9 \mathrm{~Hz}), 93.9(\mathrm{~d}, \mathrm{~J}=185.1 \mathrm{~Hz}), 88.5(\mathrm{~d}, \mathrm{~J}=15.1$ $\mathrm{Hz}), 81.8,64.3,34.3 .(\mathrm{d}, \mathrm{J}=20.5 \mathrm{~Hz}) ; \operatorname{lR}(\mathrm{KBr}) 3421,3081,1685,1478,1111 \mathrm{~cm}^{-1} ;$ HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}: 255.0769$. Found: 255.0778. Anal. Calc. $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2}: \mathrm{C}, 43.56 ; \mathrm{H}, 4.06 ; \mathrm{N}, 11.29$. Found: $\mathrm{C}, 43.59 ; \mathrm{H}, 4.11 ; \mathrm{N}, 11.17$. $\beta$ - (D) - 2',3' - Dideoxy - 2' - fluoro - 5 - fluorouridine (14b). $\mathrm{R}_{\mathrm{f}}(100 \% \mathrm{EtOAc})=0.54$; mp 152-154(C. ${ }^{1} \mathrm{H}$ NMR ( $360 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $8.41(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), $5.89(\mathrm{~d}, \mathrm{~J}=16.6$ $\mathrm{Hz}, 1 \mathrm{H}), 5.21(\mathrm{dd}, \mathrm{J}=51.5$ and $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{~m}, 1 \mathrm{H}), 4.00(\mathrm{~d}, \mathrm{~J}=12.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.67(\mathrm{~d}$, $\mathrm{J}=12.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.25-2.09(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $159.7(\mathrm{~d}, \mathrm{~J}=25.8 \mathrm{~Hz}$ ), $150.7,141.8(\mathrm{~d}, \mathrm{~J}=229.8 \mathrm{~Hz}), 126.3(\mathrm{~d}, \mathrm{~J}=36.4 \mathrm{~Hz}), 98.3(\mathrm{~d}, \mathrm{~J}=179 \mathrm{~Hz}), 91.9(\mathrm{~d}, \mathrm{~J}=37.1$ $\mathrm{Hz}), 83.6,61.9,31.9(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz})$; IR (KBr) $3417,3056,1684,1474,1105 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\mathrm{M}+\mathrm{Li}$ ] $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}:$ 255.0769. Found: 255.0764. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2}: \mathrm{C}, 43.56 ; \mathrm{H}, 4.06 ; \mathrm{N}, 11.29$. Found: $\mathrm{C}, 43.37 ; \mathrm{H}, 3.98 ; \mathrm{N}, 11.22$.
$\alpha-(D)-2^{\prime}, 3^{\prime}-$ Dideoxy - 2' - fluoro - 5-fluorocytidine (15a). $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \%$ $\mathrm{EtOAc})=0.22 ; \mathrm{mp} 198-202^{\circ} \mathrm{C}(\mathrm{dec}.) .{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 7.78(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}$, $1 \mathrm{H}), 6.07(\mathrm{~d}, \mathrm{~J}=18.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.37(\mathrm{~d}, \mathrm{~J}=54.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.59(\mathrm{~m}, 1 \mathrm{H}), 3.80(\mathrm{dd}, \mathrm{J}=12.0$ and $3.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.57(\mathrm{dd}, \mathrm{J}=12.4$ and $4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.38-2.14(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 100 MHz , $\mathrm{CD}_{3} \mathrm{OD}$ ) d $159.9(\mathrm{~d}, \mathrm{~J}=13.6 \mathrm{~Hz}), 156.5,138.3(\mathrm{~d}, \mathrm{~J}=240.4 \mathrm{~Hz}), 127.5(\mathrm{~d}, \mathrm{~J}=33.4 \mathrm{~Hz}), 93.6$
 $3098,1681,1519,1108 \mathrm{~cm}^{-1} ;$ HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \mathrm{Li}: 254.0929$. Found: 254.0929. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \cdot 1 / 2 \mathrm{H}_{2} \mathrm{O}: \mathrm{C}, 42.19 ; \mathrm{H}, 4.72 ; \mathrm{N}, 16.40$. Found: C, 41.86; H, 4.75; N, 16.36.
$\boldsymbol{\beta}$ - (D) - 2', 3' - Dideoxy - 2' - fluoro - 5-fluorocytidine (15b). $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \%$ EtOAc $)=0.37$; mp 181-183 ${ }^{\circ} \mathrm{C}(\mathrm{dec}.) .{ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \mathrm{d} 8.45(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}$, $1 \mathrm{H}), 5.92(\mathrm{dd}, \mathrm{J}=16.2$ and $1.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.18(\mathrm{dd}, \mathrm{J}=50.8$ and $4.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.46(\mathrm{~m}, \mathrm{H})$,

4:05 ( $\mathrm{dd}, \mathrm{J}=12.4$ and $2.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.72(\mathrm{dd}, \mathrm{J}=12.8$ and $2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.27-2.05(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $159.9(\mathrm{~d}, \mathrm{~J}=13.6 \mathrm{~Hz}), 156.5,138.5(\mathrm{~d}, \mathrm{~J}=240.5 \mathrm{~Hz}), 126.9(\mathrm{~d}$, $\mathrm{J}=33.4 \mathrm{~Hz}$ ), $98.4(\mathrm{~d}, \mathrm{~J}=17.9 .0 \mathrm{~Hz}), 92.5(\mathrm{~d}, \mathrm{~J}=36.4 \mathrm{~Hz}), 83.6,61.9,31.6(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}) ;$ IR (KBr) 3494, 2944, 1689, 1522, $1106 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2} \mathrm{Li}$ : 254.0929. Found: 254.0936. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}_{2}: \mathrm{C}, 43.73 ; \mathrm{H}, 4.49 ; \mathrm{N}, 17.00$. Found: C, 43.84; H, 4.47; N, 17.05 .
$\alpha$ - (D) - $N^{4}$ - acetyl-2', ${ }^{\prime}$ - dideoxy - $\mathbf{2}^{\prime}$ - fluoro - cytidine (16a). $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \%$ $\mathrm{EtOAc})=0.40 ; \mathrm{mp} 208-212^{\circ} \mathrm{C} .{ }^{\text {'H NMR }}\left(360 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}\right) \mathrm{d}^{\prime}(10.91, \mathrm{bs}, 1 \mathrm{H}), 8.05$ (d, J $=7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.25(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.08(\mathrm{dd}, \mathrm{J}=19.1$ and $2.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.42(\mathrm{~d}, \mathrm{~J}=$ $52.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.97(\mathrm{bs}, 1 \mathrm{H}), 4.54(\mathrm{~m}, 1 \mathrm{H}), 3.63(\mathrm{~d}, \mathrm{~J}=13.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.47$ ( $\mathrm{d}, \mathrm{J}=13.3 \mathrm{~Hz}$, 1H), 2.35-2.15 (m, 2H), $2.11(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO - $\mathrm{d}_{6}$ ) d 171.0, 162.6, 154.3, $145.7,94.9,92.0(\mathrm{~d}, \mathrm{~J}=183.6 \mathrm{~Hz}), 87.5(\mathrm{~d}, \mathrm{~J}=15.9 \mathrm{~Hz}), 80.2,62.6,33.3(\mathrm{~d}, \mathrm{~J}=1-1.9 .7$ Hz ), 24.4; IR (KBr) $3436,3227,1702,1661,1442,1102 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+$ Li] $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{FLi}: 278.1128$. Found: 278.1136. Anal..Calc.. $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~F}: \mathrm{C}, 48.71 ; \mathrm{H}$, 5.20; N, 15:49. Found: C, 48.73; H, 5.23; N, 15.52.
$\beta$ - (D) - $N^{\mathbf{f}^{-}}$acetyl-2', $\mathbf{3}^{\prime}$ - dideoxy - $\mathbf{2}^{\prime}$ - fluoro - cytidine ( $\mathbf{1 6 b}$ ). $\mathrm{R}_{\mathrm{f}}$ ( $15 \% \mathrm{EtOH}, 85 \%$. EtOAc $)=0.50 ; \mathrm{mp} 174-178^{\circ} \mathrm{C} .{ }^{\prime} \mathrm{H}$ NMR $\left(360 \mathrm{MHz}\right.$, DMSO $\left.-\mathrm{d}_{6}\right) \mathrm{d}(10.90, \mathrm{bs}, 1 \mathrm{H}), 8.46$
 $1 \mathrm{H}), 5.27(\mathrm{bs}, 1 \mathrm{H}), 4.39(\mathrm{~m}, 1 \mathrm{H}), 3.88(\mathrm{~d}, \mathrm{~J}=13.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.61(\mathrm{~d}, \mathrm{~J}=13.0 \mathrm{~Hz}, 1 \mathrm{H}), 209(\mathrm{~s}$, 3H), 2.20-1.85 (m, 2H); ${ }^{15} \mathrm{C}$ NMR ( 100 MHz , DMSO - $\mathrm{d}_{6}$ ) d 171.0, 162.6, 154.4, 144.7, 97.0 (d, J = 177.5 Hz ), $95.0,90.7(\mathrm{~d}, \mathrm{~J}=36.6 \mathrm{~Hz}), 82.2,60.3,30.3(\mathrm{~d}, \mathrm{~J}=19.7 \mathrm{~Hz}), 24.3$; IR ( KBr ) $3447,3245,1703,1656,1497,1122 \mathrm{~cm}^{-1}$; HRMS calculated for [M + Li]
$\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{FLi}: 278.1128$. Found: 278.1133. Anal. Calc.. $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~F}: \mathrm{C}, 48.71 ; \mathrm{H}, 5.20$; N, 15.49 . Found: C, 48.65; H, 5.22; N, 15.46.
$\alpha$ - (D) - 2', 3' - Dideoxy - 2' - fluoro - cytidine (17a). $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH} ; 85 \% \mathrm{EtOAc})=0.08$; mp $234-237^{\circ} \mathrm{C}$ (dec.). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, ~ D M S O-\mathrm{d}_{6}$ ) d $7.52(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.21$ (bm, 2H), 6.05 (dd, J = 20.4 and $3.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), $5.73(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.28(\mathrm{~d}, \mathrm{~J}=52.4 \mathrm{~Hz}$, $1 \mathrm{H}), 4.93(\mathrm{t}, \mathrm{J}=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.45(\mathrm{~m}, 1 \mathrm{H}), 3.58(\mathrm{~m}, 1 \mathrm{H}), 3.43(\mathrm{~m}, 1 \mathrm{H}), 2.26-2.13(\mathrm{~m}, 2 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO. $-\mathrm{d}_{6}$ ) $\mathrm{d} 165.8,155.0,141.6,93.3,92.2(\mathrm{~d}, \mathrm{~J}=182.8 \mathrm{~Hz}), 86.6(\mathrm{~d}$, $\mathrm{J}=15.1 \mathrm{~Hz}), 79.4,62.8,33.3(\mathrm{~d}, \mathrm{~J}=19.7 \mathrm{~Hz}) ; \operatorname{IR}(\mathrm{KBr}) 3366,3199,1659,1399,4122 \mathrm{~cm}^{-1}$;

HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{FLi}: 236.1023$. Found: 236.1014. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}: \mathrm{C}, 147.16 ; \mathrm{H}, 5.28 ; \mathrm{N}, 18.33$. Found: C, 47.40; H, 5.34; N, 18.51 .
$\beta$ - (D) - 2', 3' - Dideoxy - 2' - fluoro - cytidine (17b). Nucleoside 25 ( $0.160 \mathrm{~g}, 0.59 \mathrm{mmol}$ ) was dissolved in 10 mL of saturated methanolic ammonia. After stirring for 5 min , the reaction was complete. The methanolic ammonia was removed and the resultant white solid was placed under vacuum and heated gently in a $60^{\circ} \mathrm{C}$ water bath for 2 hrs . to remove the acetamide by-product through sublimation. The white solid was crystallized from $5 \%$ methanol / $95 \%$ methylene chloride to give a quantitative yield of a white crystalline solid. $\mathrm{R}_{\mathrm{f}}(15 \% \mathrm{EtOH}, 85 \% \mathrm{EtOAc})=0.18 ; \mathrm{mp} 191-195^{\circ} \mathrm{C}(\mathrm{dec}.) .{ }^{1} \mathrm{H} \operatorname{NMR}\left(360 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right)$ $\mathrm{d} 8.10(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.92(\mathrm{~d}, \mathrm{~J}=17.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.82(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.13(\mathrm{~d}, \mathrm{~J}=$ $50.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.39(\mathrm{~m}, 1 \mathrm{H}), 3.97(\mathrm{~d}, \mathrm{~J}=12.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.68(\mathrm{dd}, \mathrm{J}=13.0$ and $2.5 \mathrm{~Hz}, 1 \mathrm{H})$, 2.21-2.00 (m, 2H); . ${ }^{3} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 165.9, 155.0; 140.8, 97.3 (d, J = 176.8 $\mathrm{Hz}), 93.6,90.3(\mathrm{~d}, \mathrm{~J}=35.6 \mathrm{~Hz}), 81.3,60.7,31.0(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}) ; \mathrm{IR}(\mathrm{KBr}) 3397,3112$, 1680, 1400, 1178, $1070 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{FLi}: 236.1024$. Found: 236.1028. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{12} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~F}: \mathrm{C}, 47.16 ; \mathrm{H}, 5.28 ; \mathrm{N}, 18.33$. Found: C, 47.01; H, 5.21; N, 18.29 .
(L) - 5' - O - ( $t$-butyldiphenylsilyl) - 2', 3' - dideoxy - 2' - fluoro - thymidine (23). mixture of anomers $\mathrm{R}_{\mathrm{f}}\left(10 \% \mathrm{MeOH} / 90 \% \mathrm{CH}_{2} \mathrm{Cl}_{2}\right)=0.56 ; \mathrm{mp} 61-65^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR ( $360, \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \mathrm{d} 9.48(\mathrm{bs}, 1 \mathrm{H}), 7.67(\mathrm{~m}, 4 \mathrm{H}), 7.45-7.37(\mathrm{~m}, 7 \mathrm{H}), 6.15(\mathrm{dd}, \mathrm{J}=20.2$ and 3.2 Hz , 0.36 H ), $5.99(\mathrm{~d}, \mathrm{~J}=18.4 \mathrm{~Hz}, 0.64 \mathrm{H}), 5.34(\mathrm{~d}, \mathrm{~J}=51.8 \mathrm{~Hz}, 0.36 \mathrm{H}), 5.24(\mathrm{dd}, \mathrm{J}=52.2$ and 4.3 $\mathrm{Hz}, 0.64 \mathrm{H}), 4.59(\mathrm{~m}, 0.36 \mathrm{H}), 4.45(\mathrm{~m}, 0.64 \mathrm{H}), 4.17(\mathrm{dd}, \mathrm{J}=12.2$ and $2.5 \mathrm{~Hz}, 0.64 \mathrm{H}), 3.91$ (dd, $\mathrm{J}=11.9$ and $2.9 \mathrm{~Hz}, 0.36 \mathrm{H}$ ), $3.81(\mathrm{dd}, \mathrm{J}=11.5$ and $2.9 \mathrm{~Hz}, 0.64 \mathrm{H}$ ), $3.68(\mathrm{dd}, \mathrm{J}=10.8$ and $3.6 \mathrm{~Hz}, 0.36 \mathrm{H}), 2.40-2.12(\mathrm{~m}, 2 \mathrm{H}), 1.94(\mathrm{~s}, 1.08 \mathrm{H}), 1.61(\mathrm{~s}, 1.92 \mathrm{H}), 1.10(\mathrm{~s}, 5.76 \mathrm{H}), 1.07(\mathrm{~s}$, 3.24 H ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d 164.1 , $164.0,150.4,150.2,136.4,135.6,135.5$, 135.4, 135.3, 135.2, 133.0, 132.8, 132.6, 130.1, 130.0, 129.9, 127.94, 127.90, 127.8, 110.8 , $109.8,96.4(\mathrm{~d}, \mathrm{~J}=181.3 \mathrm{~Hz}), 92.1(\mathrm{~d}, \mathrm{~J}=185.8 \mathrm{~Hz}), 90.7(\mathrm{~d}, \mathrm{~J}=36.4 \mathrm{~Hz}), 86.6(\mathrm{~d}, \mathrm{~J}=15.2$ Hz ), 80.9, 79.4, 64.9, 63.6, 33.4 ( $\mathrm{d}, \mathrm{J}=20.5 \mathrm{~Hz}$ ), $32.0(\mathrm{~d}, \mathrm{~J}=21.2 \mathrm{~Hz}$ ), 27.0, 26.8, 19.4, 19.2, 12.6, 12.2; IR (thin film) $3183,3050,1696,1506,1188 \mathrm{~cm}^{-1}$; HRMS calculated for [ $\mathrm{M}+\mathrm{Li}$ ] $\mathrm{C}_{26} \mathrm{H}_{11} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}: 489.2197$. Found: 489.2175 . Anal. Calc. $\mathrm{C}_{26} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}: \mathrm{C}, 64.71 ; \mathrm{H}, 6.47$; N, 5.80. Found: C, 64.88; H, 6.56; N, 5.76.
(L) - 5' - O-(f-butyldiphenylsilyl) - $2^{\prime}, 3^{\prime}-$ dideoxy - $2^{i}$ fluoro- 5 -fluorouridine (24). mixture of anomers $R_{f}(1: 1$ hexanes $/ E t O A c)=0.48 ; \mathrm{mp} 65.71^{\circ} \mathrm{C} .{ }^{\prime} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \mathrm{d} 9.08(\mathrm{bs}, 0.4 \mathrm{H}), 9.00(\mathrm{bs}, 0.6 \mathrm{H}) 8.01(\mathrm{~d}, \mathrm{~J}=5.4 \mathrm{~Hz}, 0.6 \mathrm{H}), 7.65(\mathrm{~m}, 4 \mathrm{H}), 7.42(\mathrm{~m}$, $6.4 \mathrm{H}), 6.10(\mathrm{dd}, \mathrm{J}=20.2$ and $\mathrm{I} .4 \mathrm{~Hz}, 0.4 \mathrm{H}), 6.00(\mathrm{~d}, \mathrm{~J}=16.0 \mathrm{~Hz}, 0.6 \mathrm{H}), 5.35(\mathrm{dd}, \mathrm{J}=52.4$
and $1.6 \mathrm{~Hz}, 0.4 \mathrm{H}),(5.22, \mathrm{dd}, \mathrm{J}=51.2$ and $4 \mathrm{~Hz}, 0.6 \mathrm{H}), 4.57(\mathrm{~m}, 0.4 \mathrm{H}), 4.44(\mathrm{~m}, 0.6 \mathrm{H}), 4.22$ (dd, $\mathrm{J}=12.4$ and $2.0 \mathrm{~Hz}, 0.6 \mathrm{H}$ ), 3.91 (dd, $\mathrm{J}=11.2$ and $2.9 \mathrm{~Hz}, 0.4 \mathrm{H}$ ), $3.70(\mathrm{~m}, \mathrm{lH}), 2.45-$ $2.00(\mathrm{~m}, 2 \mathrm{H}), 1.09(\mathrm{~s}, 5.4 \mathrm{H}), \mathrm{J} .07(\mathrm{~s}, 3.6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) d $156.9(\mathrm{~d}, \mathrm{~J}=26.5$ $\mathrm{Hz}), 148.8,148.6,140.3(\mathrm{~d}, \mathrm{~J}=236.7 \mathrm{~Hz}), 140.1(\mathrm{~d}, \mathrm{~J}=23.1 \mathrm{~Hz}), 135.6,135.5 \overline{1}, 135.4$, 132.9, 132.7, 132.4, 132.3, 130.2, 130.1, 129.9, 127.9, 127.8, 125.1 (d, J = 34.9 Hz ), 123.6 (d, $\mathrm{J}=34.2 \mathrm{~Hz}$ ), $96.4(\mathrm{~d}, \mathrm{~J}=182.9 \mathrm{~Hz}), 92.0(\mathrm{~d}, \mathrm{~J}=186.6 \mathrm{~Hz}), 90.2(\mathrm{~d}, \mathrm{~J}=36.0 \mathrm{~Hz}), 86.9(\mathrm{~d}, \mathrm{~J}=$ 15.1 Hz ), 81.7, $79.8,64.8,63.0,33.2(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}), 30.9(\mathrm{~d}, \mathrm{~J}=20.4 \mathrm{~Hz}), 26.9,26.8,19.2$; IR (thin film) 3191, 1719, 1113 cm ${ }^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}_{2} \mathrm{Li}$ : 493.1946. Found: 493.1952. Anal. Calc. $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SiF}_{2}: \mathrm{C}, 61.71 ; \mathrm{H}, 5.80 ; \mathrm{N}, 5.76$. Found: C, 61.73; H, 5.83; N, 5.77 .
$\alpha-(\mathrm{L})$ - $\mathbf{2}^{\prime}, \mathbf{3}^{\prime}$ - Dideoxy - 2' - fluoro - thymidine (26a). $\mathrm{R}_{\mathrm{f}}(100 \% \mathrm{EtOAc})=0.25 ; \mathrm{mp}$ 147-149 ${ }^{\circ} \mathrm{C}$. 'H NMR ( $360 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $7.45(\mathrm{~s}, 1 \mathrm{H}), 6.11(\mathrm{dd}, \mathrm{J}=19.4$ and 2.9 Hz , 1 H ), $5.30(\mathrm{~d}, \mathrm{~J}=53.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.58(\mathrm{~m}, 1 \mathrm{H}), 3.79(\mathrm{dd}, \mathrm{J}=12.2$ and $2.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.55(\mathrm{dd}, \mathrm{J}=$ 12.2 and $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.40-2.15(\mathrm{~m}, 2 \mathrm{H}), 1.87(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 166.6, 152.3, 138.6, 110.5, $93.9(\mathrm{~d}, \mathrm{~J}=185.1 \mathrm{~Hz}), 88.3(\mathrm{~d}, \mathrm{~J}=15.1 \mathrm{~Hz}), 81.7,64.4,34.5(\mathrm{~d}, \mathrm{~J}$ $=20.5 \mathrm{~Hz}), 12.6$ IR $(\mathrm{KBr}) 3436,3166,1727,1667,1362,1186 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{10} \mathrm{H}_{13} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{FLi}: 251.1019$. Found: 251.1014. Anal. Calc.. $\mathrm{C}_{10} \mathrm{H}_{13} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}: \mathrm{C}, 49.18$; H, 5.37; N, 11.47. Found: C, 49.32; H, 5.40; N, 11.29. .
$\beta$ - (L) - 2', 3' - dideoxy - 2' - fluoro - thymidine (26b). $\mathrm{R}_{\mathrm{f}}(100 \% \mathrm{EtOAc})=0.38 ; \mathrm{mp}$ $186-188^{\circ} \mathrm{C}$. 'H NMR ( $360 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $7.94(\mathrm{~s}, \mathrm{lH}), 5.93(\mathrm{~d}, \mathrm{~J}=17.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.20(\mathrm{~d}$, $\mathrm{J}=51.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.40(\mathrm{~m}, \mathrm{IH}), 3.98(\mathrm{~d}, \mathrm{~J}=11.9 \mathrm{~Hz}, 1 \mathrm{H}) ; 3.68(\mathrm{~d}, \mathrm{~J}=13.0 \mathrm{~Hz}, \mathrm{lH}), 2.37-$ $2.10(\mathrm{~m}, 2 \mathrm{H}), 1.83(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $166.7,152.3,138.2,111.0,98.4$ $(\mathrm{d}, \mathrm{J}=178.3 \mathrm{~Hz}), 92.1(\mathrm{~d}, \mathrm{~J}=36.4 \mathrm{~Hz}), 83.1,62.4,32.5(\mathrm{~d} ; \mathrm{J}=20.5 \mathrm{~Hz}), 12.6$; IR $(\mathrm{KBr})$ $3478,3052,1684,1363,1192,1005 \mathrm{~cm}^{-1}$; Anal. Calc.. $\mathrm{C}_{10} \mathrm{H}_{13} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}: \mathrm{C}, 49.18 ; \mathrm{H}, 5.37 ; \mathrm{N}$, 11.47. Found: C, 49:29; H; 5.44; N, 11.36.
$\alpha \cdot(\mathrm{L})-2^{\prime}, 3^{\prime}$ - dideoxy - $\mathbf{2}^{\prime}$ - fluoro - 5 - fluorouridine ( $\mathbf{2} 7 \mathrm{a}$ ) $. \mathrm{R}_{\mathrm{f}}(100 \% \mathrm{EtOAc})=0.38 ; \mathrm{mp}$ $\left.155-157^{\circ} \mathrm{C}\right)$. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $7.80(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, \mathrm{lH}), 6.13(\mathrm{~d}, \mathrm{~J}=20.0 \mathrm{~Hz}$,
$1 \mathrm{H}), 5.35(\mathrm{~d}, \mathrm{~J}=54.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.63(\mathrm{~m}, 1 \mathrm{H}), 3.81(\mathrm{dd}, \mathrm{J}=11.9$ and $3.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.58(\mathrm{dd}, \mathrm{J}=$ 12.4 and $2.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.41:2.15 (m, 2H); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $159.6(\mathrm{~d}, \mathrm{~J}=25.8$ $\mathrm{Hz}), 150.7,141.5(\mathrm{~d}, \mathrm{~J}=230.6 \mathrm{~Hz}), 127.0(\mathrm{~d}, \mathrm{~J}=34.9 \mathrm{~Hz}), 93.9(\mathrm{~d}, \mathrm{~J}=184.3 \mathrm{~Hz}), 88.5(\mathrm{~d}, \mathrm{~J}=$ 15.1 Hz ), $81.9,64.3,34.3\left(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}\right.$ ); IR (KBr) $3401,3098,1661,1458,1018 \mathrm{~cm}^{-1}$; HRMS calculated for [M +Li] $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}: 255.0769$. Found: 255.0771. Anal. Talc.. $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2}: \mathrm{C}, 43.56 ; \mathrm{H}, 4: 06 ; \mathrm{N}, 11.29$. Found: C, $43.70 ; \mathrm{H}, 4.17 ; \mathrm{N}, 11.15$.
$\beta$ - (L) - $\mathbf{2}^{\prime}, \mathbf{3}^{\prime}$ - dideoxy - $\mathbf{2 '}^{\prime}$ - fluor - 5 - fluorouridine (27b). $\mathrm{R}_{\mathrm{f}}(100 \% \mathrm{EtOAc})=0.54 ; \mathrm{mp}$ $153-156^{\circ} \mathrm{C}$. 'H NMR ( $400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d $8.46(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.94(\mathrm{~d}, \mathrm{~J}=16.1 \mathrm{~Hz}$, $1 \mathrm{H}), 5.25(\mathrm{dd}, \mathrm{J}=51.6$ and $4.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{~m}, 1 \mathrm{H}), 4.05(\mathrm{dd}, \mathrm{J}=12.8$ and $2.4 \mathrm{~Hz}, 1 \mathrm{H})$, 3.72 (dd, J = 12.4 and $2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.34-2.09(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) d 159.7 $(\mathrm{d}, \mathrm{J}=25.8 \mathrm{~Hz}) ; 150.7,141.8(\mathrm{~d}, \mathrm{~J}=230.6 \mathrm{~Hz}), 126.3(\mathrm{~d}, \mathrm{~J}=35.7 \mathrm{~Hz}), 98.3(\mathrm{~d}, \mathrm{~J}=184.6 \mathrm{~Hz})$, $91.9(\mathrm{~d}, \mathrm{~J}=36.4 \mathrm{~Hz}), 83.6,61.9,31.9(\mathrm{~d}, \mathrm{~J}=20.5 \mathrm{~Hz}) ; \operatorname{IR}(\mathrm{KBr}) 3482,3037,1702,1654$, 1402, $1103 \mathrm{~cm}^{-1}$; HRMS calculated for $[\mathrm{M}+\mathrm{Li}] \mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2} \mathrm{Li}: 255.0769$. Found: 255.0764. Anal. Calc.. $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~F}_{2}: \mathrm{C}, 43.56 ; \mathrm{H}, 4.06 ; \mathrm{N}, \mathrm{I} 1.29$. Found: $\mathrm{C}, 43.59 ; \mathrm{H}$, 4.06; N, 11.17.

## PREPARATION OF L-2'-FLUORO-2',3'-UNSATURATED NUCLEOSIDES

A second facile synthesis of unsaturated 2 '-fluoronucleosides has also now been accomplished and is described below. The synthesis involves reacting a protected pyrimidine or purine base with key intermediate 309 in the presence of a Lewis acid, as described generally in Scheme 9 below. Representative compounds made according to this synthesis are described in Tables 5-6.

## Scheme 9



Fesgenta; (i) 2 -methoxypropene, OMF, P - TsOH (ii) $\mathrm{NaIO} \mathrm{O}_{4}, \mathrm{H}_{2} \mathrm{O}$ (iii) ( EHO$)_{2} \mathrm{P}$ (O) $\mathrm{CHFCO}_{2} \mathrm{EL}$, NaHMDS, THF, $-78^{\circ} \mathrm{C}$ (iv) C-HCl. EIOH (v) TBDMSCl. imidazole, $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (yi) $\mathrm{OIBAL}+\mathrm{H}, \mathrm{CH}_{2} \mathrm{Cl}_{2},-78^{\circ} \mathrm{C}$ (vil) $\mathrm{AC}_{2} \mathrm{O}$, pyridine, $\mathrm{CH}_{2} \mathrm{Cl}_{2}$.

Scheme 9


Fisagents; (i) silyteted uracl, TMSOTt, DCE (ii) sthyleted inymine; TMSOTf, DCE (iii) silytated $\mathrm{N}^{4}-\mathrm{Bz}$-cytosine,

${ }_{1}^{1}$ Scheme 9


Resgents; (i) siyleted 6-CL-Durine, TMSOTI, DCE (il) sibytated 6-Cl-2-F-purine; TMSOTi, DCE (ITI) TBAF, CH, CN (VV)


${ }^{\mathrm{a}} \mathrm{CDCl}_{3},{ }^{\text {b }}$ DMSO- $\boldsymbol{d}^{6}$
Table 3

| No. | $\mathrm{H}-1{ }^{\text {a }}$ | H-3' | H-4' | H-5' | others ; |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $24^{\circ}$ |  |  | $!$ | - - |  |
| $25^{\text {a }}$ |  |  |  |  |  |
| $26^{\text {a }}$ |  | 5.85 (s). 5.78 (s) |  | 3.85 (m) | (Bu), 0.111, 0.105, 0.097, 0.095 (45, $4 \times \mathrm{CH}_{3}$ ) |
| $27^{\text {a }}$ | 6.88 (s) | 5.77 (s) | 5.02 (s). | 3.88 (m) |  |
| $28^{\text {B }}$ | 6.81 (m) ${ }^{\text {- }}$ | ${ }_{5}^{5.84}$ (s) | 5.19 (m) | 3.81 (m) | 8.17 (s, H-8), 0.92 (s, $\left.{ }^{1} \mathrm{Bu}\right), 0.103 .0 .089\left(2 \mathrm{~s} .2 \pm \mathrm{CH}_{3}\right)$ |
| $29^{3}$ | $\cdots$ |  |  |  | : |
| $30^{\text {a }}$ | 7.00 (m) | s. 86 (s) | 5.29 (m) | 3.87 (m) | 8. 78 ( (s, H-8). 8.22 (s. H-2) |
| $31^{\text {a }}$ | 6.81 (m) | $5.73(0 . J=1.6 \mathrm{~Hz}$ ) | 4.96 (d. J = 2.8 Hz$)$ | 3.85 (m) |  |
| -32 ${ }^{\text {a }}$ | 6.78 (m) | 5.75 (s) | 4.95 (m) | 3.81 (m) |  |
| . $33^{\text {a }}$ | 6.76 (m) | 5.80 (s) |  | 3.78 (m) |  |
| $34^{\text {a }}$ | $\begin{aligned} & 6.73(\text { ps I, } J=4.4, \\ & 4.8 \mathrm{~Hz}) \end{aligned}$ | 5.80 (s) | 5.09 (m) | 3.78 (m) | 7.84 (s, H-8), 5.12 (s, $\mathrm{NH}_{2}$ ), 0.91 (s. ${ }^{\text {'Bu), }} 0.0096 .0 .082$ (s. $\mathrm{CH}_{3}$ ) |
| $35^{\text {b }}$ | - 6.90 (s) | 6.08 (s) | 4.91 (s) | 3.63 (s) |  |
| $36^{\circ}$ | $6.89(1 . J=4 \mathrm{~Hz})$ | 6.06 (s) |  | 3.57 (m) |  |
| - ${ }^{37}{ }^{\text {b }}$ | 6.94 (m) | $6.15(1 . J=1.6 \mathrm{~Hz})$ | 4.98 (s) | 3.67 (s) |  |
| $38^{\circ}$ | $\begin{aligned} & 6.87(\rho s t . J=3.6 ، \\ & 4.4 \mathrm{~Hz}) \end{aligned}$ | 6.06 (s) | 5.13 ( $1, J=3.6 \mathrm{tz})$ | 3.50 (m) | 8.26 (s, H-8), B. 08 (s. $\mathrm{H}-2)$ |

${ }^{2} \mathrm{CDCl}_{3}$. ${ }^{6}$ DMSO- $\boldsymbol{o}^{6}$

Tables

'Solvents; $\mathrm{A} ;$ ElOAc-hexanes, $\mathrm{B} ; \mathrm{CH}_{2} \mathrm{Cl}_{2}-\mathrm{MeOH}, \mathrm{C} ; \mathrm{CHCl}_{3}-\mathrm{MeOH}, \mathrm{D} ; \mathrm{THF}$.

## 40 cyclohexane, E; lyophilyzed

Previously, the synthesis of $2^{\prime}, 3^{\prime}$-unsaturated D-nucleosides has been accomplished via eleimination reaction starting from readily available nucleoside analog, which involved a lengthy modification for individual nucleosides. Several groups reported D-2'-fluoro-2',3'unsaturated pyrimidine nucleosides by the elimination of.suitable 2 'fluorinated nucleoside ' analoys (Martin, J. A., et al., J. Med. Chem. 1990, 33, 2137-2145; Stczycki, R. Z., et al., J. Med. Chem. 1990, 33, 2150-2157). This strategy for the synthesis of L-Fd4N, however, is accompanied by additional difficulties in the preparation of L-nucleosides as the starting material. There are few examples of the synthesis of $2^{\prime}, 3^{\prime}$-unsaturated purine nucleosides by direct condensation due to the lability of the 2,3 -unsaturated sugar moiety under the coupling conditions in the presence of Lewis acid, except one case of the pyrimidine analog using a thiophenyl intermediate (Abdel-Medied, A. W.-S., et al., Synthesis 1991, 313-317; Sujino, K., et al., Tetrahedron Lett. 1996, 37, 6133-6136). In contrast to the 2,3-unsaturated sugar moiety, the 2-fluoro-2,3-unsaturated sugar, which bears enhanced stability of glycosyl bond during the condensation with a hetcrocycle, was expected to become more suitable for the direct coupling reaction. Thus, ( $R$ ) -2-fluorobutenolide 506, as a precusor for the key intermediate 508, was chosen, which was prepared from L-glyceraldehyde acetonide 501.

Starting from L-glyceraldehyde acetonide, a mixture of ( $E$ )-502/(Z)-2 (9:1 by ${ }^{1} \mathrm{H}$ NMR) was obtained via the Homer-Emmons reaction in the presence of triethyl $\alpha$ fluorophosphonoacetate and sodium bis (trimethylsily 1) amide in THF (Thenappan, A., et al., J. Org. Chem., 1990, 55, 4639-4642; Morikawa, T., et al., Chem. Pharm. Bull. 1992, 40, 3189-3193; Patrick, T. B., et al., J. Org. Chem. 1994, 59, 1210-1212). Due to the difficulties in separating $(E)-502 /(Z)-502$ isomers, the mixtures were used in the following cyclization reaction under acidic condition to give the desired lactone 503 and uncyclized diol 504. The resulting mixture was converted to the silyl lactone 506 was subjected to reduction with DIBAL- H in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ at $78^{\circ} \mathrm{C}$ to give the lactol 507 . The lactol 507 was treated with acetic anhydride to yield key intermediate 508 , which was condensed with silylated 6-chloropurine under Vorburggen conditions ta afford anomeric mixtures 509. Treatment of $\mathbf{5 0 9}$ with TBAF in THF gave free nucleosides 510 and $\mathbf{5 1 1}$, which was readily separated by silica gel column chromatography. Adenine analogs 512 and 513 were obtained by the treatement of compound 510 and 511 with mercaptoethanol and NaOMe a steel bomb at $90^{\circ} \mathrm{C}$,respectively. Treatment of compounds 510 and 511 with mercaptoethanol and NaOMe afforded the inosine analogs 514 and 515 , respectively. The sterochemical assignment of
these compounds was based on th NOESY spectroscopy (cross peak between H-1' and H-4' in B-isomer 512).

Scheme 10. Synthesis of L-2'-Fluoro-d4Adenine and -Hypoxanthine by Direct

## Condensation




 (iv) $1 \mathrm{M} \mathrm{DIBAL}-\mathrm{H}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{3},-78^{\circ} \mathrm{C}$ (v) $\mathrm{Ac}_{2} \mathrm{O}$, pyx., $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (vi) siyle!ed 6-Cl-purine, TMSOTI, DCE (vii) $\mathrm{TBAF}, \mathrm{CH}_{3} \mathrm{CN}$ (viii) $\mathrm{NH}_{3} / \mathrm{MeOH}, 90^{\circ} \mathrm{C}$ (ix) $\mathrm{HS}_{\left(\mathrm{CH}_{2}\right)_{2} \mathrm{OH}, \mathrm{NaOMe} / \mathrm{MeOH} . \text { reflux }}$

Table 7. Median Effective ( $\mathrm{EC}_{50}$ ) and Inhibitory ( $1 \mathrm{C}^{50}$ ) Concentration of L-2'-Fluoro-d4Adenine and Hypoxanthine against HIV-1 in PBM

5


## Experimental section.

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonarice spectra were recorded on a Broker 250 and AMX400 400 MHz spectrometers with tetramethylsilane as the internal reference; chemical shifts ( $\delta$ ) are reported in parts per million ( ppm ), and the signals are described as $s$ (singlet), $d$ (doublet), t (triplet), q (quartet), br (broad singlet), dd (doublet of doublet), and m (multiplet). UV spectra were obtained on a beckman DU 650 . spectrophotometer. Optical rotations were measured on a Jasco DIP-370 Digital Polarimeter. Mass spectra were measured on a Micromass Inc. Autospec High Resolution double focussing sector (EBE) MS spectrometers. Infrared spectra were recorded on a Nicole 510 FT-IR spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. All reactions were monitored using thin layer chromatography on Analtech, 200 mm silica gel GF plates. Dry 1,2-dichloroethane, dichloromethane; and acetonitrile were obtained by distillation from $\mathrm{CaH}_{2}$ prior to use. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.
$\mathrm{L}-(S)$-Glyceraldehyde acetonide (302). A solution of L -gulonic- $\boldsymbol{\gamma}$-lactone ( $175 \mathrm{~g}, 0.98 \mathrm{~mol}$ ) in DMF ( 1 L ) was cooled to $0^{\circ} \mathrm{C}$ and $p$-toluenesulfonic acid ( $1.1 \mathrm{~g}, 5.65 \mathrm{mmol}$ ) was added portionwise with stirring. To the resulting solution, 2 -methoxypropene $(87.7 \mathrm{~g}, 0.92 \mathrm{~mol})$ was added dropwise through a dropping funnel at $0^{\circ} \mathrm{C}$. The reaction mixture was warmed up to room temperature and further stirred for 24 h . After the completion of the reaction, sodium carbonate ( 124 g ) was added and the resulting suspension was vigorously stirred for 3 hours. It is then filtered over glass filter and the filtrate is evaporated under vacuum. To the yellow residue, toluene ( 170 mL ) is added whereupon crystallization occurred. The solid was filtered by suction, washed with hexanes/ethanol ( $9: 1 ; 1 \mathrm{~L}$ ), and dried to give yellowish solid 301 ( $99.1 \mathrm{~g}, 65 \%$ ).

To a stirred suspension of 5,6-O-isopropylidene-L-gulono-1,4-lactone ( $70.0 \mathrm{~g}, 0.32$ $\mathrm{mol})$ in water $(270 \mathrm{~mL})$, sodium metaperiodate ( $123 \mathrm{~g}, 0.58 \mathrm{~mol}$ ) was added portionwise at $0^{\circ} \mathrm{C}$ over 30 min maintaining pH 5.5 (adjusted by addition of 2 N NaOH ). The suspension was stirred at room temperature for 2 hours, then saturated with sodium chloride and filtered. The pH of the filtrate was adjusted to 6.5-7.0 and extracted with dichloromethane ( 5 times 200 mL ) and ethyl acetate ( 5 times 300 mL ). The combined organic layer were dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure $\left(<20^{\circ} \mathrm{C}\right)$.

And then the resulting residue was distilled to give $302(23.2 \mathrm{~g}, 69 \%)$ as a colorless oil; b.p. $49-51^{\circ} \mathrm{C} / 16$ Torr. [ $\left.\alpha\right]_{\mathrm{D}} 25-66.4$ (c 6.3 , benzene).
$(E) /(Z)$-Ethyl-3- $\mid(\mathrm{R})-2,2$-dimethyl-1,3-dioxolan-4-yl]-2-fluoroacrylate (E-303 and $Z-303$ ). A solution of triethyl 2-fluorophosphonoacetate ( $39.2 \mathrm{~g}, 162 \mathrm{mmol}$ ) in THF ( 70 mL ) was cooled to $-78^{\circ} \mathrm{C}$ and a solution of sodium bis(trimethylisilyl) amide ( 1.0 M solution in THF, $162 \mathrm{~mL}, 162 \mathrm{mmol}$ ) was added dropwise. The mixture was kept for 30 min at $-78^{\circ} \mathrm{C}$, then a solution of 303 ( $19.14 \mathrm{~g}, 147 \mathrm{mmol}$ ) in THF ( 70 mL ) was added. After being stirred for 1 h at $-78^{\circ} \mathrm{C}$, the reaction mixture was treated with aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ether. The ether phase was washed with saturated NaCl , dried over $\mathrm{MgSO}_{4}$, filtered and evaporated. The residue was chromatographed on silica gel to give E-303 and $Z-303$ ( $9: 1$ by ${ }^{1} \mathrm{H} N \mathrm{NR}$ ) as a pale yellowish oil ( $34.6 \mathrm{~g}, 97.9 \%$ ). ' H NMR $\left(\mathrm{CDCl}_{3}\right) \delta 1.34,1.36\left(2 \mathrm{t}, \mathrm{J}=8 \mathrm{~Hz},-\mathrm{CH}_{2} \mathrm{CH}_{3}\right)$, $1.40,1.45\left(2 \mathrm{~s},-\mathrm{CH}_{3}\right), 3.69\left(\mathrm{~m}, \mathrm{H}_{\mathrm{a}}-5\right), 4.28\left(\mathrm{~m} ; \mathrm{H}_{\mathrm{b}}-5,-\mathrm{CH}_{2} \mathrm{CH}_{3}\right), 5.02(\mathrm{~m}, \mathrm{H}-4), 5.40(\mathrm{~m}, \mathrm{H}-4)$, 6.02 (dd, J = $8,20 \mathrm{~Hz}, \mathrm{H}-3$ ), 6.18 (dd, J $=8,32 \mathrm{~Hz}, \mathrm{H}-3$ ).
( $R$ )-(+)-4-[(tert-Butyldimethylsilyloxy)methyl]-2-fluoro-2-buten-4-olide (307). A solution of $\boldsymbol{E}-\mathbf{3 0 3}$ and $\mathbf{Z - 3 0 3}$ ( $19: 62 \mathrm{~g}, 89.89 \mathrm{mmol}$ ) in 110 mL of anhydrous EtOH was treated with 30 mL of conc. HCl and stirred at room temperature for 2 hr . The solvent was removed in vacuo and the residue was coevaporated with Toluene ( $3^{*} 300 \mathrm{~mL}$ ) to give the lactone 304 and uncyclized ester 305. The resulting yellowish syrup was used for next reaction without further purification. $t$-Butyldimethylsilyl chloride $(27.1 \mathrm{~g}, 180 \mathrm{mmol})$ was added to a mixture of $\mathbf{3 0 4}, \mathbf{3 0 5}$ and imidazole ( $12.3 \mathrm{~g}, 180 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(250 \mathrm{~mL}$ ) and the reaction mixture was stirred for 4 h at room temperature. The resulting mixture was washed with water, dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentrated, to dryness. The residue was isolated by silica gel column chromatography using 4\% Et,OAc-hexanes as an eluent to give 307 ( $28.0 \mathrm{~g}, 70.2 \%$ from compound 302) as a white crystalline solid. $\mathrm{mp} 48-50^{\circ}{ }^{\circ} \mathrm{C} ;[\alpha]^{28}{ }_{\mathrm{D}}+105.3$ (c 1.60, $\mathrm{CHCl}_{3}$ ); ${ }^{1} \mathrm{H}$ NMR ( $\mathrm{CDCl}_{3}$ ) $\delta 0.07,0.08\left(2 \mathrm{~s}, 2 \times \mathrm{CH}_{3}\right), 0.88(\mathrm{~s}, \mathrm{Bu}), 3.88(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5), 5.01(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4)$, 6.73 (ps t, $1 \mathrm{H}, \mathrm{J}=4 \mathrm{~Hz}$ ); Anal. Calcd for $\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{FO}_{3} \mathrm{Si}: \mathrm{C}, 53.63 ; \mathrm{H}, 7.77$. Found: $\mathrm{C}, 53.70 ; \mathrm{H}$, 7.75.

1-Acetyl-4-|(tert-butyldimethydsilyloxy)methyl]-2-fluoro-2-buten-4-olide (309). Lactone $307(20.58 \mathrm{~g}, 83.54 \mathrm{mmol})$ was dissolved in 200 mL of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ under nitrogen atmosphere, then the mixcture was cooled to $: 78^{\circ} \mathrm{C}$ and 1.0 M solution of DIBAL-H in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 125 mL ) was added. The resulting mixture was stirred for 2 hours at $-78^{\circ} \mathrm{C}$. The cold mixture was treated with dilute nitric acid, washed with water, and dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$. Evaporation of the
solvent gave anomers of 308 as a pale yellow oil ( 16.6 g , crude yield $80 \%$ ), which was used for the next step without further purification.
$\mathrm{Ac}_{2} \mathrm{O}(25 \mathrm{~mL}, 0.27 \mathrm{~mol})$ was added to a solution of 308 and pyridine ( $22 \mathrm{~mL}, 0.27$ $\mathrm{mol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(200 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ and the resulting mixture was stirred for 16 hours. The reaction mixture was washed with dilute HCl , saturated $\mathrm{NaHCO}_{3}$ solution, and brine. The combined organic layer was dried, filtered, and concentrated to dryness. The residue was column chromatographed ( $6.5 \%$ EtOAc/hexanes) to give 309 ( $12.6 \mathrm{~g}, 65 \%$ ) as a colorless oil.

General procedure for condensation of acetate 309 with pyrimidine bases:
A mixture of uracil ( $420 \mathrm{mg}, 3.75 \mathrm{mmol}$ ), hexamethyldisilazane ( 15 mL ) and ammonium sulfate ( 20 mg ) was refluxed for 3 hours under nitrogen. The clear solution obtained was concentrated to dryness in vacuo: TMSOTf ( $0.7 \mathrm{~mL}, 3.14 \mathrm{mmol}$ ) were added to the solution of sugar $309(728 \mathrm{mg}, 2.50 \mathrm{mmol})$ ) and the silylated base.in dry DCE $(20 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. The reaction mixture was stirred for 2 hours under nitrogen, poured into a cooled sat. $\mathrm{NaHCO}_{3}$ solution ( 30 mL ) and stirred for 15 min . The resulting mixture was washed, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography ( $3 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ ) to give $310(0.960 \mathrm{~g}, 2.73 \mathrm{mmol}, 73 \%)$ as an inseparable anomeric mixture, which was used in the next step without separation.
1-[5-O-(tert-Butyldimethylsilyl)-2,3-dideoxy-2-fluoro-L-gycero-pent-2enofuranosyl]uraci 1 (310).
UV $\left(\mathrm{CHCl}_{3}\right) \lambda_{\text {max }} 257.5 \mathrm{~nm}$.; Anal. $\left(\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{FN}_{2} \mathrm{O}_{4} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
1-[5-O-(tert-Butyldimethylsilyl)-2,3-dideoxy-2-flupro-L-gycero-pent-2-enofuranosy]]thy mine (311).

Silylated thymine ( $242 \mathrm{mg}, 1.92 \mathrm{mmol}$ ), $307(500 \mathrm{mg}, 1.72 \mathrm{mmol}$ ), and TMSOTf ( 0.5 mL , 2.25 mmol ) were reacted for 2 h to give a mixture of 311 , which was purified by silica gel column chromatography ( $3 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ ) as an inseparable anomeric mixture $(0.392 \mathrm{~g}$, $1.10 \mathrm{mmol}, 64 \%) . \mathrm{UV}\left(\mathrm{CHCl}_{3}\right) \lambda_{\text {max }} 262.0 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{FN}_{2} \mathrm{O}_{4} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
$N^{r}$-Benzoyl-1-[5-O-(tert-butyldimethylsilyl)-2,3-dideọxy-2-fluoro-(a,b)-L-glycero-pent-2-enofuranosyl]cytosine ( 312 and 313).
Silylated $N^{6}$-benzoyl cytosine ( $7.90 \mathrm{mg}, 3.67 \mathrm{mmol}$ ), $307(470 \mathrm{mg}, 1: 62 \mathrm{mmol}$ ), and TMSOTf ( $0.5 \mathrm{~mL}, 2.25 \mathrm{mmol}$ ) were reacted for 2 h to give mixtures of 312 and 313 , which were purified by silica gel column ( $30^{\circ} \%$ EtOAc/hexane) to afford $\beta$ anomer $312(0.34 \mathrm{~g}, 0.76$
$\mathrm{mmol}, 47.1 \%$ ) as a white solid and $\alpha$ anomer 313 chromatography ( $0.23 \mathrm{~g}, 0.52 \mathrm{mmol}, 31.8$ \%) as a white solid. 312: UV $\left(\mathrm{CHCl}_{3}\right) \lambda_{\max } 260.5 \mathrm{~nm}$; Anal: $\left(\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{FN}_{3} \mathrm{O}_{4} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N} . ; 513$ : UV $\left(\mathrm{CHCl}_{3}\right) \lambda_{\text {max }} 260.5 \mathrm{~nm}$.; Anal. $\left(\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{FN}_{3} \mathrm{O}_{4} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$. 5-Fluoro-1-15-O-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-(a,b-L-glycero-pent -2-enofuranosyi]cytosine (314 and 315).

Silylated 5-fluoro-cytosine ( $300 \mathrm{mg}, 2.32 \mathrm{mmol}$ ), 309 ( $360 \mathrm{mg}, 1.24 \mathrm{mmol}$ ), and TMSOTf ( $0.4 \mathrm{~mL}, 1.86 \mathrm{mmol}$ ) were reacted for 2 h to give a mixture of 314 and 315 , which was purified by silica gel column chromatography ( $3 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ) to afford $\beta$ anomer 314 as a white solid ( $168 \mathrm{mg}, 37.8 \%$ ) and $\alpha$ anomer $315(121 \mathrm{mg}, 27.1 \%$ ) as a white solid. 314 : UV $(\mathrm{MeOH}) \lambda_{\text {max }} 281.5 \mathrm{~nm} ; 315: \mathrm{UV}(\mathrm{MeOH}) \dot{\lambda}_{\text {max }} 281.5 \mathrm{~nm}$.

1-(2,3-Dideoxy-2-fluoro-( $\alpha, \beta$ )- L-gycero-pent-2-eno-furanosyl)uracil (316 and 317):
Tetra- $n$-butylammonium fluoride ( $0.6 \mathrm{~mL}, 0.6 \mathrm{mmol}$ ) was added to a mixture of 310 (177 $\mathrm{mg}, 0.52 \mathrm{mmol})$ in THF ( 15 mL ) and the reaction mixture was stirred at room temperature for 15 min . The solvent was removed and the residue was purified by silica gel column chromatography ( $2 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ ) to give $\beta$ anomer 316 ( $52.8 \mathrm{mg}, 0.23 \mathrm{mmol}, 44.5 \%$ ) and $\alpha$ anomer 317 ( $35.1 \mathrm{mg}, 0.15 \mathrm{mmol}, 29.6 \%$ ).
316: UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\max } 261.0 \mathrm{~nm}(\mathrm{pH} 7)$; Anal. $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{FN}_{2} \mathrm{O}_{4} \cdot 0.3 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N} .317: \mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right)$ $\lambda_{\text {max }} 261.0 \mathrm{~nm}(\mathrm{pH} 7)$; Anal. ( $\left.\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{FN}_{2} \mathrm{O}_{4} \mid 0.2 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

1-(2,3-Dideoxy-2-nuoro-( $\alpha, \beta$ )- L-gycero-pent-2-eno-furanosyl)thymine (318 and 319). Tetra- $n$-butylammonium fluoride ( $0.8 \mathrm{~mL}, 0.8 \mathrm{mmol}$ ) was added to a mixture of 311 ( 240 $\mathrm{mg}, 0.67 \mathrm{mmol})$ in THF ( 10 mL ) at $0^{\circ} \mathrm{C}$ and the reaction mixture was stirred at room temperature at rt for 15 min . The solvent was removed and the residue was purified by silica gel column chromatography ( $40 \% \mathrm{THF} /$ cyclohexane) to give $\beta$ anomer 318 ( $66.5 \mathrm{mg}, 0.28$ $\mathrm{mmol}, 41 \%$ ) and $\alpha$ anomer 319 ( $52.8 \mathrm{mg}, 0.23 \mathrm{mmol}, 26 \%$ ).
318: UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\max } 265.5 \mathrm{~nm}(\mathrm{pH} 7)$; Anal. $\left(\mathrm{C}_{10} \mathrm{H}_{11} \mathrm{FN}_{2} \mathrm{O}_{4} \cdot 0.4 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N} .319: \mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right)$ $\lambda_{\text {max }} 266.0 \mathrm{~nm}(\mathrm{pH} 7) ;$ Anal. $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{FN}_{2} \mathrm{O}_{4} \cdot 0.3 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
$N^{6}$-Benzoyl-1-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2-enofuranosyl)cytosine (320).
Tetra-n-butylammonium fluoride ( 1 M in THF) ( $1 \mathrm{~mL}, 1 \mathrm{mmol}$ ) was added to a solution of the $\beta$ anomer $312(280 \mathrm{mg}, 0.63 \mathrm{mmol})$ in THF $(10 \mathrm{~mL})$ and the reaction was allowed to stir at room temperature for 1 h. The reaction mixture was concentrated under the reduced pressure
and the residue was purified by flash silica gel column using $2.5 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ to give 320 ( $218 \mathrm{mg}, 0.66 \mathrm{mmol}, 75 \%$ ) as a white solid.
UV (MeOH) $\lambda_{\text {max }} 260.5 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{FN}_{3} \mathrm{O}_{4}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
$N^{b}$-Benzoyl-1-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-pent-2-enofuranosyl)cytosine (321).

Tetra- $n$-butylammonium fluoride ( 1 M in THF ) ( $1 \mathrm{~mL}, 1 \mathrm{mmol}$ ) was added to a solution of the $\alpha$ anomer $313(280 \mathrm{mg}, 0.63 \mathrm{mmol})$ in THF $(10 \mathrm{~mL})$ and the reaction was allowed to stir at room temperature for 1 h . The reaction mixture was concentrated under the reduced pressure and the residue was purified by silica gel column chromatography using $2.5 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ to give 321 ( $145.8 \mathrm{mg}, 0: 44 \mathrm{mmol}, 69 \%$ ) as a white solid.
UV ( MeOH ) $\lambda_{\text {max }} 260.5 \mathrm{~nm}$. Anal. ( $\left.\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{FN}_{3} \mathrm{O}_{4} .0 .3 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$. 1-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2-enofuranosyl)cytosine (322). A solution of the $\beta$ anomer ( $67.60 \mathrm{mg}, 0.204 \mathrm{mmol}$ ) in $\mathrm{MeOH}(5 \mathrm{~mL})$ was treated with $\mathrm{NH}_{3} / \mathrm{MeOH}(10 \mathrm{~mL}$ saturated solution) and the reaction mixture was allowed to stir at room temperature until the disappearance of starting material was observed ( 10 h ). The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative TLC using $12 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ as an eluent. The material obtained:from the plate gave $322(43 \mathrm{mg}$, $93.1 \%$ ) as a solid on trituation with hexanes and diethylether.
UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {man }} 266.5 \mathrm{~nm}(\mathrm{pH} 7) ;$ Anal. ( $\left.\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{FN}_{3} \mathrm{O}_{3} .0 .4 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
1-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-pent-2-enofuranosyl)cytosine (323). A solution of the $\alpha$ anomer $\left(65.90 \mathrm{mg}, 0.199 \mathrm{mmol}\right.$ ) in $\mathrm{MeOH}(5 \mathrm{~mL})$ was treated with $\mathrm{NH}_{3} / \mathrm{MeOH}$ ( 10 mL saturated solution) and the reaction mixture was allowed to stir at room temperature until the disappearance of starting material was observed ( 16 h ). The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative TLC using $12 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ as an eluent. The material obtained from the plate gave $322(42.5 \mathrm{mg}$, $94.5 \%$ ) as a solid on trituation with hexanes and diethylether. UV ( $\mathrm{H}_{2} \mathrm{O}$ ) $\lambda_{\text {max }} 276.0 \mathrm{~nm}(\mathrm{pH} 2), 267.0 \mathrm{~nm}(\mathrm{pH} 7)$; Anal. $\left(\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{FN}_{3} \mathrm{O}_{3}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

## 5-Fluoro-1-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2-enofuranosyl)cytosine (324).

Tetra- $n$-butylammonium fluoride ( 1 M in THF) was added to a solution of the $\beta$ anomer 314 in acetonitrile and the reaction was allowed to stir at room temperature for 1 h . The reaction mixture was concentrated under the reduced pressure and the residue was purified by flash silica gel column using $12 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ to give 324.

5-Fluoro-1-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-pent-2-enofuranosyl)cytosine (325).
Tetra- $n$-butylammonium fluoride (IM in THF) was added to a solution of the $\beta$ anomer. 315 in acetonitrile and the reaction was allowed to stir at room temperature for 1 h . The reaction mixture was concentrated under the reduced pressure and the residue was purified by flash silica gel column using $12 . \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ to give 325 .
General procedure for condensation of acetate 309 with purine bases.
A mixture of 6 -chloropurine ( $1.20 \mathrm{~g}, 7.75 \mathrm{mmol}$ ), hexamethyldisilazane ( 25 mL ) and ammonium sulfate (catalytic amount) was refluxed for 4 h under nitrogen. The clear solution was obtained was concentrated in vacuo and the residue was dissolved in dry DCE ( 10 mL ) and reacted with a solution of $307(1.50 \mathrm{~g}, 5.17 \mathrm{mmol})$ in DCE ( 40 mL ) and trimethylsilyl triflate ( $1.5 \mathrm{~mL}, 7.75 \mathrm{mmol}$ ) at room temperature. After stirring the mixture for 1 h at room temperature under nitrogen, the reaction solution was then poured into an ice cold saturated $\mathrm{NaHCO}_{3}$ solution $(20 \mathrm{~mL})$ and stirred for 15 min . The organic layer was washed with water and brine, and dried over $\mathrm{MgSO}_{4}$. The solvents were removed under reduced pressure and the residue was separated by silica gel column chromatography using $12.5 \%$ EtOAc/hexanes to give anomeric mixture 326 ( $1.25 \mathrm{~g}, 62.9 \%$ ) as a syrup.
6-Chloro-9-[5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-L-gycero-pent-2enofuranosyllpurine (326)
326: UV (MeSH) $\lambda_{\text {max }} 265.0 \mathrm{~nm}$; Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{22} \mathrm{ClFN}_{4} \mathrm{O}_{2} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
6-Chloro-2-fluoro-9-[5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fluoro( $\alpha, \beta$ )-L-gycero-pent-2-enofuranosyl]purine ( 327 and 328).
A mixture of silylated 2-fluoro-6-chloropurine [prepared from $1.170^{\circ} \mathrm{g}(6.78 \mathrm{mmol})$ of 2-fluoro-6-chloropurine and dry DCE $(40 \mathrm{~mL})$ was stirred for 16 h at room temperature. After work-up similar to that of 326 , purification by silica gel column chromatography ( $12 \%$ EtOAc/hexancs).gave $\beta$ anomer 327 ( $685 \mathrm{mg}, 1.70 \mathrm{mmol}, 30.0 \%$ ) as a white foam and $\alpha$ anomer 328 ( $502 \mathrm{mg}, 1.25 \mathrm{mmol}, 22.1 \%$ ) as an yellowish syrup.
327: UV (MeSH) $\lambda_{\text {max }} 268.5 \mathrm{~nm}$. Anal. ( $\left.\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~F}_{2} \mathrm{Cl} \mathrm{N}_{4} \mathrm{O}_{2} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N} ., 328$ : UV (MeCH)
$\lambda_{\text {max }} 269.0 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~F}_{2} \mathrm{Cl} \mathrm{N} \mathrm{N}_{4} \mathrm{O}_{2} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
6-Chloro-9-(2,3-dideoxy-2-fluoro-( $\alpha, \beta$ )-L-gycero-pent-2-enofuranosyl)purine ( 329 and 330). A solution of $326(1.2 \mathrm{~g}, 3.12 \mathrm{mmol})$ in dry $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL})$ was treated with TBAF (1 M solution in THF) ( $3.2 \mathrm{~mL}, 3.2 \mathrm{mmol}$ ) and stirred for r h. After evaporation of solvent, the
dryness was purified by column chromatography ( $3 \% \mathrm{MeOH} / \mathrm{CHCl}_{3}$ ) to obtain $\beta$ anomer 329 ( $296 \mathrm{mg}, 35 \%$ ) as a white solid and $\alpha$ anomer $330(380 \mathrm{mg}, 45 \%)$ as a foam. 329: UV (MeOH) $\lambda_{\text {max }} 265.0 \mathrm{~nm} . ; 330$ : UV (MeOH) $\lambda_{\text {max }} 265.0 \mathrm{~nm}$. (332).

6-Amino-2-fluoro-9-[5-0-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fluoro- $\beta$-l-gycero-pent-2-enofurannsyl]purine (331) and

6-Chloro-2-amino-9-[-5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent -2-enofuranosyl]purine (332)

Dry ammonia was bubbled.into a stirred solution of 327 ( $420 \mathrm{mg}, 1.04 \mathrm{mmol}$ ) in dry DME ( 35 mL ) at room temperature overnight. The salts were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography ( $25 \%$ EtOAc/hexanes) to give two compounds, 331 ( $114 \mathrm{mg}, 0.30 \mathrm{mmol}$ ) as a white solid and 332 ( $164 \mathrm{mg}, 0.41 \mathrm{mmol}$ ) as a white solid.

331:UV (MeOH) $\lambda_{\text {max }} 268.5 \mathrm{~nm}$. Anal. ( $\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~F}_{2} \mathrm{~N}_{5} \mathrm{O}_{2} \mathrm{Sij} 0.2$ Acetone) $\mathrm{C}, \mathrm{H}, \mathrm{N}, 332: \mathrm{UV}$
$(\mathrm{MeOH}) \lambda_{\text {max }} 307.5 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{FN}_{5} \mathrm{O}_{2} \mathrm{ClSi}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}, \mathrm{Cl}$.
6-Amino-2-fluoro-9-[5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fluoro- $\alpha$
-L-gycero-pent-2-enofuranosyl|purine (333) and
6-Chloro-2-amino-9-|-5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-2-fluoro- $\alpha$ -L-gycero-pent-2-enofuranosyl|purine (334).

Dry ammonia was bubbled into a stirred solution of $333(420 \mathrm{mg}, 1.04 \mathrm{mmol})$ in dry DME ( 35 mL ) at room temperature overnight. The salts were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography ( $25 \%$ EtOAc/hexanes) to give two compounds, 332 ( $150 \mathrm{mg}, 0.38 \mathrm{mmol}$ ) as a white solid and $333(69,3 \mathrm{mg}, 0.18 \mathrm{mmol})$ as a white solid.
333: UV (MeOH) $\lambda_{\text {max }} 269.0^{\circ} \mathrm{nm}$. Anal. ( $\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~F}_{2} \mathrm{~N}_{5} \mathrm{O}_{2} \dot{\mathrm{Si}} \cdot 0.3$ Acetone) $\mathrm{C}, \mathrm{H}, \mathrm{N}, 334$ : UV (McOH) $\lambda_{\text {max }} 309.5 \mathrm{~nm}$. Anal. $\left(\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~F} \mathrm{ClN}_{5} \mathrm{O}_{2} \mathrm{Si}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

9-(2,3-dideoxy-2-fluoro- $\beta$-l-gycero-pent-2-enofuranosyl)adenine (335). A solution of 329 ( $100 \mathrm{mg}, 0.369 \mathrm{mmol}$ ) and saturated $\mathrm{NH}_{3} / \mathrm{MeOH}(50 \mathrm{~mL})$ was hcated at $90^{\circ} \mathrm{C}$ in a steel bomb for 24 h . After cooling to room temperature, the solvent was removed under reduced pressure and the reșidual syrup was purified by column chromatography using $6 \%$ $\mathrm{MeOH} / \mathrm{CHCl}_{3}{ }^{\text {a }}$ as an eluent to give $335(70 \mathrm{mg}, 75 \%)$ as a white solid. 335: $\mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }}$
$258 \mathrm{~nm}(\varepsilon 18.800)(\mathrm{pH} 2), 258.5 \mathrm{~nm}(\varepsilon 18,800)(\mathrm{pH} 7), 258.5 \mathrm{~nm}(\varepsilon 19,100)(\mathrm{pH} 11)$. Anal. $\left(\mathrm{C}_{10} \mathrm{H}_{10} \mathrm{FN}_{5} \mathrm{O}_{2} .0 .2 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

9-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-penf-2-enofuranosyl)adenine (336). A solution of $\mathbf{3 3 0}(99 \mathrm{mg}, 0.366 \mathrm{mmol})$ and saturated $\mathrm{NH}_{3} / \mathrm{MeOH}(50 \mathrm{~mL})$ was heated at $90^{\circ} \mathrm{C}$ in a steel bomb for 24 h . After cooling to room temperature, the solvent was removed under reduced pressure and the residual syrup was purified by column chromatography using $6 \%$ $\mathrm{MeOH} / \mathrm{CHCl}_{3}$ as an eluent to give 336 ( $72 \mathrm{mg}, 78 \%$ ) as a white solid.
336: $\mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right) \dot{\lambda}_{\text {max }} 258 \mathrm{~nm}(\varepsilon 21,100)(\mathrm{pH} 2), 259 \mathrm{~nm}(\varepsilon 21,500)(\mathrm{pH} 7), 259 \mathrm{~nm}(\varepsilon 22,600)$ (pH II). Anal. ( $\left.\mathrm{C}_{10} \mathrm{H}_{10} \mathrm{FN}_{5} \mathrm{O}_{2}^{\prime}: 0.3 \mathrm{MeOH}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.
9-(2,3-dideoxy-2-fluoro- $\beta$-l-gycero-pent-2-enofuranosyl)hypoxanthine (337). A mixture of 329 ( $100 \mathrm{mg}, 0.369 \mathrm{mmol}$ ), $\mathrm{NaOMe}(0.5 \mathrm{M}$ solution in MeOH$)(2.94 \mathrm{~mL}, 1.46 \mathrm{mmol})$ and $\mathrm{HSCH}_{2} \mathrm{CH}_{2} \mathrm{OH}(0.1 \mathrm{~mL}, 1.46 \mathrm{mmol})$ in $\mathrm{MeOH}(20 \mathrm{~mL})$ was refluxed for 4 h under nitrogen. The reaction mixture was cooled, neutralized with glacial AcOH and evaporated to dryness under vacuum. The residue was purified by silica gel column chromatography ( $10 \%$ $\mathrm{MeOH} / \mathrm{CHCl}_{3}$ ) to afford $337(74 \mathrm{mg}, 80 \%)$ as a white solid. 37 : $\mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {mix }} 247 \mathrm{~nm}$ $(\varepsilon 12,400)(\mathrm{pH} 2), 247.5 \mathrm{~nm}(\varepsilon 13,000)(\mathrm{pH} 7), 253 \mathrm{~nm}(\varepsilon 13,100)(\mathrm{pH} 11)$. Anal. $\left(\mathrm{C}_{10} \mathrm{H}_{9} \mathrm{FN}_{4} \mathrm{O}_{3} .0 .2 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H} ; \mathrm{N}$.
9-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-pent-2-enofuranosyl)hypoxanthine (338). . A mixture of 330 ( $100 \mathrm{mg}, 0.369$ ), $\mathrm{NaOMe}(0.5 \mathrm{M}$ solution in MeOH$)(2.94 \mathrm{~mL}, 1.46 \mathrm{mmol})$ and $\mathrm{HSCH}_{2} \mathrm{CH}_{2} \mathrm{OH}(0.1 \mathrm{~mL}, 1.46 \mathrm{mmol})$ in $\mathrm{MeOH}(20 \mathrm{~mL})$ was refluxed for 4 h under nitrogen. The reaction mixture was cooled, neutralized with glacial AcOH and evaporated to dryness under vacuum. The residue was.purified by silica gel column chromatogràphy ( $10 \%$ $\mathrm{MeOH} / \mathrm{CHCl}_{3}$ ) to afford $338(70 \mathrm{mg}, 80 \%)$ as a white solid. 338: $\mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 247.5 \mathrm{~nm}$ $(\varepsilon 12,700)(\mathrm{pH} 2), 247.5 \mathrm{~nm}(\varepsilon 13 ; 700)(\mathrm{pH} 7), 252.5 \mathrm{~nm}(\varepsilon 13,100)(\mathrm{pH} 11)$. Anal: $\left(\mathrm{C}_{10} \mathrm{H}_{9} \mathrm{FN}_{4} \mathrm{O}_{3} \cdot 0.3 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, \mathrm{H}, \mathrm{N}$.

2-Fluoro-6-amino-9-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2-enofuranosyl)purine (339). A solution of $\mathbf{3 1}$ ( $101 \mathrm{mg}, 0.26 \mathrm{mmol}$ ) in dry acetonitrile ( 15 mL ) was treated with TBAF ( 1 M solution in THF) $(0.35 \mathrm{~mL}, 0.35 \mathrm{mmol})$ and stirred for 30 min . After evaporation of solvent, the dryness was purified by column chromatography: $\left(9 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}\right)$ to obtain 339 ( $64.7 \mathrm{mg}, 0.24 \mathrm{mmol}, 92.3 \%$ ) as a white crystalline solid. $\mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 269.0 \mathrm{~nm}(\mathrm{pH}$ 7).

## 2-Fluoro-6-amino-9-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-pent-2-enofuranosyl)purine

 (340). A solution of $333(73.4 \mathrm{mg}, 0.19 \mathrm{mmol})$ in dry acetonitrile ( 10 mL ) was treated with TBAF ( 1 M solution in THF) ( $0.25 \mathrm{~mL}, 0.25 \mathrm{mmol}$ ) and stirred for 30 min . After evaporation of solvent, the dryness was purified by column chromatography ( $9 \%$ $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ ) to obtain $340(46.2 \mathrm{mg}, 0.17 \mathrm{mmol}, 90.3 \%$ ) as a white crystalline solid. UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\text {max }} 269.0 \mathrm{~nm}(\mathrm{pH} 7)$.2-Amino-6-chloro-9-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2-enofuranosyl)purine (341). A solution of $332(143.5 \mathrm{mg}, 0.40 \mathrm{mmol})$ in dry acetonitrile ( 15 mL ) was treated with TBAF ( 1 M solution in THF) ( $0.6 \mathrm{~mL}, 0.60 \mathrm{mmol}$ ) and stirred for 30 min . After evaporation of solvent, the dryness was purified by column chromatography ( $5 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ ) to obtain $341(109 \mathrm{mg}, 0.382 \mathrm{mmol}, 95.5 \%)$ as a white crystalline solid. UV $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\max } 308.5 \mathrm{~nm}(\mathrm{pH}$ 7).

2-Amino-6-chloro-9-(2,3-dideoxy-2-fluoro- $\alpha$-L-gycero-pent-2-enofuranosyl)purine (342). A solution of $334(145 \mathrm{mg}, 0.36 \mathrm{mmol})$ in dry acetonitrile ( 10 mL ) was treated with TBAF ( 1 M solution in THF) ( $0.5 \mathrm{~mL}, 0.50 \mathrm{mmol}$ ) and stirred for 30 min . After evaporation of solvent, the dryness was purified by'column chromatography ( $9 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ ) to obtain 342 ( $99.9 \mathrm{mg}, 0.35 \mathrm{mmol}, 96.4 \%$ ) as a white crystalline solid. UV. $\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\max } 309.0$ $\mathrm{nm}(\mathrm{pH} 7)$.
9-(2,3-dideoxy-2-fluoro- $\beta$-L-gycero-pent-2-enofuranosyl)guanine (343). A mixture of 341 ( $63.6 \mathrm{mg}, 0.223 \mathrm{mmol}$ ), 2-mercaptoethanol ( $0.06 \mathrm{~mL}, 0.89 \mathrm{mmol}$ ) and 1 N NaOMe ( 0.89 $\mathrm{mL}, 0.89 \mathrm{mmol}$ ) in $\mathrm{MeOH}(10 \mathrm{~mL})$ was refluxed for 5 h under nitrogen. The mixture was cooled, neutralized with glacial AcOH and concentrated to dryness under reduced pressure. The residue was purified by column chromatography $\left(12 \% \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}\right)$ to obtain 343 ( $30.1 \mathrm{mg}, 0.113 \mathrm{mmol}, 50.7 \%$ ) as a white solid. $\mathrm{UV}\left(\mathrm{H}_{2} \mathrm{O}\right) \lambda_{\max } \cdot 253.5 \mathrm{~nm}(\mathrm{pH} 7)$.

Referring to Scheme 11, starting from diethyl diallylmalonate (701), the 4-carbethoxy-1,6heptadiene (702) was synthesized in 78\% yield (W. A. Nugēnt, J. Am. Chem. Soc., 1995;-117, 8992-8998). Compound 703 was synthesized from compound 702 in $71 \%$ yield (L. E. Martinez, J. Org. Chem., 1996, 61, 7963-7966), and compound 705 was synthesized from compound 704 in $43 \%$ yield (D. M. Hodgson, J. Chem. Soc. Perkin Trans.' I, 1994, 33733378). The key intermediate cis-( $\pm$ )-3-acetoxy-5-(acetoxymethyl)cyclopentene (708) can be alternatively synthesized from cyclopentadiene and formaldehyde in acetic acid using a Print reaction (E. A. Saville-Stones, J. Chem. Soc. Parkin Trans. I, 1991, 2603-2604) albeit it suffers low yield and inseparable problems; or from a bicyclic lactone which was synthesized by multiple steps through 4 steps (F. Burlina, Bioorg. Med. Chem. Lett., 1997, 7, 247-250). The latter methodology gave a chiral 708 [( - )-enantionier], although it needed to synthesized a chiral bicyclic lactone. $N^{4}$-Acetyl-5-fluorocytosine was synthesized from 5 -fluorocytosine and $\rho$-nitrophenyl !acetate (A. S. Stcinfeld, J. Chem. Research (M), 1979, 1437-1450).

Scheme 11


## Experimental Part

General. All reagents were used as received unless stated otherwise. Anhydrous solvents were purchased from Aldrich Chemical Co. Melting points (M.p.) were determined on an Electrothermal digit melting point apparatus and are uncorrected. ${ }^{1} \mathrm{H}$ and ${ }^{1}{ }_{3} \mathrm{C}$ NMR spectra were taken on a Varian Unity Plus 400 spectrometer at room temperature and reported in ppm downfield from internal tetramethylsilane.
4-Carbethoxy-1,6-heptadiene (702). A mixture of diethyl diallymalonate (701; $50 \mathrm{~g}, 208$ mmol), sodium cyanide ( $20.7 \mathrm{~g}, 422 \mathrm{mmol}$ ) and DMSO ( 166 mL ) was heated at $160^{\circ} \mathrm{C}$ for 6 h. After being cooled to r.t., the mixture was added to 400 mL of water and the product was extracted into hexane ( $4 \times 100 \mathrm{~mL}$ ). After evaporation of the solvent at reduced pressure, the residue was distilled $\left(42-43^{\circ} \mathrm{C} / 1 \mathrm{Torr}\right)$ to give $27.34 \mathrm{~g}(78 \%)$ of 702 as a colorless liquid. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 5.80-5.70\left(\mathrm{~m}, 2 \mathrm{H}, 2 \mathrm{CH}=\mathrm{CH}_{2}\right), 5.10-5.02\left(\mathrm{~m}, 4 \mathrm{H}, 2 \mathrm{CH}=\mathrm{CH}_{2}\right)$, $4.14\left(\mathrm{q}, 2 \mathrm{H}, \mathrm{J}=7.2 \mathrm{~Hz}, \mathrm{OCH}_{2}\right), 2.54-2.48(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}), 2.41-2.34,2.29-2.23(2 \mathrm{~m}, 4 \mathrm{H}, 2$ $\left.\mathrm{CH}_{2}\right), 1.25\left(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$. ( $\pm$ )-3-Cyclopentenecarboxylic Acid, Ethyl Ester (703). A flame-dried 500 mL flask was charged with 2,6 -dibromophenol ( $1.20 \mathrm{~g}, 4.76 \mathrm{mmol}$ ), tungsten oxychloride ( $0.813 \mathrm{~g}, 2.38$ mmol ), and anhydrous toluene ( 25 mL ). The resulting suspension was heated at reflux under nitrogen for 1 h , and then the :solvent was evaporated in vacuo. The solid residue was broken up with a spatula and dried in vacuo for 30 min . To the residue were added toluene ( 160 mL ), $E L_{4} \mathrm{~Pb}(1.54 \mathrm{~g}, 4.76 \mathrm{~mL})$, and $702(22 \mathrm{~g}, 131.0 \mathrm{mmol})$. The mixture was heated at $90^{\circ} \mathrm{C}$ under nitrogen for 1.5 h . After being cooled to r.t., the mixture was filtered through a celite, and the celite was rinsed with $t$-BuOMe. The combined filtrates were washed with $1 \% \mathrm{NaOH}$ soln, water, and brine, and concentrated by evaporation at reduced pressure. The residue was distilled ( $37.38^{\circ} \mathrm{C} / 1$ Torr) to give $13.06 \mathrm{~g}(71 \%)$ of 703 as a colorless liquid. ${ }^{1} \mathrm{H}$ NMR ( 400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.67(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}=\mathrm{CH}), 4.14\left(\mathrm{q}, 2 \mathrm{H}, \mathrm{J}=7.2 \mathrm{~Hz}, \mathrm{OCH}_{2}\right.$ ), 3.11 (pentuplet, $\mathrm{J}=$ $7.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}), 2.65$. ( $\mathrm{d}, \mathrm{J}=7.6 \mathrm{~Hz}, 4 \mathrm{H}, 2 \mathrm{CH}_{2}$ ), $1.27\left(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$.
( $\pm$ )-1-(Hydroxymethyl)-3-cyclopentene (704). To a cold $\left(-78^{\circ} \mathrm{C}\right)$ solution of $703 \mathbf{( 7 \mathrm { g } ; 5 0}$ mmol ) in dry THF ( 150 mL ) was added $\mathrm{LiAlH}_{4}(1 \mathrm{M}$ soln in THF, $25 \mathrm{~mL}, 25 \mathrm{mmol}$ ), and the reaction solution was stirred at $-78{ }^{\circ} \mathrm{C}$ under argon for 4 h . Then the reaction solution wasallowed to warm to $0^{\circ} \mathrm{C}$, and 2.5 mL of water, 2.5 mL of $15 \% \mathrm{NaOH}$, and 7.5 mL of water were added sequentially. After warming to r.t., the precipitates were filtered through a celite,
and the elite was washed with hot EtOAc. The combined filtrates were washed with 0.1 N NaOH , and brine, dried $\left(\mathrm{MgSO}_{4}\right)$, filtered, concentrated and dried in vacuo to give 4.294 g $(84 \%)$ of 704 as a pale yellow liquid. ${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.68(\mathrm{~s}, 2 \mathrm{H}, 2 \mathrm{CH}=\mathrm{CH})$, $3.57\left(\mathrm{~d}, \mathrm{~J}=6.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{OH}\right), 2.54-2.48\left(\mathrm{~m}, 3 \mathrm{H}, \mathrm{CH}+\mathrm{CH}_{2}\right), 2.15-2.10\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right)$., cis-(土)-4-(Hydroxymethyl)-1,2-epoxycyclopentane (705). To a solution of 704 ( 930 mg , 9.1 mmol ), and vanadyl acetylacetonate ( 10 mg ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL})$ was added $t$ $\mathrm{BuO}_{2} \mathrm{H}\left[3 \mathrm{M}\right.$ soon in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, prepared from a mixture of $t-\mathrm{BuO}_{2} \mathrm{H}$ ( $70 \%$ by weight in water, $41 \mathrm{~mL}, 0.3 \mathrm{~mol})$ and $\mathrm{CH}_{2} \mathrm{Cl}_{2}(59 \mathrm{~mL})$ by drying ( $2 \times \mathrm{MgSO}_{4}$ ) and storage over $4 \AA$ molecular sieve, $10 \mathrm{~mL}, \sim 30 \mathrm{mmol}]$ drop wise. After stirring at rit. for 24 h , aqueous $\mathrm{Na}_{2} \mathrm{SO}_{3}$ ( $15 \%$ soln, 60 mL ) was added, and the mixture was stirred at rt. for 6 h . The organic layer was separated, washed with sat. $\mathrm{NaHCO}_{3}$, and brine, and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexane/EtOAc (2:1) to give 460 mg ( $43 \%$ ) of 705 as a colorless liquid. ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.54\left(\mathrm{~s}, 2 \mathrm{H},(\mathrm{CH})_{2} \mathrm{O}\right), 3.49(\mathrm{t}, \mathrm{J}=4.0 \mathrm{~Hz}$, $2 \mathrm{H}, \mathrm{CH} \mathrm{H}_{2} \mathrm{OH}$ ), 2.95 (bs, $1 \mathrm{H}, \mathrm{OH}$ ), 2.44-2.40(m, $1 \mathrm{H}, \mathrm{CH}$ ), 2.05-2.02 (m, $\left.4 \mathrm{H}, 2 \mathrm{CH}_{2}\right) .{ }^{13} \mathrm{C}$ NMR ( $\left.100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 66.9\left(\mathrm{~d},(\mathrm{CH})_{2} \mathrm{O}\right), 59.2\left(\mathrm{t}, \mathrm{CH}_{2} \mathrm{OH}\right), 36.5(\mathrm{~d}, \mathrm{CH}), 31.4\left(\mathrm{t}, 2 \mathrm{CH}_{2}\right)$. cis-(土)-3-Acetoxy-5-(acetoxymethyl)cyclopentene (708). To a solution of diphenyl diselenenide ( $2.70 \mathrm{~g}, 8.65 \mathrm{mmol}$ ) in anhydrous $\mathrm{EtOH}(100 \mathrm{~mL})$ was added $\mathrm{NaBH}_{4}$ in portions. The solution was stirred until the yellow color turned to colorless, and then a solution of $705(1.70 \mathrm{~g}, 14: 4 \mathrm{mmol})$ in anhydrous THF ( 10 mL ) was added. The reaction solution was heated at reflux for 1 h under nitrogen, and then the solvent was evaporated in vacuo. To the residue was added EtOAc $(80 \mathrm{~mL})$ and water ( 30 mL ). The organic phase was separated, washed with brine, dried $\left(\mathrm{MgSO}_{4}\right)$, filtered, concentrated and dried in vacuo. The obtained ( $\pm$ )-1-hydroxy-4-(hydroxymethyl)-2-(phenylselenenyl)-cyclopentane ( 706 ; light yellow oil) was used for the next reaction directly without further purification. To the crude product 706 were added anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(60 \mathrm{~mL}), \mathrm{Et}_{3} \mathrm{~N}(30 \mathrm{~mL}, 216 \mathrm{mmol})$, and DMAP $(50 \mathrm{mg})$. The resulting solution was cooled to $0^{\circ} \mathrm{C}$, and $\mathrm{Ac}_{2} \mathrm{O}(14.7 \mathrm{~g}, 144 \mathrm{mmol})$ was added dropwise. After being stirred at rit. under argon overnight, evaporation of the solvent provided ( $\pm$ )-1-acetoxy-4-(acetoxymethyl)-2-(phenylselenenyl)-cyclopentane (707; light yellow oil). To a cold $\left(0^{\circ} \mathrm{C}\right)$ solution of 707 in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$ containing 3 drops of pyridine was added $30 \%{ }^{\prime} \mathrm{H}_{2} \mathrm{O}_{2}$ soln ( 20 mL ) over a period of 5 min . After being stirred at 0 ${ }^{\circ} \mathrm{C}$ for 30 min and at rt. for another 30 min , the reaction mixture was diluted by addition of $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$. The organic phase was separated, washed with water, sat. $\mathrm{NaHCO}_{3}$, and '
brine, dried $\left(\mathrm{MgSO}_{4}\right)$, filtered, and concentrated by evaporation in vacuo. The residue was .purified by flash chromatography on silica gel eluting with $0-10 \%$ EtOAc in hexane to give $2.254 \mathrm{~g}\left(79 \%\right.$, for the three steps) of 708 as a pale brown-liquid. ${ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 6.01-6.00,5.92-5.90(2 \mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}=\mathrm{CH}), 5.66-5.64(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-3), 4.04(\mathrm{~d}, \mathrm{~J}=6.8$ $\mathrm{Hz}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{O}$ ), 2.98-2.92 (m, $\left.1 \mathrm{H}, \mathrm{H}-5\right), 2.53-2.46(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4 \mathrm{a}), 2.08,2.04\left(2 \mathrm{~s}, 6 \mathrm{H}, 2 \mathrm{CH}_{3}\right)$, $1.60-1.54(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-4 \mathrm{~b}) .{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 171.1,170.9(2 \mathrm{~s}, 2 \mathrm{C}=0), 137.0$, $131.4(2 \mathrm{~d}, \mathrm{CH}=\mathrm{CH}), 79.2(\mathrm{~d}, \mathrm{C}-3), 67.4\left(\mathrm{t}, \mathrm{CH}_{2} \mathrm{O}\right), 43.7(\mathrm{~d}, \mathrm{C}-5), 33.4(\mathrm{t}, \mathrm{C}-4), 21.3,20.9(2 \mathrm{q}$, $2 \mathrm{CH}_{3}$ ).
cis-( $\pm$ )-Carbocyclic $5^{\prime}$ - 0 - acetyl-2', $3^{\prime}$-didehydro- $\mathbf{2}^{\prime}, 3^{\prime}$-dideoxy-5-fluorocytidine (709)..A suspension of 5 -fluorocytosine ( $258 \mathrm{mg}, 2 \mathrm{mmol}$ ) and $\mathrm{NaH}(58 \mathrm{mg}, 2.4 \mathrm{mmol}$ ) in anhydrous DMSO ( 15 mL ) was heated in a pre-warmed oil bath at $70^{\circ} \mathrm{C}$ for 30 min . Then the resulting solution was cooled to r.t., and $\operatorname{Pd}\left(\mathrm{PPh}_{i}\right)_{4}^{d}(73 \mathrm{mg}, 0.063 \mathrm{mmol})$ and a solution of $708(298$ $\mathrm{mg}, 1.5 \mathrm{mmol}$ ) in anhydrous THF ( 2 mL ) were added respectively. The reaction mixture was stirred at $70^{\circ} \mathrm{C}$ under argon for 3 days. After removal of the solvent by evaporation in vacuo, the residue was treated with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$. The precipitates were filtered through a celite, and the celite was washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The combined filtrates were concentrated, and the residue was purified by flash chromatography on silica gel eluting with $0-5 \% \mathrm{MeOH}$ in. $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $40 \mathrm{mg}(10 \%)$ of 709 as a light brown solid. Recrystallization from $\mathrm{McOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ /hexane provided pure product as white powders. M.p. 182-184 ${ }^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.43(\mathrm{~d}, \mathrm{~J}=6.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-6), 6.18-6.16\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-\mathrm{s}^{\prime}\right), 5.83-5.81(\mathrm{~m}$, $\left.1 \mathrm{H}, \mathrm{II}-2^{\prime}\right), 5.73-5.71\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 4.23-4.21,4.08-4.04\left(2 \mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{O}\right), 3.14-3.12(\mathrm{~m}, 1 \mathrm{H}$, H-4'), 2.92-2.84 (m, 1H, H-6'a), 2.08 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ), 1.41-1.35 (m, 1H, H-6'b).
cis-( $\pm$ )-Carbocyclic $N^{4}, 5^{\prime}$-O-diacetyl-2', $3^{\prime}$ '-didehydro- $2^{\prime}, 3^{\prime}$-dideoxy- 5 -fluorocytidine (710). In an analogy manner to the procedure for 709, the title compound 710 was prepared from 708 ( $560 \mathrm{mg}, 2.828 \mathrm{mmol}$ ) and $N^{4}$-acetyl-5-fluorocytosine ( $726 \mathrm{mg}, 4.24 \mathrm{mmol}$ ): 560 $\mathrm{mg}(64 \%$, brown oil). This crude product was used directly for the next reaction without further purification.
cis-(土)-Carbocyclic $N^{4}, 5^{\prime}$ - $O$-diacetyl-2', $3^{\prime}$-didehydro- $2^{\prime}, 3^{\prime}$-dideoxycytidine (711). In an analogy manner to the procedure for 709, the title compound 711 was prepared from 708 (272 $\mathrm{mg}, 1.37 \mathrm{mmol}$ ) and $N^{4}$-acetylcytosine ( $316 \mathrm{mg}, 2.06 \mathrm{mmol}$ ): $108 \mathrm{mg}(27 \%)$ of white powders. M.p. $169.5-171.5^{\circ} \mathrm{C} .{ }^{\mathrm{I}} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.80(\mathrm{bs}, 1 \mathrm{H}, \mathrm{NH}), 7.72(\mathrm{~d}, \mathrm{~J}=$
$\left.6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-6), 7.39(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5), 6.19-6.17(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-3)^{\prime}\right), 5.86-5.81^{\prime}(\mathrm{m}, 1 \mathrm{H}$, H-2'), 5.77-5.75 (m, $\left.1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 4.17-4.13,4.07-4.02\left(2 \mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{O}\right), 3.18-3.10(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-$ $4^{\prime}$ ), 2.96-2.88 (m, $\left.1 \mathrm{H}, \mathrm{H}-6^{\prime} \mathrm{a}\right), 2.27,2.06\left(2 \mathrm{~s}, 6 \mathrm{H}, 2 \mathrm{CH}_{3}\right), 1.43-1.37\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-6^{\prime} \mathrm{b}\right) .{ }^{3} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 170.8(\mathrm{~s}, 2 \dot{\mathrm{C}}=\mathrm{O}$ ), $162.0(\mathrm{~s}, \mathrm{C}-4), 155.6(\mathrm{~s}, \mathrm{C}-2), 145.3(\mathrm{~d}, \mathrm{C}-6), 139.2(\mathrm{~d}$, C-3'), 130.0 ( $\left.\mathrm{d}, \mathrm{C}-2^{\prime}\right), 96.8$ (d, C-5), 66.3 ( $\left.\mathrm{t}, \mathrm{C}-5^{\prime}\right), 62.8\left(\mathrm{~d}, \mathrm{C}-1^{\prime}\right), 44.2$ (d, C-4'), 34.7 (t, C-6'), 25.0, 20.9 ( $2 \mathrm{q}, 2 \mathrm{CH}_{3}$ ).
cis-( $\mathbf{~}$ )-Carbocyclic $\mathbf{2}^{\prime}, 3^{\prime}$-didehydro-2', $3^{\prime}$-dideoxy-5-fluorocytidine (712). To a flask containing 709 ( $33 \mathrm{mg}, 0.12 \mathrm{mmol}$ ) was added NaOMe ( 0.5 M soln in $\mathrm{MeOH}, 0.5 \mathrm{~mL}$ ). The reaction solution was stirred at r.t. for 1 h , and then the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel eluting with $5-10 \% \mathrm{MeOH}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $17 \mathrm{mg}(61 \%)$ of 712 as a light brown solid. Recrystalization from $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ /hexane provided pure product as white powders. M.p. $205.5-206.0^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}_{6}$ ) $\delta 7.66(\mathrm{~d}, \mathrm{~J}=6.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-6), 7.60,7.40\left(2 \mathrm{bs}, 2 \mathrm{H}, \mathrm{NH}_{2}\right), 6.06-$ $6.05\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-3^{\prime}\right), 5.68-5.65\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-2^{\prime}\right), 5.53-5.50\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 4.77-4.75\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4^{\prime}\right)$, 3.50-3.48, 3.41-3.37 ( $2 \mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5^{\prime}$ ), 2.79-2.77 (m, 1H, H-6'a), 1.34-1.27 (m, 1H, H-6'b). ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}$ ) $\delta 157.0(\mathrm{~d}, \mathrm{~J} \mathrm{C}-\mathrm{F}=11.9 \mathrm{~Hz}, \mathrm{C}-4), 154.0(\mathrm{~s}, \mathrm{C}-2), 139.2\left(\mathrm{~d}, \mathrm{C}-3^{\prime}\right)$, $135.8\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=241.3 \mathrm{~Hz}, \mathrm{C}-5\right), 130.2\left(\mathrm{~d}, \mathrm{C}-2^{2}\right), 126.8\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=11.8 \mathrm{~Hz}, \mathrm{C}-6\right), 63.5\left(\mathrm{t}, \mathrm{C}-5^{\prime}\right)$, 61.3 (d, C-1'), 47.2 (d, C-4'), 33:3 (t, C-6'). MS (FAB) m/e $226\left(\mathrm{MH}^{+}\right)$. Anal. ( $\left(\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{FN}_{3} \mathrm{O}_{2}\right)$ calcd C 53.33, H 5.37, N 18.66; found C 53.10, H 5.40, N 18.44. In an analogy manner to the above procedure, the title compound 712 was also prepared from 710 ( $750 \mathrm{mg}, 2.42 \mathrm{mmol}$ ): 320 mg ( $59 \%$, white powders).
cis-( $\pm$ )-Carbocyclic $2^{\prime}, 3^{\prime}$-didehydro-2', $3^{\prime}$-dideoxycytidine (713). In an analogy manner to the procedure for 712 , the title compound 713 was prepared from $711(75 \mathrm{mg}, 0.257 \mathrm{mmol})$ : $48 \mathrm{mg}\left(90 \%\right.$, white solid). M.p. $200-201^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta 7.40$ ( $\mathrm{d}, \mathrm{J}=7.2$ $\mathrm{Hz}, \mathrm{IH}, \mathrm{H}-6), 7.03,6.95$ ( $2 \mathrm{bs}, 2 \mathrm{H}, \mathrm{NH}_{2}$ ), $6.07-6.05(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-3$ '), 5.67 (d, J = $7.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-$ 5), 5.65-5.64 (m, 1H, H-2'), 5.55-5.52 (m, 1H, H-1'), 4.71-4.68 (m, 1H, H-4'), 3.43-3.36 (m, 2H, H-5'), 2.78-2.76 (m, 1H, H-6'a), 1.24-1.18 (m, 1H, H-6'b). ${ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO$\left.d_{6}\right) \boldsymbol{\delta} 165.5(\mathrm{~s}, \mathrm{C}-4), 155.8(\mathrm{~s}, \mathrm{C}-2), 142.2(\mathrm{~d}, \mathrm{C}-6), 138.6\left(\mathrm{~d}, \mathrm{C}-3^{\prime}\right), 130.5\left(\mathrm{~d}, \mathrm{C}-2^{2}\right), 93.7(\mathrm{~d}, \mathrm{C}-$ 5), 63.9 (t, C-5'), 60.8 (d, C-1'), 47.3 (d, C-4'), 34.0 (t, C-6'). MS (FAB) m/e $208\left(\mathrm{MH}^{+}\right)$. Anal. $\left(\mathrm{C}_{10} \mathrm{H}_{13} \mathrm{~N}_{3} \mathrm{O}_{2}\right)$ calcd D 57.96, H 6.32, N 20.28; found C 57.35, H 6.27, N 20.02. HRMS (FAB) calcd for $\left(\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{~N}_{3} \mathrm{O}_{2}\right): 208.1086$; found 208.1088:
cis－（土）－Carbocyclic $2^{\prime}, 3^{\prime}$－dideliydru－2＇，3＇－dideoxy－5－fluorocytidine $5^{\prime}$－triphosphate， tricthylhydrogenammonium salt（714）．To a solution of 712 （ 10 mg ）in anhydrous DMF $(0.3 \mathrm{~mL})$ and pyridine $(0.1 \mathrm{ml})$ was added a 1 M solution of 2 －chloro－ $4 \mathrm{H}-1,3,2-$ benzodioxaphosphorin－4－one in anhydrous 1,4 －dioxane $(0.05 \mathrm{~mL})$ ．The reaction solution was stirred at ret．for 15 min ．Then，a solution of 1 M pyrophosphoric acid－ $\mathrm{Bu}_{3} \mathrm{~N}$ in anhydrous IMF（ 0.12 mL ），and Bu $3 \mathrm{~N}(0.05 \mathrm{~mL})$ was added sequentially．After stirring at r．t．for another 15 min ，a solution of $\mathrm{I}_{2} / \mathrm{H}_{2} \mathrm{O} /$ pyridine $/ \mathrm{THF}$ was added to the above solution dropwise until the iodine color persisted（about 0.5 mL ），and then the mixture was concentrated by evaporation in vacuo．The residue was dissolved in water（ 2 mL ），washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 1$ mL ），filtered，and purified by FPLC（column：HiLoad 26／10 Q Sepharose Fast Flow；buffer A： $0.01 \mathrm{M} \mathrm{Et}_{3} \mathrm{NHCO}_{3}$ ；buffer B： $0.7 \mathrm{M} \mathrm{Et} 3 \mathrm{NHCO}_{3}$ ；flow rate： $10 \mathrm{~mL} / \mathrm{min}$ ；gradient： increasing buffer B from $0 \%$ at beginning to $10 \%$ at 4 min ，then to $100 \%$ at 64 min ）． Collection and lyophilization of the appropriate fractions afforded 714 as a colorless syrup． HPLC［column： $100 \times 4.6 \mathrm{~mm}$ Raining Hydropore SAX ionic exchange；buffer A： 10 mM $\mathrm{NH}_{4} \mathrm{H}_{2} \mathrm{PO}_{4}$ in $10 \% \mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$（pH 5．5）；buffer B： $125 \mathrm{mM} \mathrm{NH}_{4} \mathrm{H}_{2} \mathrm{PO}_{4}$ in $10 \% \mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$ （pH 5．5）；flow rate： $1.0 \mathrm{~mL} / \mathrm{min}$ ；gradient：increasing B from $0 \%$ at beginning to $100 \%$ at 2.5 $\mathrm{min}]$ retention time： $11.9 \mathrm{~min} . \mathrm{MS}$（FAB）me 464 （［M－H］$)^{+}$．
cis－（土）－Carbocyclic $2^{\prime}, 3^{\prime}$－didehydro－ $2^{\prime}, 3^{\prime}$－dideoxycytidine $5^{\prime}$－phosphate（715）．In an analogy manner to the procedure for 714 ，the title compound 715 was prepared from 713. HPLC（same conditions as above）retention time： 12.1 min ．MS（FAB）me 446 （ $[\mathrm{M}-\mathrm{H}]^{+}$）． Inhibitory effect of（土）－Carboxy－D4FC－triphosphate against HIV－1 reverse transcriptase．
Extension assays were performed using a $\mathrm{r}(\mathrm{I})_{\mathrm{n}} \cdot(\mathrm{dC})_{12-18}$ homopolymer template－ primer（Pharmacia，Piscataway，NJ）and the HIV－1 heterodimer p66／51 reverse transcriptase（RT，Biotechnology General，Rehovat，Israel）．The standard reaction mixture（ $100 \mu \mathrm{l}$ ）contained 100 mM This hydrochloride（ pH 8.0 ）， $50 \mathrm{mM} \mathrm{KCl}, 2 \mathrm{mM}$
 and $1 \mu \mathrm{M}^{3} \mathrm{H}-\mathrm{dCTP}(23 \mathrm{Ci} / \mathrm{mmol})$ ． 3 TCTP $(0.001-50 \mu \mathrm{M})$ was the positive control． Compounds were incubated I hr at $37^{\circ} \mathrm{C}$ in the reaction mixture with 1 unit HIV－1 RT．The reaction was stopped with the addition of an equal volume of cold $10 \%$ TCA $/ 0.05 \%$ sodium pyrophosphate and incubated 30 minutes at $4^{\circ} \mathrm{C}$ ．The precipitated
nucleic acids were harvested onto fiberglass filter paper using a Packard manual harvester (Meriden, CT). The radiolabel uptake in counts per minute (cm) was determined using a Packard 9600 Direct Beta counter.

## IV. Anti-HIV Activity

In one embodiment, the disclosed compounds or their pharmaceutically acceptable derivatives or salts or pharmaceutically acceptable formulations containing these compounds are useful in the prevention and treatment of HIV infections and other related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDSrelated neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections. In addition, these compounds or formulations can be-used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The ability of nucleosides to inhibit HIV can be measured by various experimental techniques. One technique, described in detail below, measures the inhibition of viral replication in phytohemagglutinin (PHA) stimulated human peripheral blood mononuclear (PBM) cells infected with HIV-I (strain LAV). The amount of virus produced is determined by measuring the virus-coded reverse transcriptase enzyme. The amount of enzyme produced is proportional to the amount of virus produced.

Antiviral and cytotoxicity assays: Anti-HIV-1 activity of the compounds is determined in human peripheral blood mononuclear (PBM) cells as described previously (Schinazi, R. F.; McMillan, A.; Cannon, D.; Mathis, R.; Lloyd, R. M. J.; Peck, A.; Sommadossi, J. IP.; St. Clair, M.; Wilson, J.; Furman, P. A.; Painter, G.; Choi, W.-B.; Liotta, D. C. Antimicroh. Agents Chemother. 1992, 36, 2423; Schinazi, R. F.; Sommadossi, J.-P.; Saalmann, V.; Cannon, D.; Xie, M.-Y.; Hart, G.; Smith, G.; Hahn, E. Antimicrob. Agents Chemother. 1990, 34, 1061). Stock solutions ( $20-40 \mathrm{mM}$ ) of the compounds were prepared in sterile DMSO and then diluted to the desired concentration in complete medium.
3'-azido-3'-deoxythymidine (AZT) stock solutions are made in water.' Cells are infected with the prototype $\mathrm{HIV}-1_{\text {LA }}$ at a multiplicity of infection of 0.01 . Virus obtained from the cell supernatant are quantitated on day 6 after infection by a reverse transcriptase assay using poly $(\mathrm{rA})_{\mathrm{n}}$.olio $(\mathrm{dT})_{i 2-18}$ as template-primer. The DMSO present in the diluted solution (< $0.1 \%$ ) should have no effect on the virus yield. The toxicity of the compounds can be
assessed in human PBM, CEM, and Vero cells. The antiviral $E C_{50}$ and cytotoxicity $\mathrm{IC}_{50}$ is obtained from the concentration-response curve using the median effective method described by Chou and Talalay (Adv. Enzyme Regul. 1984, 22, 27).

Three-day-old phytohemagglutinin-stimulated PBM cells $10^{6}$ cells $/ \mathrm{ml}$ ) from hepatitis B and HIV-1 seronegative healthy donors are infected with HIV-1 (strain LAV) at a concentration of about 100 times the $50 \%$ tissue culture infectious dose (TICD 50) per ml and cultured in the presence and absence of various concentrations of antiviral compounds.

Approximately one hour after infection, the medium, with the compound to be lested ( 2 times the final concentration in medium) or without compound, is added to the flasks ( 5 ml ; final volume 10 ml ). AZT is used as a positive control.

The cells are exposed to the virus (about $2 \times 10^{5} \mathrm{dpm} / \mathrm{ml}$, as determined by reverse transcriptase assay) and then placed in a $\mathrm{CO}_{2}$ incubator. HIV-1 (strain LAV) is obtained from the Center for Disease Control, Atlanta, Georgia. The methods used for culturing the PBM cells, harvesting the virus and determining the reverse transcriptase activity are those described by McDougal et al. (J. Immun. Meth. 76, 171-183, 1985) and Spira et al. (J. Clin. Meth. 25, 97-99, 1987), except that fungizone was not included in the medium (see Schinazi, et al., Antimicrob. Agents Chemother ${ }_{2}$ 32, 1784-1787 (1988); Id., 34:1061-1067 (1990)).

On day 6, the cells and supernatant are transferred to a 15 ml tube and centrifuged at about 900 g for 10 minutes. Five m of supernatant are removed and the virus concentrated by centrifugation at $40,000 \mathrm{rpm}$ for 30 minutes (Beckman 70.1 Ti rotor). 'The solubilized virus pellet is processed for determination of the levels of reverse transcriptase. Results are expressed in $\mathrm{dpm} / \mathrm{ml}$ of sampled.supernatant. Virus from smaller volumes of supernatant ( 1 ml ) can also be concentrated by centrifugation prior to solubilization and determination of reverse transcriptase levels.

The median effective ( $\mathrm{EC}_{30}$ ) concentration is determined by the median effect-method (Antimicrob. Agents Chemother; 30, 491-498 (1986). Briefly, the percent inhibition of virus, as determined from measurements of reverse transcriptase, is plotted versus the micromolar concentration of compound. The $\mathrm{EC}_{50}$ is the concentration of compound at which there is a $50 \%$ inhibition of viral growth.
-Mitogen stimulated uninfected human PBM cells ( $3.8 \times 10^{5}$ cells $/ \mathrm{ml}$ ) can be cultured in the presence and absence of drug under similar conditions as those used for the antiviral assay described above. The cells are counted after 6 days using a hemacytometer and the
trypan blue exclusion method. as described by Schinazi et al., Antimicrobial Agents and Chemotherapy, 22(3), 499 (1982). The $\mathrm{IC}_{50}$ is the concentration of compound which inhibits $50 \%$ of normal cell growth.

Table 7 provides data on thề anti-HIV activity of selected compounds. Using this assay, it was determined that ( $\pm$ )-carbocyclic-D4FC-TP ( $2^{\prime}, 3^{\prime}$-unsaturated-5-fluorocytidine) exhibited an $E C_{50}^{\dagger}$ of $0.40 \mu \mathrm{M}$, and ( $\pm$ )-carbocyclic-D4C-TP ( $2^{\prime}, 3^{\prime}$-unsaturated cytidine) exhibits an $\mathrm{EC}_{50}$ of $0.38 \mu \mathrm{M}$.

## V. Anti-Hepatitis B Activity

The ability of the active compounds to inhibit the growth of hepatitis virus in 2.2.15 cell cultures (HepG2 cells transformed with hepatitis virion) can be evaluated as described in detail below.

A summary and description of the assay for antiviral effects in this culture system and the analysis of HBV DNA has been described (Korba and Milman, 1991, Antiviral Res ${ }_{i}$, 15:217). The antiviral evaluations are optimally performied on two separate passages of cells. All weils, in all plates, are seeded at the same density and at the same time.

Due to the inherent variations in the levels of both intracellular and extracellular HBV DNA, only depressions greater than 3.5 -fold (for HBV virion DNA) or 3.0 -fold (for HBV DNA replication intermediates) from the average levels for these HBV DNA forms in untreated cells are considered to be statistically significant ( $\mathrm{P}<0.05$ ). The levels of integrated HBV DNA in each cellular DNA preparation (which remain constant on a per cell basis in these experiments) are used io calculate the levels of intracellular HBV DNA forms, thereby ensuring that equal amounts of cellular DNA are compared between separate samples.

Typical values for extracellular HBV virion DNA in untreated cells ranged from 50 to $150 \mathrm{pg} / \mathrm{ml}$ culture medium (average of approximately $76 \mathrm{pg} / \mathrm{ml}$ ). Intracellular HBV DNA replication intermediates in untreated cells ranged from 50 to $100 \mu \mathrm{~g} / \mathrm{pg}$ cell DNA (average approximately $74 \mathrm{pg} / \mu \mathrm{g}$.cell DNA). In general, depressions in the levels of intracellular HBV DNA due to treatment with antiviral compounds are less pronounced, and occur more slowly, than depressions in the levels of HBV virion DNA (Korba and Milman, 1991, Antiviral Res:, 15:217).

The manner in which the hybridization analyses can be performed for these experiments resulted in an equivalence of approximately 1.0 pg of intracellular HBV DNA to

2-3 genomic copies per cell and $1.0 \mathrm{pg} / \mathrm{ml}$ of extracellular HBV DNA to $3 \times 10^{5}$ viral particles/ml.

Toxicity analyses were performed to assess whether any observed antiviral effects are due to a general effect on cell viability. The method used herein are the measurement of the uptake of neutral red dye, a standard and widely used assay for cell viability in a variety of virus-host systems, including HSV and HIV. Toxicity analyses are performed in 96-well flat bottomed tissue culture plates. Cells for the toxicity analyses are cultured and treated with test compounds with the same schedule as described for the antiviral evaluations below. Each compound are tested at 4 concentrations, each in triplicate cultures (wells "A", "B", and "C"). Uptake of neutral red dye are used to determine the relative level of toxicity. The absorbance of internalized dye at $510 \mathrm{~nm}\left(\mathrm{~A}_{\text {sin }}\right)$ are used for the quantitative analysis. Values are presented as a percentage of the average $A_{\text {sin }}$ values in. 9 separate cultures of untreated cells maintained on the same 96 -well plate as the test compounds.

## VI. Anti-Hepatitis C Activity

Compounds can exhibit anti-hepatitis C activity by inhibiting HCV polymerase, by inhibiting other enzymes needed in the replication cycle, or by other known methods. A number of assays have been published to assess these activities.

WO 97/12033, filed on September 27, 1996, by Emory University, listing C.
Hagedorn and A. Reinoldus as inventors, and which claims priority to U.S.S.N. 60/004,383, filed on September 1995, describes an HCV polymerase assay that can be used to evaluate the activity of the compounds described herein. This application and invention is exclusively licensed to Triangle Pharmaceuticals, Inc., Durham, North Carolina. Another HCV polymerase assays has been reported by Bartholomeusz, et al., Hepatitis C virus (HCV) RNA polymerase assay using cloned HCV non-structural proteins; Antiviral Therapy 1996:1(Supp 4) 18-24.

## VI. Treatment of Abnormal Cellular Proliferation

In an alternative embodiment, the compounds are used to treat abnormal cellular proliferation. The compound can be evaluated for activity by testing in a routine screen, such as that performed cost by the National Cancer Institute, or by using any other known screen, for example as described in WO 96/07413.

The extent off anticancer activity can be easily assessed by assaying the compound according to the procedure below in a CEM cellor other tumor cell line assay. CEM cells are
human lymphoma cells (a T-lymphoblastoid cell line that can be obtained from ATCC: Rockville, MD). The toxicity. of a compound to CEM cells provides useful information regarding the activity of the compound against tumors. The toxicity is measured as $\mathrm{IC}_{50}$ micromolar). The $\mathrm{lC}_{50}$ refers to that concentration of test compound that inhibits the growth of $50 \%$ of the tumor cells in the culture. The lower the $\mathrm{IC}_{50}$, the more active the compound is as an antitumor agent. In general, 2'-fluoro-nucleoside exhibits antitumor activity and can be used in the treatment of abnormal proliferation of cells if it exhibits a toxicity in CEM or other immortalized tumor cell line of less than 50 micromolar, more preferably, less than approximately 10 micromolar, and most preferably, less than 1 micromolar. Drug solutions, including cycloheximide as a positive control, are plated in triplicate in $50 \mu \mathrm{l}$ growth medium at 2 times the final concentration and allowed to equilibrate at $37^{\circ} \mathrm{C}$ in a $5 \% \mathrm{CO}_{2}$ incubator. Log phase cells are added in $50 \mu \mathrm{l}$ growth medium to a.final concentration of $2.5 \times 10^{3}$ (CEM and SK-MEL-28), $5 \times 10^{3}$ (MMAN, MDA-MB-435s, SKMES-1, DU-145, LNCap), or $1 \mathrm{x}{ }^{\prime}$ $10^{4}$ (PC-3, MCF-7) cells/well and incubated for 3 (DU-145, PC-3, MMAN), 4 (MCF-7, SK-MEL-28, CEM), or 5 (SK-MES-1, MDA-MB-435s, LNCaP) days at $37^{\circ} \mathrm{C}$ under a $5 \% \mathrm{CO}_{2}$ air atmosphere. Control wells include media alone (blank) and cells plus media without drug. After growth period, $15 \mu \mathrm{l}$ of Cell Titer 96 kit assay dye solution (Promega, Madison, WI) are added to each well and the plates are incubated 8 hr at $37^{\circ} \mathrm{C}$. in a $5 \% \mathrm{CO}_{2}$ incubator. Promega Cell Titer 96 kit assay stop solution is added to each well and incubated $4-8 \mathrm{hr}$ in the incubator. Absorbance is read at 570 nm , blanking on the medium-only wells using a Biotek Biokinetics-plate reader (Biotek, Winooski, VT). Average percent inhibition of growth compared to the untreated control is calculated. $\mathrm{IC}_{50}, \mathrm{IC}_{90}$, slope and r value are calculated by the method of Chou and Talalay. Chou T-C, Talalay P. Quantitative analysis of dose-effect relationships: The combined effects of multiple drugs or enzyme inhibitors. Adv Enzyme Regul 1984, 22:27-55.

The active compound can be administered specifically to treat abnormal cell proliferation, and in particular, cell hyperproliferation. Examples of abnormal cell proliferation include, but are not limited to: benign tumors, including, but not limited to papilloma, adenoma, firoma, chondroma, osteoma, lipoma, hemangioma, lymphangioma, leiomyoma, rhabdomyoma, meningioma, neuroma, ganglioneuroma, nevus, pheochromocytoma, neurilemona, fibroadenoma, teratoma, hydatidiform mole, granuosatheca, Brenner tumor, arrhenoblastoma, hilar cell tumor, sex cord mesenchyme, interstitial
cell tumor, and thyoma as well as proliferation of smooth muscle cells in the course of development of plaques in vascular tissue; malignant tumors (cancer), including but not limited to carcinoma, including renal cell carcinoma, prostatic adenocarcinoma, bladder carcinoma, and adenocarcinoma, fibrosarcoma, chondrosarcoma, osteosarcoma, liposarcoma, hemangiosarcoma, lymphangiosarcoma, leiomyosarcoma, rhabdomyosarcoma, myelocytic leukemia, erythroleukemia, multiple myeloma, glioma, meningeal sarcoma, thyoma, cystosarcoma phyllodes, nephroblastoma, teratoma choriocarcinoma, cutaneous T-cell lymphoma (CTCL), cutaneous tumors primary to the skin (for example, basal cell carcinoma, squamous cell carcinoma; melanoma, and Bowen's disease), breast and other tumors infiltrating the skin, Kaposi's sarcoma, and premalignant and malignant diseases of mucosal tissues, including oral, bladder, and rectal diseases; preneoplastic lesions, mycosis fungoides, psoriasis, dermatomyositis, rheumatoid arthritis, viruses (for example, warts, herpes simplex, and condyloma acuminata), molluscum contagiosum, premalignant and malignant diseases of the female genital tract (cervix, vagina, and vulva). The compounds can also be used to induce abortion.

In this embodiment, the active compound, or its pharmaceutically acceptable salt, is administered in an effective treatment amount to decrease the hyperproliferation of the target cells. The active compound can be modified to include a targeting moiety that concentrates the compound at the active site. Targeting moieties can include an antibody or antibody fragment that binds to a protein on the surface of the target cell, including but not limited to epidermal growth factor receptor (EGFR), c-Esb-2 family of receptors and vascular endothelial growth factor (VEGF).

## VII. Pharmaceutical Compositions

Humans suffering from anyof the disorders described herein can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable derivative or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form. A preferred dose of the compound for all of the abovementioned conditions will be in the range from about 1 to $50 \mathrm{mg} / \mathrm{kg}$, preferably 1 to 20 $\mathrm{mg} / \mathrm{kg}$, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically

IPO DELHI 23-05-2015 15:0081
acceptable derivatives can be calculated based on the weight of the parent nucleoside to be delivered. If the derivative exḥibits activity in itself; the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg , preferably 70 to 1400 mg of active ingredient per unit dosage form. A oral dosage of $50-1000 \mathrm{mg}$ is usually convenient.

Ideally the active ingredient should be administered to achieve peak plasma .concentrations of the active compound of from about 0.2 to 70 pM , preferably about 1.0 to 10 $\mu \mathrm{M}$. This may be achieved, for example, by the intravenous injection of a 0.1 to $5 \%$ solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be neted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration fanges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of admimistration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating àgent such as alginic acid, Primogel, or com starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silipon dioxide; a sweetening agent such as sucrose or saccharin; or a
flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit Corms can contain various other materials which modify the physical form of the dosage unit. for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable derivative or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that ${ }_{\text {; }}$ supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulate delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alva Corporation.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for
example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipids) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

This invention has been described with reference to its preferred embodiments.
Variations and modifications of the invention, will be obvious to those skilled in the art from the foregoing detailed description of the invention.

IPO DELHI 23-06-2015 16:00

## We Claim:

1. A 2'- $\alpha$-fluoro-nucleoside of the formula:

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{\prime}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$R^{2}$ is $H$, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vico, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof.
2. The compound of claim 1, wherein the base is a purine base, $\mathrm{R}^{2}$ is H ; monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt thereof.
3. The compound of claim 2, wherein the purine base is selected from the group consisting of guanine, adenine, hypoxanthine, 2,6-diaminopurine and 6-chloropurine, or a pharmaceutically acceptable salt thereof.
4. The compound of claim 1 , wherein the base is a pyrimidine base, $\overrightarrow{\mathrm{R}}^{2}$ is H , monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt thereof.
5. The compound of claim 5 . wherein the base is selected from the group consisting of thymine, cytosine, 5 -methylcytosine, uracil, and 5-fluorouracil, or a pharmaceutically acceptable salt thereof.
6. A pharmaceutical composition comprising an effective treatment amount of the compound of the formula:

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which. when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester íncluding alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent s as described in the definition of aryl given above, a. lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.
7. The composition of claim 6 , wherein the base is a purine base selected from the group consisting of guanine, adenine, hypoxanthine, 2,6-diaminopurine and 6chloropurine, or a pharmaceutically acceptable salt thereof:
8. The composition of claim 6 , wherein the base is a pyrimidine base selected from the group consisting of thymine, cytosine, 5 -methylcytosine, uracil, and 5 -fluorouracil, or a pharmaceutically acceptable salt thereof.
9. Use of a 2'-fluoronucleoside in the manufacture of a medicament useful for the treatment of hepatitis B infection -in humans wherein the 2 '-fluoronucleoside has the formula:

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl! given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
10. Use of a 2 'fluoronucleoside in the manufacture of a medicament useful for the treatment of hepatitis C infection in humans wherein the 2 'fluoronucleoside has the formula:

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{\prime}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F : or $\mathrm{CF}_{3}$, lower alkyl. amino, loweralkylamino, di(lower)alkylamino, or ulkoxy;
$\mathrm{R}^{2}$ is H , phosphate; including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl; or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
11. Use of a $2^{\prime}$-fluoronucleoside in the manufacture of a medicament useful for inhibiting the replication of HIV in humans wherein the $2^{\prime}$-fluoronucleoside has the formula:

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$R^{2}$ is $H$, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which . when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterel; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a
pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
12. Use of a 2'-fluoronucleoside in the manufacture of a medicament useful for the treatment of abnormal cell proliferation in humans wherein the 2 -fluoronucleoside has the formula:
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{\prime}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optIonally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier:
13. A $2^{\prime}$-fluoro-nucleoside of the formula:

$\mathrm{Y}=\mathrm{O}, \mathrm{S}, \mathrm{CH}_{2}, \mathrm{CHF}$
wherein
Base is a purine or pyrimidine base:
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$R^{2}$ is $H$, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including mellanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with ore or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof.
14. The compound of claim 13 , wherein the base is a purine base, $\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt thereof.
15. The compound of claim 13, wherein the purine base is selected from the group consisting of guanine, adenine, hypoxanthine, 2;6-diaminopurine and 6-chloropurine, or a pharmaceutically acceptable salt thereof.
16. The compound of claim 13 , wherein the base is a pyrimidine base, $\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt thereof.
17. The compound of claim. 16, wherein the base is selected from the group consisting of thymine, cytosine, 5 -methylcytosine, uracil, and 5 -fluorouracil, or a pharmaceutically acceptable salt thereof.
18. A pharmaceutical composition comprising an effective treatment amount of a 2'-fluoro-nucleoside of the formula:



$$
\mathrm{Y}=\mathrm{O}, \mathrm{~S}, \mathrm{CH}_{2}, \mathrm{CHF}
$$

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H ; phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate $\lfloor$ or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, ora pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.
19. The composition of claim 18 , wherein the base is a purine base selected from the group consisting of guanine; adenine, hypoxanthine, 2,6-diaminopurine and 6 chloropurine, or a pharmaceutically acceptable salt thereof.
20. The composition of claim 18, wherein the base is a pyrimidine base selected from the group consisting of thymine, cytosine, 5-methylcytosine, uracil, and 5-fluorouracil, or a pharmaceutically acceptable salt thereof.
21. Use of a 2 '-fluoronucleoside in the manufacture of a medicament useful for the treatment of hepatitis B infection wherein the 2'-fluoro-nucleoside has the formula:

$\mathrm{Y}=\mathrm{O}, \mathrm{S}, \mathrm{CH}_{2}, \mathrm{CHF}$
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino. loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally'substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in viva, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically: acceptable carrier.
22. Use of a 2'-fluoronuclcoside in the manufacture of a medicament useful for the treatment of hepatitis C infection wherein the 2'-fluoro-riucleoside has the formula:

$\mathrm{Y}=\mathrm{O}, \mathrm{S}, \mathrm{CH}_{2}, \mathrm{CHF}$
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vico, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent s as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{j}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
23. Use of a 2 'fluuronucleoside in the manufacture of a medicament useful for the inhibition of the replication of HIV wherein the 2'-fluoro-nucleoside has the formula:
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$R^{2}$ is $H$, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
24. Use of a 2 '-fluoronucleoside in the manufacture of a medicament useful for the treatment of abnormal cell proliferation in humans wherein the 2 'fluoro-nucleoside has the formula:

## wherein

Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, Jowerulkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
25. A $2^{\prime}$-fluoro-nucloeside of the formula:
wherein
Base is a purine or pyrimidine base;
$y$
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H} . \mathrm{OR}^{3}, \mathrm{~N}_{3}$ : CN , halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino. loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is II or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an aminu acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof.
25. The compound of claim 24 , wherein the base is a purine base, $\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt thereof.
26. The compound of claim 25 , wherein the purine base is selected from the group consisting of guanine, adenine, hypoxanthine, 2,6-diaminopurine and 6-chloropurine, or a pharmaceutically acceptable salt thereof.
27. The compound of claim 24 , wherein the base is a pyrimidine base, $\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate or acy!, or a pharmaceutically acceptable salt thereof.
28. The compound of claim 27, wherein the base is selected from the group consisting of thymine, cytosine, 5-methylcytosine, uracil, and 5-fluorouracil, or a pharmaceutically acceptable salt thereof.
29. A pharmaceutical complosition comprising an effective treatment amount of a 2'-fluoro-nucloeside of the formula:


95
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{\prime}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is $H$, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester. including alkyl or arylalkyl sulfoniyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent s as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.
30. The composition of claim 29 , wherein the base is a purine base selected from the group consisting of guanine, adenine, hypoxanthine; 2,6 -diaminopurine and 6 chloropurine, or a pharmaceutically acceptable salt thereof.
31. The composition of claim 29, wherein the base is a pyrimidine base selected from the group consisting of thymine, cytosine, 5 -methylcytosine, uracil, and 5-fluorouracil, or a pharmaceutically acceptable salt thereof.
32. . Use of a 2'-fluoronucleoside in the manufacture of a medicament useful for the treatment of hepatitis B infection wherein the 2 '-fluoro-nucleoside has the formula:
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{\prime}$ is $\mathrm{OH}, \mathrm{H}^{\prime}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamina, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monnophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and,
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a ' pharmaceutically acteptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
33. Use of a 2'-fluoronucleoside in the manufacture of a medicament useful for the treatment of hepatitis C infection wherein the 2 'fluoro-nucleoside has the formula:

$\mathrm{X}=\mathrm{S}, \mathrm{CH}_{2}$
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{\prime}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive: is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
34. Use of a 2 '-fluoronucleoside in the manufacture of a medicament useful for the inhibition of HIV wherein the 2 'fluoro-nucleoside has the formula:

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vico, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
35. Use of a 2'-fluoronucleoside in the manufacture of a medicament useful for the treatment of abnormal cellular proliferation in humans wherein the 2 'fluoro-nucleoside has the formula:


Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; ácyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid; peptide, or cholesterol; and .
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vico, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
36. A 2 '-fluoro-nucleoside of the formula:
$\bullet$
wherein
Base is a purine or pyrimidine, base;
$\mathrm{R}^{\prime}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceurically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or mure substiluents as described in the definition of aryl given above, a lipid, an amino acid; peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vico, is capable of being cleaved to the parent compound; or a pharmaceutically acceptable salt thereof. consisting of thymine, cytosine, 5 -methylcytosine, uracil, and 5-fluorouracil, or a pharmaceutically acceptable salt thereof.
41. A pharmaceutical composition comprising an effective treatment amount of a 2'-fluoro-nucleoside of the formula: monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable salt thereof.
38. The compound of claim 37 , wherein the purine base is selected from the group consisting of guanine, adenine, hypoxanthine, 2,6-diaminopurine and 6-chloropurine, or a pharmaceutically acceptable salt thereof.
39. The compound of claim 36 , wherein the base is a pyrimidine base, $\mathrm{R}^{2}$ is H , monophosphate, diphosphate, triphosphate or acyl, or a pharmaceutically acceptable-salt thereof.
40. The compound of claim 39 , wherein the base is selected from the group

$\mathrm{X}=\mathrm{S} ; \mathrm{CH}_{2}$
100
wherein
Base is a purine or pyrimidine base;
. $\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphusphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vico, is capable of providing a compound wherein $\mathrm{K}^{2}$. is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl; alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.
42. The composition of claim 43, wherein the base is a purine base selected from the group consisting of guanine, adenine, hypoxanthine, 2,6 -diaminopurine and 6 chloropurine, or a pharmaceutically acceptable salt thereof:
43. The composition of claim 42 , wherein the base is a pyrimidine base selected from the group consisting of thymine, cytosine, 5 -methylcytosine, uracil, and 5 -fluorouracil, .or a pharmaceutically acceptable salt thereof.
44. Use of a 2 'fluoronucleoside in the manufacture of a medicament useful for the 1 treatment of hepatitis $B$ infection wherein the 2 '-fluoro-nucleoside has the formula:

$\mathrm{X}=\mathrm{S}, \mathrm{CH}_{2}$
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{\prime}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is $H$, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in viva, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other phamaceutically acceptable leaving group which when administered in vico, is capable of being cleaved to the parent compound, or a pharnaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
45. Use of a 2'-fluoronucleoside in the manufacture of a medicament useful for the treatment of hepatitis C infection wherein the 2 '-fluoro-nucleoside has the formula:

$\mathrm{X}=\mathrm{S}, \mathrm{CH}_{2}$
wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$R^{3}$ is acyl, alkyl, phosphate. or other pharmaceutically acceptable leaving group which when administered in viva, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
46. Use of a 2 'fluoronucleoside in the manufacture of a medicament useful for the inhibition of HIV wherein the 2'-fluoro-nucleoside has the formula:

wherein
Base is a purine or pyrimidine base;
$R^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3}, \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vive, is. capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituent as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathbf{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vive, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
47. Use of a 2'-fluoronucleoside in the manufacture of a medicament useful for the treatment of abnormal cellular proliferation in humans wherein the 2 'fluoro-nucleoside has the formula:


$$
\mathrm{X}=\mathrm{S}, \mathrm{CH}_{2}
$$

wherein
Base is a purine or pyrimidine base;
$\mathrm{R}^{1}$ is $\mathrm{OH}, \mathrm{H}, \mathrm{OR}^{3}, \mathrm{~N}_{3_{7}} \mathrm{CN}$, halogen, including F , or $\mathrm{CF}_{3}$, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy;
$\mathrm{R}^{2}$ is H , phosphate, including monophosphate; diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of providing a compound wherein $\mathrm{R}^{2}$ is H or phosphate; sulfonate ester including alkyl ọ arylalkyl sulfonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, an amino acid, peptide, or cholesterol; and
$\mathrm{R}^{3}$ is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group which when administered in vivo, is capable of being cleaved to the parent compound, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT


INTERNATIONAL SEARCH REPORT
PCT/US 99/04051
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

9-(2,3-Dideoxy-2-fluoro-beta-D-threo
- pentofuranosyl) adenine (beta~fddA).
Introduction of a 2@?-beta-fluoro
Substituent via Inversion of a Readily
Obtainable 2@?-alpha-Fluoro Isomer"
TETRAHEDRON LETTERS,
vol. 39, no. 13 ,
26 March 1998 ( $1998-03-26$ ), page 1657-1660
XP004108441
ISSN: 0040-4039
page 1658 , scheme 1
1-3,11,
Approach to the Clinically Useful,
13-15
Anti-Hiv-Active Nucleoside
----


# EFFECTS OF FLUORINE SUBSTITUTION ON DRUG METABOLISM: PHARMACOLOGICAL AND TOXICOLOGICAL IMPLICATIONS* 

B. KEVIN PARK ${ }^{\dagger}$ and NEIL R. KITTERINGHAM Department of Pharmacology and Therapeutics University of Liverpool Liverpool, England

l. INTRODUCTION ..... 606
II. PHYSICOCHEMICAL PROPERTIES OF FLUORINATED DRUGS ..... 607
III. EFFECT OF FLUORINE SUBSTITUTION ON DRUG METABOLISM ..... 609
A. Anesthetics ..... 611

[^4]B. Analgesics ..... 614
C. Carcinogens ..... 616
D. Corticosteroids ..... 619
E. Drugs Used in the CNS ..... 620
F. Nucleosides and Nucleotides ..... 623
G. Estrogens ..... 626
H. Prostanoids ..... 626
I. Vitamin D ..... 628
IV. REPLACEMENT OF A HYDROXYL GROUP WITH FLUORINE ..... 630
V. METABOLITE DEFLUORINATION ..... 631
VI. FLUÖRINATED COMPOUNDS AS ENZYME INHIBITORS ..... 633
VII. CONCLUSION ..... 637
Acknowledgment ..... 638
References ..... 638

## I. INTRODUCTION

Fluorine substitution can have profound effects on the biological activity of small molecules [1-6]. Many fluorinate .compounds are currently widely used in the treatment of disease and include anticancer drugs, antiviral agents, anti-inflammatory agents, antidepressants, antipsychotics, and steroids, as well as general anesthetics. In a recent compendium of over 700 therapeutic drugs [7], 48 contained one or more fluorine atoms. It has been estimated that, in recent years, half of the fine chemical patents have involved fluorine-containing molecules [8]. The chemistry and medicinal chemistry of fluoroorganic compounds have been reviewed [4-6, 9]. The inclusion of a fluorine atom in a drug molecule can, in theory, influence: both the disposition of the drug and the interaction of the drug with its pharmacological target (Fig. 1). The effects of fluorine substitution on the inter- and intramolecular forces which affect binding of ligands at cholinergic and adrenergic receptors are particularly well documented [10-13]. Less information is available concerning the effect of fluorine substitution on drug disposition. The purpose of this review is to analyze the effects of fluorine substitution on the metabolism of a drug in terms of the chemistry of the molecule, and then to consider the pharmacological and toxicological implications of such changes with respect to drug design.


FIG. 1. Effects of fluorine substitution on chemical structure and drug action.

## II. PHYSICOCHEMICAL PROPERTIES OF FLUORINATED DRUGS

Fluorine can be substituted into a drug molecule in place of hydrogen without introducing any major steric changes since the van der Walls radius of fluorine is similar to that of hydrogen $\left(r_{F}=1.35 \AA, r_{H}=1.20 \AA\right)$ and less than that of other halogens or oxygen (Table 1). The radius of an atom is dictated by the number of protons in the nucleus and by the number of shells containing electrons. Fluorine has nine protons which strongly interact with the same number of electrons whereas hydrogen has only one proton interacting with one electron. The strong attraction between electrons and protons in a fluorine atom means that its atomic radius is contracted to such an extent that it is similar in size to a hydrogen atom, and therefore fluorine is able to mimic hydrogen with respect to steric requirements at binding sites on receptors and enzymes.

In contrast to their similarity in size, hydrogen and fluorine have quite different electronic properties. Fluorine is the most electronegative element in the periodic table (Table 1). When fluorine is substituted for hydrogen the resulting change in the electron distribution in the molecule can alter the $\mathrm{pK}_{u}$, dipole moments, and overall reactivity and stability of neighboring functional groups within the molecule. The magnitude of the change in

## TABLE 1

Physical Properties of the Carbon-Fluorine Bond [4]

these electronic properties is determined in a predictable fashion, by the bonding between the fluorine atom and the functional group. Thus the presence of a fluorine atom ortho to a phenolic group is associated with a reduce $\mathrm{pK}_{\mathrm{a}}$ of $1: 2$, whereas meta and para fluorosubstitution have much less effect (Table 2). In contrast, the presence of fluorine in an aromatic system will produce a systematic increase in the $\mathrm{pK}_{山}$ of an amino group.

Fluorine forms a strong bond with carbon (bond energy $C-F=112$ $\mathrm{kcal} / \mathrm{mol}$ ) which has an increased oxidative and thermal stability compared with the carbon-hydrogen bond ( $\mathrm{C}-\mathrm{H}=98 \mathrm{kcal} / \mathrm{mol}$ ). The carbon-fluotine bond is one of the strongest known in organic chemistry. In addition to the formation of covalent bonds, a fluorine atom present in a molecule can also form reversible, electrostatic bonds with certain functional groups. Fluorine can participate in hydrogen bonding, as a hydrogen bond acceptor,

## TABLE 2

Effect of Fluorine Substitution on the $\mathbf{p K}_{\mathbf{a}}$ of Simple Phenols and Anilines

and in this respect the bonds formed are of energy comparable to those formed to oxygen ( $\mathrm{O}-\mathrm{H}-\mathrm{O}$ ) and stronger than those formed by other halogens. The carbon-fluorine bond has a strong dipole and this may interact, either positively or negatively, with other dipoles. This may. lead to an alteration in the $\mathrm{pK}_{\mathrm{a}}$ of a particular functional group or alter the overall conformation of the molecule. For example, it is thought that, in fluorimated derivatives of noradrenaline, interactions between a ring carbonfluorine bond and the hydroxyl group on the heta-carbon in the side chain determine the conformation of the molecule, and hence the position of the fluorine atom in the aromatic ring can determine receptor selectivity [10].

The presence of a fluorine atom may influence the lipophilicity of a molecule and hence affect the partitioning of the drug into membranes, and also facilitate hydrophobic interactions of the drug molecule with specific binding sites, on either receptors or enzymes. The replacement of a single aromatic hydrogen atom usually results only in a modest increase in lipophilicity, whereas the $\mathrm{CF}_{3}$ group is among the most lipophilic of all substituents (Table 3). This is particularly important in the case of centrally acting drugs where the presence of fluorine atoms increases the rate of absorption and transport of the drug across the blood-brain barrier and into the CNS [14].

Fluoride ion is a good leaving group. being the conjugate base of a strong acid. Therefore, fluoride ion can be lost in both displacement and elimination reactions, an aspect of fluorine chemistry that can be utilized in the design of drugs or chemical agents which.form stable covalent bonds with target receptors or enzymes as part of their pharmacological response, and that is the basis of the "lethal synthesis" concept of Peters [15].

The presence of fluorine can alter the oxidation potential of an aromatic system and thus alter the rate of autoxidation and formation of quinones and quinoneimines. Sequential introduction of fluorine atoms into the nuclaus of paracetamol produced an increase in the oxidation potential of the molecule as measured by cyclic voltammetry• [16]. However, in some instances fluorine substitution may not alter the rate of autoxidation, as exemplified by the selective denervation agent 5.7-dihydroxytryptamine [17].

## III. EFFECT OF FLUORINE SUBSTITUTION ON DRUG METABOLISM

The introduction of fluorine into a molecule can be used to alter the rate, route, and extent of drug metabolism. Such effects are most commonly achieved by fluorine substitution at the site of metabolic attack by virtue of IPO DELH altered chemical reactivity of the carbon-fluorine bond, in comparison $H_{t o t h a t ~ o f ~ t h e ~ c a r b o n-h y d r o g e n ~ b o n d ~ S i t e-s p e c i f i c ~ m e t a b o l i c ~ b l o c k a d e ~ h a s ~}^{\text {B }}$

TABLE 3
Physicochemical Parameters for Some Commonly Used Aromatic Substituent


Note. $\delta$ is the Hammett ionization constant for substituent in the meta $\left(\delta_{m}\right)$ and para $\left(\delta_{j}\right)$ positions. $f^{H}$ is the fragment constant for aromatic substituents, and MR is the molar refractivity, a function related to molar volume by the Lorentz-Lorenz equation. For precise definitions of these constants and a comprehensive list of values, see Ref. 104.
been used for three main purposes: first, as an integral part of pharmacological action, as exemplified by antimetabolites and "suicide" enzyme inhibitors; secondly, to modify the pharmacokinetics of a drug in terms of distribution; rate, and/or route of metabolism; thirdly, as a "chemical probe'" to investigate the role of specific oxygenation reactions in the physoological activation of compounds and the bioactivation of toxins/carcinogens. Substitution at sites adjacent to and, in some instances, distal to the site of metabolic attack can alter both rates and routes of drug metabolism by either inductive/resonance :(through-bond) effects or conformational and electrostatic (through-space) effects. The presence of a fluorine atom adjacent to a site of metabolic attack could, in theory, either increase or decrease the rate of biotransformation depending on whether (1) the metabolic attack is nucleophilic or electrophilic in nature and (2) inductive or resonance effects of the fluorine atom predominate in the reaction. For exampile, in a simple saturated system the inductive effect of fluorine could be expected to reduce the reactivity of adjacent groups to electrophilic attack by P450 enzymes. In contrast, it might be anticipated that the presence of
fluorine orth to a phenolic group might increase its reactivity as a nucleophile in methylation and glucuronidation reactions, and there is some avidance to support this hypothesis [18, 19].

Fluorine substitution can therefore have complex effects on drug metabolism which in turn may have implications for drug efficacy and/or drug safety. We therefore use the mechanistic framework outlined in Fig. 1 to consider the role of metabolism in the action of various classes of fluorimated compounds, with particular consideration of factors which may be of relevance to the design of safer drugs.

## A. Anesthetics

Halothane (1) was the first of the modern fluorocarbon anesthetics to be introduced. The metabolic fate of halothane is relevant to its hepatotoxicity. The National Halothane Study [20] showed that two forms of hepatic injury occur with halothane: the first a mild increase in up to $20 \%$ of patients, and the second a more severe form, referred to as halothane hepatitis, characterized by massive liver necrosis occurring in 1 in 35,000 patients on first exposure and in 1 in 3700 patients on multiple exposure. Halothane hepatitis is regarded as a model for immune-mediated hepatotoxicity. A high proportion of patients with halothane hepatitis have been found to have cell-specific antibodies and lymphocytes directed against halothane-derived liver neoantigens. These antigens correspond to at least five different polypeptides ( $100,76,59,57$, and 54 kDa ) that are expressed predominantly in the microsomal fraction of liver [21|. There are two major pathways of halothane metabolism, as shown in Fig. 2, both of which are thought to be catalyzed by CYP2EI (although the evidence for this isozyme mediating halothane reduction is not definitive). Reduction leads to the formation of reactive intermediates or free radicals, such as 2 -chloro-1,1,1-trifluoroethane (2) which can undergo further reduction to a carbanion and then, following fluorine elimination, give rise to $\mathrm{CF}_{2}=\mathrm{CHCl}(3)$. It is the reductive pathway that is thought to be responsible for the mild form of hepatitis.

Oxidation of halothane is believed to proceed via a reactive intermediate, trifluoroacetyl chloride (5). This species can either react directly with water to form the nontoxic trifluoroacetic.acid (6) and be excreted in urine, or it can react with any adjacent nucleophiles to form trifluoroacetyl (TFA) adducts. It is the formation of such adducts with proteins that has been postulated as a mechanism for the immunological or severe form of halothane hepatitis [22].

Chlorofluorocarbons (CFCs) are fluorinated compounds of environmental significance because of their ability to deplete stratospheric ozone. There is


FIG. 2. Simplified metabolic scheme for halothane, indicating the reductive pathway (leading to mild, type I hepatitis) and the oxidative pathway (thought to be responsible for the severe form of halothane hepatitis).
an intense research effort aimed at developing substitutes for CFCs, with the hydrochlorofluorocarbons (HCFCs) undergoing extensive toxicity testing as potential alternatives. The structural similarity between the HCFCs and halothane has led some investigators to look for TFA-protein adducts in livers of animals exposed to a variety of HCFCs [23-25]. Some HCFCs, notably 2,2-chloro-1,1,1-trifluoroethane, gave rise to TFA-proteins to an extent similar to that seen with halothane itself. In addition, urinary fluoride and trifluoroacetic acid concentrations were enhanced after exposure to HCFCs, indicating that both oxidative and reductive processes are involved in the metabolism of these compounds [26].

Fluorinated anesthetics provide a fascinating example of how the presence of fluorine in a molecule can be the cause of toxicity, and yet further substitution with fluorine can, paradoxically, prevent the same toxicity by reducing the extent of drug metabolism.

Methoxyflurane (7) was widely used in clinical anesthesia during the IPO DELHI ${ }^{1960} \mathrm{~s}_{3}$ However, it was discovered that there was an association of the drug







Isoflurane (9)
(<1\%)


FIG. 3. Effect of fluorine substitution on the extent of metabolism (\%dose) of general anesthetics.
with nephrotoxicity, and use of the agent in anesthesia progressively diminished. A high urine output syndrome leading to dehydration, and in some cases fatal renal failure, was related to the extensive ( $40 \%$ ) metabolism of methoxyflurane and high serum concentrations of inorganic fluoride. Inorgenic fluoride ions inhibit chloride transport in the ascending limb of the loop of Hence [27]. Methoxyflurane has been shown to be metabolized in man and animals to oxalic acid and free fluoride [28]. Defluorination probably occurs, as outlined in. Fig. 3. Compared with methoxyflurane, enflurance (8) and isoflurane (9) undergo $3 \%$ and $<1 \%$ metabolism, respectively.

[^5]with these agents, and there are only occasional reports of nephrotoxicity for enflurane and none at all for isoflurane [29-31].

Inspection of the chemical structures of the three anesthetics reveals that increasing fluorine substitution can result in a reduction in overall metabolism, and specifically biotransformations leading to defluorination. However, the position of fluorine substitution is critical for both determining the occurrence of metabolic defluorination and for limiting the overall extent of metabolism of the compound. If the initial step in the metabolism of methoxyflurane is demethylation, then it would appear that replacement of two hydrogens with fluorine in the $O$-methyl group reduces the reactivity of the remaining hydrogen atom toward abstraction by the cytochrome P-450 enzymes.

In man, enflurane is metabolized to fluoride ion, difluoromethoxydifluoracetic acid, and an unidentified acid metabolite. The predicted products of oxidation of the difluoromethyl group have not been detected [32]. Inorganic fluoride and trifluoroacetic acid have been identified as end products of isoflurane metabolism [33]. These products are thought to arise by a sequence which begins with insertion of an active oxygen atom into the bond connecting hydrogen to the ethyl $\alpha$-carbon, a reaction catalyzed by cytochrome P4502EI in man [34]. In a rat model, the cytochrome P-450 inhibitor cimetidine decreased inorganic plasma fluoride production [35].

Desflurane (10), in which the chlorine atom in isoflurane is replaced by a fluorine atom, is excreted by the lungs and appears resistant to biotransformation. The oil/gas partition coefficient for desflurane (18.7) is considerably less than that of isoflurane (91), which explains the more rapid rates of onset and offset of anesthesia of the former [36, $\cdot 37$ ].

## B. Analgesics

The widely used analgesic paracetamol (11) causes"fulminant hepatic necrosis when taken in overdosage 138, 39]. After administration of a therapeutic dose of paracetamol, the major pathways of metabolism are glucuronidation and sulfation |Fig. 4(a)|. The hepatotoxicity is thought to be caused by an electrophilic metabolite, $N$-acetyl-p-benzoquinone imine (12). Introduction of fluorine into the paracetamol molecule (13-17) alters the oxidation potential in a manner dependent on the number and position of the fluorine atoms [16]. The presence of fluorines at the 2 -and 6 -positions (16) increases the oxidation potential of paracetamol sufficiently to reduce the propensity of the molecule to undergo oxidative bioactivation, as measured by the depletion of hepatic glutathione and excretion of thioether conjugates, and thereby reduces the in vivo toxicity of the molecule |Fig. 4(b)|


FIG. 4. (a) The metabolism and mechanism of toxicity of paracetamol. (b) The effect of fluorine substitution on the oxidation potential, bioactivaton, and toxicity of paracetamol. Each compound was administered to mice IPO DEL HaL a dose of 2 E 65 or 831.64 mine $/ \mathrm{kg}[40]$.

140]. Introduction of fluorine did not affect either the glucuronidation or sulfation pathways. However, introduction of fluorine into the acetyl group resulted in extensive hydrolysis to give aminophenol, a biotransformation not observed with paracetamol. Unfortunately, 2,6 -fluorine substitution also resulted in a loss of analgesic activity in a mouse model [16], which was attributed to a loss of conjugation between the acetyl group and the aryl ring, an effect similar to that observed with 2,6 -methyl substitution.

It is also pertinent to consider the metabolism of drugs in current therepeutic use which might, in theory, undergo metabolism if it were not for the presence of a fluorine atom. In the search for novel nonsteroidal antiinflammatory drugs, fluorinated derivatives of salicylic acid have exhibited high analgesic potency in addition to their anti-inflammatory activity. Two such examples are diflunisal and flufenisal, which are potent inhibitors of prostaglandin synthesis, in particular prostaglandin $E_{1}$, through their action on the enzyme cyclooxygenase. Diflunisal, because of its lipophilicity, is well absorbed and extensively metabolized, with less than $5 \%$ of the drug being excreted unchanged. Metabolism results entirely from ether and ester glucuronide formation. There is no oxidative metabolism of the difluorophenyl group |41].

## C. Carcinogens

Precarcinogenic polycyclic aromatic hydrocarbons are metabolically activated by cytochrome P-450 enzymes to arene oxides which bind covalently to DNA and other essential macromolecules and thereby cause mutagenesis and carcinogenesis. Oxygenation can be suppressed by introduction of fluorine at the site of metabolic attack. It is thought that the strength of the C-F bond and the electron-withdrawing effects of fluorine combine to block the electrophilic attack of an oxygen species at an aromatic center. Of particular importance in this respect is the possibility of blocking the formation of bay ring epoxides. However, it is also important to note in interpretation of data concerning the activation of carcinogens, that fluorine can have distal effects on bioactivation. Electrostatic potentials have been derived for 1,2,3,4-tetraḥydro-7,12-dimethylbenz|a|anthracene derivatives which show that the presence of fluorine in one ring can have a marked effect in adjacent rings, with a concomitant alteration in oncogenic posentaal |42|.

Fluorine substitution was used as a tool in the early mechanistic investigations of carcinogenicity (Fig. 5). Miller and Miller [43] found that substitution of fluorine in the 3-position of 7-methyl-1,2-benzanthracene (18) virtually abolished the carcinogenic activity of this hydrocarbon toward


(14)


10





Fluorine substitution at the 5 -position in
7-methyl-1,2-benzanthracene eliminates carẹinogenic action [43]: However fluorine substitution at other positions enhances ( $6,8,9,10$ ) [44].

1-F, 2-F and 5-F 7, 12-dimethylbenz-(u)-anthracene were cither inactive or required more than lool-fnld lingliur duse line the purest comperund $\mid$.is):

The akin and tumour initiating activities of $7-, 8-$, 9-, and 10 -fluornbenzo-(a)-pyrenes were negative in (emile mice ${ }^{46}$ ).

2,10 dilluorodibenzo-(a,i)-pyrene is not carcinogenic in contrast to the parent compound [47].

8, y-difluoroindeno [1,2,3-e d]pyrene weakly, but still tumorigenic [48\}

FIG. 5. The effect of fluorine substitution on the oncogenic potential of aromatic hydrocarbons.
mouse skin. However, fluorine substitution at other positions may enhance carcinogenicity [44].

Similar suppression of carcinogenic activity has been reported with the fluorinate derivatives of 7,12-dimethylbenz(a)anthracene (DMBA) (19). The 1-, 2-, and 5 -fluorinate derivatives were either inactive or required more than a 1000 -fold higher dose to induce a comparable mutagenic response to DMBA. These results suggest that carbon positions 1 and 2 of DMBA, which are located in the bay region, and position 5, located in the K -region, are involved in the metabolic activation of DMBA into mutagenic and carcinogenic metabolites [45].

Benzo-(a)-pyrene (BP) (20) was the first member of the polycyclic aromatic hydrocarbon class of compounds for which proximate and ultimate carcinogens were defined. The metabolic pathway to the chemically reactive species responsible for the tumorigenicity of BP consists of cytochrome P-450 oxidations and epoxide hydrolysis leading to the ultimate carcinogen, 7.8-dihydroxy-9, 10-epoxytetrahydrobenzpyrene. Accordingly, tumorigenicity studies showed that 7-.8-,9- and 10-fluorobenz(a)pyrenes were not turitorigenic in the mouse, and that fluorine substitution, at each position, had blocked formation of the respective diol-epoxides [46]. It has also been shown that fluorine substitution in the angular rings of dibenzo-(a,i)-pyrene (21) reduces both tumorigenicity and dihydrodiol formation [47]. Fluorine can be used as a metabolic probe to assist in the identification of those positions within an aromatic hydrocarbon that are critically associated with its tumorigenic activity. Indeno[1.2;3-cd]pyrene (IP) (22) is a nonalterant polycyclic hydrocarbon, found throughout the environment, which is active as a tumor initiator when assayed on mouse skin. Metabolic studies have shown that the compound is metabolized in both the A- and D-rings. Fluorinated derivatives were therefore synthesized and assessed for their tumor-initiating activity on mouse skin and formation of DNA,adducts, using ${ }^{32} \mathrm{P}$-postlabeling $148 \mathrm{]}$. The weak tumorigenic activity of 8,9 -difluoro=IP as compared to IP was held to be consistent with IP undergoing metabolic activation in the D-ring, although no formal metabolism study was undertaken. It was anticipated that location of fluorine at the 8 - and 9 -positions would suppress formation of 7,8-, 8,9-, and 9,10-epoxides of IP. However, although the number of tumors/animal was reduced, a significant percentage ( $40 \%$ )-of tumor-bearing mice was still observed which was attributed to some A-ring activation.

The metabolic activation of 5 -methylchrysene ( $5-\mathrm{MeC}$ ) (23) has been of interest because this carcinogen is typical of the class of methylated polynuclear aromatic hydrocarbons and is the most carcinogenic of all the methylchrysene isomers. In order to investigate the chemical mechanisms of bioactivation of this molecule, Hecht et al. 149] investigated the comparative mutagenicity, carcinogenicity, and in vitro metabolism of seven derivatives fluorinated at the $1-, 3-, 6-7-9-11-$, and 12 -positions, respectively. All seven compounds were mutagenic in the presence of a rat liver homogenate. Investigation of mouse skin tumor formation showed that the 6., 7-, 9., 11-fluorinated derivatives were as carcinogenic as $5-\mathrm{MeC}$; 12fluoro was significantly less potent, whereas both $1-\mathrm{F}$ and 3-F were inactive as complete carcinogens (Fig. 6). Examination of the in vitro metabolism of the fluorinated compounds indicated that fluorine substitution inhibited the oxidative metabolism at the position of attachment and at neighboring positions. Thus, in the case of 1 F - and $3 \mathrm{~F}-\mathrm{MeC}$ formation of the 1,2-


FIG. 6. The effect of fluorine substitution on the carcinogenicity of 5methylchrysene ( $5-\mathrm{MeC}$ ) in the mouse (adapted from Ref. 49).
dihydrodiol was inhibited and was reduced in the presence of a 12-fluoro atom. The results were therefore consistent with the concept that the metaboric activation of $5-\mathrm{MeC}$ in mouse skin proceeds primarily by formation of a 1.2-dihydrodiol-3,4-epoxide. These data also indicate that the structural requirements for tumorigenic activity are more specific than for mutagenic activity in $S$. typhimurium.

## .D. Corticosteroids

Fluorination of natural hormones can lead to molecules with enhanced quantitative efficacy, and also to qualitative differences in activity. The introduction of a fluorine atom into the steroid nucleus can have complex effects on biological activity, which may involve many factors including conformational changes in the steroid nucleus and altered receptor binding. Here we focus on the effect of fluorine substitution on metabolism. The first fluorination of a steroid hormone observed to enhance biological activity was the synthesis of $9 \alpha$-fluoro-hydroxycorticosteroids [2]. Fluorocortisone acetate is a potent mineralocorticoid with considerable glucocorticoid activity; ie., introduction of the $9 \alpha$-fluors enhances the glucocorticoid and mineralocorticoid activity 10 - and 125 -fold, respec-
lively. Further modification of the molecule, and in, particular introduction of a double bond in the A-ring, produces selective anti-inflammatory agents such as dexamethasone. There are several ways in which the $9 \alpha$-fluor group might enhance activity. First, the enhanced acidity of the $11 \beta$ hydroxyl group might increase receptor binding, although there is no direct evidence for this. Secondly, X-ray crystallography reveals a small conformational change, in which the A-ring is bent underneath the plane of the molecule as a result of a nonbonding interaction between the $9 \alpha$-fluor group and the axial substituent on Cl [50].

A feature of $9 \alpha$-fluorination is a dramatic reduction in some of the major routes of metabolism seen with cortisol (24) (Fig. 7). The most striking finding is the lack of oxidation of the $11 \beta$-hydroxyl group to a ketone (25), which occurs rapidly with cortisol and leads to a loss of biological activity. Such a biotransformation was not observed in either in vive or in vitro studlies. A similar effect was observed for other $9 \alpha$-fluorinate steroids [51], and also with a vicinal $12 \alpha$-fluors group in cortisol (Table 4). The $9 \alpha-$ fluorine atom alters the rate at which the $11 \beta$-hydroxyl group can be oxidized by both enzymes, and by chemical oxidants such as chromic acid. Hence, in vive, there is a shift in the enzymatic equilibrium between the biologically inactive 11 -ox compounds and the active reduced $11 \beta$-hydroxy form [52]. In vitro studies have shown that, while cortisone and A-ring reduced metabolites are the major products of cortisol metabolism in the liver, $9 \alpha$-fluorocortisol undergoes preferential . $6 \beta$-hydroxylation (26), and $20 \alpha$-reduction (28) (Fig. 7) [53].

## E. Drugs Used in the CNS

The two most common functional groups containing fluorine found in therapeutic drugs of this class are the 4 -fluorophenyl group and the trifluoromethyl group. Both groups are extremely lipophilic and will therefore have a marked effect on drug penetration and drug distribution. In many cases this factor may be the most significant in improving pharmacological activity. Indeed, the majority of the drugs which contain these functional groups are centrally acting agents. In addition, both groups are generally resistant to metabolic attack. The 4 -fluorophenyl is usually resistant to aromatic hydroxylation, especially at the 4-position, although aromatic hydroxylation at the unsubstituted positions has been reported. Defluorination of the fluoromethyl group is even less common, although 5-trifluoromethyluracil is converted into 5 -carboxyuracil in man with concomitant excretion of inorganic fluoride [54].




FIG. 7. The effect of $9 \alpha$-fluorine substitution on the metabolism of cortisol by human hepatic microsomes. The metabolic routes undergone by cortisol are indicated by the light arrows, while the heavy arrows (labeled $F$ ) indicate the principal routes of the fluorinated analogues.

The trifluoromethyl group ( $\mathrm{CF}_{3}$ ) group, although isosteric with a methyl group, is-more lipophilic and is, like fluorine itself, a strong electronwithdrawing group in aromatic systems, in contrast to a methyl group which has a positive inductive effect (Table 3). The $\mathrm{CF}_{3}$ group is not known to undergo metabolic degradation, although metabolic attack, by cytochrome P450 enzymes, may occur alpha to the trifluoromethyl group in alkyl systems and at the ortho and para positions when the $\mathrm{CF}_{3}$ group is attached directly to an aryl group. In molecules such as fluphenazine, which contain two chemically equivalent rings, apart from one being substituted with a $\mathrm{CF}_{3}$ group, hydroxylation occurs in the unsubstituted ring because of the deactivating effect of the $\mathrm{CF}_{3}$ group [55].

There are three categories of psychotropic agents which act by blocking dopamine receptors in the CNS: tricyclics, butyróphenones, and diarylbutylamines. Many of these drugs, contain either a $\mathrm{CF}_{3}$ group or fluorophenyl group which presumably contribute to the overall pharmacological activity of the compounds by enhancing CNS penetration, and retarding metabolic degradation. Several clinically useful phenothiazines have been introduced [4]. Trifluoropromazine, trifluperazine, and fluphenazine are all more ac-
live than chlorpromazine, 5, 50, and 100 times, respectively. The most widely used butyrophenone is haloperidol. It has been established that the para-fluorophenyl group is optimal for neuroleptic activity of the butsrophenones. In the search for more potent neuroleptics it was found that the diarylbutylamines pimozide and fluspirilene, which contain two fluorophenyl groups, were longer acting than haloperidol. Fluspirilene appears to have the longest duration of action, with single weekly doses better than or equal to daily doses of haloperidol in 795 schizophrenic patients.

## F. 'Nucleosides and Nucleotides

Fluorine has been substituted into both the base and the sugar residue of nucleosides and nucleotides, and the resulting compounds (29-37) now represent an important group of drugs (Fig. 8).

A major breakthrough in the 1950s was the synthesis of nucleic acid antagonists by substitution of fluorine for hydrogen in naturally occurring purimes and pyrimidines [3.,56]. It was found that an antimetabolite could be produced by fluorination at a metabolic site in a natural substrate. 5Fluorouracil (29) has been one of the major antimetabolites used in the treatment of solid cancers. 5-Fluorouracil is converted into a pharmacologically active metabolite, S-fluoro-deoxyuridine monophosphate (FdUmp) (39), which inhibits the enzyme thymidylate synthetase, resulting in reduce formation of thymidine (41) and hence DNA [57]. Inhibition is ascribed to the presence of the unreactive fluorine atom at C-5 which blocks the essential addition of formate (Fig. 9). 5-Fluorouracil, as FdUmp, is also incorporated into mRA. Since 5 -fluorouracil and its anabolites are concentrated in cancer cells, the enzymatic blockade inhibits tumor growth.

5-Fluoro-2'-deoxyuridirie (FdUrd) (30), a potent cytotoxic agent in cell culture, is substantially degraded in vive to the free pyrimidine base, 5 fluorouracil, by the enzyme thymidine phosphorylase, which is less potent on a molar basis than FdUrd. A second fluorine substitution in the ribose ring (31) [58], while reducing the overall activity of the compound, improved the stability of the nucleosidic linkage toward cleavage. It has also been shown that fluorination at the $3^{\prime}$-position can improve metabolic stability of the glycosidic bond.

The success of 5 -fluorouracil as an antimetabolite has prompted the continued search for fluorinated purine and pyrimidine compounds as potential anticancer agents and, more recently, as drugs for use in the treatment of HIV disease. Among the dideoxypurine nucleosides, $2^{\prime}, 3^{\prime}$-dideoxyadenosine (ddAdo) and $2^{\prime}, 3^{\prime}$-dideoxyinosine (ddlno) have an in vive virustatic effect and appear to improve immune function in patients with AIDS and severe



(31)

(3.3)

(34)


FIG. 8. Chemical structures of fluorinated nucleosides and nucleotides that have undergone pharmacological evaluation.

AIDS-related complex. However, because of the extreme acid lability of their glycosidic bonds, these compounds require administration either with antacids or in an enterically coated tablet to be orally bioavailable. A $2^{\prime}$ fluoroarabinosyl substitution in ddAdo ( $2^{\prime} \mathrm{F}$-dd-ara-A), has been found to render the molecule (32) acid stable without loss of antiretroviral activity [59]. In addition, it has been shown that $2^{\prime}$-F-dd-ara-A is much less susceptible to enzymic deamination in human T-cell (MOLT4) extracts, but could still form the active antiviral $5^{\prime}$-triphosphate anabolite; $2^{\prime}$-F-dd-ara-ATP.

(29)




1

FIG. 9. The effect of C-5. fluorination of uracil in the metabolic pathways involved in thymidine synthesis.

2-Fluoroadenine nucleosides are resistant to deamination by the catabolic enzyme deaminate. Thus 2-fluoroformycin, 2-fluoroadenosine (33), 2-fluoro-8-azadenosine (34), and 9-arabinofluranosyl-2-fluoroadenine are poor substrates for adenosine deaminase [60-62]. In addition the 2-fluoro substituent does not seriously impair phosphorylation by adenosine kinase. However, in the case of 2-fluoroformycin, although formation of the monophosphate occurs in various cell lines, it does not proceed to the triphosphate, which may explain its decreased cytotoxicity in L12 10 cells [62].

Fluorine-substituted analogues are of interest in the development of antiAIDS drugs. Alovudine (36) ( $3^{\prime}$-fluorothymidiné; FddThd; FLT) is the direct fluorine analogue of zidovudine (35) (AZT, 3'-azidothymidine), the only currently licensed drug for the treatment of AIDS. From a metabolic viewpoint. it has been shown that FLT is well phosphorylated in relevant cell lines to the 5 -triphosphate which is the active inhibitor of HIVassociated reverse transcriptase [63]. In addition, the compound could, like AZT, act as a terminator of DNA synthesis, because of the lack of the 3'-hydroxyl group, but unlike AZT would not form a toxic 3'. -amino metaboolite. FLT was found to exhibit an anti-HIV-7 potency similar to that of AZT but with slightly better selectivity of effects and with higher intracelIular active metabolite levels [64]. The elimination half-life of FLT in rats
and monkeys is slightly longer than AZT, which may reflect the fact that FLT is excreted in urine as unchanged drug, unlike AZT which undergoes some glucuronidation $[64,65]$.

Further fluorine substitution, at the $3^{\prime}$-position, produces an inactive analogue $3^{\prime}, 3^{\prime}$-difluoro- $3^{\prime}$-deoxythymidine (37) (DFLT). Although the difluoro compounds assume a conformation similar to other thymidine analogues aclive against HIV, it has been proposed that the lack of activity is due to the direction of the dipole created by the two $\mathrm{C}-\mathrm{F}$ bonds at $\mathrm{C}-3^{\prime}$ lying much closer to the plane of the deoxyribose rather than pointing downward (as in AZT and FLT), and thus preventing DFLT from serving as a substrate for thymidine kinase and for its 5 -triphosphate to be a poor substrate for reverse transcriptase [66].

## G. Estrogens

Synthetic and natural estrogens have been associated in humans with a variety of vaginal, breast, hepatic, and cervical cancers. The mechanism(s) of carcinogenesis have not been elucidated, but it has become clear that hormonal potency cannot be directly correlated with carcinogenic activity, and it has been suggested that oxidative metabolism plays a role in the carcinogenicity of steroid estrogens. The natural estrogens, estrone and estradiol, are known to undergo extensive oxygenation to 2 -hydroxylated and 4-hydroxylated (catechol) metabolites, in humans and experimental animals. Catechols can be oxidized to chemically reactive species (quinones and semiquinones) which can form covalent bonds with proteins and DNA. Lehr 1675 found that 2 -fluoroestradiol (42) was ais estrogenic as estradiol but noncarcinogenic in the Syrian hamster, and assumed that 2-fluorination had blocked catechol formation. However, Li et al. 168] subsequently demonstrated that 2 -fluoroestradiol undergoes defluorination by hepatic microsomes. In vive studies (Ref. 69: Salford, unpublished data), in the hamster and rat, showed that the presence of a 2 -fluor substituent diverted the metabolism of the steroid from 2-hydroxylation to glucuronidation, thus providing a metabolic rationale for the observations of Lehr [67] (Fig. 10).

## H. Prostanoids

Numerous fluorinated derivatives of prostaglandins $E_{2}$ and $F_{24}$ have been synthesized, with most attention being focused on the development of phatmacodynamic selectivity-smooth muscle vs. antifertility.

The prostanoids prostacyclin and thromboxane play an essential physiological role in the regulation of the cardiovascular system and platelet func-




methylation
(43)

glucuronidation




FIG. 10. Effect of fluorine substitution on the metabolism of estradiol.
ion. Both compounds have short ( $<5 \mathrm{~min}$ ) half-lives in vivo. Consequently there has been a concerted effort to synthesize analogues with altered pharmacokinetic properties, and in particular, enhanced stability and activity (Fig. II).

Thromboxane $\mathbf{A}_{2}\left(\mathrm{TxA}_{2}\right)$ causes aggregation of platelets and constriction of vascular smooth muscle. It has a half-life of only 32 sec under physiological conditions. Incorporation of fluorine into the oxetane ring alpha to the acetalic linkage, reduces the rate of carbonium ion formation and acid hydrolysis. Thus model compounds related to 7,7-difluoro-TxA ${ }_{2}$ (45) have a rate of hydrolysis which is $10^{k}$ times slower than that of $\mathrm{TXA}_{2}[70]$ while 10,10 -difluoro- $\mathrm{TxA}_{2}$ is also a stable analogue and retains thromboxane-like activity [71].

Prostacyclin $\left(\mathrm{PGI}_{2}\right)$ is a vasodilator and inhibitor of platelet aggregation. It contains an acid-labile enol ether group which is responsible for its short biological half-life. Electrophilic attack of a hydroxonium ion at the enol ether double bond is the rate-limiting step in the metabolic degradation of the compound. It was therefore anticipated that fluorination alpha to the labile group would reduce the electron density on the enol ether group, and thus improve the stability of the molecule toward acid hydrolysis. 10,10 -Difluoro-13-dehydroprostacyclin (46) exhibited a half-life 150 times greater than that of $\mathrm{PGI}_{2}$ and was equal in potency to the natural compound in

628
PARK AND KITTERINGHAM

(45)

(46)

(47)

FIG. 11. Chemical structures of fluorinate prostanoids.
terms of vasodilator activity [72]. In addition, substitution of the acetylenic group for the 13,14-double bond blocked inactivation by 15 -hydroxyprostaglandin dehydrogenase. Similarly, the 7 -fluors derivative of $\mathrm{PGI}_{2}$ (47) stabilized the enol by reducing the electron density of the double bond at $\mathrm{C}-5$ through the inductive effects of fluorine. The half-life of $7(S)-7$-fluors- $\mathrm{PGI}_{2}$ was greater than 1 month under conditions where the half-life of $\mathrm{PGI}_{2}$ was 10 min [73]. Stability was further demonstrated by measurement of platelet aggregation. The activity of the 7 -fluors derivative was maintained under conditions in which $\mathrm{PGI}_{2}$ had decreased to $1 / 1(\mathrm{xx})$ of its activity. In each case, the stability of the fluorinate compound can be attributed to the inductive effect of fluorine reducing the basicity of the ether group.

## I. Vitamin D

During the past 20 years much progress has been made in elucidating the role of metabolism in the physiological activation of vitamin $D_{3}$ (48), and fluorine substitution has been used to investigate the anabolism and the catabolism of the vitamin (Fig. 12). Vitamin $D_{3}$ undergoes sequential 25and 1-hydroxylation in the liver and kidney, respectively. The resulting product, 1,25-dihydroxyvitamin $\mathrm{D}_{3}$. should be regarded as a hormone play-


FIG. 12. Structure of yitamin $D_{3}$ indicating positions in which fluorine substitution has been used to investigate physiological metabolic activation.
ing a central role in the metabolism of phosphorus and calcium. Accordingly, it has been found that blocking the 1-and 25 -hydroxylations with fluorine groups markedly reduces the biological activity of vitamin $D$ compounds [74, 75]. In competitive binding assays $1 \alpha-\mathrm{OH}-25 \mathrm{~F}-\mathrm{D}_{3}$ is about equipotent with $1-\alpha-\mathrm{OH}-\mathrm{D}_{3}$, indicating that the fluorine group is mimicking hydrogen, not hydroxyl, at the 25 -position. The compound also had reduced activity in vive [76].

Halloran et al. [77] looked at 24,24-difluoro-25-hydroxyvitamin $\mathrm{D}_{3}$ and found it to be equally active to 25 -hydroxy-vitamin $D_{3}$ which indicated that 24-hydroxylation is not required for activity, on the assumption that fluerine substitution would block 24 -hydroxylation. There was no evidence for defluorination, although the metabolism of the fluorinate compound was not studied directly.

Fluorine substitution has also been used to investigate the possible metabolic inactivation of vitamin $D$ compounds. It was found that $26,26,26$, 27,27,27-hexafluoro-1,25-dihydroxyvitamin $D_{3}$ is approximately 10 times more active, and longer acting in vive, than $1,25-(\mathrm{OH})_{2}-\mathrm{D}_{3}$ itself [78], indicating that it undergoes less rapid metabolism to inactive products. However, it has also been postulatedithat multiple fluorine substitution in the vicinity of the 25 -hydroxyl group can markedly enhance the affinity of a compound for the receptor by increasing the acidity of the 25 -hydroxyl group [78]. These observations emphasize the need to carry out formal metabolism studies when using fluorine substitution as a probe for defining key metabolic steps in physiological bioactivation. It cannot be presumed that replacement of hydrogen with fluorine will block metabolism in every situation and at every position. In this context, it is of interest to note that

6-fluoro-vitamin $D_{3}$ actually behaves as an antagonist at the intestinal receptor for $1,25-(\mathrm{OH})_{2}-\mathrm{D}_{3}$ [79].

## IV. REPLACEMENT OF A HYDROXYL GROUP WITH FLUORINE

The $\mathrm{CF}_{2}$ and CFH groups have been proposed as reasonable isosteric and isopolar replacements for the hydroxyl group because of their size, electrondistribution, and ability to act as hydrogen bond acceptors [80-82]. The $\mathrm{CF}_{2} \mathrm{H}$ group is particularly favored due to its ability to act as a hydrogen donor [83], potentially allowing interaction with solvent and biological molecules. In addition, fluorine can mimic a hydroxyl group either through a dipole-dipole interaction or through an acceptor role in an hydrogen bond. It has been demonstrated that fluorine is capable of interacting significantly with proton donors in enzymatic sites [84, 85].

The potential clinical usefulness of centrally, acting dopamine receptor agonists and antagonists has stimulated an extensive search for novel dopaminergic compounds. Dopamine itself is not suitable as a therapeutic agent in this context because it does not cross the blood-brain barrier and it is a good substrate for catechol-o-methyl transferase (COMT) and monoamtine oxidase (MAO) enzymes. Replacement of the 4-hydroxyl group in dopamine with fluorine produced a compound which retained affinity for both $D_{1}$ and $D_{2}$. receptors without being able to discriminate between the receptor subtypes [86], but which should also no longer be a substrate for COMT or MAO.

Chloramphenicol is a drug of choice in the treatment of infections caused by Salmonella typhi. The worldwide emergence of bacterial resistance to this drug, especially in Salmonella, prompted a reexamination of structureactivity relationships of the amphenicols [87]. The clinically important resistance to chloramphenicol in bacteria is usually due to the presence of specific inactivating enzymes, chloramphenicol acetyltransferases, which catalyze an acetyl-coenzyme A-dependent acetylation of the 1 - or 3-hydroxy. group or both. Replacement of the primary hydroxyl group in chloramphenicol by a hydrogen, chlorine, or bromine atom results in a complete or significant loss of potency. 3-Fluoro-3-deoxychloramphenicol, which has conformational properties similar to chloramphenicol, was found to be highly active against both chloramphenicol-susceptible and chloramphenicol acetyltransferase-producing resistant organisms. In contrast, it was found that replacement of the secondary alcohol (at the 1 -position) by a fluorine results in loss of activity [88].

## V. METABOLIC DEFLUORINATION

Despite the strength of the carbon-fluorine bond, defluorination can readily occur, under certain circumstances, because of the stability of the fluoride ion (Fig. 13). If a molecule is sufficiently electrophilic to undergo direct reaction with nucleophilic groups present in proteins and amino acids, such as the amino group in lysine. the hydroxyl group in serine and the sulfhydryl group in cysteine, then reactions can proceed spontaneously with the direct displacement of the fluoride ion. Such compounds can therefore be highly toxic, the type of toxicity depending on the target macromolecule. Two examples are given to illustrate this point. A well-known example of this type of reaction is the phosphorylation of the serine residue at the active site of the enzyme acetylcholinesterase by diisopropyl phosphorofluoridate (DFP) (49). In vivo exposure to DFP produces nonselective inhibition of cholinesterase enzymes and is therefore highly toxic. Dinitrofluorobenzene (51) is a model immunogen, widely used to study humoral and cellular immune responses. The compound reacts directly with lysine residues in proteins, with direct displacement of fluoride ion, to form the dinitrophenyl hapten (52). In this respeçt dinitrofluorobenzene is more reactive than dinitrochlorobenzene [89]. In vivo, approximately $10 \%$ of the compound binds to protein, whereas most of the compound undergoes metabolic detoxication by conjugation with glutathione (53) [90].

The production of fluoride ion during biological oxidation of aryl fluorides has been observed in several systems [91]. Hydroxylation of 4-fluoro-L-phenylalanine (54) by phenylalanine hydroxylase results in l-tyrosine (55) and fluoride ion [92]. Also, hydroxylation of 3,5-difluoro-4-hydroxybenzoic acid (56) results in 3-fluorobenzoquinone-5-carboxylic acid (57) and fluoride ions [93).

The enzymes responsible for metabolism of 4 -fluoro- $N$-methylaniline (58) have been investigated in detail, both in vitro and in vivo using ${ }^{19} \mathrm{~F}$ NMR [94]. The major enzyme responsible for $N$-demethylation and aromatic ring hydroxylation was the cytochrome P-450 system, whereas the contribution for flavin-containing monooxygenase to formation of defluorinated ring hydroxylated products would be about 3-10 times higher than that of cytochromes P-450. It was suggested that defluorination, which accounted for $40 \%$ of recovered metabolites, could have resulted from $N$-oxidation rather than metabolic ring hydroxylation. In keeping with this hypothesis, it has been suggested that 4 -defluorination of pentafluoraline ( 60 ) proceeds by formation of fluoride anion and a reactive benzoquinoneimine which undergoes subsequent reduction to an aminophenol (61) [95].

2-Fluoroethýnylestradiol (62), unlike 2-fluoroestrádiol, undergoes partial defluorination in vivo in the rat to produce 2-hydroxyethynylestradiol

$$
1779
$$








(58)




FIG. 13. Metabolic defluorination.
(63) [18]. The reaction, catalyzed by cytochrome P-450 enzymes, is thought to involve rearrangement of an intermediate epoxide with concomitant loss of fluoride ion, and subsequent reduction of the resulting quinone to the catechol.

Amodiaquine (64) is an antimalarial drug which undergoes extensive bioactivation in vive to a quinone imine metabolite which is excreted in bile as the 5 -glutathionyl metabolite (65). Attempts were made to block the biotransformation by substitution of a fluorine at the 5 -position [112]. However, it was discovered that the major metabolite of 5 -fluoroamodiaquine was again 5 -glutathionylamodiaquine, which was thought to be formed by elimination of hydrofluoric acid from an intermediary gluetathione adduct.
The release of fluoride from aliphatic compounds is readily achieved by hydroxylation alpha to the carbon-fluoride bond and elimination of hydrofluoric acid, to yield a ketone or an acyl halide as described earlier for the metabolism of methoxyflurane.

## VI. FLUORINATED COMPOUNDS AS ENZYME INHIBITORS

Although the main theme of this review is concerned with the effects of fluorination on drug metabolism, it is pertinent to mention briefly compounds which act as mechanism-based enzyme inhibitors by virtue of the presence of various fluorinated functional groups.

Fluoroacetic acid (66) is a highly toxic substance found naturally in a number of plants. When fluoroacetic acid is ingested it enters the tricarboxylic acid cycle and is converted by "lethal synthesis" into fluorocitric acid (68) [15], which is a potent inhibitor of the enzyme aconitase (Fig. 14). Therefore, the enzyme is unable to effect the elimination of water from fluorocitric acid [96], and instead the false substrate becomes irreversibly bound to the enzyme, in a process in which fluorine acts as a good leaving group [97].
The toxicity of fluoroacetate is of relevance to drug design involving metabolically labile fluoroalkyl groups. In an investigation of a series of fluoroalkylamine derivatives of narcotic analgesics in rats, elevated serum concentrations were detected, implicating in vive oxidative deamination of the $N$-(fluoroalkyl) substituent to fluoroacetate [98].
As mentioned above, 5 -fluorouracil is converted in vivo into 5 -fluoro-$2^{\prime}$-deoxy- $\beta$-uridine, which is a potent competitive inhibitor of thymidylate synthetase. The inhibition is ascribed to several properties of fluorine. The size of the fluorine atom and the strength of the carbon-fluorine bond al-

inhibition of aconitase
FIG. 14. Fluoroacetate inhibition of the tricarboxylic acid by "lethal synthesis.'.
low the molecule to enter the active site without metabolism. However, the potency of the molecule as an enzyme inhibitor is a function of the affinity of the antimetabolite for the enzyme whic̣h is 1000 -fold greater than the natural substrate; which is a consequence of the decreased $\mathrm{pK}_{\mathrm{a}}$ of the nitrogen in 5 -fluorouracil (8.15) compared with uracil (9.45).

The presence of a fluorine atom at an appropriate position in the molecule, or metabolite, where it can be eliminated as fluoride ion provides a mechanism for suicide enzyme inhibition. The use of fluorinated ketones and fluoroamino acids in this respect is well documented.

Fluorinated amino acids have been successfully employed as suicide inhibitors. Such inhibitors form a reversible complex with the target enzyme. While bound to the enzyme, the substrate is transformed in such a way as to activate the latent functionality present in the molecule. The activated suicide inhibitor then undergoes an irreversible reaction with a nucleophilic group on the enzyme and thus inactivates the enzyme.

Fluoromethylated amino acids have been recognized as potential suicide inhibitors of enzymatic decarboxylation reactions for some time [99]. The enzymatic deactivation is thought to be dependent on loss of fluoride ion from the intermediate Schiff base formed betweeh pyridoxal phosphate and the fluoromethylated amino acid ( $\alpha$-fluoromethyldopa) at the active site (Fig. 1S). Loss of fluoride generates a reactive Michael-type acceptor which can conjugate to an enzyme-bound nucleophilic group. $\alpha$-Fluoromethyldopa is active in both the periphery and the brain [100]. Such mechanismbased enzyme inhibitors have also been developed for ornithine decarböylase, GABA transaminase, arginine decarboxylase, and histidine decarboxylase [6].

The enzyme $S$-adenosyl-L-homocysteine (SAH) hydrolase is an attractive target for the development of antiretroviral agents. It regulates biolog-



FIG. 15. Selective enzyme inhibition by fluoromethyldopa.
ical methylation reactions indirectly, and thus the methyl group 5'-capping which the mRNA of many viruses require for binding to ribosomes. Mechanism-based inhibitors of SAH hydrolase have been designed based on the enzymatic pathway for conversion of SAH to adenosine (76) (Fig. 16). These compounds showed antiretroviral activity against Moloney leukemia virus [101]. Enzymatic turnover of the vinyl fluoride would give a $\beta$-fluoro$\alpha, \beta$-unsaturated ketone, which is susceptible to addition of an enzyme nucleophile followed by elimination of fluoride in a Michael-type reaction.

Several approaches to blockade of the renin-angiotensin system have been studied for the treatment of hypertension. Since angiotensinogen is the only known substrate for renin, inhibition of this stage of the renin-angiotensin system might offer some advantage over ACE inhibitors. Sitedirected inhibitors of the enzyme have been designed which contain a readily hydrated difluoroketone that is thought to mimic the tetrahedral intermediate that forms during the enzyme-catalyzed hydrolysis of a peptide bond |102|. Thus the compounds behave as transition-state analogues. In

vino, several such compounds showed good oral activity in the salt-depleted normotensive cynomologous monkey.

Fluorinate ketones may also act as quasi-substrate inhibitors by readily forming a hemiketal adduct with the nucleophilic serine residue present at the active site of the enzyme [103] as a consequence of the enhanced reaptivity of the ketone due to the inductive effect of the adjacent fluorine atoms.

## VII. CONCLUSION

The introduction of fluorine into a molecule can alter both the rate and route of drug metabolism, in a manner dependent on the site of fluorination in relation to the sites of metabolic attack in the nonfluorinated molecule. Fluorine substitution can also influence the disposition of a drug, and fluorinated drugs have the distinct advantage that their in vive tissue pharmacokinetics can be monitored noninvasively by ${ }^{19} \mathrm{~F}$ magnetic resonance spectroscopy. Substitution of fluorine for hydrogen at the site of oxidative attack can block metabolism or can deflect metabolism along an alternative route. However, oxidative: defluorination can occur, in both aromatic and aliphatic systems, and therefore formal metabolic studies must always be undertaken when using fluorine substitution to investigate the role of a particular biotransformation in a physiological or toxicological process.

The effects of fluorine substitution at sites adjacent to, or distal to, the site of metabolic attack are less easy to predict. The presence of a highly electronegative fluorine atom may inhibit the interaction of the drug with enzymes which effect nucleophilic attack at the molecule. Alternatively, the inductive effect of a fluorine atom adjacent to a phenolic group might enhance the rate of electrophilic attack at this center by UDPGA catalyzed by glucuronyl transferase.

In terms of drug design, fluorine substitution can be used to alter the rate of drug metabolism and thereby produce a drug with a longer duration of action, and such an approach has already been used successfully for several classes of drugs. Alternatively, introduction of fluorine could, in theory, improve the therapeutic ratio of drugs which cause toxicity in man by the formation of chemically reactive metabolites. This could be achieved by fluorine substitution, at the appropriate site of the molecule, with an alteration in the balance between activation and detoxication processes; provided, of course, that fluorine is introduced into the molecule in such a way that it does not interfere with the interaction between the drug and its phar= macological site of action.

## ACKNOWLEDGMENT

B.K.P. is a Wellcome Principal Research Fellow. We thank Dr. P. M. Morgan and Dr. A. H. Harrison for helpful discussions.

## REFERENCES

[1] P. Buffa and R. A.• 'eiers, J. Physiol.; 110,488 (1950).
[2| J. Fried and E. F. Sabo, J. Am. Chem. Soc., 76, 1455 (1954).
[3] C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E: Pleven, and J. Scheiner, Nature, 179, 663 (1957).
[4] G. Resnati, Il Pharmaco, 45, 1066 (1990).
[5] G. Resnati, Il Pharmaco. 45, 1137 (1990).
[6] J. T. Welch, Tetrahedron.43, 3123 (1987).
[7] C. T. Dollery, A. R. Boobis, D. Burley, D. M. Davies, D. S. Davies, P. I. Harrison, M. L.E. Orme, B. K. Park, and L. I. Goldberg, Therapeutic Drugs, Churchill Livingstone, Edinburgh, 1991.
[8] S. M. Brown and M. C. Bowden, Chem. Ind., 1993, p. 143.
[9] J. Mann, Chem. Soc. Rev., 16, 381 (1987).
[10] K. L. Kirk, O. Olubajo, K. Buchold, G. A. Lewandowski, F. Gusovsky, D. McCulloh, J. W. Daly, and C. R. Creveling, J. Med. Chem., 29, 1982 (1986).
[II] J. F. DeBernardis, D. J! Kerkman, M. Winn, E. N. Bush, D. L. Arendsen, W. J. McCleilan, J. J. Kyncl, and F. Z. Basha, J. Med. Chem., 28, 1398 (1985).
[12] A. S. Bàss, J. D. Kohli, A. Adejare, K. L. Kirk and L. I. Goldberg, Eur. J. Phurmacol., 187, 87 (1990).
[13] P. Bravo, G. Resnati, P. Angeli, M. Frigerio, F. Viani, A. Arnone, G. Marucci, and F. Cantalamessa, J. Med. Chem., 35, 3102 (1992).
[14] A. J. Elliott, in Aspects of Fluorine Chemistry (R. Fuller and Y. Kobayashi, eds.). Elsevier Biomedical Press, New York, 1982.
[15] R. A. Peters, in Carbon-Fluorine Compounds: Chemistry, Biochemistry and Biological Activities (K. Elliott, 'ed.), Elsevier, Amsterdam, 1957.
[16] S. Barnard, R. C. Storr, P. O'Neill, and B. K. Park, J. Pharm. Pharmacol., 45, 736 (1993).
[17] M. Kawase, A. K. Sinhababu, and R. T. Borchardt. Chem. Pharm. Bull., 38, 2939 (1990).
[18] P. Morgan. J. L. Maggs, P. C. B. Page, and B: K. Park, Biochem. Pharmacol:, 44, 1717 (1992).

FLUORINE EFFECTS ON DRUG METABOLISM
[19] K. L. Kirk, D. Cantacuzene, B. Collins, G. T. Chen, Y. Nimit, and C. R. Creveling, J. Med. Chem., 25, 680 (1982).
[20] National Halothane Study..J. Am. Med. Assoc., 197, 121 (1966).
[21] L. R. Pohl, J. G. Kenna, H. Satoh, and D. Christ, Drug Metab. Rev., 20, 203 (1989).
[22] J. G. Kenna, H. Satoh, D. D. Christ, and L. R. Pohl, J. Pharmacol. Exp. Ther., 245, 1103 (1988).
[23] J. W. Harris; J: P. Jones, J. L. Martin, A. C. LaRosa, M. J. Olson, L. R. Pohl, and M. W. Anders, Chem. Res. Toxicol., 5, 720 (1992).
[24] J. W. Harris and M. W. Anders, Chem. Res. Toxicol., 4, 180 (1991).
[25] J. W. Harris, L. R. Pohl, J. L. Martin, and M. W. Anders, Proc. Natl. Acad. Sci. USA, 88; 1407 (1991).
[26] D. E. Dodd, W. T. Brashéar, and A. Vinegar, Toxicol. Letl., 68, 37 (1993).
[27] R. J. Roman, J. R. Carter, W. C. North, and M. L. Kauker, Anesthesiology, 46, 260 (1977)..'
[28] R. I. Mazze, J. R. Trudell, and M. J. Cousins, Anesthesiology, 35. 247 (1971).
[29] R. I. Mazze, M. J. Cousins, and G. A. Barr, Anesthesiology, 10, 536 (1974).
[30] R. I. Mazze, R. K. Calverley, and N. T. Smith, Anesthesiology, 46, 265 (1977).
[31] E. I. Eger, E. A. Smuckler, L. D. Ferrell, C. H. Goldsmith, and B. H. Johnson, Anesth. Analg., 65, 21 (1986).
[32] R. L. Carpenter, E. I. Eger, B. H. Johnson, J. D. Unakadt, and L. B'. Sheiner, Anesth. Analg., 65, 575 (1986).
(33) B. A. Hitt, R. I. Mazze, M. J. Cousins, H. N. Edmunds, G. A. Barr, and J. R. Trudell, Anesthesiology, 40, 62 (i974).
[34] K. E. Thummel, E. D. Kharasch, T. Podoll, and K. Kunze, Drug Metab. Dispos., 21, 350 (1993).
[35] M. Wood, J. Uetrecht, J. M. Phythyon, S. Shay, B. Sweetman, O. Shaheen, and A. J. J. Wood, Anesth. Analg., 65, 481 (1986).
[36] D. D. Koblin, E. I. Eger, B. H. Johnṣon, K. Konopka, and L. Waskell, Anesth. Analg., 67, 534 (1988).
[37] R. M. Jones, D. D. Koblin, J. N. Casihman, E. I. Eger, B. H. Johnson, and D. C. Damask, Br. J. Anaesth., 64, 482 (1990).
[38] D. G. D. Davidson and W. M. Eastham, Br. Med. J., 2, . 497 (1966).
[39] D. C. Davis, W. Z. Potter, D. J. Jollow, and J. R. Mitchell, Life Sci., 14, 2099 (1974).
[40] S. Barnard. D. F. Kelly, R. C. Storr, and B. K. Park, Biochem. Pharmacol., 46, 841 (1993).
[41] D. J. Toc̣co, G. O. Breault, A. G. Zacchei, S. L. Steelman, and C. V. Perner, Drug Metab. Dispos., 3, 453 (1975).
142] S. D. Black. P. K. Sharma, J. C. Galluchi, A. C. Blackburn, J. W. Downs, S. J. Rinderle, and D. T. Witiak. Carcinogenesis, 13, 1337 (1992).
[43] E. C. Miller and J. A. Miller, Cancer Res., 20, 133 (1960).
[44] D. M. Jerina, H. Yagi, W. Levin, and A. H. Conney, in Drug Design and Adverse Reactions (H. Bundgaard, P. Juul, and H. Kafod, eds.), Academic Press, New York, 1977.
[45] E. Huberman and T. J. Slaga, Cancer Res., 39, 411 (1979).
[46] D. R. Buhler, F. Unlu, D. R. Thakker, T. J. Slaga, M. S. Newman, W. Levin. A. H. Conney, and D. M. Jerina, Cancer Res., 42, 4779 (1982).
[47] S. Hecht, E. Lavoie, V. Bedenko, L. Pingàro, S. Katayama, D. Hoffman. D. Sardella, E. Boger, and R. Lehr, Cancer Res., 41, 4341 (1981).

148] J. E. Rice, E. H. Weyand, C. Burrill, and E. J. Lavoie, Carcinogenesis, II, 1971 (1990).
1491 S. S. Hecht, E. LaVole, R. Mazzarese, N. Hirota, T. Ohmori, and D. Hoffman, J. Natl. Cancer Inst., 63, 855 (1979).
[50] C. M. Weeks; W. L. Duax, and M. E. Wolff, J. Am. Chem. Soc., 95, 2865 (1973).
[51] I. E. Bush and V. B. Mahesh, Biochem. J.. 93, 236 (1964).
[52] I. E. Bush and V. B. Mahesh, Biochem. J., 71,718 (1959).
[53] S. M. Abel, D. J.. Back, J. L. Maggs, and B. K. Park, J. Steroid Biochem. Molec. Biol., 46, 833 (1993).
[54] C. Heidelberger, in Carbon-Fluorine Compounds: Chemistry, Biochemistry and Biological Activities (K. Elliot, ed.), Elsevier, Amsterdam, 1972, pp. 125-140.
[55] M. W. Dysken, J. I. Javai, S. S. Chang, C. Schaffer, A. Shahid, and J. M. Davis, Psychopharmacology, 17, 205 (1981).
[56] R. Duschinsky, E. Pleven, and C. Heidelberger, J. Am. Chem. Soc., 79, 4559 (1957).
[57] H. M. Pinedo and G. F. J. Peters, J. Clin. Oncol., 6, 1653 (1988).
158| S. Ajmera, A. R. Bapat, K. Danenberg, and P. V. Danenberg, J. Med. Chem., 27, II (1984).
[59| R. Masood, G. Ahluwalia, D. Cooney, A. Fridland, V. Marquez, J. Driscoll, Z. Hao, H. Mitsuya, C. Perno, S.: Broder, and D. Johns, Mol. Pharmacol., 37, 590 (1990).
|60| R. W. Brockman, Y. C. Cheng, F. M. Scabel, and J. A. Montgomery, Cancer Res., 40, 3610 (1980).
$161 \mid$ J. A. Montgomery. A. T. Shortnacy, and J. A. Secrist, J. Med. Chem., 26. 1483 (1983).

FLUORINE EFFECTS ON DRUG METABOLISM
[62] J. A. Secrist, A. T. Shortnacy, and J. A. Montgomery, J. Med. Chem., 28, 1740 (1985).
[63] E. Mathews, C. Lehmann, D. Scholz, H. A. Rosenthal, and P. Langen, Biochem. Biophys. Res. Commun., 153, 825 (1988).
[64] X. B. Kong, Q. Y. Zhu, P. M. Vidal, K. A. Watanabe, B. Polsky, D. Armstrong, M. Ostrander, S. A. Lang. E. Muchmore, and T. C. Chou, Antimicrob. Agents Chemother., 36, 808 (1992).
[65] L. Stahle, E. Guzenda, and E. Ljungdahl-Stahl, J. Acquir. Immune Defic. Syndr., 6, 435 (1993).
[66] D. Bergstrom, A. Mott, E. De Clercq, J. Balzarini, and D. Swartling, J. Med. Chem., 35, 3369 (1992).
[67] J. G. Liehr, Mol. Pharmacol., 23, 278 (1983).
[68] J. J. Li, R. H. Purdy, E. H. Appelman, J. K. Klicka, and S. A. Li, Mol. Pharmacol., 27, 559 (1985).
[69] P. Morgan. J. L. Maggs. P. C. Bulman-Page, F. Hussain, and B. K. Park, Biochem. Pharmacol., 43, 985 (1992).
[70] J. Fried, E. A. Hallinan; and M. J. Szwedo, J, Am. Chem. Soc., 106, 3871 (1984).
[71] T. A. Morinelli, A. K. Okwu, D. E. Mais, P. V. Halushka, V. John, C. K. Chen; and J. Fried, Proc. Natl. Acad. Sci. USA., 86, 5600 (1989).
[72] J. Fried, D. K. Mitra, M. Nagarajan, and M. M. Mehrotra, J. Med. Chem., 23, 234 (1980).
[73] K. Bannai; T. Toru, T. Oba, T. Tanaka, N. Okamura, K. Watanabe, A. Hazato, and S. Kurozumi, Tetrahedron. 39, 3807 (1983).
[74] J. L.-Napoli, M. A. Fivizzani, H. K. Schnoes, and H. F. DeLuca, Biochemistry, 17, 2387 (1978).
[75] J. L. Napoli, M. A. Fivizzani, H. K. Schnoes, and H. F. Deluca, Biochemistry, 18, 1641 (1979).
[76] Y. Kobayashi and Y. Taguchi, in Biomedical Aspects of Fluorine Chemistry (R. Filler and Y. Kobayashi, eds.), Elsevier, Amsterdam, 1982, pp. 33-53. ${ }^{\prime}$
[77] B. P. Halloran, H. F. Deluca, E. Barthell, S. Yamada, M. Ohmori, and H. Takayama, Endocrinology, I08, 2067 (1981).
[78] Y. Tanaka, H. F. Deluca, Y. Kobayashi, and'N. Ikekawa, Arch. Biochem. Biophys., 229, 348 (1984).
[79] F. Wilhelm, W. G. Dauben, B. Kohler, A. Roesle, and A. W. Norman, Arch. Biochem. Biophys., 233, 127 (1984).
[80] D. Bergstrom, E. Romo; and P. Shum, Nucleos. Nucleot., 6, 53 (1987).
[81] D. E. Bergstrom and P. W. Shum, J. Org. Chem., 53, 3953 (1988).
[82] G. M. Blackburn, F. Eckstein, D. E. Kent, and T. D. Peree, Nucleos.
[83| D. D. Nelson, G. T. Fraser, and W. Klemperer, Science, 238, 1670 (1987).
[84] P. Murray-Rust, W. C. Stallings, C. T. Monti, R. K. Preston, and J. P. Glusker, J. Am. Chem. Soc., 105, 3206 (1983):
[85] L. H. Takahashi, R. Radhakrishnan, R. E. Rosenfield, E. F. Meyer, and D. A. Trainor, J. Am. Chem. Soc., III, 3368 (1989).
[86] F. Claudi, M. Cardellini, G. M. Cingolani, A. Piergentili, G. Peruzzi, and W. Balduini. J. Med. Chem.. 33. 2408 (1990).
[87] T. L. Nagabhushan. D. Kandasamy, H. Tsai, W. N. Turner, and G. H. Miller, in Current Chemotherapy: Proceedings of IIth Internarional Congress on Chemotherapy, American Society of Microbiology, 1980, vol. 106, pp. 442-443.
[88] T. Tsushima, K. Kawada, T. Tsuji, and K. Tawara, J. Med. Chem., 28, 253 (1985).
[89| M. D. Tingle, J. B. Clarke, N. R. Kitteringham, and B. K. Park, Int. Arch. Allergy Appl. Immunol., 91, 160 (1990).
1901 N. R. Kitteringham, J. G. Kenna, C. McLean, J. B. Clarke, and B. K. Park, Drug Metab. Dispos., 20. 625 (1992).

191] G. M. K. Hughes and B. C. Saunders, Chem. Ind., 1954, p. 1265.
192| S. Kaufman, Biochim. Biophys. Acta, 51.619 (1961).
193| M. Husain, B. Entsch, D. P. Ballou, V. Massey, and P. J. Chapman, J. Biol. Chem., 255, 4189 (1980).

194| M. G. Boersma, N: H. P. Cnubben, W. J. H. Van Berkel, J. Vervoot, and I. M. C. M. Rietjens, Drug Metab. Dispos., 21, 218 (1993).
[95] I. M. C. M. Rietjens and J. Vervoot, Chem.-Biol. Interact., 77, 263 (1991).
[96] R. Peters, R. W. Wakelin, and P. Buffa, Proc. Roy., Soc., B/40, 497 (1952).
[97] H. L. Carrell, J.'P. Ģlusker, J. J. Villafranca, A. S. Mildvan, R. J. Dummel, and E. Kun, Science, I70, 1412 (1970).
[98| W. G. Reifenrath, E. B. Roche, and W. A. Alturk,J. Med. Chem., 23, 985 (1980).
[99] J. Kollonitsch, A. Patchett, S. Marburg, A. Maycock, L. Perkins, G. Doldouras, D. Duggan, and S. Aster, Nature, 274, 906 (1978).
[100] P. Bey, M. J. Jung, J. Kochweser, M. G. Palfreyman, A. Sjoerdsma, J. Wagner, and M. Zraika, Br. J. Pharmacol., 70, 571 ( 1980).
[101] J. R. McCarthy, E. T. Jarvi, D. P. Matthews, M. L. Edwards, M. J. Prakash, T. L. Bowlin, S. Mehdi, P. S. Sunkara, and P. Bey, J. Am. Chem. Soc., 111, 1127 (1989).
[102] A. Doherty, I. Sircar, B. E. Kornberg, J. Quin, R. T. Winters, J. S. Kaltenbronn, M. D. Taylor, B. L. Batley, S. R. Rapundalo, M.J. Ryan. ànd C. A. Paincthaud, J. Med. Chem., 35, 2 (1992).
[103] U. Brodbeck. K. Schweikert, R. Gentinetta, and M. Rottenberg, Biochim. Biophys. Acta, 567. 357 (1979).
[104] C. Hansch and A. J. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley, New : York, 1979.
[105] S. M. Abel. D. J. Back, J. L. Maggs, and B. K. Park, J. Steroid Biochem. Molec. Biol., 43, 712 (1992).
[106] F. J. Frey and B. M. Frey, J. Lab. Clin. Med., 101, 593 (1983).
[107] A. A. Sandberg and W. R. Slannwhite, J. Clin. Endocrinol., 17, 1040 (1957).
[108] J. Kripalani, A. 1. Cohen, 1. Weliky, and C. Schreiber, J. Pharm. Sci., 64, 1351 (1975).
[109] D. Murphy' H. F. West, and A. M. Bethel, Acta Endocrinol. (Copenh.), 45, 498 (1964).
[110] J. Butler and C. H. Gray, J. Endocrinol., 46, 379 (1970).
[111] K. Minagawa, Y. Kasuya, S. Baba, G. Knapp, and J. P. Skelly, Steroids, 47, 175 (1986).
[112] A. C. Harrison, B. K: Park, P. M. O'Neill, R. C. Storr, and M. R. Kitteringham, Br. J. Clin. Pharmacol., 34, 148P (1992).
$\cdots$

ORGANIC LETTERS

# Synthesis and Potent Anti-HIV Activity of L-3'-Fluoro-2', $3^{\prime}$-Unsaturated Cytidine 

Giuseppe Gumina, ${ }^{\dagger}$ Raymond F. Schinazi, ${ }^{\ddagger}$ and. Chung K. Thu ${ }^{*}{ }^{1 /}$<br>Department of Pharmaceutical and Biomedical Scichtes, College of Pharmacy,<br>The University of Georgia, Athens, Georgia 30602, and Emir University School of Medicine/Vetcrams Affairs Medical Center, Deccuthr: Georgic 300.33<br>"chusi(iurx. ॥ga.ect"

Received September 24, 2001



L-2', $3^{\prime}$-Didehydro- $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-fluorocytidine ( $\mathrm{L}-3^{\prime}-\mathrm{FAAC}$ ), a novel potent anti-HIV agent ( $\mathrm{EC}_{50} 0.03 \mu \mathrm{M}$ in PBM cells), has been synthesized from t-xylose in 14 steps.

Nucleoside analogues have been the cornerstone of antiviral therapy over the past thirty years. In the effort 10 discover effective antiviral agents against AIDS and viral hepatitis, a large number of nucleoside analogues have been synthesized and evaluated. Although structure --activity relationship studes have not led to a pharmacophore model for the antiviral activities of nucleosides, tome sinuctural features have been particularly successful. For example, all six of the nucleoside reverse transcriptase inhibitors approved by the FDA for the treatment of AIDS' can be considered as $2^{\prime}, 3^{\prime}$-dideoxynucleosides. In addition, among ring substituents, electronwithdrawing groups such as azido ${ }^{2}$ and fluorine ${ }^{3}$ have often

[^6]produced potent antiviral agents. Another structural feature that is often beneficial for antiviral activity is a $2^{\prime}, 3^{\prime}$ unsaturated bond. We have extensively explored these substitutions in nucleoside analogues, particularly with the synthesis and biological evaluation of D - and $\mathrm{L}-2^{\prime}, 3^{\prime}$ -didehydro- $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}$-fluor nucleosides (Figure 1). ${ }^{3 \mathrm{~s}-\mathrm{r}}$


Figure 1. Structures of D- and L-2', $3^{\prime}$-didehydro- $2^{\prime}, 3^{\prime}$-dideoxy- $2^{\prime}$ fluor nucleosides.

Among them, the cytosine and 5 -fluorocytosine derivatives displayed potent anti-HIV and anti-HBV activity. without significant cytotoxicity. For this reason, we decided to explore the chemistry and biology of $2^{\prime}, 3^{\prime}$-didehydro- $2^{\prime}, 3^{\prime}$ -dideoxy- $3^{\prime}$-flupronucleosides. In this series, the D-cytidine and D-thymidine analogues were previously synthesized and shown to have low to moderate anti-HIV-I activity without cytotoxicity. ${ }^{4}$ The D-adenine derivative also showed moderate anti-HIV activity with some toxicity. ${ }^{4 \mathrm{a}}$ In view of the fact

Scheme 1. Synthesis of $1 .-2^{\prime}, 3^{\prime}$-Didehydro- $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-fluorocytidine

${ }^{"}$ Reagents and conditions: (a) ref 5 ; (b) $\mathrm{NaH}, \mathrm{THF}$, from $0^{\circ} \mathrm{C}$ to room temperature, 1 h , then $\mathrm{BnBr}, \mathrm{TBAl}$, from $0^{\circ} \mathrm{C}$ to room temperature, overnight; (c) $1: 2(4.0 \mathrm{M} \mathrm{HCl} /$ dioxane $) / \mathrm{MeOH}$, room temp, 1.5 h ; (d) (i) $\mathrm{PhOC}(\mathrm{S}) \mathrm{Cl}, \mathrm{DMAP}, \mathrm{Tol}, 90^{\circ} \mathrm{C}, 3 \mathrm{~h}$, (ii) $\mathrm{Bu} \mathrm{H}_{3} \mathrm{SnH}$, AIBN, reflux, 1 h ; (e) $\mathrm{H}_{2}(55 \mathrm{psi}), 10 \% \mathrm{Pd} / \mathrm{C}, ~ \mathrm{EtOH}$, room temp, 72 h ; (f) $\mathrm{CrO}_{3}, \mathrm{Ac}_{2} \mathrm{O}, \mathrm{Py}, \mathrm{CH}_{2} \mathrm{Cl}_{2}$, room temp, 15 min ; (g) DAST, $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, reflux, 36 $h$; (h) concentrated $\mathrm{H}_{2} \mathrm{SO}_{4}, \mathrm{Ac}_{2} \mathrm{O}, \mathrm{AcOH}, 0^{\circ} \mathrm{C}, 5 \mathrm{~min}$; (i) persilylated $N^{4}$-benzoylcytosine, TMSOTf, MeCN, from $0^{\circ} \mathrm{C}$ to room temperature, 72 h ; (j) saturated $\mathrm{NH}_{3} / \mathrm{MeOH}$, room temp, 4 h ; (k) MeONa, DMF, room temp, overnight.
that among the $2^{\prime}$-fluors derivatives $L$-isomers have potent antiviral activity with no toxicity or less toxicity than their D-counterparts, it was of interest to synthesize $1 .-2^{\prime}, 3^{\prime}$. didehydro- $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-fluorocytidine ( $\mathrm{L}-3^{\prime}-\mathrm{Fil4C}$ ) 1 (Scheme 1). Our synthetic method can also provide in entry. to the $\mathrm{L}-2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}, 3^{\prime}$-difluoro nucleoside 11 .

The starting material of our synthetic approach (Scheme 1) was $L$-xylose, which was converted to the protected L-ribose analogue $\mathbf{2}$ in four steps in $73 \%$ overall -yield by a well-known procedure in our laboratory. ${ }^{5}$ Benzylation of 2 was easily accomplished by treatment with sodium hydride, followed by benzyl bromide and catalytic tetrabutylammonium iodide. Methanolysis of the resulting benzyl ether gave the intermediate 3 as the sole isomer. 'H NMR showed the signal related to the H-1 as a singlet, which indicates the $\beta$-stereochemistry. ${ }^{6}$ Comparison of the proton spectrum with that of the known enantiomer ${ }^{7}$ confirmed the assignment. Conversion of 1 to the phenoxythiocarbonyl derivative followed by the radical deoxygenation of the latter gave protected $t$ - 2 -deoxyribose 4 . Compound 4 wis rather uncleactive toward catalytic hydrogenation, and its palladiumcatalyzed debensylation required treatment with hydrogen

[^7]at 55 psi for 3 days. Although the yield was modest ( $60 \%$ ), most of the unreacted starting material could be recovered and recycled. Oxidation of the debenzylated product 5 by chromic anhydride/pyridine/acetic anhydride gave ketone 6 in $88 \%$ yield. Treatment with (diethylamino)sulfur trifluoride (DAST) afforded difluorinated intermediate $7^{8}$ in $66 \%$ yield. Compound 7 was converted to the acetate 8 by the modificatimon of a known literature method. ${ }^{9}$. Condensation of the acetate 8 with persilylated $N^{4}$-benzoylcytosine was effected under Vorbrüggen conditions using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst. The epimeric products 9 and 10 were chromatographically separable, and the $\beta$-isomer was more abundant. In fact, ${ }^{1} \mathrm{H}$ NMR of the crude reaction-mixture showed an epimeric ratio of 5:4. Deprotection of each isomer was accomplished by ammonolysis to give difluorinated nucleosides $11^{10}$ and 12. Elimination by treatment with sodium methoxide in DMF

[^8]afforded the target unsaturated nucleosides $1^{11}$ and 13 in 53 and $51 \%$ yields, respectively.
Intermediate 7 could have been obtained from 2 through a more straightforward route (Scheme 2) involving oxidation

Direct reaction of intermediate 7 with $N^{4}$-benzoylcytosine in the standard Vorbrüggen conditions did not give the expected protected nucleosides. Instead, the inseparable epimeric mixture $16^{14}$ (Scheme 3) was iṣolated in $60 \%$ yield.

Scheme 3. Ring-Opening of 7 in Vorbrüggen Conditions


The stereochemistry of condensation products 9 and 10 has been established by 2D NMR NOESY experiments. Thus, the NOESY spectrum of epimer 9 showed clear correlations between protons $\mathrm{H}_{1^{\prime}}$ and $\mathrm{H}_{4}$. Correlations between $\mathrm{H}_{4^{\prime}}$ and $\mathrm{H}_{2^{\prime} \alpha}$ and between the latter and $\mathrm{H}_{1}$, were also observed. In the case of 10 , the $\mathrm{H}_{4^{\prime}}$ proton strongly correlated with one of the $\mathrm{H}_{2^{\prime}}$ protons (which could thus be identified as $\alpha$ ), while the other $\mathrm{H}_{2^{\prime}}(\beta)$ correlated with $\mathrm{H}_{1^{\prime}}$.


Figure 2. NOE correlations and stereochemistry of 9 and 10.

In summary, $\mathrm{L}-2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}, 3^{\prime}$-difluoro- and $\mathrm{L}-2^{\prime}, 3^{\prime}$ -didehydro- $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-fluoro nucleosides have been synthesized from t-xylose in 13 and 14 steps, respectively. The target compounds were obtained by condensation of a difluorinated intermediate 8 with a nucleobase in a process of general applicability. The key difluorination step of ketone 6 proceeded with a $66 \%$ yield. Our approach seems to be more convenient and versatile than the reported synthesis of the D -thymidine analogue. ${ }^{\text {I }}$

[^9]

Preliminary biological evaluation of the synthesized compounds showed that L-3'-FUHC: 1 has potent ami-HIV activity ( $\mathrm{EC}_{54} 003 \mu \mathrm{M}$ in PBM cells) with lite or no significant toxicny $\left(\mathrm{IC}_{50}=86.9 \mu \mathrm{M}\right.$ in PBM cells and $\mathrm{IC}_{91}$ $>100 \mu \mathrm{M}$ in $\mathrm{CI}: \mathrm{M}$ cells). ${ }^{10}$ The difluorinated analogue 11 was inactive. These promising results prompt us to symblesize other pyrimidine and purine analogues in order to study the
(16) Whereas AZT showed $\mathrm{EC} \mathrm{c}_{0}$ of 0.0444 M , with $\mathrm{CC}_{40}>100$ in $\mathrm{PB} . \mathrm{M}$ cells and $I C_{50}=14.1$ in CEM cells (ref 3 d ).
full structure-activity relationships, which is in progress in our laboratory.

Acknowledgment. This research was supported by the U.S. Public Health Service Research Grant AI 32351 from the National Institute of Allergy and Infectious Diseases, NIII. We thank Dr. Michael Bartlett of the College of Pharmacy, The University of Georgia, for performing the high-resolution mass spectra.

OL.0168059

# Fluorinate nucleosides 

Krzysztof W. Pankiewicz*<br>Pharmasset Inc.; 1860 Montreal Road, Turk er, Atlanta,-G:A-30084,- LS. 4<br>Received 8 February 2000; accepted 7 March 2000


#### Abstract

The synthesis and biological activity of deoxyfluoro nucleosides are reviewed. © 2000 Elsevier Science Ltd. All rights reserved.


Keywords: Fluorinate nucleosides; Fluorinate sugars; Antiviral; Anticancer -
Contents1. Introduction . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . ... . . . . . 87
2. Nucleosides containing a fluorine atom at $\mathrm{C}-2$ ..... 88
3. Nucleosides doubly fluorinate at $\mathrm{C}-\mathbf{2}^{\prime}$ ..... 97
4. 3'-Deoxy-3'-Huoro nucleosides ..... 98
5. Nucleosides fluorinated at C-4' ..... 100
6. Nucleosides containing fluorine(s) at C.S' ..... 101
7. Miscellaneous studies ..... 102
Acknowledgements ..... 104
References ..... 104

## 1. Introduction

This review on fluorinate nuckosides is. part of a series of mini-reviews on fluorinate sugars launched as a project by Carbohydrate Research (for a previous review on fluorinate nucleosides, see: [1]). Consequently, this article focuses on nucleosides that contain a fluorinoted glycone moiety, and it does not cover a large group of nucleosides fluorinated at the nucleobase. Beilstein's CROSSFIRE search

[^10]revealed 362 structures containing a fluorine atom at the sugar moiety of nucleosides. These consist of 238 compounds fluorinate at C-2', 40 nucleosides doubly fluorinate at C$2^{\prime}, 29$ derivatives substituted at $\mathrm{C}-3^{\prime}, 13$ compounds. with fluorine atoms at both the $2^{\prime}$ - and 3'-position, two analogs containing fluorine at $\mathrm{C}-4^{\prime}$, and finally a group of 42 nucleosides substituted at C-5',

The objective of this chapter is not to present a list of known fluorinate nucleosides but rather to show the development of the field. Since some early-synthesized $2^{\prime}$-deoxy- $2^{\prime}$ fluor nucleosides showed promising theta-
peutic potential (mainly antiviral and antieancer), the synthesis of new generations of 2'-fluorinated nucleosides flourished in hope of new drug discovery. Thus, more than $77 \%$ of fluorinated nucleosides synthesized to date contain fluorine atom(s) at $\mathrm{C}-2^{\prime}$ of the sugar. This also shows how frantic the competition was to produce new $2^{\prime}$-fluoro substituted analogs with improved biological activity. Several analogs reached clinical trials; however, up to date only one (gemcitabine) has been approved as a drug. As the field developed, great knowledge of structure-activity relationships has been accumulated that allows today for the design and synthesis of new compounds inaccessible ever before and for generating new ideas reaching well beyond the old limits.

To the best of this author's knowledge, none of formerly published reviews [1] have covered the topic of fluorinated nucleosides extensively, although many aspects of the chemistry of fluorinated nucleosides have been reviewed. For example, Bergstrom and Swarling [2] published a special issue on 'Fluorine Substituted Analogues of Nucleic Acid Componeints', Herdewjin et al. [3] described 'Synthesis of Nucleosides Fluorinated in the Sugar Moiety', and Pankiewicz and Watanabe [4] discussed 'Synthesis of 2'- $\beta$-1/luoro-substiluted Nucleosides by Direct Approach'.

Introduction of fluorine atom(s) into components of nucleic acids in general and nucleosides in particular frequently leads to a dramatic change in their biological activity. For example, replacement of the $2^{\prime}-\beta$-hydrogen atom (arabino configuration) or the $3^{\prime}$-hydroxyl group of natural thymidine by fluorine afforded new nucleosides with potent antiviral properties, FMAU [5] and FLT [6]; respectively. Substitution of both hydrogens of $\mathrm{C}-2$ ' of deoxycitine with geminal fluorines' (e.g., replacement of the $-\mathrm{CH}_{2}-$ group by a $-\mathrm{CF}_{2}-$


Scheme 1.

group at the 2 '-position) resulted in the formation of gemcitabine [7], a nucleoside with potent anticancer activity.

A fluorine atom at a sugar carbon in nucleosides causes only a minor change of the shape of the modified structure. Fluorine is a good mimic of a proton (small size) or hydroxyl group (similar polarity) and is able to form hydrogen bonding (as an acceptor). However, fluorine seriously affects stereoelectronic properties of the molecule. These in turn restrict conformational equilibria [8] of the sugar-fluorinated nucleoside [9]' 'locking' the sugar ring into a preferred conformation, stabilize the glycosylic bond (if placed in its proximity) towards hydrolysis, as well as affect the susceptibility of cytosine and adenosine analogs for enzymatic deamination. The $-\mathrm{CF}_{2}$ - group has been suggested by Blackburn [10] as an isopolar and isosteric substituent for oxygen. Analogs of di- and triphosphates in which the $-\mathrm{CF}_{2}-$ group has replaced the pyrophosphate oxygen have been used as substrates in enzymatic reactions. Since then the $-\mathrm{CF}_{2}$ - group, as well as -CHF-, were used extensively to modify not only nucleotide but also nucleoside analogs.

## 2. Nucleosides containing a fluorine atom at C-2'

The first nucleoside with fluorine in the sugar moiety, $2^{\prime}$-deoxy-2'-fluorouridine (2, $X=H$ ), was synthesized in 1961 . by Codington

[^11]

Scheme 2.
et al. [11]. Since hydrogen or a hydroxyl group at $\mathrm{C}-2^{\prime}$ distinguishes nucleosides as components of deoxyribonucleic acids (DNA) or ribonucleic acids (RNA), it was interesting to investigate the biological properties of nucleosides containing fluorine that could mimic both H or OH to some extent. Compound 2 $(\mathrm{X}=\mathrm{H})$ was prepared by cleavage of the anhydro linkage of $2,2^{\prime}$-anhydrouridine (1) with anhydrous HF (Scheme 1). Later, Fox and co-workers [12] at the Sloan-Kettering Institute have synthesized 2'-fluoro- $\beta$-D-ribosylthymine and the 2'-fluoro analog of 5 -fluorouridine ( $2, X=F$ ).

Such a direct introduction of fluorine into the carbohydrate moiety of a nucleoside has obvious limitations restricting the substitution to the ribo configuration of pyrimidine nucleosides. In the 1960s 1-( $\beta$-D-arabinofuranosyl)adenine (ara-A) and -cytosine (aru-C), nucleosides containing an -OH group in the 2'-arabino configuration, were evaluated as potential anticancer drugs. It was found that the efficiency of both agents suffered due to enzymatic deamination to the corresponding inactive metabolites, ara-I and ara-U, respectively. It was therefore desirable to synthesize fluoro derivatives of these compounds, such as F-ara-A and F -ara-C, and compare their biological activity with the parent nucleosides. The direct displacement


of a good leaving group at $\mathrm{C}-2^{\prime}$ in ribo configuration with fluorine attacking from the $\beta$-face had not been considered to be successful due to the steric hindrance provided by the aglycone positioned above the sugar face. Also, the inductive effects from the aglycone and the lactol ring oxygen make the substitution at the $\mathrm{C}-2^{\prime}$ position difficult. In addition, in the case of pyrimidine nucleosides, neighboring group participation of the carbonyl group at $\mathrm{C}-2$ of the base resulted in formation of $2,2^{\prime}$-anhydro nucleosides, followed by introduction of fluorine in the ribo configuration (vide suppra). Indeed, it was demonstrated that treatment of the methyl 2,3 -anhydro-5-O-ben-zyl- $\beta$-d-riboside (3, Scheme 2) with $\mathrm{KHF}_{2}$ gave exclusively methyl 3-deoxy-3-fluoro- $\beta$-Dxylofuranoside (4) [13], whereas similar reaction of the corresponding $\alpha$-D-riboside (5) afforded a mixture of the desired 2-deoxy-2-fluoro- $\alpha$-D-arabinofuranoside (6, as the major product) and the xylo-substituted derivative 7 [14]. These compounds were separated on silica gel column, converted into their corresponding glycosyl bromides, and used for coupling with adenine and cytosine to give F-ara-A, F-ara-C, as well as the xylo-substituted derivatives [14,15]. It was also confirmed that a direct reaction of adenosine $2^{\prime}, 3^{\prime}$-anhydride derivative with a fluoride resulted in a nucleophilic attack at the 3 '-position, exclusively [16].

Since F-ara-C was reported [15] to show as potent inhibitory activity against L1210 leukemic cells as a clinically used anticancer: agent, ara-C, large amounts of F -ara-C were required for further biological studies. However, such fluorinated nucleosides were barely accessible by the above-mentioned method due to low yield of preparation of the 2 -fluoro sugar 6. Although, the introduction of a fluorine atom at $\mathrm{C}-2$ of the carbohydrate by nucleophilic displacement reaction is rather difficult, the similar reaction at C-3 is not. This guided Watanabe and co-workers [17] to synthesize! 3-deoxy-3-fluoro-D-glucose and then convert it into 2 -deoxy-2-fluoro-D-arabinose. The key step of the synthesis (Scheme 3 ) is oxidation of the 3-deoxy-3-fluoro-D-glucose derivative 10 with sodium metaperiodate, which afforded the 2-deoxy-2-fluoro-D-ara-
binose that cyclized simultaneously (anomeric aldehyde and C-4-hydroxyl group) forming exclusively the desired $2^{\prime}$-deoxy-2-fluoro furanose 11. The final glycosyl bromide 12 was then prepared and used extensively for the synthesis of numerous pyrimidine and purine nucleosides containing fluorine in the $\mathrm{C}-2^{\prime}$ arabino configuration. However, $2^{\prime}$-deoxy-2'-fluoro-ara-C showed little antitumor activity in mice.

The first antiviral nucleoside, $2^{\prime}$-deoxy-5-iodo-uridine (Iduviran), was synthesized by Prusoff [18]. The glycosylic bond of this compound is not stable in acidic conditions. Therefore, it was interesting to prepare analogs of Iduviran containing a fluorine atom at C-2', which stabilizes the glycosylic linkage. Consequently, a number of 5 -substituted uracil and cytosine nucleosides with fluorine in the arabino configuration were designed and prepared by Watanabe et al. [5]. Among them, FIAC, FEAU, and FMAU showed not only potent activity agaipst HSV, but also an excellent activity against hepatitis $B$ virus (HBV) and other viruses such as varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). In addition FMAU was highly active against murine leukemias resistant to ara-C. Such a broad and promising biological activity of these new $2^{\prime}$-deoxy-2'-fluoroarabino nucleosides stimulated the progress of the field in the coming years. Indeed, in number of syn-
thetic procedures have been developed in order to make new analogs with even better chemotlierapeutic potential.


IDUVIRAN


FIAC


FEAU

FIAC and FMAU were selected as candidates for-clinical trials. This-motivated-Tann and researchers [19] at Bristol-Myers to develop an even more efficient method for the synthesis of FMAU. They found that direct displacement of 2 -imidazoylsulfonate (13a) with $\mathrm{KHF}_{2}$ gave a $63 \%$ yield of the desired 2-deoxy-2-fluoro sugar 14 (Scheme 4). It is worthwhile to note that treatment of 13a with TBAF gave only elimination products. The displacement of mesyl or triflate group at the 2-position (13b or 13c) with $\mathrm{KHF}_{2}$ or TBAF as well as reaction of 13d with diethylaminosulfur trifluoride (DAST) did not afford the desired product either. Bromination of 14 produced quantitatively the glycosyl bromide 15, which was coupled with silylated thymine to give FMAU in $95 \%$ (as a mixture of $\alpha, \beta$ anomers in the ratio of 1:7).

The easy access to the 2-deoxy-2-fluoroarabino sugar resulted in an avalanche of studies


Scheme 3.


Scheme 4.

IPO DELHI 23-06-2015•16:01
on the synthesis of $2^{\prime}$-deoxy- $2^{\prime}$-fluormated nueleosides. For example, Martin and researchers [20] at Roche prepared a number of $2^{\prime}$-deoxy- $2^{\prime}$-fluoro-containing pyrimidine analogs of anti-HIV nucleosides. Among them analogs of ddC such as 16 , its $2^{\prime}, 3^{\prime}$-difluoro derivative $17,2^{\prime}-\mathrm{F}-\mathrm{d} 4 \mathrm{C} 18$, and $2^{\prime}-\mathrm{F}-\mathrm{d} 4 \mathrm{~T} 19$ showed significant activity against HIV.


16


17


18


19


20

The analog of ddC containing fluorine in the $2^{\prime}$-ribo configuration was not active. Sterzycki et al. [21] (Bristol-Myers) synthesized an analog of AZT 20 as well as some of the above compounds and found they exhibit. a potent antiviral activity, that was, however, not superior to that of AZT. Marquez et al.
[9] examined the relationship between preferred ring-puckering of fluorine-substituted dideoxynucleosides in solution and their antiHIV activity. He concluded that, for various aglycone moieties, a fluorine atom at positions 3'-down' or $2^{\prime}$ '-up' correlates with anti-HIV activity, whereas, nucleosides with fluorine atoms in the same positions but in inverted configuration are inactive. Interestingly, he prepared difluorodideoxy xylo-uridine (24) and xylo-cytidine (25) (Scheme 5) and found them inactive. With exception of ara-C analog 17, earlier-synthesized difluoro derivatives of (rra-U [20], ara-T [22] (26, 27), as well as compounds containing two fluorine atoms in the ribo configuration (28-30) [22,23] did not show any activity.


$17 \mathrm{~B}=\mathrm{C}$
$26 \mathrm{~B}=\mathrm{U}$
$27 \mathrm{~B}=\mathrm{T}$
$28 \mathrm{~B}=\mathrm{C}$
$29 \mathrm{~B}=\mathrm{U}$
$30 \mathrm{~B}=\mathrm{T}$
The C-nucleoside analog of FMAU (CFMAU, Scheme 6) is an isosteric and isoelectronic isomer of FMAU, and therefore it was believed it might exhibit an antiviral activity similar to that of FMAU. Thus, the Watanabe group at Sloan-Kettering Institute synthesized C-FMAU [24] as well as its $3^{\prime}$-azido-3-


Schume 5 .


Scheme 6.


Scheme 7.
doxy analog (33) [25], an analog of C-AZT. The key intermediate was 4,5'-anhydro-1-methyl-pseudouridine (31); in which oxygen at $\mathrm{C}-4$ in the uracil ring is linked to $\mathrm{C}-5^{\prime}$ and thereby precludes its participation in nuclcophilic reaction that occurs on $\mathrm{C}-2^{\prime}$.

Fluorination went relatively smoothly when 31 was treated with tris(dimethylamino)sulfur (trimethylsilyl)-difluoride (TASF) to give 32 in $40 \%$ yield. Hydrolysis of the anhydro linkage afforded C-FMAU, which was further conversed into 33. These compounds did not exhibit any significant antiviral activity. It is interesting to note that treatment of natural nucleoside $3^{\prime}-O$-acetyl - 2, $5^{\prime}$ - anhydro - $2^{\prime}$ - $O$ -triflyl-uridine (34, Scheme 7) with a mucleowhile such as LiCl or $\mathrm{LiBr}(\mathrm{LiX})$ resulted in: the formation of the $5^{\prime}$-substituted- $2,2^{\prime}$-antidrouridine (35) due to preferential attack at $\mathrm{C}-5^{\prime}$ that liberated the 2-oxide, which then displaced the $\mathrm{C}-2^{\prime}$-triflyl function forming the $2,2^{\prime}$-anhydro linkage [2( $]$.

At the same time, the synthesis of carbocylic nucleosides became of considerable interest due to discovery of such nucleosides as aristeromycin and neplanocin in nature. These
natural products and analogs such as carbodine and cyclaridine have been synthesized and have been shown to have antiviral properties.


Carbodine


Aristeromycin


Cyclaridine $(X=O H)$
$36(X=F)$

carb-FAC

carb-FMAU

Since the presence of a 2'-ara-fluoro substituent has been found to confer potent antiviral activity, the Glaxo researchers [27] prepared a number of deoxy-fluoro carbocylic nucleoside analogs, among them an analog of cyclaridine 36, a carbocylic analog of $2^{\prime}$-de-oxy-2'-fluoro-arabino-C (carb-FAC), and carbocyclic FMAU. All carbocyclic pyrimidine nucleosides containing fluorine at the C-2'arabino configuration were synthesized by construction of an appropriate pyrimidine base from the corresponding amino fluorocyclopentanediol 41 (Scheme 8) [28]. In the case of the carbocyclic analog of ribose, the fluorine atom can be introduced into the $2^{\prime}$ -


Scheme 8.
ara position by treatment of 3,5 -tetraiso-propyldisiloxanyl-protected triol 38 a with DAST. The amino group of 38 must be protected with an electron-withdrawing group, such as a 2,4 -dinitrophenyl moiety (DNP), to reduce the electron density on the nitrogen: Otherwise, as in the case of the trityl protected compound 38b, the corresponding aziridine derivative 39 has been obtained exclusively. Interestingly, this work demonstrated the usefulness of the silyl protection in the reaction with DAST. In a similar manner the carbocylic analog of $2^{\prime}, 2^{\prime}$-diffuoro thymidine hids been synthesized from 38a. This conipound was oxidized to give the 2 -keto derivative, which upon treatment with DAST afforded amino 2,2-difluorocyclopentanediol derivative 42, in low yield. Deprotection of 42, followed by treatment with $\mathrm{EIOCH}=\mathrm{C}(\mathrm{Me}) \mathrm{CONCO}$, afforded the desired $2^{\prime}, 2^{\prime}$-difluoro-carb-T [29].
Since there is no aglycone involvement in neigirboring group participation at $\mathrm{C}-2^{2}$ in purine nucleosides, the Biggadike and Borthwick group at Glaxo [28] treated. $3^{\prime \prime}, S^{\prime}$ 'teltraisopropyldisiloxanylaristeromysin with D $\wedge$ ST and obtained the corresponding fluoro derivative, albeit in only $5 \%$ yickl. However. the similar reaction of $3^{\prime}, 5^{\prime}, N^{\prime \prime}$-tribenzoylaristeromycin with DAST afforded, after debenzoylation, the desired $2^{\prime}$-fuoro-arabino analog 36 in $50 \%$ yield. Among pyrimidine fluoro carbocyclic nucleoside analogs; the most active against HSV-1 was carb-FMAU, although it was 88 -fold less active than FMAU. No activity was found against HSV-2. Activity of other carbocylic compounds was inferior to that of the parent nucleosides. In contrast, the $2^{\prime}$-fluoro analog of cyclaridine was shown to be 10 times.more active than cyclaridine itself against $\mathrm{HSV}-1$ and $\mathrm{HSV}-2$ and more active than acyclovir against $\mathrm{HSV}-2$ in the mouse systemic test.

A similar rationale was behind the synthesis of fluorinated analogs of acyclic nucleosides, such as $2^{\prime}$-deoxy-2'-fluoro-1',2'-seconucleosides. Uridine ( 44 ), thymine (45), 5 -iodouridine (46), ribavirin (47), and guanosine (48) analogs were oblained by coupling of $(R, R)-2-$ (chloromethoxy)-1,3-bis(benzyloxy)-4-fluorobutane (43) with an appropriate base, followed by debenzylation. The desired isomer of the sugar mimic 43 was prepared from D-

isoascorbic acid in five steps. These compounds were evaluated against RNA viruses and found to be inactive [30].

A najority of regular $2^{\prime}$ - $\beta$-fluoro nucleosides have been synthesized by condensation of the nucleobase and sugar. In contrast to simple and efficient glycosylation of pyrimidines, however, the condensation of purines with 2-deoxy-2-fluoro-D-arabinofuranosyl halide is rather difficult. In fact, some purine bases do not react with the glycosyl halide. For example, F-ara-A was originally synthesized [14] by fusion of the fluoro sugar derivative with 2,6-dichloropurine, followed by conversion into the adenine derivative, Later, 6 -chloropurine was condensed with the fluoro ' sugar to give a mixture of four isomers (7-, or 9 -substituted, $\alpha, \beta$ anomers) from which the desired isomer was separated in low yield and converted into F-ara-A $[31,32]$.

Direct nucleophilic displacement of a good leaving group in the $2^{\prime}$-ribo configuration with fluorine has been considered to be difficult, if not impossible, not only due to poor activity of $\mathrm{C}-2^{\prime}$, but also due to the weak nucleophilicity of fluorine, which in addition is known as a rather strong base. Indeed, treatment of $2^{\prime}-O$-triflyl- $3^{\prime}, 5^{\prime}$-di- $O$-benzyl- $N^{\prime}$-benzylinosine (49) with TASF afforded elimination products 50 and 51 as expected (Scheme 9) [33]. Facile elimination of $\mathrm{CF}_{3} \mathrm{SO}_{3} \mathrm{H}$ from 49 with the formation of olefins 50 and 51 is due to the fact that the sugar of 49 is in the C-3'-endo conformation. The presence of the electronegative substituent (triflyl group) forced 49 to


Scheme 9
assume the $\mathrm{C}-3^{\prime}$-end conformation [34].


C 3'- ${ }^{\prime}$ ado


C 2'-endo

In such conformation the triflyl group and the hydrogen at $\mathrm{C}-3^{\prime}$ are in a trans di-axial configuration, which favors elimination. Pankiewicz et al. $[35,36]$ assumed that if the furanose ring conformation could be shifted toward C-2'-endo by using bulky protecting groups at $\mathrm{C}-5^{\prime}$ and $\mathrm{C}-3^{\prime}$ of the purine nucleoside $2^{\prime}$-triflate, then nucleophilic substitution might be possible. The C-2'-endo conformation of the furanose ring is unfavorable for trans elimination. Indeed, when $N^{\prime}$ -benzyl-3', $5^{\prime}$-di- $O$-trityl-inosine $2^{\prime}$-tritlate was treated with TASF, the desired 2'fluoro-arabono nucleoside was obtained in $30 \%$ yield [33]. The reaction is even more efficient when the $2^{\prime}-$ hydroxyl group of the $N^{1}-3^{\prime}, 5^{\prime}$-di- $O$-trityl-benzylinosine is converted into the 2'fluoro function by DAST [35]. F-ara-A and F-ara-G were also prepared by reaction of the corresponging $3^{\prime}, 5^{\prime}$-ditrityl derivatives with DAST [36]. Recently it was reported [37] that a combination of a $5^{\prime}-O$-trityl group with $3^{\prime}-O$-benzoyl protection also worked efficiently in terms
of the introduction of fluorine at the 'up'-side of C-2'. Since the benzoyl group could be introduced regioselectively (via stannylation) at the 3 '-position of nucleosides as, well as the trityl group at $\mathrm{C}-5^{\prime}$, there was no need for separation of the $3^{\prime}, 5^{\prime}$ - and $2^{\prime}, 5^{\prime}$-ditrityl derivalives.
$2^{\prime}, 3^{\prime}$-Dideoxy purine nucleosides have potent anti-HIV activity, and the inosine analog (dd) is in clinical use. The instability of these compounds in acidic conditions complicates oral administration. The $2^{\prime}$-fluorinate analogs were found, as expected, to be indefinitely stable to acidic conditions that completely decomposed ddI and IdA in minutes. While the erythro isomers were inactive, the threo isomers F-ara-ddI and F-ara-ddA were just as potent as parent drugs. A new convenient route to F -ara -dd has been recently developed by Marquez and co-workers [38] at NIH (Scheme 10). It started with the facile introducton of fluorine at $\mathrm{C}-2^{\prime}$ from the $\alpha$-side of protected ara-A, followed by dimethoxytritylation and mesylation to give 54. Elimination of methanesulfonic acid from 54 afforded a stable vinyl intermediate 55.

Inversion of stereochemistry at C-2' was accomplished via stereoselective reduction of the double bond to give the desired F -ara-ddA.

The same group reported [39] an interesting chemistry of the DAST fluorination of $3^{\prime}-\mathrm{de}-$ oxy-4'-thiopyrimidine nucleosides. Since $2^{\prime}, 3^{\prime}$ -dideoxy-4'-thiocytidine showed a moderated anti-HIV activity, they attempted to improve its activity by incorporation of fluorine into the sugar ring. Treatment of hydroxylated perecursors 56 or 57 with DAST did not proceed with the usual inversion of configuration to give derivatives containing fluorine on the $\alpha$ side of the sugar ring. Instead retention of configuration was observed, e.g., fluor substi-

tution occurred from the $\beta$-face to give 58 or 59 (Scheme 11). The authors explain that participation of the $4^{\prime}$-thiofuranose sulfur was responsible for a double-inversion mechanism that resulted in retention of configuration.

Interestingly, attempted fluorination of $3^{\prime}$ -deoxy-4'-thiouridine protected with a MEM group at $\mathrm{N}-3$ (60) gave the $3^{\prime}$-deoxy- $\mathbf{2}^{\prime}$-fluor derivative 62 with retention of configuration (Scheme 12). Formation of the very reactive N -3-MEM- $\mathrm{O}^{2}$, 2'anhydronucleoside interme- $^{2}$-an date 61 that reacted with fluorine ion explains retention of the configuration [40].

Although, the synthesis and chemotherapeutic activity of 1-(2-deoxy-2-fluoro- $\beta$-D-ara-binofuranosyl)-pyrimidines such as FMAU, FIAU, FIAC stimulated the synthesis of a variety of nucleoside analogs containing a fluorine atom at the C-2'-arabino configuraton, the clinical application of lead compounds ended up with disappointment and failure. Phase I trials of FMAU as. an antileukemic agent were terminated by severe neurologic toxicity [41]. Fialuridine (FIAU) exhibited delayed toxicities due to the interference of mitochondrial function resulting in lactic acidosis and hepatic failure [42].

Recently, however, a number of nucleosides with the unnatural L -configuration have been reported as potent agents against HIV, HBV, and certain cancers. These include 3 TC, FTC, L-FddC, and L-FMAU.'


aTC


L-FddC


Interestingly, these L-nucleosides exhibit potent biological activity, while showing a much lower toxicity than their D-counterparts. Chi and co-workers [43] at the University of Georgia prepared the 2-fluoro L-arabinosyl bromide from L-ribose according to the method of Can [19] that was used for the synthesis of d-FMAU. The starting L-ribose derivative was obtained first from L-xylose and then more efficiently from L -arabinose [44]. The L-glycosyl bromide was coupled with a number of nucleobases to give, among others, the L-nucleosides depicted below.



- Scheme 11.


Scheme 12.


L-FMAU was found to be the most active as an anti-HBV agent among the synthesized compounds. It did not show any toxicity profiles that caused withdrawal of the D-counterpart from clinical studies. L-FMAU is currently considered as a clinical candidate for treatment of chronic HBV infection.

In addition to pyrimidine nucleosides, the group of Thu [45] has prepared a number of purine F-ara-L-nucleosides and found that $\mathrm{L}-$ F-ara-A and L-F-ara-I exhibit good anti-HBV activity without significant toxicity. Also, the synthesis of $2^{\prime}$-fluoro- $2^{\prime}, 3^{\prime}$-unsaturated 1 -nucleosides has been explored [46]. This was accomplished by condensation of the key $2^{\prime}$ vinylic fluoride acetate 63 with the appropriate heterocycles. The most potent compound in this series was an L-analog of 5-fluorocytidine derivative 67.


During all these years application of $2^{\prime}$ fluorinate nucleosides has not been limited to their use as potential chemotherapeutics. Repeatedly, these compounds have been used for incorporation into oligonucleotides, and such modifications have been examined in terms of specific interactions with DNA, RNA and ;ioproved affinity to nucleic acid components. For example, it was demonstrated that modification of the Dickerson dodecamer with FMAU or FAC dramatically increases catlytic efficiency of Eco 1 endonuclease relative to the unmodified sequence [47] and that the presence of FMAU has a large stabilizing effect on the duplex $[48,49]$.

Cook and co-workers [50] at Isis Dharmaceuticals incorporated 2'-deoxy-2'-fluoroadenosine, -guanosine, -uridine, and -cytidine making 'uniformly' modified phosphodiester or phosphorothioate oligonucleotides. These compounds hybridized with RNA forming the duplex, which fully adopts the A-form conformation. It was also found that the modified phosphorothioate oligos were highly nuclease resistant and retained exceptional binding affinity to the RNA targets. An RNA hybrid duplex with uniformly $2^{\prime}$-fluoro-modified oligos did not support RNase H activity.

On the other hand it was found by Damha et al. [51] that $2^{\prime}$-deoxy- $2^{\prime}$-fluoro- $\beta$-D-arabino nucleic acids ( $2^{\prime} \mathrm{F}$-ANA) showed an excellent binding affinity to RNA, and $2^{\prime}$ F-ANA/RNA duplexes are recognized and degraded by RNase H as well as DNA/RNA hybrids. Among over 60 types of modified oligos, none of them except phosphorothioates, boranophosphates, and now $2^{\prime}$ F-ANAs could trigger the activity of RNase H .

Recently, interesting studies that make use of $2^{\prime}$-deoxy- $2^{\prime}$-fluorouridine and its $2^{\prime}$-fluorsarabino isomer have been published by Stivers et al. $[52 ; 53]$ These authors took advantage of great stability of the glycosylic bond in $2^{\prime}$ fluorinate nucleosides to solve the mechanism of action of Escherichia coli uracil DNA glycosylase, which flips uracil from the DNA helix and then. cleaves it in order to repair DNA. Since the $2^{\prime}$-fluorinate uridines incorprorated into DNA could be flipped but not cleaved, the kinetic mechanism of damage site recognition has been conveniently observed.

## 3. Nucleosides doubly fluorinated at C-2.

Gemcitabine (2'-deoxy-2', 2'-difluorocytidine) has been recently approved by the FDA for treatment of pancreatic cancer, and its hydrochloride (Gemzar) is now marketed in many countries. Gemcitabine showed a complicated mechanism of action inhibiting the synthesis of DNA and RNA as well as inhibiting ribonucleotide reductase [54].. 2'-Deoxy$2^{\prime}, 2^{\prime}$-difluoroguanosine was reported to exhibit a similar activity [55].

Gemcitabine was synthesized by Hertel and co-workers at Lilly Research Laboratories [7] by condensation of a silylated cytosine with 2-deoxy-2,2-difluoro-D-ribofuranose, prepared in a stereocontrolled manner (Scheme -13). Thus, ( $R$ )-2,3- $O$-isopropylideneglyceraldehyde (72) was coupled with bromodifluoroacetate under Reformatskii conditions to give a $3: 1$ mixture of diastereoisomers 73 and 74. These compounds were separated on a silica gel column, and the major isomer 74 was hydrolyzed with Dowex-50W $\left(\mathrm{H}^{+}\right)$to give cyclized lactone 75.. The lactone was protected with tert-butyldimethylsilyl (TBDMS) groups to give 76 and then reduced to 78 . Mesylation
of 78 ( $\mathrm{R}=$ TBDMS) afforded 79, a starting material for coupling with silylated cytosine and other nucleobases. Condensation of 79 with cytosine in the presence of trimethylsilyl triflate gave a $40 \%$ yield of the $\alpha$ anomer and only $10 \%$ of the desired $\beta$ anomer 80 . Later this procedure was improved [56] by selecting the benzoyl instead of the TBDMS group as the protection for hydroxyl groups. With this modification selective crystallization of the lactone 77 from a distereomeric mixture containing the lactone obtained from 73 was possible. In addition, condensation of $79(\mathrm{R}=\mathrm{Bz})$ with the base afforded a $1: 1$ mixture of $\alpha, \beta$ anomers (instead of $4: 1$ as in case of TBDMS protection) from which the desired gemcitabine 80 could be separated by crystallization.

Recently, a number of pyrimidine and purine L -nucleosides containing. $-\mathrm{CF}_{2}-$ at the $2^{\prime}$-position have been synthesized and studied [57,58]. These nucleosides were designed to take advantage of good activity and low toxicity of other L-nucleosides with potent antiviral properties such as ( - )-FTC or L-FMAU. Unfortunately none of these new L-difluoro nucleosides showed expected biological activities.


Scheme 13.


81


FLT


82

Scheme 14.


## 4. 3'-Deoxy-3'-Huoro nucleosides

FLT was originally synthesized in 1971 by Langen and co-workers [6] by opening the 2,3'-anhydro linkage of 2, $3^{\prime}$-anhydrothymidine (81, Scheme 14) with $\mathrm{HF} / \mathrm{AlF}_{3}$. Later, Herdewijn's group [59] synthesized FLT by treatment of 1-(2-deoxy-5-O-trityl- $\beta$-D-threopentofuranosyl)thymine (82) with DAST. In 1988 it was discovered "that FLT was very active against HIV $[60,61]$, and the compound was proved [62] to be even more potent as an inhibitor of HIV replication than AZT. The corresponding deoxyuridine, deoxycytidine, deoxyadenosine, and deoxyguanosine (FLG) derivatives have been prepared and found to ,be less active than FLT $[59,62,63]$. FLG has been shown to inhibit human and duck heptitis $B$ virus [64]. All these compounds are potential inhibitors of viral reverse transcriptare (RT) and chain terminators. Unfortunately they were found to be highly cytotoxic. A similar synthesis of $2^{\prime}, 3^{\prime}$-dideoxy- $3^{\prime}$-fluors5 -fluorouridine by opening of the $2,3^{\prime}$-anhydro linkage of the $2^{\prime}$-deoxy-5-flusrouridine derivalive has been reported [65]. Since $2^{\prime}$-deoxy-5fluorouridine, a potent cytotoxic agent, is cleaved in the cell extensively by thymidine phosphorylase, to give 5 -fluorouracil, itself a potent cytotoxic agent but with a different mode of action than that of 5 -fluorouridine, the idea was to synthesize a $2^{\prime}$-deoxy-5-
fluorouridine derivative resistant to the action of thymidine phosphorylase. Indeed, replacemont of the $3^{\prime}-\mathrm{OH}$ group of $2^{\prime}$-deoxy-5lluorouridine with a fluorine atom afforded a desired compound with a much more stable glycosylic linkage; however, its activity was. found to be inferior to that of the parent drug.

A simple synthesis of $3^{\prime}$-deoxy- $3^{\prime}, 3^{\prime}$-difluorothymidine (85) has been reported by Bergstrom et al. [66] (Scheme 15). Although nucleoside 85 resembles conformationally and sterically other thymidine analogs (which are active against HIV), compound 85 was found to be inactive.

The success of AZT inspired Prisbe and co-workers at Synthex to synthesize $4^{\prime}$-azidothymidine [67]. Although this compound retain $3^{\prime}$-hydroxyl group, it acts as a chain terminator. and RT inhibitor. Since FLT is one of the most potent. inhibitors of HIV known, it was interesting to learn if the presence of a fluorine at C-3' of $4^{\prime}$-azido-T would lead to better activity. $5^{\prime}$-Iodination of FLT, followed by methoxide-induced elimination, afforded $4^{\prime}, 5^{\prime}$-unsaturated derivative $\mathbf{8 6}$ (Scheme 16), which upon $\mathrm{IN}_{3}$ addition gave 87. Oxidative displacement the of $5^{\prime}$-iodide failed. However, protection of N-3 with a benzoyl group, followed by treatment of 88 with tetramethylammonium acetate in $N^{1}, N^{3}$ dimethyltetrahydropyrimidone, gave the desired 5'-O.-acetyl nucleoside 89. Deprotec-
timon with ammonium hydroxide furnished the desired $4^{\prime}$-azido-3'-deoxy-3'-fluorothymidine (90). Contrary to expectation, 90 was much less active than AZT, $4^{\prime}$-azido-T, or FLT [68].

The activity of FLT and AZT inspired I In et al. [69] to synthesize $3^{\prime}$-deoxy-3'-C-branched-chain substituted nucleosides. Condensation of the sugar precursors 91 and 93 (Scheme 17) with a silylated thymine afforded 92 and 94, the corresponding analogs of FLT and AZT, respectively. None of these compounds demonstrated significant antiviral activity.

Synthesis of a number of nucleosides contraining $3^{\prime}$-deoxy- $3^{\prime}$-fluors- and $2^{\prime}$-azide- $2^{\prime}, 3^{\prime}$ -dideoxy-3'-fluoro-D-ribofuranoside has been reported by Mikhailopulo et al. [70]. These compounds were prepared by coupling an appropriate sugar 95 or 99 with heterocyclic bases (to give among others 96 and 98) and were evaluated as antiviral or anticancer agents. 3'-Deoxy-3'-fluoroadenosine (96) was found to be the most active, both as a cytotoxic compound and as an antiviral. Morizawa et al. [71] reported the first synthesis of 96 by a glycosylation method, and later Van Aershot et al. [72,73] prepared 96 by DAST treatment of the $2^{\prime}, 5^{\prime}$-di-O-tritylated adenine nucleoside containing the $3^{\prime}$-hydroxyl group in the xylo configuration (97), followed by detritylation.


95


96



98

Since it was discovered that $2^{\prime}, 5^{\prime}$-olioadenylates ( $2-5 \mathrm{~A}$ ) play a key role in the antivival action of interferon [74], it was interesting to study the role of the $3^{\prime}$-hydroxyl group of 25 A in binding to $2-5 \mathrm{~A}$-dependent endoribonuplease (RNase L). In this connection, 2-5A oligomers containing 96 and its xylo isomer were prepared, and it was found that their susceptibility to degradation is dependent upon the conformation of a modified 2-5A [75].

Since F and $\mathrm{CF}_{3}$ showed comparatively close inductive effects, it was interesting to perepare nucleosides containing the $3-C$-ri-fluoromethyl- $\beta$-D-ribofuranose moiety and evaluate their biological activity. Thus, 1,2-O-isopropylidéne- $\alpha$-D-xylofuranose (100, Scheme


Scheme 17.


IPO DELHI 23-06-2015:15:01


Scheme 19.


Scheme 20.
18) was selectively benzoylited to give compound 101, which was thell oxidized to the 3-keto derivative 102. Reaction of 102 with $\mathrm{CF}_{3} \mathrm{SiMe}_{3}$.in the presence of tetrabutylammonium fluoride led to desired trifluoromethyl derivative 103 as the only isomer. This compound, upon hydrolysis with $\mathrm{CF}_{3} \mathrm{COOH}$, followed by acetylation, afforded starting material 104 for Vorbrüggen condensation with the appropriate silylated base. 9-(3-C-Trifluoromethyl- $\beta$-D-ribofuranosyl)-thymine, -uracil, and -adenine were prepared, and interestingly adenine nucleoside 105 was found to be active against HSV-1 [76].

Carbocyclic nucleosides containing fluorine at $\mathrm{C}-3^{\prime}$ have attracted some attention, For example, neplanocin A has been efficiently converted in three steps into its $3^{\prime}$-deoxy- $3^{\prime}$ -fluoro-xylo-analog. Again the tetraisopropyldisiloxanyl protecting group proved to be useful for treatment with DAST (see Scheme 8). Slow addition of $3^{\prime}, 5^{\prime}$-tetraisopropyldisiloxanylneplanocin A (106, Scheme 19) to a mixture of DAST-pyridine in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ at $0^{\circ} \mathrm{C}$ gave the $3^{\prime}$-fluoro derivative 108 in $65 \%$ yield, with only a small amount ( $5 \%$ ) of the diol 107. Deprotection of 108 afforded the $3^{\prime}$-deoxy-3'-fluoro-xylo-neplanocin A (109) in good yield [77].

## 5. Nucleosides fluorinated at C-4'

Nucleocidin (113), an antitrypanosomal antibiotic, was first isolated [78] in 1957. The structure of nucleocidin (was established by Morton et al. [79], and the compound was synthesized by Moffat and co-workers [80] (Scheme 20). 4'-Fluoro-2', $3^{\prime}$ - $O$-isopropylideneadenosine (110) was converted into $5^{\prime}-O-$ tributylstannylene derivative 111, which was treated directly with sulfamoyl chloride to give 112. Deprotection of 112 afforded nucleocidin in good yield.

The reaction of several $4^{\prime}, 5^{\prime}$-dehydronucleosides with iodine and iodine fluoride were studied by Verheyden and Moffat [81]. They found, for example, that treatment of uridine derivative 114 with lodine fluoride afforded $5^{\prime}$-deoxy - $4^{\prime}$-fluoro- $5^{\prime}$-iodo- $2^{\prime}, 3^{\prime}$ - $O$-isopropyli-



cheme 21 .


Scheine 22.
deneuridine (115). The iodo function of $\cdot 115$ was then converted into various $5^{\prime}$-substituted 4'-fluorouridines, including $4^{\prime}$-fluorouridine (Scheme 21, 116).

Recently, Chu and co-workers published [82] an interesting work on an asymmetric fluorination of the tertiary carbon of nucleosides. They used the [3,3]-sigmatropic Claisen rearrangement reaction to introduce the required tert-fluorinated carbon. Thus, 2,3-O-isopropylidene-D-glyceraldehyde
(Scheme 22, 117) reacted with triethylphosphonoacetate to give ( E )- $\alpha, \beta$-unsaturated fluoro ethyl ester 118. This compound was deisopropylidenated and selectively.' (via dibutyl tin oxide) benzylated to give 119, which was subjected to the Claisen rearrangement conditions to give tertiary fluoro ethyl ester 120. Ozonization afforded aldehyde 121, which was reduced with DIBAL-H to give lactol 122. Further conversion of 122 into a key derivative 123 and condensation with silylated $N^{4}$-benzoylcytosine or 6 -chloropurine under Vorbrüggen conditions afforded an anomeric mixture of the corresponding nucleosides. The desired $\beta$ anomers were separated and. converted into $3^{\prime}$-fluoro-apionucleosides of cytosine $\mathbf{1 2 4}$ and adenine 125 , respectively. In this iso-nucleoside numbering system, the fluorine atom is in the $3^{\prime}$-position; however, it can be considered as an equivalent to the 4 '-position of regular nucleosides.

In a similar manner a number of $3^{\prime}$-fluoroapionucleosides in the L series have been prepared [83], and their biological activity is now under evaluation.

## 6. Nucleosides containing fluorine(s) at $\mathbf{C - 5}$

The last group of compounds to be discussed contain a fluorine atom at C -5'. Some of them were synthesized in order to eliminate the possibility of phosphorylation of these nucleosides to the corresponding mono-, di-, and triphosphates in cells. It was then investigated if these $5^{\prime}$-deoxy- $5^{\prime}$-fluoro compounds would show any activity, which would not be dependent on their conversion into the corresponding nucleotides. These compounds were prepared either by condensation of $1-\mathrm{O}-$ acetyl-2,3-di- $O$-benzoyl-5-deoxy-5-fluoro- $\alpha, \beta$ -D-ribofuranose with an appropriate nucleobase [84] or by direct fluorination of nucleosides at $\mathrm{C}-5^{\prime}$, which is not a difficult task. A variety of methods could be applied such as a nucleophilic displacement of mesylates (tosylates) with KF or tetrabutylammonium fluoride as well as direct displacement with DAST (see Herdewijn's review [3]). However, it is reasonable to expect that such $5^{\prime}$-fluorination of adenosine protected with the $2^{\prime}, 3^{\prime}-O-$ isopropylidene group should not proceed well. It is known that acetonide protection brings $\mathrm{N}-3$ of the adenine base and $\mathrm{C}-5^{\prime}$ of the sugar moiety to a close proximity. Thus, an intro-

$5^{\prime} \cdot O$-tosyl-2', 3'-O-isopropylideneadenosine


3,5'-cyclo-derivative
duction of a good leaving group at $\mathrm{C}-5^{\prime}$ leads to the intramolecular displacement by $\mathrm{N}-3$ resulting in the formation of the corresponding $3,5^{\prime}$-cyclonucleoside [85]. This can be avoided either by acylation of the $\mathrm{N}-6$ of adenine or by protection of the $2^{\prime}$ - and $3^{\prime}$-hydroxyls with groups that do not cause such conformational rigidity as acetonide protection.

More challenging was a replacement of the oxygen of the $5^{\prime}$-hydroxyl function with añisopolar and isosteric - $\mathrm{CF}_{2}$ - group in order to synthesize difluoromethylene phosphonate nucleotides, e.g., to make the $-\mathrm{CH}_{2}-\mathrm{CF}_{2}-\mathrm{P}$ - linkage a good mimic of the $-\mathrm{CH}_{2}-\mathrm{O}-\mathrm{P}-$ moiety of nalural nucleotides. Groups such as - CHF-! and $-\mathrm{CF}_{2}$ - has been incorporated in place of $3^{\prime}$ - or $5^{\prime}$-oxygens of nucleosides or as replacement for bridging oxygens in the corresponding di- and triphosphates. For example, the synthesis of 9-(5,5-difluoro-5-phosphonopentyl)guanine (126) was reported. This compound was designed as a potent multisubstrate inhibitor of purine nucleoside phosphorylase and indeed showed an excellent inhibitory activity ${ }^{\text {[ }} 86$ ].


A general method for synthesis of $5^{\prime}$-difluoromethylene phosphonates was described by Matulic-Adamic et al. [87]. They found that a direct displacement of $5^{\prime}$-deoxy- $5^{\prime}$-iodo- $2^{\prime}, 3^{\prime}$ -$O$-isopropylideneuridine with $\mathrm{LiCF}_{2} \mathrm{P}(\mathrm{O})$ $(\mathrm{OEt})_{2}$ or reaction of the $5^{\prime}$-aldehyde function of the uridine derivative with the same reagent did not work. However, an efficient synthesis of the sugar precursor 128, followed by condensation with nucleobases, afforded the desired phosphonates. Thus, treatment of the triflate derivative 127 with $\mathrm{LiCF}_{2} \mathrm{P}(\mathrm{O})(\mathrm{OEt})_{2}$, followed by acetolysis under mild acidic conditions, gave the key sugar derivative 128. It is
interesting to note that a similar displacement of the triflate group of the methyl furanoside 129 did not lead to a similar product due to intramolecular reaction of the 1 -methoxy group with the 5 -triflate function of 129 . Finally, condensation of 128 with silylated nucleobases afforded the corresponding phosphonates $130(B=U, C$, and $A)$ in moderate yield. The rationale herein was to use these new compounds as starting

131

materials for synthesis of phosphonate analogs of biologically important molecules. Indeed, analogs of ATP and cAMP (131 and 132), as well as oligonucleotides containing non-hydrolyzable $\mathrm{P}-\mathrm{C}$ bonds such as 133 , were successfully prepared [87], and their biological properties were evaluated.

## 7. Miscellaneous studies

It has been demonstrated in recent years that even such radically modified nucleoside analogs as the oxirane analog 134 and its more stable cyclopropane analogs 135 and 136 showed a potent inhibitory activity


134


135


136
against herpesviruses $[88,89]$, which inspired Qu and Zemlicka [90] to synthesize new nucleoside analogs containing the difluorocyclopropane moiety as potential antiviral and/or antitumor agents. The difluorocyclopropane moiety is a close steric and electronic mimic of an oxirane ring, and in addition, gemcitabine and other nucleosides described in this review that contain the seminal difluoromethylene moiety showed an interesting antitumor or antiviral activity. cis-2-Butene-1,4-diol (137, Scheme 23) was monobentylated and then converted into benzoate 13y. Addition of difluorocarbene afforded 1.40, which after debenzoylation, followed by bromination, afforded a key derivative 142 for condensation with nucleobases. Thus, reaction of appropriate bases with 142 using $\mathrm{K}_{2} \mathrm{CO}_{3}$ in DMF gave, after deprotection, the desired nucleosides 143 in good yield $(\mathrm{B}=\mathrm{A} ; \mathrm{G}, \mathrm{C}, \mathrm{T})$.

It is worthwhile to mention the recent publication by Townsend et al. [91] which shows that an idea of the introduction of a fluorine atom at $\mathrm{C}-2^{\prime}$ in the arabino configuration in order to increase the stability and antiviral activity of nucleosides is still "an attractive alternative. In the advanced stage of development at Glaxo Wellcome is now 2,5,6-trichloro-1- $\beta$-D-ribofuranosylbenzimidazole (TCRB) discovered in Townsend's laboratory as an anti-human-cytomegalovirus (HCMV) agent. This compound did not inhibit DNA, RNA, or protein synthesis, but acted by a unique mechanism, which involves inhibition
of viral DNA processing and virus assembly. However, the glycosidic bond of this nucleoside is not very stable, and accumulation of the aglycone in blood was observed. Therefore, the synthesis of F-ara-TCRB (Scheme 24) was accomplished by both a direct method of fluorination $[33,35,36]$ of the corresponding $3^{\prime}, 5^{\prime}$-ditrityl derivative of TCRB 144, as well as by condensation of a sugar derivative 15 [14,17,19] with $2,5,6$-trichlorobenzimidazole. Indeed, the compound was found to be stable, and the activity was retained.

4'-Thionucleosides show antiviral and anticancer activities [92,93]. Several new 2:modified $2^{\prime}$-deoxy-4'-thiocytidines, including $2^{\prime}$-fluoro 145 and $2^{\prime}, 2^{\prime}$-difluoro derivatives 146 , have been prepared by Yoshimura et al. [94,95].


Among them the $2^{\prime}$-fluor analog was found to have potent antineoplastic properties in vitro. Recently, Jeong et al. [96,97] synthesized the corresponding compounds in L-series, 147 and 148 expecting to combine the properties of 4 '-thio- and L-nucleosides. None of these compounds, however, showed antitumor activity.


Scheme 23.

tIRE


F-ara-TCRB


15

Scheme 24.

## Acknowledgements

I wish to thank Prof. David C, Baker for his help in search of the literature and helpful comments.

## References

[1] T. Tsuchiya, Adl. Carbohydr. Chem. Biochem., 4 S (1990) 91-278.
[2] D.E. Bergstrom, D.J. Swartling, in J.F. Libenain, A. Greenberg, W.R. Dolbier Jr. (Eds.), Fhorine Comuining Molentes. Strucure, Reactivity, and Applications, VCH, New York, 1988. pp. 259 -308 (Chapter 11).
[3] P. Herdewijn, A. Van Aerschot, L. Kerremans, Nucleosides Nucleoticles. 8 (1989) 6.5.
[4] K.W: Pankiewict, K.A. Watanabe, J. Fhorine Clıom., 64 (1993) 15-36.
[5] K.A. Watanahe. U. Reichman, K. Hirota, C. L.ope\%, J.J. Fox, J. Med. Chitl., 22 (1979) $21: 24$.
[6] G. Etzold, R. Hintsche, G. Kowollik, I'. Langen. Tetrahedron, 27 (1971) 2463.
[7] L.W. Hertel, J.S. Kroin, J.W. Misner, J.M. Tustin, /. Org. Cheml. 53 (1988) 2406-24()9.
[8] C. Thibaudeau, N. Nishizono, Y. Sumita, A. Matsuda, J. Chattopadhyiayi, Nucleosides Nucleotides.- 18 (1999) 1.035-1053, and references therein.
[9] V.E. Marquez. B:B. Lim, J.I. Barchi, M.C. Nicklians, in C.K. Chu, D.C. Baker (Eds.), Nucleosides and Nucleotides as Antimmor and Antiviral Agents, Plenum, New York, 1993, pp. 265-284
[10] G.M. Blackburn. D.E. England, F. Kolkmann, I. Chem. Soc., Chem. Commum., (1981) 930-.932.
[1I] J.F. Codington, I. Doerr, D. Van Praag, A. Bendich, J.J. Fox, J. Ain. Chim. Soc., 83 (1961) 5030-5031.
[12] J.F. Codington, I. Doerr, I). Van Praag, A. Bendich, J.J. Fox, J. Org. Chrm., 29 (1964) 558-564.
[13] J.A. Wright, N.F. Taylor, Carbọlydr. Res., 6 (1908) 347.
[14] J.A. Wright, N.F. Taylor, J.J. Fox, J. Org. Chim., 34 (1969) 2632--26.36.
[15].J.A. Wright, D.P. Wilson, J.J. Fox, J. Med. Chem., 13 (1970) 269-272.
[16] M.J. Robins, Y. Fourun, R. Mengel, J. Org. Chem., 39 (1974) 1564.
[17] U. Reichman, K.A. Watanabe, J.J. Fox, Carlohydr. Res., 42 (1975) 233-240.
[18] W.H. Prusoff, Biochem. Biophys. Acta, 32 (1959) 296... 297.
[19] C.H. Tann, P.R. Brodfuehrer, S.P. Brundidge, Sapino Jr., H.G. Howell, J. Org. Chem., 50 (1985) 3644 . 3647.
[20] J.A. Martin, D.J. Bushnell, I.B. Duncan, S.J. Dunsdon, M.J. Hall, P.J. Machin, J.H. Merrert, K.E.IB. Parkes, N.A. Roberts, G.J. Thomas, S.A. Galpin, J. Merl. Chem., 33 (1990) 2137--2145.
[21] R.Z. Sterzycki, 1. Ghazzouli, V. Brenkovan, J.C. Martin, M.M. Mansuri, J. Med. Chem., 33 (1990) 2150-..2157.
[22] J.-T. Huang, L.-C. Chen, L. Wang, M.-H. Kim, J.A. Warshaw, D. Armstrong, Q.-Y. Zhu, T.-C. Chou. K.A. Watanabe, J. Matulic-Adamic, J. Med. Chem., 34 (1991) 1640.
[23] A. Van Aerschot, J. Balzarini, R. Pauwels, L. Kerremans. E. De Clerq. P. Herdewijn, Nucleosides Nucleorides, 8 (1989) 1121.
[24] K.W. Pankiewicz, B. Nawrot, H. Gadler, R.W. Price, K.A. Watanabe, J. Med. Chem., 30 (1987) 2314-2316.
[25] E. Soċhacka, B. Nawrot, K.W. Pankiewicz, K.A. Watanabe, J. Med. Chem., 33 (1990) 1995-1999.
[26] K.W. Pankiewicz, K.A. Watanabe, Chem. Pharm. Bull., 35 (1987) 4494-4497.
[27] K. Biggadike, A. Borthwick, A.M. Exall, B.E. Kirk, R.A. Ward, J. Chem. Soc., Chem. Commun., (1988) 898-900.
[28] K. Biggadike, A.D. Borthwick, D. Evans, A.M. Exall, B.E. Kirk, S.M. Roberts, L. Stephenson, P. Youds, A.M.Z. Slawin, D.J. Williams, J. Chem. Soc., Chem. Commun., (1987) 251-254.
[29] A. Borthwick, D.N. Evans, B.E. Kirk, K. Biggadike, A.M. Exall, P. Youds, S.M. Roberts, D.J. Knight, J.A.V. Coates, J. Med. Chem., 33 (1990) 179-186.
[30] P. Vemishetti, R. Saibaba, R.P. Panzica, E. Abushanab, J. Mell. Chem., 33 (1990) 681-686.
[31] C:K. Chu, J. Matulic-Adanic, J.-T. Iluang, T. =C. Chou, J.H. Burchenal, J.J. Fox, K.A. Watanabe, Chem. Pharm. Bull., 37 (1989) 336-339.
[32] V.E. Marquez, C.K.-H. Tseng, H. Mitsuya, S. Aoki, J.A. Kelley, H. Ford Jr., J.S. Roth, S. Broder, D.G. Johns, J.S. Driscoll, J. Med. Chem., 33 (1990) 978 --985.
[33] J. Krzeminski, B. Nawrot, K.W. Pankiewicz, K.A. Watanabe. Nucleosides Nucleotides, 10 (1991) 781 -. 798.
[34] S. Uesugi, H. Niki, M. Ikehara, H. Iwahashi, Y. Kyogoku, Tetrahedron Lett., (1979) 4073.
[35] K.W. Pankiewicz, J. Krzeminski, L.A. Ciszewski, W.-Y. Reni, K.A. Watanabe, J. Org. Chem., 57 (1992) 553-559.
[36] K.W. Pankiewicz, J. Krzeminski, K.A. Watanabe, J. Org. Chem., 57 (1992) 7315-7321.
[37] T. Maruyama, S. Takamatsu, S. Kozai, Y. Satoh, K. Izawa, Chem. Pharm. Bull., 47 (1999) 966-970.
[38] M.A. Siddiqui, J.S. Driscoll, V.E. Marquez, Teirahedron Letl., 39 (1998) 1657-1660.
[39] L.S. Jeong, M.C. Niclaus, C. George, V.E. Marquez, Tetrahedron Lett., 35 (1994) 7569-7572.
[40] L.S. Jeong, M.C. Niclaus, C. George, V.E. Marquez, Tetrahedron Lett., 35 (1994) 7573-7576.
[41] J.L. Abbruzzese, S. Schmidt, M.N. Raber, J.K. Levy, A.M. Castellanos, S.S. Legha, I.H. Krakoff, Invest. New Drugs, 7 (1989) 195-201.
[42] R. McKenzie, M.W. Fried, R. Sallie, H. ConJee Varam, A.M. Di Bisceglie, Y. Park, B. Savararese, D. Kleiner, M. Tsokos, C. Luciano, T. Pruett, J.L. Stotka, S.E. Straus, J.H. Hoofnagle, N. Engl. J. Med., 333 (1995) 1099-1105.
[43] T. Ma, S.B. Pai, Y.L. Zhu, J.S. Lin, K. Shanmuganathan, J. Du, C. Wang, H. Kim, M.G. Newton, Y.C. Cheng, C.K. Chu, J. Med. Chem., 39 (1996) 2835-2843.
[44] J. Du, Y. Choi, K. Lee, B.K. Chun, J.H. Hong, C.K. Chu, Nucleosides Nucleotides, 18 (1999) 187-195.
[45] T. Ma, J.S. Lin, M.G. Newton, Y.C. Cheng, C.K. Chu, J. Med. Chem.; 40 (1997) 2750-2754.
[46] K. Lee, Y. Choi, E. Gullen, S. Schleuter-Writz, R.F. Schinazi, Y.C. Cheng, C.K. Chu, J. Med. Chem., 42 (1999) 1320-1328.
[47] P. Kois, K.A. Watanabe, Nucleic Acids Symp. Ser., 29 (1993) 215-216.
[48] P. Kois, Z. Tocik, M. Spassova, W.Y. Ren, I. Rosenberg, J. Farras Soler, K.A. Watanabe, Nucleosides Nucleotides, 12 (1993)-1093-1109.
[49] I. Rosenberg, J. Farras Soler, Z. Tacik, W.Y. Ren, L.A. Ciszewski, P. Kois, K.W. Pankiewicz, M. Spassova, K.A. Watanabe, Nucleosides Nucleotides, 12 (1993) 381401.

- [50] A.M. Kawasaki, M.D. Casper. S.M. Freier, E.A. I.esnik,
- M.C. Zounes, L.L. Cummins, C. Gonzales, P.D. Cook, J. Med. Chem.. 36 (1993) 831-S41.
[51] M.J. Damha, C.J. Wilds, A. Nóronha, I. Brukner, G. Borkow, D. Arion, M.A. Darniak, J. Am. Chem. Soc., 120 (1998) 12476-12977.
[52] J.T. Stivers, K.W. Pankiewicz. K.A. Watanabe, Biochemistry, 38 (1949) 952-963.
[53] A.C. Drohat, G. Xiao, M. Tordova. J. Jagadeesh. K.W. Pankiewicz, K.A Watanabe, G. Gilliland, J.T. Stivers, Biochomistry, 38 (1999) 11876-11886.
[54] W. Plunkell, P. Huang, V. Ganghi, Nucleosides Nucteutides, 16 (1997) 1261-127).
[55] V. Gandhi, S. Mineishi, P. Huang, A.J. Chapman, Y. Young, F. Chen. B. Nowak, S. Chubb, L.W. Hertel, W. Plunkett, Cancer Res., 55 (1995) 1517-1524.
[56] T.S. Chou, P.C. Heath, L.E. Patterson, L:M. I'oteet, R.E. Lakin, A.II. Hunt, Synthesis, (1992) 565-570.
[57] Y. Xiang, L.P. Kotra, C.K. Chu, R.F. Schinari, Bioorg. Med. Chem. Lett, 7 (1995) 743--748.
[58] L.P. Kotra, Y'. Xiang, M.G. Newton, R.F. Schinazi, Y'C. Cheng, C.K. Chu, J. Med. Chem., 40 (1997) $3635-$ 3644.
[59] P. Herdewijn, J. Balzarini, E. De Ćlercq, R. Pauwels, M. Baba, S. Broder. H. Vanderhaeghe, J. Med. Chem.; 30 (1987) 1270.
[60] H. Hartmann, M.W. Vogt, A.G. Durno, M.S. Hirsch, G. Hunsinann, F. lickstein, AIDS Res. Hum. Retrovir., 4 (1988) 457.
[61] R. Kushida, S. Cox, J. Harmenberg, G. Gilljum, B. Wahren, Antimicrob. Agents Chumother., 33 (1989) 2083.
[62] J. Balzarini, M. Baba, R. Pauwels, P. Herdewijn, E. De Clerica, Biochem. Pharincol., 37-(1988) 2847-2856.
[63] P. Herdewijn, R. Pauwels, M. Baba, J. Balzarini, E. De Clercq, J. Med. Chem., 30 (1987) 2132.
[64] I. Schroder, B. Holmgren, M. Oberg, B. Lofgren, Antiviral Res., 37 (1998) 57-66.
[65] S. Ajmera, A.R. Bapat, K. Danenberg, P.V. Danenberg, J. Med. Chem., 27 (1984) 11-14.
[66] D.E. Bergstrom, A.W. Mott, E. De Clercq, J. Balzarini, J.D. Swartling, J. Med. Chem., 35 (1992) 3369-3372.
[67] H. Maag, R.M. Rydzewski, M.J. McRoberts, D. Craw-ford-Ruth, J.P.H. Verheyden, E.J. Prisbe, J. Med. Chern., 35 (1992) 1440.
[68] E.J. Prisbe, H. Maag,_J.P.H. Verheyden, R.M. Rydzewski, in C.K. Chu, D.C. Baker (Eds.), Nurleepsides and Nucleotides as Antitumor and Antiviral Agents, Plenum, New York, 1993, pp. 101-113.
[69] T.S. Lin, J.-L. Zhu. G.E. Dutschman, Y.-C. Cheng, W.F. Prusoff, J. Med. Chem., 36 (1993) 353-362.
[70] I.A. Mikhailopulo, N.E. Poopciko, T.I. Pricota. G.G. Sivets, E.I. Kvasyuk, J. Balzarini, E. De Clercq, J. Med. Chein., 34 (1991) 2195-2202.
[71] Y. Morizawa, T. Nakayama, A. Yasuda, K. Uchida, Bull. Chem. Soc: Jpu., 62 (1994) $2119-2120$.
[72] A. Van Aershot, P. Herdewijn, G. Jansen, M. Cools, E. De Clercq, Antiviral Res., 12 (1989) 133-150.
[73] D.F. Smee, J.L.B. Morris. D.L. Barnard, A. Van Aerschot, Antiviral Res., 18 (1992) 151-162.
[74] P.F. 'Torrence, J. Imai, K. Lesiak, J. Warrinnier, J.

Balzarini, E. De Clercq, J. Med. Chem., 26 (1983) 1674-- 1678.
[75] (a) E.N. Kilinichenko, T.L. Podkopaeva, M. Kelve, M. Saarma, I.A. Michkhailopulo, Biochem. Biophys. Res. Commun., 167 (1990) 20-26. (b) T. Kovacs, A. Pabuccuogulu, K. Lesiak, P.F. Torrence, Bioorg. Chem., 21 (1993) 192-208.
[76] C.R. Johnson, D.R. Bhumaralkar, E. De Clercq, Nucleosides Nucleotides,. 14 (1995) 185-194.
[77] A.D. Borthwick, K. Biggadike, Tetrahedron Leti., 33 (1992) 3237-3240.
[78] S.O. Thomas, V.L. Singleton, J.A. Lowery, R.W. Sharpe, L.M. Pruess, J.N. Porter, J.H. Mowat, N. Bohonos, Antibiot. Ann., 716 (1956/1957).
[79] G.O. Morton, J.E. Lancaster, G.E. Van Lear, W. Fulmor, W.F. Meyer, I. Am. Chem. Soc., 91 (1969) 15351537.
[80] I.D. Jenkins, J.P.H. Verheyden, J.G. Moffatt, J. Am. Chem. Soc:, 98 (1976) 3346.
[81] G.R. Owen, J.P.H. Verheyden, J.G. Moffatt, J. Org. Chem.. 41 (1976) 3010.
[82] J.H. Hong, K. Lee, Y. Choi, C.K. Chu, Tetrahedron Letl., 39 (1998) 3443-3446.
[83] K. Lee, Y. Choi, J.H. Hong, R.F. Schinazi, C.K. Chu, Nucleosides Nucleotides, 18 (1999) 537-540.
[84] M. Sharma, Y.-X. Li, M. Ledvina, M. Bobek, Nucleosides Nucleotides, 14 (1995) 1831-1852.
[85] W. Jahn, Chem. Ber., 98 (1965) 1705-1708.
[86] S. Halazy, A. Ehrhard, C. Danzin, J. Am. Chem. Soc., 113 (1991) 315.
[87] J. Matulic-Adamic, P. Haeberli, N. Usman, J. Org. Chem., 60 (1995) 2563-2569.
[88] T. Sekiyama, S. Hatsuya, Y. Tanaka, M. Uchiyama, N. Ono, S. Iwayama, M. Oikawa, K. Suzuzki, M. Okunishi, T. Tsuji, J. Med. Chem., 41 (1998) 1284--1298:
[89] W.T. Ashton, L.C. Meurer, C.L. Cantone, A.K. Field, J. Hannah, J.D. Karkas, R. Liou, G.F. Patel, H.C. Perry, A.F. Wagner, E. Walton, R.L. Tolman, J. Med. Chein., 31.(1988) 2304-2315.
[90] Y.-L. Qiu, J. Zemlicka, Nucleosides Nucleotides, 18 (1999) $2285 \cdots 2300$.
[91] L.B. Townsend, K.S. Gudmundsson, S.M. Daluge, J.J. Chen, Z. Zhu, G.W. Koszalka, L. Boyd, S.D. Chamberlain, G.A. Freeman, K.K. Biron, J.C. Drach, Nucleosides Nucleotides, 18 (1999) 509-519.
[92] M.R. Dyson, P.L. Coe, R.T. Walker, J. Chem. Soc:, Chem. Commun., (1991) 741-742.
[93] J.A. Secrist III, K.N. Tiwari, J.M. Riordan, J.A. Montgomery, J. Med. Chem., 34 (1991) 2361-2366.
[94] Y. Yoshimura, K. Kitano, H. Satoh, M. Watanabe, S. Miura, S. Sakata, S. Sasaki, A. Matsuda, J. Org. Chem., 61 (1996) 822-823.
[95] Y. Yoshimura, K. Yamada, H. Satoh, M. Watanabe, S. Miura, S. Sakata, S. Sasaki, A. Matsuda, J. Org. Chem., 62 (1997) 3140-3152.
[96] L.S. Jeong, H.R. Moon, S.J. Yoo, S.N. Lee, M.W. Chun, Y.H. Lim, Tetrahedron Letl., 39 (1998) 5201,-5204.

1971 L.S. Jeong, H.R. Moon, Y.J. Choi, M.W. Chun, H.O. Kim, J. Org. Chim., 63 (1998) 4821-4825.

2 N NaOH , bring), dried $\left(\mathrm{MgSO}_{4}\right)$, and concentrated in vacuo. The residue, a red oil ( 7.4 g), was chromatographic on neutral III alumina made up in pentano. Elution by pentane gave 2.11 g which was discarded. Elution by other gave 2.bis(tert-butylthio)mothylpytidine ( $3.05 \mathrm{~g}, 0.0113 \mathrm{~mol}, 11$ ) which was distilled in a short path apparatus: bp $80^{\circ}$ ( 0.1 mm ); ir (film) 1588 ( s ), 1508 (m), 1470 (s), $1432(\mathrm{~s}), 1364(\mathrm{~g}), 1164(\mathrm{~s}), 880(\mathrm{~m}), 742(\mathrm{~m}), 718(\mathrm{~m}) \mathrm{cm}^{-1}, \mathrm{uv}$
 $=6 \mathrm{~Hz}), 7.64(\mathrm{~m}, 2), 7.10(\mathrm{q}, 1), 6.16(\mathrm{~s}, 1), 1.28(\mathrm{~s}, 18)$.
Anal. Waled for $\mathrm{C}_{12} \mathrm{H}_{22} \mathrm{NS}_{2}: \mathrm{C}, 62.43 ; \mathrm{H}, 8.64$ : $\mathrm{N}, \mathrm{B}, 20$. Found: C . 62.40; H, 8.95; N, 6.22.

Pyridine $(7.9 \mathrm{~g}, 0.1 \mathrm{M})$ was treated with mothyllithium $(78 \mathrm{ml}$ of a 1.60 M solution, 0.12 mol ) and tert-butyl disulfide ( $17.6 \mathrm{~g}, 0.1$ mol) in an analogous manner. The bulk of the products were water soluble, presumably 2 -picoline. The material eluted from neutral
 mass spectrum) with 2.bis(tert-butyithiohnethylpyridine propared above. Comparison was also made by the (silica gel GF eluted by $\mathrm{CHCl}_{3}$-ethyl ace! tate $4: 1$ ).

Acknowledgment. Wo wish to acknowledge the support and encouragement of Dr. Max Wilhelm and monty helpful discussions with Mr. Louis Dorfman and Professor Peter Yates. We thank Mr. Dorfman's staff for microanalyses and spectra.
Registry No .-Sa, $53730 \cdot 69.1 ; 3 \mathrm{HCl}, 53730.70-4 ; 3 \mathrm{c}, 63730-$ $71.6 ; 4 \mathrm{a}, 53730-72.6 ; \mathrm{db} ; 63730-73.7$ dc, $63730-74.8 ; 5 \mathrm{a}, 63730.75$. 0; $3 \mathrm{~b}, 53730-76.0 ; 5 \mathrm{c}, 53778.52-2 ; 6 \mathrm{a}, 53730.77 .1 ; 6 \mathrm{c}, 53730-78-2$; Ta, $53730.79-3 ; 7 \mathrm{f}$, о $3730-80-6 ; 7 \mathrm{c}, 53730-81.7$; 7d, 63730.82.8; 7 o $\mathrm{HCl}, 53730 \cdot 83 \cdot 9 ; 7 f, 53730 \cdot 8 \mathrm{~A} \cdot 0 ; 8 \mathrm{a}, 53730 \cdot 85 \cdot 1 ; 8 \mathrm{~h}, 63730 \cdot 86 \cdot 2 ; \mathrm{g}_{\text {, }}$ 33730-87-3; 11, 63730-88-4; pyridine, 110-80.I; phenylsulfanyl
chloride, 931 -59.9; phenyl disulfide, 882-33.7; dimothyl disulfide, B24.02-0; m -chloroperbenzoic acid, 037-14-4; trinuoroacotic anhy dido, 407-25.0; ethyl 2-bromopropionate, 535-11.6; ethyl 4.bromobutyrato, $2969.81 \cdot 5$; butyl disulfide, $629.45 \cdot 8$; othyl $\alpha$.bromo. isohutyrate, 600.00 .0 ; ethyl bromoacetate, 105-36-2; 2.bis(tertbutylinio)methylpyidine, 53730-89-5; 2-picoline, 109-06-8.

## References and Notes

(i) H. L. Mate in "the Chemistry of Heterocycino Compounds." Vol. 14, A Wolssborgor, Ed., "Pyridine and hs Derivatives." PrIV, E. Kungsberg. Ed., Wiley, Now York, N.Y., Chapter XV.
(2) H. M. Wast Anat E. H. Sakai, J. Amor. Chem. Soc., 73, 1210 (1951).
(3) L. L. Bembas. J. Amer. Chem. Soc., 67, 688 (1945).
(4) H. First and H. J. Olatz, J. Pratt. Chem., 4, 147 (1950).
(5) M. Hotzalg. Vf: Cobol, and H, J. Konlg, J. Pratt. Chem., 311, 174 (1989).
(8) J. Deterge, Pharm. Acla Hell, \$4, 637 ( 1969).
(7) E. Plazok and E. Sucharda, Chem. Bor., 59,2282 (1928)
(8) A. D. Wostland, R. A. Cooley, J. L. Holmes, y. S. Hong. M. H. Un, M. L. Zwioslor, and M. M. Grensn, J. Med. Chant, 18, 319 (1973).
(9) K. F. King and L. Bauer, J. Org. Chem., 36, 1841 (1971).
(10) C. S. Glam end J. L. Stout, Chem. Commun, 478 (1970).
(11) R. Levine and W. M. Kadunce, Chem. Commune, 821 (1970).
(12) C. S. Glam and J. L. Stout, Chem. Commun., 142 (1989).
(13) Q. Fraonkol and J. C. Cooper, Toltahedron Lott., (1825 (i868)
(14) C. S. Glam and E. E. Knaus, Tetrahedron Lett. 4861 (1971).
(15) R. F. Francis, W. Davis, and J. T. Wiener, J. Org. Cham., 39, 59 (1974).
(16) N. Finch and H. W. Gschivend, J. Org. Chem, 38,1483 (1871).
(17) L. E. Tenenbaum, rel I'Chapier v.
(19) M.E. Kuohno. J. Org. Chem., 28,2124 (1983).
(19) Molting points were obtained in a Thomas-Hoovor molting point apparaUss and are uncorrected. Nmr spectra were obliged on a Varia A. 60 hatrumonk, infrared spectra on a Perkin-Emer 2 or 521 , na ss special. on an A MS902 at 70 ob, and ultravblet spectra on a Carey 14 insultmont.

# New Fluorinating Reagents, Dialkylaminosulfur Fluorides ${ }^{1}$ 

Williain Middleton<br>Central Research Department, E. I. du Mont do Nemours and Company, Experimental Station,<br>Wilmington, Delaware 19898<br>Rocciued September 23, 1974

Dialkylaminasuliur iniluorides (2) and bla(dialkylanino)sulfur difluorides (5) are easy to handle fluorinating reagents useful for replacing hydroxyl and carbonyl oxygen with fluorine under vary mild conditions. The trifluorides (2) were prepared by the reaction of dialkylaminotrimothylsilanes (1) with $\mathrm{SF}_{4}$, and the difluorides ( $\delta$ ) were prepared by tho reaction of 2 with 1. Those fluorides are particularly useful in fluorinating sensitive alcohols and aldehydes. For example, reaction of diethylaminogulfur trifluorido (DAST) with isobutyl alcohol gave isobutyl fluoride as tho principal product, reaction of DAST' with pivaldohydo at $25^{\circ}$ gave ( $\left.\mathrm{CH}_{3}\right)_{3} \mathrm{CCHF} \mathrm{F}_{2}$ in $78 \%$ yield, and reaction of $\mathrm{Me}_{3} \mathrm{NSF}_{2} \mathrm{NE}_{2}$ with crotyl alcohol at $25^{\circ}$ gave crotyl fluoride in $78 \%$ yield.

Sulfur tetianluoride is a useful fluorinating agent for replacing oxygen with fluorine in organic compounds. ${ }^{2}$ Tho substitution of one or two of the fluorine atoms in sulfur totrafluoride with dialkylamino groups would result in ami. nosulfur fluorides that also may be expected to be fluerinating agents. We have examined the preparation and chemical properties of dialkylaninosulfur trifluorides and bis(dialkylanimo)sulfur dilluorides with tho hope of developing nov selective fluorinating reagents.

Preparation. Tho dialkylaminosulfur' (rifhnorides (2) were propared by an adaptation of a literature procedure, ${ }^{3}$ which consists of treating sulfur tetrafluoride with a dials. ylaninotrimethylgilane (t), Diathylaminosulfur trinuorided (DAST), dimethylaminosulfur trifluoride, ${ }^{3}$ and the now pyrrolidinosulfur trifluoride were prepared by this method. When this reaction is conducted in trichlorofluoromethane (bp $25^{\circ}$ ) at $-70^{\circ}$, high yiolds of a product of very high pupity are obtained, since the only appreciable by-product is Iugrotrimothylsilane (3), an oasily soparatod low -boiling (bp $17^{\circ}$ ) material. These three (rifluorites are stable prod-
uts that can be distilled and stored in plastic bottles at room temperature.


Disopropylaminosulfur trifluoride $\left(2, \mathrm{R}_{2} \mathrm{~N} \Rightarrow\right.$ diisopropylamino) was plo prepared, but it why unstable to distilJation and decomposed to isopropyliminosulfur difluoride (4) when heated above $60^{\circ}$.

$$
\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CHN}=\mathrm{SF}_{1}
$$

4

$$
\mathrm{R}_{2} \mathrm{~N}-\mathrm{SF}_{2}-\mathrm{NR}_{2}^{\prime}
$$

5

Bis(dialkylamino)sulfur difluorides (6) have not been prepared previously. We prepared them by the reaction of a dialkylaminotrimethylsilane (1) with a dialkylaminosul. fur trifluoride (2) at $25^{\circ}$. The sulfur difluorides were not stable to distillation, but they could bo easily purified by removing the volatile solvent ( $\mathrm{CCl}_{3} \mathrm{~F}$ ) and byproduct (3) by ovaporation at reduced pressure. The ${ }^{19} \mathrm{~F}$ nmr spectra of

Table
Reactions of Alcohols with $\mathrm{Et}_{2} \mathrm{NSF}_{3}$


- All reactions ware carried out between -50 and $-78^{\circ}$ unless othenwioc noted. © Yield of isolated products unless otherwise noted. © $Y$. Kobayashi, C. Akashi, and K. Morinaga, Chem. Pharm. Bul., 1784 (1988). ${ }^{\text {© K. Wiechart, C. Gruenert, and H. J. Preibisch, Z. Chem., } 8 \text {, }}$ 64 (1968). M. Mloissan, J. Chem. Soc., 931 (1888). / K. A. Cooper and E. D. Hughes, J. Chem. Soc., 1183 (1937). Product was not isolated

 887 (1936). ${ }^{1} \mathrm{M}$. Hanack, Chem. Br., 94, 1082 (1901). m Anal. of saluple separated by gie. Waled for C،H7F: C, 64.8; H, 9.0̆; F, 2ī.6. Found:


 J. Amer. Chem. Soc., 82, 2535 (1900).
the difluorides at $-80^{\circ}$ and at $30^{\circ}$ show a single sharpest. nance at 5 to 10 ppm downfield from $\mathrm{CCl}_{3} \mathrm{~F}$. This relatively high field absorption and lack of spin-spin coupling indi. cate that tooth fluorine atoms are equivalent and are probe. bly in the axial position. These spectra are in contrast to the specter of the trifluorides (2), which show both equato. rial and axial nuorines coupled to each other. ${ }^{5}$


## Fluorination with Aninosulfur Fluorides

Markovakij, Pashimnik, and Kirsanov ${ }^{6}$ recently reported that the dialkylaminosulfur trifluorides are useful in replacing carbonyl oxygen of aldehydes and ketones with fluorinc. The work that we have done inctopendently fully supports these observations. In addition, wo have found that tho dialkylaminosulfur trifluoridos are perhaps even
more useful in replacing the hydroxyl groups of sensitive alcohols with fluorine, and the bis(dialkylamino)sulfur difluorides are also useful reagents for preparing organofluofine compounds.

Fluorination of Alcohols
The reaction of DAST and the oiler dialkylaminosulfur trifluorides with alcohols to replace the hydroxyl group with fluorine appears to be a broadly general reaction with distinct advantages over other. reagents used for this parpose, including. $\mathrm{SF}_{4}{ }^{7} \quad \mathrm{SeF}_{4} \cdot$ pyridine, ${ }^{8} \cdot \alpha$-fluorinate amines, ${ }^{7}$ and $H F$ and $H F$-amine reagents. ${ }^{9}$ Primary, seconday, and-tetliary alcohols all react, with high yields of the unrearranged fluoride usually resulting.

These reactions can be conducted under very wild condi-
tions so that other groups, including ester groups and other halogens, can also be present. Typically, the alcohol can be added slowly to a solution of DAST in an inert solvent cooled to -80 to $-78^{\circ}$. For many alcohols, the reaction occurs rapidly evon at this lotv tomperature. Diglyme is a convenient solvent for the preparation of low- looiling funrides because the product can be distilled out of the reaction mixture and the HF that is formed in the reaction remains behind complexed with the diglyme. For the praparation of higher boiling fluorides, lower boiling solveints such as pentane, methylene chloride, 'or trichlorofluoromuthane are useful. Table 1 contains a list of the alcohols that have been converted to fluorides.
I'wo problems can occur when replacing the OH groups of an alcohol with fluorine: carbonium ion type rearrangements and dehydration. The carbonium ion type rearrangements are less likoly to occur when DAST is used than when other known fluorinating agents arc used. For example, fluorination of isobutyl alcohol with DAST gave more than a $2: 1$ ratio of isobutyl fluoride (6) to tert-hutyl fluoride, whereas fluorination with $\mathrm{SeF}_{4}$-pyridine is reported ${ }^{8}$ to give only the reartanged tert-butyl fluoride. However, the nore easily rearranged exo- und endo-borncol gave the rearranged thoride 7 .


Dehydration (elimination) also appears to be less of a problem with DAST than with other fluorinating reagents. For example, cyclooctanol reacts with DAS'T. 10 give a 70:30 ratio of cyclooctyl fluoride (8) to cyclooctone, whereas $\mathrm{Et}_{2} \mathrm{NCF}_{8} \mathrm{CHClF}$ reacts to give only cyclooctene.


Crotyl alcohol (9) is sensitive to both double-bond rearrangement and dehydration. For example, it reacts with $\mathrm{SF}_{4}$ to give a $90 \%$ yield of butadiene, a 956 yield of 3 -fluoro-1-butene (11), and only a trace of crotyl fluoride (10). Reactions of DAST with crotyl alcohol under the same conditions (diglyme solvent) gave virtuatly no butadiene and a
high yield of monofluorides consisting of a 72:28 ratio of 11-10.

Reaction of DAST with crotyl alcohol in a less polar solvent (isooctane) gave larger amounts of 10 (36\%), but still gave the rearranged 11 as the major product ( $64 \%$ ). Fluorination of the ioomeric alcohol, 0-buten:2-ul (12), gave the same two products, but in differont satios (seo Tablo I). Since both 9 and 12 should form the same carbonium ion, it appers that a free carboniun ion is not involved in the reaction, but from tho reareanged producls ubsurved in these reactions and in the reactions with borneol, it is clear that these fluorination reactions do have considerable carbonium ion character.
The bis(dialkylamino)sulfur difluorides (5) are also use. ful reogents for replacing bydroxyl groups with fluorine in sensitive alcohols. Although they are less reactive, the difluorides have certain advantages over the trifluorides in that they cause less rearrangement and elimination. For example, diethylaminodimethylaminosulfur difluorido ( $5, \mathrm{R}$ $=\mathrm{CH}_{3} ; \mathrm{R}^{\prime}=\mathrm{C}_{2} \mathrm{H}_{5}$ ) reacts with crotyl alcohol (9) to give the umearranged 10 as tho principal product, with only smaller amounts of the rearranged 11 formed (ratio 72:21). The difluorides of also causo less delaydrations of easily dolydirated alcohols, such as cyclohexanol, as compared to the reaction of the same alcohols with the trifluorides (2).

The smaller amounts of rearrangement and dehydration products that are formed in the fluorination of alcohols with the difluorides 5 , as opposed to the trifluorides 2 , can be rationalized by assuning that both reactions go through an unisolated intermediato in which one of tho fluorines on sulfur has been replaced by an alkoxide group (13). This intermediate coisld then dissociate to give an ion pair consisting of a carbonium ion and a sulfur oxide anion (14). The sulfur oxide ion containing two amino groups $(14, X=$ $\mathrm{NR}_{2}$ ) would be expected to lose fluoride more readily than the anion containing only one amino group (14, X=F), and therefore have a shorter lifetime. Since the ion pair formed in the reaction of the difluoride 5 with an alcohol would have a shorter lifetime than the ion pair formed from 2 and an alcohol, less carbonium ion type reactions would occur.
An alternate explanation would be hased on leaving group ability linstead of fluoride ion transfer. Since the leaving ability of $\mathrm{R}_{2} \mathrm{NSF}_{2} \mathrm{O}^{-}$should be greater than $\left(\mathrm{R}_{2} \mathrm{~N}\right)_{2} \mathrm{SFO}^{-}$, the decomposition of intermediate 13 ( $\mathrm{X}=$ F) to give products should involve more carbonium ion ${ }^{\text {. }}$ characler than decomposition of $13\left(\mathrm{X}=\mathrm{NR}_{2}\right)$, and therefore would be subject to more extensive rearrangement and eliminnation.

$13, X \sim F_{1} N R_{2} \quad 14, X=F, N R_{2}$
Fluorinatlon of Aldehydes and Ketones. DAST is a convenient reagent for replacing the carbonyl oxygen of aldehydes and ketones with two fluorine atoms (See Table II). This reagent is particularly useful for fluorinating aldehydes and ketones that are sensitive to acidic conditions or contain other functional groups that are unstablo in the presence of acid, since no acid other than adventitious HF is formed in the reactions and no additional aciclic catalyst is needed. Even aqucous work-ups do not result in the formation of acidic solutions, since the only hy-product, diethylaminosulfinyl tuoride (16), is hydrolyzed to give sulfur dioxide and diothylamino hydrofluoride.

Table II
Reaclions of Carbonyl Conipounds with DAST:

${ }^{2}$ Glc yield. ${ }^{\circ}$ Anal. Caled for $\mathrm{C}_{3} \mathrm{H}_{10} \mathrm{~F}_{2}: \mathrm{C}, 85.8 ; \mathrm{H}, 0.3 ; \mathrm{F}, 35.1$. Found: $\mathrm{C}, 030.7 ; \mathrm{H}, 9.4 ; \mathrm{F}, 35.0 .9$ Anal. Caled for $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{~F}: \mathrm{C}, 68.2 ; \mathrm{H}, 10.3 ; \mathrm{F}$, 21.6. Found: $C$, 88.3; $H, 10.6 ; F, 21.8$, d Anal. Found; $C, 05.3 ; H, 9.3 ; F, 35.4$, ' W. R. Hasek, W. C, Smith, and V. A. Engelhardt, J. Amer.
 61.7; H, 10.4; F, 27.8. Found: C, 82.1; H, 10.2; F, 28.1: ${ }^{\wedge}$ K. Matsuda, J. A. Sedlak. J. S. Noland, and G: C. Cleckler, J. Org. Chem., 27.
 (pentane-ether). ${ }^{\wedge}$ Anal. Caled for $\mathrm{C}_{30} \mathrm{H}_{4} \mathrm{~F}_{7} \mathrm{O}: \mathrm{C}, 03.8 ; 11$, 7.6; $\mathrm{F}, 20.2$. Found: $\mathrm{C}, 63.1$; Hn 7.3; F, 20.8.

Tablo III
Effect of Solvent on Product Dlstribution in the Fluorinatlon of Plvaldeliyde with DAS'T

| Solveat | K ol producu (sic y yoidu). |  |
| :---: | :---: | :---: |
|  | $\left(\mathrm{CH}_{3}\right)_{3} \mathrm{CCH}_{2}$ | $\begin{gathered} \mathrm{CH}_{2}=\left(\mathrm{CH}_{3}\right)-\mathrm{HC}_{\left(\mathrm{CH}_{3} 2_{2}^{2}\right.} \\ \mathrm{CHFCH}_{3}-\mathrm{CHECH}_{3} \end{gathered}$ |
| $\mathrm{CCl}_{3} \mathrm{~F}$ | 88 | 2 . 10 |
| Pentane . -- | 87 | 3. 10 |
| $\mathrm{CCl}_{3} \mathrm{H}$ | 72 | . 3 . 25 |
| $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ | 72 | 2.28 |
| Xylene | 84 | 8 - 28 |
| Tetrahydrofuran | 65 | $20-15$ |
| Plvaldehyde | 60 | 1030 |
| Diglyme | 30 | 3238 |
| $\mathrm{R}_{\mathrm{i}} \mathrm{C}=0 \mathrm{O}+\mathrm{DAS}$ | $\rightarrow \mathrm{R}_{2} \mathrm{CF}_{3}$ |  |

Pivaldehydo (16) is an examplo of an noid-sensitive alde. hyde. Previous attempts to prepare the corresponding gem. difluoride have resulted in rearrangemonts or trimerization. However, pivaldehyde can be successfully, fluorinated to 17 by the use of DAST in a nonpolar solvent such as pentane or $\mathrm{CCl}_{3} \mathrm{~F}$. Carbonium ion type rearrargements will occur, however, if more polar solvents aro used (See Table III). Thus, if diglyme (a basic, polar golvent) is used, fhe rearranged products 18 and 19 are formed, and if chloroform is used (a nonbasic, poler solvent), considorable rearrangement product 19 is formed, but only a small amount of the olimination product 18 is formed. The solvont dependancy of this reaction is consistent with the reaction shown in Schome I.

Scheme I


Dialkylaminosulfur Trifluorides (Table IV). The four trifluo. rides listed ir Table IV were prepared by the reaction of an amino. trimethylsilane with gulfur tetrafluoride in $\mathrm{CCl}_{3} E$, as illuatrated by the preparation of diethylaminosulfur trifluoride (DAST)..
A solution of 98 g ( 0.68 mol ) of diathylaminutrimathylsilane in 100 ml of $\mathrm{CCl}_{3} \mathrm{~F}$ was added dropwisa to a solution of 40 ml (measured at $-78^{\circ}, 0.72 \mathrm{~mol}$ ) of sulfur tetrafluoride in 200 ml of $\mathrm{CCl}_{3} \mathrm{~F}$ at -65 to $-60^{\circ}$. The reaction mixture was watmed to room teanporature and then distilled to give 88.9 y ( $84 \%$ ) of DAST as a pale yellow liquid.

IIs(dielkylamino)sulfur Difluoridos (Table IV). The four

Table IV
Aminosulfur Fluorides

difluorides listed in Tablo IV were prepared by the reaction of dimethylaminosulfur tiflluoride or DAST with an aminotrimethylsilane, as lllustrated by the preparation of bis(dimethylamino)sulfur difluoride.

A $29.25 \cdot \mathrm{~g}$ ( 0.25 mol ) sample of dimethyleminotrimethylsilano was added dropwise to a solution of 33.2 g ( 0.26 mol ) of dimethyln. minosulfur trinuoride in 100 inl of $\mathrm{CCl}_{3} \mathrm{~F}$ conled to $-78^{\circ}$. The reaction mixture was warmed to $26^{\circ}$ and then filtered under nitro. gen to remove a small amount of suspended solid. The filtrato was evaporated to dryness under reducod pressuro to give 23.5 g (609\%) of bis(dimethylamino)sulfur difluoride as a white cryatattino solid.
$N$-Isopropyliminosulfur Difluozlö̃o (4); Atterpted distilla. tion of crude diisopropylaminosulfur trifuorlde caused this product to decompose at about $60^{\circ}$ ( 2 nim ). The volatile decomposition products were collected in a cooled trap and redistilled to give an 80\% yiold of 4 as a liyht yellow liquid: bp $63^{\circ}$; ${ }^{18} \mathrm{~F}$ nmr $\left(\mathrm{CCl}_{3} F\right)$; $72.9 \mathrm{ppm} ;{ }^{1} \mathrm{H}$ nmr $\left(\mathrm{CCl}_{3} \mathrm{~F}\right) \delta 1.28 \mathrm{ppon}(\mathrm{d}, J=6.6 \mathrm{~Hz}, 6 \mathrm{H})$ and 4.17 ppmin (septet, $J w 6.5 \mathrm{~Hz}, 1 \mathrm{H}$ ).
Anol. Cald for $\mathrm{C}_{3} \mathrm{H}_{7} \mathrm{~F} 2 \mathrm{NS}: \mathrm{C}, 28.3 ; \mathrm{H}, 5.6 ; \mathrm{F}, 29.0 ; \mathrm{N}, 14.0 ; \mathrm{S}$ 25.2. Found: C, 28.4; H, $6.6 ;$ F, 20.5 ; N, 14.0; S, 25.4.

Fluorination of Alcohols (Table 1). Tbe alcohols listed in T'able I wore added to a solution of DAST or dimethylimingsulfur trifluoride in an inert solvent cooled to $-60 \mathrm{l}_{0}-78^{\circ}$. The reaction mixture was then warmed to room temperature or higher. An ins. tial exothormic reaction usually occurred at low temporature. In some cases, a sccond exothermic reaction was evidont during the warm-up period. The lower-boiling product fluorides were distillud out of the reaction mixture at reduced pressuro. Reaction mixtures containing higher-boiling fuorides were mixed with water, and the organic layer was separated and dried, and the solvent was dis. tilled off. The product nuorides were puritied by diatillation, 10 . crystallization, or column chromscography. The following are representative examples.
Ethyl 2.Fluoroproplonato. A solullon of $1.18 \mathrm{~g}(0.01 \mathrm{~mol})$ of ethyl lectate in 2 ml of methylene chloride was slowly added to a solution of $1.25 \mathrm{~g}(0.01 \mathrm{~mol})$ of DAST in 6 ml of muthylene chlorite cooled to $-78^{\circ}$. The reaction mixture was warmed to coom temperaturo and mixud with culd water. The lowor layar wes separnted, washed with water, dited ( $\mathrm{Mg}_{\mathrm{g}} \mathrm{SO}_{4}$ ), and distilled to dive 0.93 g of ethyl id nurropropionare ${ }^{20}$ as a colorless liquid.

1-Bromu-2. Fluoroothano. Lithylene bromohydrin, $31.2 \overline{0}$ y 10.25 mol), wat udded dropwise to alution of $33 \mathrm{~g}(0.2 \mathrm{~h} \mathrm{~mol})$ of di. mothylan wosulfur trinuoride in 180 ml of diglyme curlod to $-50^{\circ}$. The cuaction mixture was wallied to rooin tomporaturu, and 60 ml of the most volatile purtion was distilled out at reduced pressure. The distillate was mixed with water, washed with $6 x$ codium bicar. bonate solution, dried $\left(\mathrm{M}_{\mathrm{B}} \mathrm{SO}_{4}\right)$, and redistilied to give 22.2 z of 1 . bromo-2-fluoroothanatl as a colorless liquid.
Fluorlnation of Crotyl Alcohol with (Diethylamino)(dimethylamino)sulfur Difluoride. A solution of $1.44 \mathrm{~g}(0.02 \mathrm{~mol})$ of crotyl alcohol (2-buten- $1 \cdot 01$ ) in 2 ml of diethyleno glycol dinieth. yl ether was slowly addad to a stirred solution of $3.7 \mathrm{~g}(0.02 \mathrm{~mol})$ of (diothylamino)(dimethylamino)sulfur difluoride in 10 ml diethylene glycol dimethyl ether cooled to $-78^{\circ}$. The reaction mixture was warmed to $25^{\circ}$ and the volatile products wore distlled out under reduced pressuro to give 1.3 ml nf colorless liquid. Redistil lation gavo $1.08 \mathrm{~g}(72 \%)$ of a mixtire containing $79 \%$ 1.17uoro.2.
butone (crotyl fluoride) and 21\% 2.fluoro-3-butene, bp 24-27 ${ }^{\circ}$.
When the reaction was repeated, using isooctune in the place of diathylene glycol dimethyl ather as the reaction solvent, a $06 \%$ ylold of fuorobutene was obtained consisting of $87 \% 1$-luoro.2. butone and $13 \%$ 2-fluoro- 3 -buteno.
Fluorination of Aloohols with ( $\mathrm{Me}_{2} \mathrm{~N}_{2} \mathrm{SF}_{1}$, A solution of 1.08 g ( 0.01 mol ) of benzyl alcohol in 2 ml of methylene chloride was added slowly to a solution of 0.0066 mol of bis(dimethylamino) sul fur difluoride in 6 ml of methylone chloride cooled to $-78^{\circ}$. The reaction mixture was warmed to room temperature and mixed with wator. The organic layer was separated, washed with water, and then $6 \%$ sodium bicarbonate, and dried ( $\mathrm{MgSO}_{4}$ ). Analysis by glo and ${ }^{19} \mathrm{~F} \mathrm{~nm}$ showed that benzyl nuoride had been formed in $91 \%$ yield. Cyclohexanol was nuorinated in a similar manner to give fuorocyclohexane, ${ }^{19} \mathrm{~F}$ ninr ( $\mathrm{CCl}_{3} \mathrm{~F}$ ) $\delta-161.2 \mathrm{ppm}(\mathrm{m})$
Fluoriuation of Aldohydes and Ketoucs with DAST (Tablo II). The ketones and aldehydes in Table II ware fluorinated by stirxing them in an inert solvont with DAST at temporatures and for times indicated. The fluorinated products wero isolated, by pouring the reaction mixture into water, and then separating drying, and distilling the orgnnic layer. The following exaraple il lustrates this procedure.
Fluorinatlou of Isovaleraldehyde, A 1.72 gg ( 0.02 mol ) sample of isovaleraldehyde was slowly added to a solution of $2.5 \mathrm{ml}(0,02$ moi) of DAST in 10 ml of $\mathrm{CCl}_{3} F$ at $25^{\circ}$. The reaction mixture was slirred for 30 min , and then mixed with 25 ml of wator. Tho lower urganic layer was separated, washed with water, dried ( $\mathrm{M}_{8} \mathrm{SO}_{4}$ ), and'distillod to give 1.73 g ( 80 N ) of 1,1 -difuoro- 3 -methylbutane as a colorless liquid
 M.9.6; F, 35.l.

Megistry No.-1 ( $\mathrm{R}=$ Mo), 2083-91-2; $1(\mathrm{R}=\mathrm{Et}), 996.50-9 ; 1$ $1 \mathrm{R}_{2}=-\left(\mathrm{CH}_{2}\right)_{4}-1,15097.49-1 ; 1(\mathrm{R}=\mathrm{Pri}), 17425.88 .6 ; 4,63731.08$. 1; sulfur tetrafluoride, 7783.60.0.

## References and Notes

(1) (a) Portions of this paper were presented at the Sacond Winter Fluorino Conterence, St. Pelergburg. Fla., Fob 1974; (b) Contributlon No. 2183
(2) W. C. Smth, Angsw, Cham, Int. Ed. Engl., 1, 467 (1962)
(3) O. C. Osmlias, R. A. Kent, and A. O. MacDlarmld, Chent, ind. (London) 44, 1712 (1964).
(4) S. P. Von Halasz and O. Glamser, Chem. Bor., 104,1247 (1971)
(6) D. G. Dboll and A. F. Janzon, Can. J. Cham., 50,2428 (1972)
(6) L. N. Markovskil, V. E. Pashinnik, and A. V. Kirsenov, Synihegls, 787 (1973).
(7) W. A. Sheppard and C. M. Sharts, "Organic Fluorlne Chemistry," W. A Bonjamin, Now York, N.Y., 1969
(8) O. A. Olah, M. Nolima, añd I. Kerekes, J. Amer. Cham. Soc., 86, 925 (1974).
(8) O. A. Olah, M. Nojma, and I. Kerekes, Synihosls, 786 (1973).
(10) Melling points and boilling polnts ara unccrrected, ${ }^{19} \mathrm{~F}$ nent spectra were obialned with a Varlan A58-60 spectromater. Poak center postlons are reported in paris per millien downitald from $\mathrm{CCl}_{5}$ fused as an Interna reference. The olalkylaminoslanes used were prepared by the reaction of socondary amines with tilmethyichlorosilane.
(11) J. A. Brocks, R. Kosfold, P. Sartorl, and M. Schmelsser, Chem. Oor., 1982 (1970).
(12) F. L. M. Patilson, O. A. V. Petors, and F. H. Dean, Can. J. Chom., 43 1669 (1895).

NUCLEOSIDES \& NUCLEOTIDES, $8(1), 65-96$ (1989)

SYNTHESIS OF NUCLEOSIDES FLUORINATE IN TEE SUGAR MOIETY. THE-APPLIOATLOH-OF DIETIMLANSHOGUIFUR- TRIFILOREDE TO THE SYNTHESIS OF FLUORINATE NUCLEOSIDES
P. Herdewijn ${ }^{\ddagger}$, A. Van Aergchot \& I.. Kerremans

Regal Institute for Medical Research, Katholleke Uaiversiteit Leaven, B-3000 Leven, Belgium

ABSTRACT. A survey is given of the different methods that have been used for the synthesis of nucleosides fluorinate in the carbohydrate moiety. In this article we describe the uso of diethylaminosulfur trifluoride (DAST) as a fluorinating agent in the nucleoside field.

The introduction of a fluorine substituent in organic compounds has frequently led to a dramatic change in their biological activity. This is perhaps most clearly shown in the field of the anti-inflamatory steroids where inclusion of fluorine atom, ot either the fa- or 9a-position, generally leads co marked increase in their potency. A more recent example is the intergating development in che field of the antibacterial quinolne derived from nalidixic acid. The introduction of a fluorine atom in the 6-poaltion has potentiated the antimicrobial activity and has broaderned their antibacterial npectrum. A well known example in the carbohydrate
 the grociose metabolism and also as a diagnostic agent.

The interest of medicinal chemists in the construction of fluorine containing drugs is derived from the relative stability of the carbonfluorine bond, both chemically and metabolically, and from the strong electronegative character of fluorine, which alter the electronic properties of a molecule. In cost examples, fluorine has taken the place of a hydrogen at os. fluorine and hydrogen have indeed similar Van der Hals radii, but they strongly differ in electronegative character. Physicochemisally apeaklng, there are much more similarities between a fluor group and an hydroxyl group; for example in their bond lengths to carbon and in the dipole moments of these bonds. In solution, the conformation of a fluorine compound of ten resembles that of the parent hydroxyl compound ra-

65

Copyright © 1989 by Marcel Dekker, Inc.
ther than that of che hydrugen analogue: for example z'-iluorö-2'-deoxyribonucleosides ${ }^{l a}$ and $2^{\prime}$-fluoro-2'-daoxyarabinonucleosides ${ }^{l b}$. In. these examples, the conformation is strongly related to the electrostatic interactions between the fluorine substitucnt and the vicinal hydroxyd group ${ }^{2}$. These resulics $\boldsymbol{f}^{\circ}$ o not always in conformity with crystallographic data. To oeplain chese diyorallogriphlc data. it has been. guggested that an alteruntive conformation can be stsbllized by an intramolecular bydrogen bond $\left(3^{1-O H} \ldots .\right)^{3}$. On the other liant, a lluoro group can only be a proton acceptor, while a hydroxyl group can function both as an acceptor and as a donor in the formation of hydrogen bonds. Therefore it seems very difficult to predice the molecule's blological behaviour when a $C-H$ or a $C-O l l$ group has been displaced by a $C-F$ group.

There is only a very small number of naturally occuring organic fluorine compounds, an example of which is "nucleocidin", 1 , an antibiotic, isolated from Streptomyces clavus ${ }^{4}$. The compound's structure, $4^{i}$ -fluoro- $5^{\prime-0-s u l f a m o y l a d e n o s i n e, ~ w a s ~ c l u c i d a t e d ~ i n ~} 1969^{5}$ and its aynthesis. vas described in $1971^{6}$ and $1976^{7}$.

Still. the fluorinated nucleosides from synchetic origin are far more tmportant. S-Fluoro-2'-deoxyuridine, 2, (as 5-fluorouracil) is a widely used anticumor compound, wilch is elther used single or in combination therapy for the treatment of different metastatic cancers. Trifluorothymidine, 3 . is one of the oldest antiviral compounds, used in copical treatrent of herpetic eye infections (acute keratitis). The introduction of a fluorine substituent in the 2-position of $9-\beta-D-a r a b i n o f u r a n o s y l a d e n f n e$

enhances its stability cowards enzymatic deamination. This compound, 9-8-D-arabinofuranosyl-2-f luoroadenine, $4^{k}$, shows good activity against experimental animal cancers ${ }^{9} \because$ The $2^{\prime}-f$ luoro- $2^{\prime}$-deoxy- 0 -D-arabinofuranosylpyrimidine compounds 5 a and sb were found to be very active against che herpes
simplex virus type $I$ and type If infections with very low eytotoxicity ${ }^{10}$. More recently, the 5 -ethyl analogue $5 c$ was described as a promising new antiherpes agent 11,12 .




$\begin{array}{ccc} & \underline{X} & \frac{r}{r} \\ \underline{S O} & \mathrm{NH} & \mathrm{I} \\ \underline{S O} & \mathrm{OH} & \mathrm{CH}_{3} \\ \underline{\Sigma} & \mathrm{OH} & \mathrm{C}_{2} \mathrm{H}_{5}\end{array}$




CHEMISTRY

Due to solvation, the fluoride ion is a relatively poor nucleophile In protic solvents. In polar aprotic solvents, however, only cations are strongly solvated and the nucleophilicity of the fluoride ion is significanty enhanced. Extremely nucleophilic fluoride ions have been obtained by the use of crown-ethers and of fluoride loaded exchange resins. Despite this, the synthesis of fluorinate nucleosides is $\dot{s}$ fill a difficult task. A frequently encountered problem is the fluoride ion catalysed elimination reaction. Frequently vigorous reaction conditions are required and even then, the yields of the desired compounds are $10 \%$. In this article weill give a literature survey of the nucleosides fluorinate d in the sugar molety, and veil describe the use of diethylaminosulfur trifluoride. (DAST), 6, for the synthesis of some selected compounds. This allows the preparetimon of these compounds in good yield, under very mild conditions and with normal glassware.

Three basic methods were used to synthesize nucleosides fluorinated in the sugar moiety : .

- epoxide cleavage by fluoride ions,
- displacement of a sulfonyloxy group by fluoride ions.

IPO DELHI 23-06-2015 1GBag Assigned Page \#13954

- opening of the anhydrn hond formed by the sugar and the base part. The latter reaction is restricted to pyrimidine- and some related nucleosidis.
All thecae reactions occur with inverstim of configuration.


## A. Nugleophilic oxiraae ring opening with fluoride fur

Fluoride ring opening of oxiranes has been used for the synthesis of
 trice, $63 \%$ ) and of 9-(3-deoxy-3-fluoro-B-D-acabinofuranosyl)adenine ${ }^{14}$ (8) (WHF 2 in ethylene glycol, 41 ). In the case of 2 and 8 , regiospecificity vas reported and no other isomers were mentioned. Nevertheless, when 1-(5-0-benzoyl-2,3-epoxy-8-D-1yxofuranosyl)uracil was treated with $10 \% \mathrm{HF}$ in dioxane ${ }^{15}$, the two isomers $\underline{9}(25 z)$ and $\underline{10}(11 z)$ were isolated, together with uracil and $1-B-D-x y l o f u r a n o s y l u r a c i l$.

These methods are subject to several drawbacks related to the vigorus reaction conditions which are needed for the ring opening. With $\mathrm{KHF}_{2}{ }^{14}$ or $\mathrm{HF}^{15}$. decomposition occurred and respectively adenine or uracil were formed. The method with tetraechylamiontum fluoride ${ }^{13}$ suffers from the disadvantage of the strictly anhydrous conditions required for the reaction. The problems associated with the drying of tetraalkylamonilum fluoride and the stability of this reagent under the conditions mentioned were studied by Shame et al. ${ }^{16}$ When we repeated the synthesis of 7 follow wing the literature procedure, the fluortnared nucleoside was isolated io a 40 z yield. The two other compounds, isolated after debenzoylation with methanol saturated with ammonia, are 9-B-D-xylofuranosyladenine, 11, and S-amino-1-(3-deoxy-B-D-xylofuranosyl) imidazole-4-(N-benzoyl) carbnxamide-$\mathrm{N}^{5}-3^{\prime-}$-cyclonucleoside, 12 .






IPO DELHI 23-DE-2015 1 Bag Assigned Page \#13955

FLUORINATED NUCLEOSIDES

Bx - benzoyl



II

12

The, formation of 11 was also reported in the original manuscript and results from traces of moisture which are introduced into the reaction mixture. The N-benzoyl group of the cyclonucleoside 12 , which is formed via an attack of $\mathrm{N}^{3}$ on the époxide followed by ing opening ${ }^{13}$, is stable against mild debenzoylation conditions ( $\mathrm{MeOH}, \mathrm{NH}_{3}$ )..A rather strange re-

suit was obtained by ring opening of the epoxide, 1-(2,3-epoxy-8-D-1yxofuranosyl)uracil, with liquid hydrogen fluoride (10 \%) in dioxane ${ }^{17}$. Togathen with the expected 3'-fluoro-3'-deoxyarabinouridine, 13 (13 $\pi$ ) and uracil, 3'-fluoro-3'-deoxyurldine, 14, (11 2) was obtained.

The later was formed frow 13 during the reaction.: The authors didn't speculate on possible reaction mechanism. Epoxide opening of the same product in dalogous reaction conditions ${ }^{18}$ gave 13 in 3. $z$ yield together with two other unidentified products containing fluorine. This demonatrated that in such vigorous reaction conditions it is very difficult to obtain reproduceable results.

The ring opening of apoxides (KHF 2 in ethylene ${ }^{i}$ glycol) on carbohydrateas hag also been used by Wright et al. In their total synthesis of $I$ and 15 ${ }^{19,20}$. in their synthesis of the cytidine analogues $16,17,18$ and $1^{19-23}$ and for the synthesis of the $2^{\prime}$-fluor analogues of $9-(8-D-a r a b 1-$ nofuranosyl)adenine. 20, and the a-analogue $\underline{21}^{23}$. Normally, the opening of epoxides is very easy with HP in the presence of an organic base, such as
tetrahydrofuran or dioxin. This is ty be ultrlbuted co che increased dissociation of the hydrofluoric acid ${ }_{i}^{24}$ and its most important application






20

21
can be found lon the steroid field. Potassium hydrogen fluoride, however, gave better results on carbohydrates ${ }^{20}$. Besides, high HF-concentrations are incompatible with the acid sensitive glycosidic bond of nucleosides.
8. Nucleuphilic displacement of sulfonates by fluoride ion

This reaction has been used mow often for che introduction of a fluorine atom in the $5^{\prime}$-position of different nucleosides because the displacement of primary sulfonates in a reaction with fluorine is more easily achieved than the same reaction on a secondary carbon. The reaction was carried out on, either mesylates, or tosylates with potassium fluoride in ethylene glycol (or methanol) ( $130-150^{\circ} \mathrm{C}$ ) or with tetrabutylamonium fluorride in. dimethylformanide at $50^{\circ} \mathrm{C}$. Yields then range from 152 to $92 \%$. The reaction with hydrofluoric acid in dioxane, however, was reported to give better yields ${ }^{25}$. Scheme 1 gives a clear view of the compounds aynthesized by this method. Some of the ribo-analogues were opened between the $2^{\prime}-$ and $3^{\prime}$-position by treatment with $\mathrm{NaIO}_{4}$ in rater ${ }^{40}$.

To introduce fluorine on a. secondary carbon atom, a more reactive leaving group is preferred. The use of triflate as leaving group has'allowed a good yield-preparation of fluorine containing nucleosides and this under very mild conditions ( $\mathrm{Bu} \mathrm{a}_{4} \mathrm{~N}^{+} \mathrm{F}^{-}$, THE, $\mathrm{O}^{\circ} \mathrm{C}$ ). A lot of publications have
 trahydrofuranyl group ${ }^{42}$ proved to be wore suitable than the tetrahydropyranyl group for protection of the $3^{\prime}$,- and $5^{\prime}$-hydroxyl group because it is
 zed in the same manner ( $\mathrm{Bu}_{4} \mathrm{~N}^{+} \mathrm{F}^{-}$, THF, R.T.) from 2-N-isobutyryl-3', $5^{\prime}-\mathrm{di-}$ O-tecrahydrof uranyl-9-B-0-arabinofuranosylguanine in a 40 yield. ${ }^{47}$ Ni-

( 1271 (281 (33)
(35) (36) 1381

C 1271
U 127 (361
A 1271
S. fluoroU (27)

$X=F: Y=F: 1321$
$X=F: Y=N_{1} 1311$
$X=F: Y=H$ $X=F: Y=H|x|$

different bases $(39)$

C 1301
U(30) (37)

5-Ifuoro U 1261

$X=O H: Y=H(34)$

SCHEME I
rite deamination of 22a resulted in 2'-deoxy-2'-fiuoroinosine inc. . $^{\text {28,49 }} \mathrm{A}$ useful alternative, which has only recently found its application in the nucleoside field ${ }^{50}$, is the use of tris(dimethylamino) sulfonium difluorotrimethylailicate (TASF) ${ }^{51}$ on crifluoromethanesulfonyl derivatives. The reaction has been reported on C-nucleusides, $23{ }^{50}$. Still, the reaction on a $N$-nucleoside ${ }^{50}$ was unsuccessful. The difficulties encountered with a direct introduction of the fluorine atom in the 2 '-"up" position of N-nucleosides could be caused by the unfavorable. Interaction between the approaching nucleophile and the anoweric substituent. Another -factor might be the bond length of the C-N bond which Ls shorter than that of the C-C bond.

The displacement of primary and secondary sulfonates has also been used for the preparation of fluorocarbohydrates which function as starting material for the synthesis of nucleosides by a sugar-base condensation reaction. The most relevant example is the synthesis of the 2-deoxy-2-fluoro-D-arabinofuranose derivative $\underline{24}^{52}$. This compound has been used for the preparation of many analogues of PIAC Sa. The synthesis described is suitable for large scale preparations. The reason for this total synthesis Lies in the facile neighbouring group participation reaction of the C-2

## 1226



The = cetrahydrofuranyl; Ac acetyl; fl = triflate
carbonyl group with a leaving group in the $2^{\prime}-p o s i t i o n, ~ w h i c h ~ p r e v e n t s ~ d i-~$ rect introduction of a fluor group in the $2^{" 4}$ up" position. The key step In this reaction sequence is the direct displacement of a secondary sulfanyloxy group by a fluorine aton with potassium fluoride in acetamide in a 65 Z yield., The reaction sequence leading to 24 proceeds with an overall yield of $25 \%$.


3-0-acetyl-5-0-benzoy1-2-deoxy-2-fluoro-D-arabinofuranosylbrowide 24, was condensed with several triethylsilylated bases. Deprotection with ammona in methanol provided the $\beta$-nucleosides in good yield ${ }^{11,12 ; 21 ; 52-64}$. Other analogues were made by modification of the base $59-70$ or the sugar colet ${ }^{71}$ after condensation.

An alternative procedure for the synthesis of the same sugar (25) was published by Tan et al. ${ }^{72,73}$ They started with $1,3,5-t r 1-0$-benzoyl-a-Dribofuranose (26) ${ }^{74}$, used imidazolylbulfonates ${ }^{75}$ as leaving group and zuggested a sulphonylfluoride $\left(\mathrm{SO}_{2} \mathrm{~F}\right)$ as reactive intermediate, We compared the two methods. The method of the Bristol-Myers group was indeed wore
straightforward chan the lengthy procedure carried out by Retchman et al. ${ }^{\text {2 }}$ The stoan-kettering procedure could be reproduced exactly as described in tho described yields. When we used the method of P.R. Brodfuehrer ${ }^{74}$ and C.H. Panic ${ }^{72}$, we didn't follow the fluorination with KHF 2 by HPLC but after 1 hour, 52,2 cyrstaline material was obtained (literature 63 ).

C. Nucleophilic attack on anhydro bonds

This is the most widely used method for the introduction of a flofine atom into the carbohydrate moiety of nucleosides. The method is restricted to pyrimidine nucleosides. Elimination as a side reaction is most pertinent in the doxy aeries in kaleidoscope of examples exists for the introduction of fluorine in the $2^{\prime}$ - and the $3^{\prime}$-position.
a) Introduction of fluorine in the 2' -position by opening of the $o^{2}, 2^{\prime}=$ bond

Attack of fluoride ion occurs on the sugar carbon atom. Normally about 10 z HP in dioxane, at an elevated temperature, was used ${ }^{76-81}$. A yield optimization study has been carried out for the work with [18]f ${ }^{82}$. Yields ranging from 10 to $50 z$ dependent on reaction rife and reaction temperature were obtained. In some cases $\mathrm{AlF}_{3}$ was used as a catalyst 30,84 . The use of potassium fluoride in the presence of crown aethers 85 appeared to be the best method for the synthesis of the cytosine analogue. Simple heating of $0^{2}, 2$-anhydro-1-A-D-aradinofuranosylcytosine hydrofluoride in dimethyllormamide ${ }^{86}$ gave lower yields. Scheme II gives an overall view of the nucleosides synthesized by chis method.


(30)

(Bb)

SCHEME 11

b) Opening of the $0^{3}$,3'-bond of cycionucleosides

This reaction was used for the synthesis of $2^{\prime}$, $\mathbf{3}^{\prime \prime-d i d e o x y n u c l e o s i d e s . ~}$ Only two other, examples exist. Reaction of $0^{2}, 3^{\prime}$-anhydro-1- $B-D$-xylofuranosyluracil with 12 .IF In dioxane in the presence of $\mathrm{AlF}_{3}$ afforded two fluorine containing nucleosides ${ }^{87}: 21(312)$ and $28(47 \%)$. The formation of the latter has been explained through a rearrangement of the starting material to the thermodynamically more stable $0^{2}, 2^{\prime}$-anhydronucleoside
 this rearrangement and $3^{\prime-f l u o r o-3 '-d e a x y u r i d i n e ~ w a s ~ o b t a i n e d ~ i n ~ g o o d ~}$ yield. (66 $z$ ). This compound is the only example of a $3^{\prime}$-fluoro-3'-deoxy-. B-D-ribofuranose-nucleoside described in literature.


- 39



,

27
28

SCHEME 111

As mentioned before, the group of $P$. Langen concentrated on the $2^{\prime}$ deoxypyrimidine nucleosides. The introduction of a. fluorine atom in the $3^{\prime}$-position was carried out successfully ( $30 \%$ yield) with hF in dimethylformamide or 1 a dioxin on the $5^{\prime-0-m e s y l a t e, ~ 298 . ~ T h e ~ m e s y l a t e ~ g r o u p ~ o f ~}$ 30 can be easily removed because of the possibility that an intermediate $0^{2}, 5^{\prime}$-anliydro bond forms. The use of $5^{\prime}-0$-tritylated or $5^{\prime}$-0-unprotected $0^{2}, 3^{\prime}$-anhydro compounds give lover yields of the $3^{\prime}$-fluor analogue ${ }^{88,89}$. The same authors introduced the use of an electrophilic catalyst, such as AIF 3. For the opening of the anhydro bond. In these circumstances, the concentration of the needed Hf could be lowered. Also HF excesses could be reduced (e.g. 0.1 I $\mathrm{HF}, \mathrm{AlF} \mathrm{F}^{\prime}$, dioxane or DMF, $150-200^{\circ} \mathrm{C}$ ) $29,32,33,90-94$. The $5^{\prime}-0$-wesylated- $3^{\prime}$-fluoroihymidine. 30 , vas obtained in 66 yield 30.94 . The $5^{\prime}$-O-mesylate group could $\forall C$ removed by heating with potassium acetate In acetic anhydride 94 . This reaction may also be carried out without che $5^{\prime}$-0-mesylate group $29,33,90,91$. Nevertheless, the Alp $3^{\prime}$ s solubility in dioxane. Ls very low and its exact function is not very clear. Another altetnative is the application of $\mathrm{KHF}_{2}$ or $\mathrm{NH}_{4} \mathrm{~F}$ in diethylene glycol $33,89,90$ onto $0^{2}, 3^{\prime-a n h y d r o-1-(2-d e o x y-B-i n-t h r e o-p e n t o f u r a n o s y l) t h y m i n e ~ a n d ~ 3 '-0-~}$ mesyl-2'-deoxythymidine. The products synthesized by these methods are summarized in Scheme IV. The reaction also works on pyranoses 84 .


SCHEME IV

196)

(97)


(30) (95)

(34)

(97)

(97)

SCHEME V
c) Opening of the $0^{2}$ 5' -bond of cyclonucleogides

These anhydronucleosidos can function as reactive intermediates during the synthesis of 5'-fluoropyriondines. They were rarely used. as starting material for the synthesis of such compounds. ${ }^{37,95}$,
D. Miscellaneous methods

A lot of tluorinated nucleosides have been synthesized by condensecion of fluorinate carbohydrates with purine or pyrimidine bases. Most of these fluorocarbohydrates have ween synthesized by one of the methods discribed harebefore. A discussion of their synthesis iss beyond the scope of this short review. Of che.non-mencioned products, only a tabular. review is given (Scheme V).

Further modiflearions of che known fluorinate nucleooides, either in the base, or in the sugar part have led to compounds depicted in Scheme VI. The 4-thio analogues were synthesized as intermediates in the conversion of an uracil base into a cytosine base. The inotine analogues vera obtained by enzymatic deaminate of tho adenine counterpart. The base modfled 2'-fluoro-2'-deoxyarabinonucleosides are not mentioned, Many of them are described in patent literature as for instance under ref. 56 and 59. Some compounds ( 31 and 32) verse constructed by a gradual build up of the base part, starting from the appropriate sugar (Scheme VII).

Because the formation and opening of anhydro bonds is impossible for naturally occuring purine nucleosides, the $3^{\prime}-f 1 u o r o-2^{\prime}, 3^{\prime}-d i d e o x y n u c i e o-$ sides with adenine, $3 \underline{3}^{110 \mathrm{a}}$, guanine, $34^{110 \mathrm{~b}}$, or benzimidazoie, $35^{11 \mathrm{l}}$, as base part have been synthesized by transglycosylation of a fluorinate byriwidine nucleoside with the gilylated purine base.


Only one example exists of a branched chain fluoronucleoside: 1-\{3-deoxy-3-fluoro-3-C-hydroxymethyl-B-D-xylofuranosyl)uracil, 36. It was synthesized by a sugar-base condensation reaction ${ }^{112}$.


Bobek et al. synthesized several 2'-fluorinated pyrimidine isonucleosides, 37, by means of a nucleophilic displacement on gem-difluoro-carbohydrates 113,114 .


B: uracil, thymine, 5-fluorouracil. cytosine


$$
\begin{aligned}
& \text { ( } \\
& \text { = } \\
& \text { 鿾 }
\end{aligned}
$$




## SCHEME VI (continued)



31 neg


32 (8)

SCHEME VII

Recently, publications have mentioned two examples where nucleosides were substituted by a gem-difluoro group. $2^{\prime}, 3^{\circ}$-bideoxy- $3^{\prime}, 3^{\prime}$-difluorothyaiding. 38, 115 has been synthesized from the $3^{\prime}$-keto derivative with diethylaminosulfur trifluoride. Different $2^{\prime \prime} .2^{\prime \prime}$-difluoró- $\mathbf{2}^{\prime}$-deoxynucleosides 39 were synthesized by the Eli Lilly Research group ${ }^{116}$ and by Merrill Dow Pharmaceuticals ${ }^{1 / 7}$. Both started with the appropriate base and with ethyl 2-bromo-2,2-difiuoroacetate. The 5-halogeno-, 5-halogenovinylpyrimidine ${ }^{116}$ and different purine analogues ${ }^{117}$ are also mentioned.

herdewljn, van aerschot, and kerremans

The gyntheute of nucieooidino, $1,6,7$ wac aocompliched via an addition reaction of iodine IIuorlde ( $A_{g} P, I_{2}$ ) on the $4^{\prime} .5^{\prime}$-unsaturated nucleoside. Some ocher $4^{\circ}$-C-fluoronucleosides, as for example the uracil 118,119 and the thymine ${ }^{l / 9}$ analogue of nuclēcidine, and cite $5^{\prime}$-amino- and $5^{\prime-}$-deoxyanalogue of $4^{\prime-C-f l u o r o a d e n o s i n e ~}{ }^{119}$, have been described by the same group. Ag F in pyridine has also been voided for the introduction of a flub. tine atom in the $s^{\prime}$-position of uridine with iodine as leaving group ${ }^{89}$. The $0^{2}, 5^{\prime}$-anhydro compound wis suggested as reactive intermediate.

Finally, several 4-fluorinated carbocyclic nucleosides were described in a Syntax patent ${ }^{121}$.

'X:H,F:X':F

## E. Reaction of a free hydroxyl group with dlethylaminosulfur rifluoride

Dialkylaminosulfur criflunide, 6. ${ }^{122,123}$ shows the same chemical characteristics as sulfur (IV )fluoride. Markovskif and Middleton introduced it in organic chemistry for the synthesis of, among others, gem-difluoroalkanes ${ }^{124}$ and acid fluorides ${ }^{124,125}$. The reagent has been successfully applied for the replacement of a hydroxyl group by a.fluorine atom ${ }^{126}$ and for the replacement of on anoweric hydroxyl group in the preparation of Blycosyl fluorides ${ }^{127,128}$. It also reacts easily with tertiary alcohols (for example ref. $126,129,130$ ). Dist has been extensively used for the inproduction of fluorine into carbohydrates ${ }^{13!}$.

The reaction with DAST affords products resulting from Walden inversion. Nevertheless, there are a feu examples in which the reaction proceeds with retention of configuration. An elimination reaction was not often encountered, although problems still. exist when trans-elimination can easily take place ${ }^{132}$. DAST offers the advantage that it can be "used for direct displacement of a hydroxyl group by fluorine. Very mild condilions suffice for the alcohul-fluorlde conversion: with DAST. Moreover, DAST can be used on acid sensitive substances and the reaction can be carried out with normal laboratory glass equipment. This direct introducecion of a fluorine starting with an alcohol has been done in the past with several other reagents, for example: 2-chluroul.f,2-tcifluorocriethylamine ${ }^{133}$ and diphenylerifluorophosphorane and analogues ${ }^{134}$. In spite of
thin, only the first reagent has been used for the synthesis of a fluormated nucleoside, namely the $5^{\prime}$-fluor derivative of pseudouridine ${ }^{135 a}$. The reaction on thymidine with the same reagent but in different circumstances gave the $0^{2}, 3^{\prime}$-anhydro compound ${ }^{135 b}$.


The synthesis of $3^{\prime}$-fluoro-2', 3'-dideoxynucleosides resorts under $P$. Langen et al.'s work. Their synthesis is restricted to pyrimidine nucleosides ${ }^{32,33,88-94}$. The purine analogues were obtained by a trans-glycosyla timon procedure ${ }^{110,111}$. In order to find a more generally applicable methad, we tested the reaction of diethylaminosulfur. trifluoride on 5-0-pro-tected-2-deoxy-1-B-D-thrso-pentofuranosyl-nucleosides. The reactions with pyrimidine nucleosides are summarized in Scheme VIII. Except for the use of distilled dichloromethane, dried on $\mathrm{CaCl}_{2}$, no special precautions were taken and apart from, the uridine analogue, syntheses axe described in a previous paper ${ }^{136}$. No attempts were made to optimize the described yields. The synthesis of $3^{\prime}$-fluoro-2'. 3'-dideoxyuridine 1 is analogous to the one described for the chymidine derivative. Dichloromethane can be used as solvent for ald the nucleosides


B: chywin-l-yl; uracil-1-yl; 5-ethyluracil-1-yl; cytosin-1-yl; adenin-9gl; N-trityl-2,6-diaminopurin-9-yl; guanin-9-yl

1) when $R=$ trityl: $80 \mathrm{ZHOAC}, 100^{\circ} \mathrm{C}$; when $R$ a monomethoxytrityl 2 z prom luenesulfonic acid, RT, $\mathrm{CHCl}_{3}-\mathrm{MeOH}$ (4:1)

SCHEME VIII


1) monomethoxytrityl chloride pyridine; ii) phenoxythiocarbonyl chloride, DAP, $\mathrm{CH}_{3} \mathrm{CN}$; iii) AIBN, cributyltin hydride, toluene; iv), p-toluenesulfony chloride, $\mathrm{CHCl}_{3}$. MeOH .

SCHEME IX.

The same reaction was also carried out on different purines. The reactions with adenine ${ }^{137}$ and guanine ${ }^{138}$ as base were described earlier. It is noteworthy to say that the protection of an anjnc group of adenine or cytosine with a benzoyl group gives complex reaction mixtures. In all cases, only some traces of elimination products were detected. The synthesis of 9-(2-fluoro-2,3-dideoxym-B-erychro-pentofuranosyl)adenine, 40, and 9-(2'-finoro-2', 3'-dideoxy-B-D-threo-pentofuranosyl)adenine, tl, was also described ${ }^{137}$. The purification of the latter was arduous and the yield was low ( 10 i ). Fox et al.'s $\mathrm{s}^{52}$. method is still the method to be chosen when greater amounts of a compound with the $2^{\prime}$-up configuration are needed.'


60


41

A partical problem is the synthesis of the adenosine analogue with a Elvoro group in the $3^{\prime}$-"up" configuration 42. This product could not be obtained by reaction of DAST with 5'-0-protected-2'-deoxyadenosine because of the attack of nitrogen in position-3 on the activated C-3'. This proflem was resolved as shown in Scheme $I x^{137}$. The starting material for this synthesis, 9-(3-fluoro-3-deoxy-B-D-xylofuranosyl)adènine, I. can be obcained with DAST (see further).
The compounds 40 and 41 were also described by Marquez et al. $139^{\circ}$ For the synthesis of 40 , they used the nucleophilic substitution of a triflate with tetra-n-butylamonium fluoride. For the synthesis of 41, an analogous reaction sequence was used as in that of Scheme IX.


In all previous cases, the trityl~ or monomethoxytrityl group was used for the $S^{\prime \prime}$-protection, the reason therefore lies in the selective introduction of this protecting group at a primary hydroxyl group. In case of a monomethoxytrityl group,: gome detritylation was always taking place durlng the reaction. Therefari, we suggest the, s'-o-benzoyl group, as a useful alternative (Scheme $X$ ). Also the yielde ate better with this pro, tecting group. Mónobenzoylation of 9 ( (2-deoxy-b-D-thré ranenfuranosyl)adenine, 43 , with 1 equivalent of benzoyl chloride (added dropwifa in pyridine at $0^{\circ} \mathrm{C}$ ), afforded the $5^{\prime}$-O-benzoylated derivative 44 in an 80 " yield. This compound was created with 3 equivalents of DAST in dichloromethane for 1.30 h . After the normal work-up procedure and the chromatographic purification; the $3^{\prime}-f l u o r o ~ c o m p u o n d ~ 45$ was obtained in an $80 z$ yleld. Debenzoylation vith amionta in methanol gave 9-(3-fluoro-2,3-dideo-xy-8-D-erythro-pentofuranosyl) edenine, 33, in a 917 yield.

The most observed side reaction during the fintroduction of a fluorine atom by a nucleophilic substitution reaction is the fluoride catalyzed elimination reaction. The extent to uhich this side reaction occurs is decermined by the stereochemical configuration of the substrate. a very Interesting example is the fluorination of $1,2: 5,6-d i \dot{C}^{\circ} 0-i s o p r o p y l i d e n e-a-0-$ allofuranise (A). The reaction with DAST ${ }^{132}$ yields the product from the nucleophilic displacewent (B). The same resultis are obtsined with other fluorinasing reagente (Amberlyst $\left.A 26 / V^{-}\right)^{140}, \mathrm{Bu}_{4} \mathrm{NF}^{141}$, , TASF ${ }^{142}$ ) after 3-0activation. The fluoride actack occure from the exo-side of the bicyclo[3.3.0]octane ring system. In the opposite situation, $3^{i-0 m a c t i v a t e d ~}$ 1,2:5,6-d1-0-1sopropylidene-a-D-glucofurapose (C) is strongly resistent co the nucleophiles' actack. Elimination wich che favorably disposed C-4 hydrogen 15 che predominanc reaction (D) (DAST ${ }^{132}, \mathrm{Bu}_{4} \mathrm{NF}^{141}, ~ T A S F^{142}$ ). The bame results were obtained on the $S$-O-benzoylated (or tritylated) derivative 46 (with DAST on the alcohol, with $\mathrm{Bu}_{4} \mathrm{NF}$ or CBF on the 3-0-triflate or $3-0-t o s y l a t e)^{143}$. So, each sugar exhibits a unique reactivity pattern.

(A)


(B)

(c)

13

(D)


66

It is well known that changes in the conformation of the ribose ring upon protection may alter the course of the reaction. Therefore the rearcion with DAST was tested on tritylated 9-B-D-xylofuranosyladenine, 47 . This reaction yielded the expected $3^{\prime}$-fluor compound 48 well (78 7) (Scheme $X I$ ). The yield of the deprotection step was rather disappointing (46 z) .

The importance of the use of a non-participating protecting group in 2'-position may be illustrated by the reaction of 9-(5-0-benzoyl-3-0-to-syl-2-0-acetyl-8-D-xylofuranosyl)adenlne with tetra-butylamonium fluoride in a mixture of cetrahydrofuran-acetonitrile which gave the epoxide 50 in a 63 x yield ${ }^{143}$.


The synthesis of fluorinate nucleosides with this reagent is also applicable to other nucleosides as illustrated by che preparation of $2^{\prime}$ -deoxy-2'-fluorouridine (Schema XII). The product was found to be identical



SCHEME XII
-fth that described by Cushley et al. ${ }^{16}$ The choice of the $3^{\prime}$-0-protecting groups was arbitrary.

A rather strange observation was made when $6-\mathrm{i}, 5^{\prime}-0-\mathrm{d} 1$ (monowethoxy-erityl)-3'-0-tert-butyldimethyl.eilyl-adenosine, 51 , obtained as aide compound in our synthesis of the $2^{\prime}-0-811 y 1$ derivative ${ }^{137}$, was treated with VAST ( $5 \mathrm{~h}, \mathrm{RT}, \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ). The reaction mixture was fairly complex, but only one fluorinate compound, 52, was isolated ( 302 yield). This. product was detritylated. The non-introducion of a fluorine substituent in 2 '-poricion follows from the coupling constants in the ${ }^{1} H$ NMR- and ${ }^{13} C$ NMR spectrim. The isolated compound has the same mp, $U W,{ }^{1} H$ NMR spectrum, ${ }^{13} C$ NMR spectrum and Rf in TLC is 9-(3-fluoro-3-deoxy-B-D-xylofuranosyl)adenine. An enslogons observation "was made by $S$. Roberts with adenosine protected on $3^{\prime}$ and $5^{\prime}$ with the tetriaisopropyldisiloxane group ${ }^{144}$. The theoretical possibility that DAST first cleaves the silylerher moiety and only thereafter converts di(monomethoxytrityl)adenosine into 7 was ruled out by the observation that the reaction did not give the same results when starting from $6-\mathrm{N}, \mathrm{s}^{\prime}$ - 0 -ditrityladenosine. The following reaction mechanism is proposed (Scheme XIII). Due to its very electrophilic nature, diethylaminosulfur crifluoride first reacts with the hindered $2^{\prime}$-OH group. It thus generates the intermediate 53. Removal of the silyl protecting group with an

concomitant attack of thẹ alkoxyde, generated from this fluoride induced desilylation, on, sulphur gives a cyclic intermediate; 54, which gives rise to the $3^{\prime}-\mathrm{fluoro-2'-sulfinate}$ 5S, after attack of fluoride ion on the less hindered 3 '-position. This intermediate is unstable and is hydrolyzed during work-up by attack on sulphur.

Previously, the opening of cyclic sulfates with fluoride ion by attack on carbon was described by Tewson et al. ${ }^{145,146}$. Nevertheless, the same reaction with cyclic sulfite was very slow and the yields were rathe low ${ }^{145}$.

The existence of a labile sulfinate as intermediate and the imperdance of the use of properly protected nucleosides for the introduction of a fluorine group can be illustrated by some reactions done on $2^{\prime}, 3^{\prime}$-ecouridine. Reaction of $5^{\prime}-0-t r i t y 1-2 \prime, 3^{\prime}$-secouridine, 5 56, with DAST at low temperature and interrupting the reaction so as to enable the isolation of the intermediate. produced only one spot in TLC. After a flash chromategraphy, however, a second compound appeared with a lower Rf on TLC. Both products ware isolated and it was shown that the most apolar compound could be easily converted in the most polar compound, for example, by

## 1



56

$59 \mathrm{~d} \cdot \mathrm{R}=\mathrm{Ir}$ $59 \dot{B} \cdot \mathrm{R}=\mathrm{H}$.

$\mathrm{Et}_{2} \mathrm{~N}$


58

SCHEME XIV
stirring in MeOW in the presence of silica. The unstable product was adentiffed as 57, and the other compound as 58 (Scheme XIV). These products are the result of a neighbouring group participation reaction of the C-2 carbonyl groups on $C-2^{\prime}$. When te tried to introduce a fluorine atom in the $2^{\prime}$-position with potassium fluoride and crown ether in monoglyme or dinethylformamide, in the presence of p-toluenesulfonic acid, the reaction mixture contained two products. The first was the starting material, the second 59a, resulted from a neighbouring group attack of the free HO-group on $C-2^{\prime}$. Without $p$-toluenesulfonic acid, no such ring closure occurred. The product vas further identified after detritylation to 59 b .

When we compare the ${ }^{1} H$ NMR; and ${ }^{13} C$ NMR spectra in DMSO-d 6 of the fluorinate $B$-adenosine analogues we can conclude as follows :
 range coupling is -found between the $H-8$ and fluorine in. the ${ }^{\prime} H$ NMR spectrim and between $C-8$ and fluorine in the ${ }^{13} C$ NMR spectrum.

- When the fluorine atom is.sicuated in the $3^{\prime \prime}$ up" position, only the signat for $C-8$ is split into a doublet. No $H-8, F$ coupling was found.
- With e fluorine atom in the $2^{\prime}$ - or $y^{\prime \prime}$ down" position, neither of the two occurred.


## EXPERIMENTAL PART

Melting points were determined in capillary tubes with a Büchi-Tottoll apparatus and are uncorrected. Ultraviolet spectra were recorded with
a Beckosin UV 5230 epactrophotompter. Mags cpagtra care dotormincd with an AEI MS -12 apparatus. The ${ }^{2} H$ NAK and ${ }^{13} \mathrm{C}$ NHR spectra were determined by means of a $J E O L F X$ 90Q spectrometer $v i t h$ tetramethylgilane as internal
 coated Merck silica gel $F 254$ plates were used for TLC, and the spots were examined with uV light find a guphuric.acid-anisaldehyde spay y. Column chromatography was performed on Merck silica gel ( $0.063-0.200$ mon). Ashydrous solvents were obtained as follows: pyridine was refluxed overnight in p-toluenesulfonyl chloride, distilled, refluxed overnight in potassium hydroxide, and distilled again; dichloromechane was. stored for 1 week on anhydrous calcium chloride, filtered, and distilled.

## 3'-Fluoro-2'.3'-dideoxyuridipe

This product was described formerly. ${ }^{32}$, although with little physical constants. It was synthesized in the sane way as described for the thymedine analogue ${ }^{136}$. except that dichloromethane was used as solvelli.
Dp $183-184^{\circ} \mathrm{C}$.
UV ( MeOH ) $\wedge_{\max }: 260 \operatorname{mm}(c 10,100)$.
MS ( $m / \mathrm{e}$ ) $230\left(\mathrm{~K}^{+}\right)$.
 (dr, J $4^{\prime}, F=27 \mathrm{~Hz}, \mathrm{H}-4^{\prime}$ ): $5.30\left(\mathrm{~m}, \mathrm{~J}_{3}, \mathrm{~F}=54.5 \mathrm{~Hz}, \mathrm{H}-3^{\prime}\right): 5.67\left(\mathrm{~m}, 5^{\prime}-\mathrm{OH}\right.$,
 (bye, NH).
${ }^{13} \mathrm{C} \underset{\operatorname{NiR}(\text { pyridicne-d }}{5}$ ) $: 38.8\left(\mathrm{~d}, \mathrm{~J}=20.9 \mathrm{~Hz}, \mathrm{C}-2^{\prime}\right) ; 61.8(\mathrm{~d}, \mathrm{~J}=11.0 \mathrm{~Hz}$, C-5'); 85.6 ( $\mathrm{B}, \mathrm{C}-\mathrm{I}^{\prime}$ ) ; 86.2 ( $\mathrm{d}, \mathrm{J}=24 \mathrm{~Hz}, \mathrm{C}-4^{\prime}$ ) ; $95.6(\mathrm{~d}, \mathrm{~J}=175.9 \mathrm{~Hz}$, C-3'); $102.9(\mathrm{~B}, \mathrm{C}-5) ; 140.3(\mathrm{~A}, \mathrm{C}-6) ; 151.6(C-2) ; 164.1(C-4)$.

## 9-(3'-Fluoro-2', $3^{\prime}$-dideoxy-8-D-erythro-pentofuranosyl)-2,6-diaminopurine

A solution of 1.58 ( 2 mall) of 9-(2-deoxy-5-0-tricyl-B-D-threo-pen-tofuranosyl)-N-trityl-2,6-diaminopurine in 50 ml of anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was treated with $l$ mi of DAST for 75 min at room temperature. The mixture was poured in 40 ml of 10 z sodium bicarbonate. The organic layer was separared, dried, evaporated and purified by column chromatography to yield 1.17 8 (78 2) of the 3 -fluor compound. $\therefore \quad:$ ${ }^{2} \mathrm{H}$ NR R ( $\mathrm{CDCl}_{3}$ ) $\delta: 1.91-2.80$ ( $\mathrm{m}, \mathrm{H}-2^{\prime}, \mathrm{H}-2^{\prime \prime}$ ); $3.22^{\circ}$ (m, H-5', H-5'); 4.2!
 at 5.25 ppra$) ; 5.72$ (m, H-1'); 6.12 ( NH ); 6:87-7.64 (m, trityl).
The product was further identified after detritylation. Therefore, 1 mol ( 0.75 g ) was dissolved in 80 I acetic acid and heated for 25 min at $80^{\circ} \mathrm{C}$. The mixture was evaporated, coevaporaced with toluene and purified by co-

Juan chromatography ( $\mathrm{CHCl}_{3}-\mathrm{HeOH} ; 95: 5$ ), thus yielding $145 \mathrm{mg}(54 \mathrm{Z})$ of the stele compound which vas crystallized from MeCH.
np $192-193^{\circ} \mathrm{C}$.
MS ( $\mathrm{B} / \mathrm{C}$ ) 268 ( $\mathrm{K}^{+}$),


$I^{\prime} \operatorname{NarR}\left(\mathrm{CO}_{3} \mathrm{OD}\right) 6: 2.47-2.85$ and $3.00-3.36$ ( $\mathrm{m}, 2 \times 1 \mathrm{H},{ }^{\circ} \mathrm{H}-2^{\prime}$ ' and $\mathrm{H} 2^{\prime \prime}$ ); 3.82 ( $\mathrm{a}, 2 \mathrm{H}, \mathrm{H}-\mathrm{s}^{\prime}$ and $\mathrm{H}-5^{\prime \prime}$ ) ; 4.35 (dz, $1 \mathrm{H}, \mathrm{J}_{4^{\prime}, \mathrm{F}}=27.5 \mathrm{~Hz}, \mathrm{H}-4^{\prime}$ ); 5.40 (dd, 1 H , $\left.J_{3^{\prime}, F}=54.7 \mathrm{~Hz}, \mathrm{H}-3^{\prime}\right) ; 6.30$ (dd, $1 \mathrm{H} ; \mathrm{J}=5.9 \mathrm{~Hz} ; 9.2 \mathrm{~Hz}$ and $\left.0.6 \mathrm{~Hz}, \mathrm{H}-1 \mathrm{l}^{\prime}\right) ;$ 1.96 (s, MH, slowly exchangeable); 7.94 (d. $\mathrm{J}=0.6 \mathrm{~Hz}, \mathrm{H}-8$ ) ppm.
${ }^{13} \mathrm{C}$ NR $\left(\mathrm{CD}_{3} \mathrm{OD}\right) 39.0\left(\mathrm{~d}, \mathrm{~J}=20.75 \mathrm{~Hz}, \mathrm{C}-2^{\prime}\right) ; 63.5\left(\mathrm{~d}, \mathrm{~J}=12.2 \mathrm{~Hz},\left(\mathrm{C}-5^{\prime}\right)\right.$; $87.3\left(\mathrm{~s}^{\prime}, \mathrm{C}-\mathrm{I}^{\prime}\right)$; $88.05\left(\mathrm{~d}, \mathrm{~J}=22.0 \mathrm{~Hz},\left(\mathrm{C}^{\prime}\right)\right.$; $96.50\left(\mathrm{~d}, \mathrm{~J}=175.8 \mathrm{~Hz},\left(-3^{\prime}\right)\right.$; $138.8(\mathrm{~s}, \mathrm{c}-8)$.

3'-Fluoro-3'-deoxyadenosine, 49
A mixture of 2 mmol of $\mathrm{B}-\mathrm{D}-\mathrm{xylofuranosyladenine} \mathrm{and} 12$. Wal of riphenylmethylchloride in anhydrous pyridine ( 30 ml ) was heated for 2.5 days at $80^{\circ} \mathrm{C}$. After cooling to room temperature and adding Me OM, we concentrated the mixture to 10 ml and then poured it into $\mathrm{H}_{2} \mathrm{O}$ and extracted with $\mathrm{CHCl}_{3}$. The organic layer was dried, evaporated and purified by colum a chromatography : 1) $\mathrm{CHCl}_{3}$, 2) $\mathrm{CHCl}_{3}-\mathrm{MeOH}(99: 1)$. The product 47 crystallized from MeCH ( 1 mol, 502,18 ).
np $240^{\circ} \mathrm{C}$.
UV ( $\mathrm{CHCl}_{3}$ ) $\lambda_{\max }: 275^{\circ} \mathrm{nm}(\mathrm{E} 23,400)$.
${ }^{\prime} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta: 3.50$ (m, $\left.\mathrm{H}-\mathrm{S}^{\prime}, \mathrm{H}-5^{\prime \prime}\right) ; 3.96$ (dd, $\mathrm{H}-3^{\prime}$ ); 4.29 (m, $\mathrm{H}-\mathrm{C}^{\prime}$ ); 4.57.(d, H-2'). The presence of three trityl groups was confirmed by intergration of the multiplet at $\delta 7.30$ and compared with the integration of the doublet at $\delta 5.45$ ( $\mathrm{H}-\mathrm{l}^{\prime}$ ); 7.76 ( s , purine H ).
A solution of 1 mol ( 993 mg ) of this compound in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 50 ml ) was treated. with DAST ( $0.3 \mathrm{ml}, 2 \mathrm{mal}$ ) for 4 h at room temperature. The reaction mixture vas poured into 50 ml of 10 z sodium bicarbonate, the orgenic layer was dried and evaporated. Column chromatographic purification $\left(\mathrm{CHCl}_{3}\right)$ yielded $720 \mathrm{mg}(72 \cdot 2)$ of tritylated $3^{\prime}$-fluoro-3'-deoxyadenosine, 48.
$\mathrm{T}_{\mathrm{H}}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta: 3.04\left(\mathrm{~m}, \mathrm{H}-5^{\prime}\right) ; 3.30\left(\mathrm{~m}, \mathrm{H}-5^{\prime \prime}\right.$ and one half of $\left.\mathrm{H}-3^{\prime}\right)$; 3.90 (bId, one half of $\mathrm{H}-3^{\prime}$ ): 4.23 (dr, $\mathrm{J}_{4}, \mathrm{~F}=27 \mathrm{~Hz}, \mathrm{H}-4^{\circ}$ ): 5.12 (dad, $\mathrm{J}_{2}^{\prime}, \mathrm{F}=21.5 \mathrm{~Hz}, \mathrm{~J}=3.7$ and $7.5 \mathrm{~Hz}, \mathrm{H}-\mathbf{2}^{\prime}$ ); $6.25\left(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, \mathrm{H}-\mathrm{I}^{\prime}\right) ; 7.32$ ( $\mathrm{m}, \mathrm{trityl}$ ); 7.82 and 7.86 ( $2 \times \mathrm{m}, \mathrm{H}-2$ and $\mathrm{H}-8$ ).
In comparison with the normal position of the $\mathrm{H}-\mathbf{3 '}^{\prime}$ proton, the $\mathrm{H}-\mathbf{3 '}^{\prime}$ proton
is situated at a much higher field. This suggests the situation of this proton in. che shielding zone of an aromatic protecting group. An explanacion by a close proximity of $\mathrm{H}-\mathrm{J}^{\prime}$ to tho $\mathrm{N}-3$ lone pair of electrons can be exrlinded because the some phenomenon was also observed for the thymine analogue (data not shown).
 $82.5\left(\mathrm{~J}=23.2 \mathrm{~Hz}, \mathrm{C}-4^{\prime}\right): 86.7\left(\mathrm{~s}, \mathrm{C}-1^{\prime}\right) ; 90.5\left(\mathrm{~d}, \mathrm{~J}=185 \mathrm{~Hz}, \mathrm{C}-3^{\prime}\right)$.
This compound ( 0.720 mol. 716 . mg) was diluted with 20 ml of 80 z acetic acid and stirred overnight at room temperature and 30 min at $100^{\circ} \mathrm{C}$. We then evaporated che mixture, coevaporated it with toluene and purified it by column chromatography: 1) $\mathrm{CHCl}_{3}-\mathrm{MeOH}$ ( $99: 1$ ), 2) $\mathrm{CHCl}_{3}-\mathrm{MeOH}$ (90:10). The title compound 49 crystallized from MeCH: 70 mg ( 0.26 mol, 46 Z).
top $164^{\circ} \mathrm{C}$ (dec): .
uv (MeCH) $\lambda_{\text {wax }}$ : $259 \mathrm{~nm}(c \mid 5,070)$.
MG (me) $260\left(\mathrm{M}^{+}\right)$.
 $H .4^{\prime}$ ) ; 4.95 (dod, $J=4.2$ and $7.5 \mathrm{~Hz}, J_{2}, F=25.0 \mathrm{~Hz}, \mathrm{H}-2^{\prime}$ ); 5.10 (dd, $\mathrm{J}=$ $4.2 \mathrm{~Hz}, \mathrm{~J}_{3}, . \mathrm{F}=54.0 \mathrm{~Hz}, \mathrm{H}-3^{\prime}$ ) ; $5.95\left(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz} ; \mathrm{H}-\mathrm{I}^{\prime}\right.$ ); 7.38 ( $\mathrm{Drs}, \mathrm{NH}_{2}$ ); 8.16 and $8.36(2 \times s, H-8$ and $H-2)$.
${ }^{1 J} \mathrm{C} \operatorname{NHR}\left(\mathrm{DMSO}_{6}\right): 61.2\left(d, J=11.0 \mathrm{~Hz}, \mathrm{C}-5^{1}\right) ; 72: 2(\mathrm{~d}, \mathrm{~J}=15.9 \mathrm{~Hz}$. $\left.C-2^{\prime}\right) ; 84.1\left(d, J=22 H z, C-4^{\prime}\right) ; 87.1\left(s, C-1^{\prime}\right) ; 93.2(d, J=181.9 \mathrm{~Hz}$, $\left(-3^{\prime}\right) ; 119.5(\mathrm{~s}, \mathrm{C}-5) ; 140.3(\mathrm{~s}, \mathrm{C}-8) ; 149.3(\mathrm{~s}, \mathrm{C}-4) ; 152.6(5, \mathrm{C}-2)$; $156.2(\mathrm{~s}, \mathrm{C}-6)$.
Elem. Anal. calculated $C: 44.61 \mathrm{H}: 4.49 \mathrm{~N}: 26: 0.1$

$$
\text { found } \quad C \because 44.72 \quad 11: 4.64 \quad N: 26.22
$$

(3-0-Trtiyl-0 ${ }^{2}, 2^{\prime}$-anhydror $2:, 3^{\prime}$-secouridine, 58.
$5^{\prime}$-0-Trityl-2', $3^{\prime}$-setouridine ( $3 \mathrm{mmol}, 1.4 \mathrm{~m}_{\mathrm{g}} \mathrm{g}$ ) was dissolved in 15 ml of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, cooled co $-70^{\circ} \mathrm{C}$, and $0.73 \mathrm{ml}(6 \mathrm{mmol})$ of DAST was added. The reaction mixture was warmed up to $-20^{\circ} \mathrm{C}$ over a period of 40 min , and pourred into $\$ Z$ sodium bicarbonate solution, cooled in ice: The organic layer was separated, washed with water and dried. TLC revealed only one spot. After flash chromatography (CHC1 ${ }_{3}-\mathrm{MeOH} \cdot 96: 4$ ) on silica gel, a second compound appeared with lower Rf. Both products were isolated in a total. yield of approximately 60 z .
 57
MS (moe) no molecular ion could be detected, high rel. intensity was found at $470\left(M^{+}-\right.$SONE $\left._{2}+H\right)$ and $120\left(\right.$ NONEt $\left._{2}\right)$.
 ( $4, \mathrm{CH}_{2} \mathrm{CB}_{3}$ ) : 32.6 (m, R-5', $\mathrm{H}-5^{\prime \prime}$ ); 3.52-4.24 (AB part from ABX spectrum, H-3'. partially overlapped with $H-4^{\prime}$ ): 4.63 ( $A B$ part of $A B X$ spectrum;
 $7.5 \mathrm{~Hz}, \mathrm{H}-5$ ) ; 6.06 ( $\mathrm{Q}, \mathrm{J}=5.7$ and 2.6 Hz, $\mathrm{H}-\mathrm{I}^{\prime}$ ); 7.3 ( m, tritgl and $\mathrm{H}-6$ ). ${ }^{13}{ }_{f} \operatorname{MRR}\left(\mathrm{CDCl}_{3}\right) ; 13.6\left(\mathrm{CH}_{3}\right) ; 36.2{ }^{\prime}\left(\mathrm{CH}_{2} \mathrm{CH}_{3}\right) ; 63.0$ and $63.5\left(\mathrm{C}-2^{\prime}\right.$ and C-5'); $73.2\left(C-3^{\prime}\right) ; 79.5\left(\mathrm{C}-4^{\prime}\right) ; 87.1\left(\mathrm{C}_{3}\right) ; 87.5\left(\mathrm{C}-1^{\prime}\right) ; 109.5(\mathrm{C}-5)$; 127.0, 127.6, 128.2, 142.8 (trityl); 135.3 (C-6); 160.1 (C-2); 171.8 (C-4).

ap $181^{\circ} \mathrm{C}$.
MS (me) $470\left(\mathrm{M}^{+}\right)$.
UV ( MeOH ) $\lambda_{\max }: 252 \mathrm{~nm}$ (sh.).
 $\left.\mathrm{H}-4^{\prime}\right) ; 4.65\left(\mathrm{~m}, \mathrm{H}-2^{\prime}, \mathrm{H}-2^{\prime \prime}\right) ; .5 .80(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, \mathrm{H}-5) ; 6.23(\mathrm{t}, \mathrm{J}=4 \mathrm{~Hz}$, H-1'); 7.47 (m, 'trotyl); 7.57 (d, H-6).
${ }^{13} \mathrm{C} \operatorname{NaR}\left(\mathrm{CDCl}_{3}\right) 63.1$ and $63.7\left(\mathrm{C}-2^{\prime}\right.$ and $\left.\mathrm{C}-5^{\prime}\right)$; $74.2\left(\mathrm{C}-3^{\prime}\right) ; 82.4\left(\mathrm{C}-4^{\prime}\right)$; $87.0\left(C \phi_{3}\right) ; 81.9(C-1!) ; 109.2(C-5) ; 136.4(C-6) ; 160.5(C-2) ; 172.8$ (C-4). Other signals for the city groups are not mentioned.
$1-(R)-(6-(R)$-hydroxymethyl-1,4-dioxan-2-yl)uracil
Reaction of $5^{\prime}-0-t r i t y l-0^{2}, 2^{\prime}$-anhydro- $2^{\prime}, 3^{\prime}$ - secouridine, 58 (or the $3^{\prime-0-d i e t h y l s u l f i n a t e), ~ w i t h ~ p o t a s s i u m ~ f l u o r i d e ~(10 ~ e q), ~[18]-c r o w n-[6]-~}$ polyether, in monoglyme in the presence of p-toluenesulfonic acid andydross for 6 h at reflux temperature gave 48 Z of the starting material and 30 z .of the 1.4 -dioxane derivative 59a. The yield of 59 a . 1 s 60 z when the reaction is carried out in DHF at reflux overnight. UV (MeOW) 260 tu.
${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta$ : signals for $\mathrm{H}-3, \mathrm{H}-5, \mathrm{H}-6$ and the $\mathrm{CH}_{2} \mathrm{OTr}$ protons are concentrated in one multiple ranging from 2.9 to 4.2 ppm 5.7 (d; $\mathrm{H}-5$ ); 5.75 (dd, $\mathrm{J}=2.8$ and $9.4 \mathrm{~Hz}, \mathrm{H}-3 \mathrm{l}$ ): 7.23 (trityl and $\mathrm{H}-6$ ).
${ }^{13} \mathrm{C} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): 63.1\left(\mathrm{CH}_{2} \mathrm{OTr}\right) ; 67.8$ and $68.0\left(\mathrm{CH}_{2} \mathrm{OCH}_{2}\right) ; 75.9$ (C-6i); 78.7 ( $\mathrm{C}-2^{\prime}$ ); 102.6 ( $\mathrm{C}-5$ ); 139.3 ( $\left.\mathrm{C}-6\right)$; 149.7 ( $\left.\mathrm{C}=0\right) ; 162.8$ ( $\mathrm{C}=0$ ).

The product was further identified after detritylation with $80 \%$ of acetic acid at $100^{\circ} \mathrm{C}$ for 25 min and isolated in 83 Z yield after column chromategraph ( $\mathrm{CHCl}_{3}$ - $\mathrm{MeOH}, 97-3$ ). This product, 59 b , has been described previous$1 y^{147,148}$.
mp $164-165^{\circ} \mathrm{C}$.

UV ( HeOH ) $\lambda_{\text {max }}: 260 \mathrm{~nm}$ ( $(\varepsilon 9.700)$.
HS (m/e) $228\left(M^{+}\right)$.
${ }^{\prime} \mathrm{H} \operatorname{NHR}\left(\mathrm{CO}_{3} \mathrm{COCO}_{3}\right) \delta: 3.3-4.15$ (m; $\mathrm{H}-3^{\prime}, \mathrm{H}-5^{\prime}, \mathrm{H}-6^{\prime}$ and $\mathrm{CH}_{2} \mathrm{OH}$ ); 5.65 (d, $J=8 \mathrm{~Hz}, \mathrm{H}=5$ ) ; 5.75 (dd, J 9.7 and $2.9 \mathrm{~Hz}, \mathrm{H}-2^{\prime}$ ): 7.72 (d, H-6) ppm.
${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CD}_{3} \mathrm{COCD}_{3}\right)=61.6\left(\mathrm{CH}_{2} \mathrm{OH}\right) ; 67.2$ and $67.6\left(\mathrm{CH}_{2} \mathrm{OCH}_{2}\right) ; 77.9$ and 78.9 $\left(C-2^{\prime}\right.$ and $\left.C-G^{\prime}\right) ; 102.0(C=5) ; 140.5(C-6) ; 150.3(C=0) ; 162.8(C=0)$.

## Acknowledgment

He are indebted to Dr. C. Cosselfn of the "Université des Sciences et Techniques du Languedoc" for kindly providing his research results. Dr. P. Herdewijn is a research associate of the Belgian National Fund of Scientific Research. We thank Laurent Palmaerts, Christiane Callebaut and Kaat Cumps for fine editorial help.

## REFERENCES

1. (a) Blandin, M.; Son, T.-D.; Catlin, J.C.; Guschlbauer, W. Blochim. Biophys. Acca 361. 249 (1974); (b) Lipnick, R.L.; Eissekis, J.D. Biochim. Blophys. Acta 608, 96 (1980).
2. Klimke, G.; Cuno, I, Ludemann, H.-D.: Mengel, R.; Robins. K.J. Z. Naturforsch. 35, 853 (1980).
3. Marck, C.; Lesyng, B.; Saenger, W. J. Molec. Struct. 82, 77 (1982).
4. Thomas, S.o.; Singleton, V.L.; Lowery, J.A.; Sharpe. R.W., Pruess, L.M.: Porter, J.N.; Mowat, J.H.; Bohonod, N. Ancibiotics Ann. 716 (1956-1957).
5. Morzon, G.O.; Lancaster, -J.E.; Van Lear, G.E.; Fulmor, W.; Meyer, W.E. J. Am. Chew. Soc. 91. 1535 (1969).
6. Jenkins, T.j.; Verkeyden, J.P.H. J. Am. Chem. Soc. 93.4323 (1971).
7. Jenkins. I.D.; Verheyden, J.P.H., Moffatt, J., G. J. Am. Chem. Soc. 98, 3346 (1976).
8. Monegomery, J.A.; Hewson; K. J. Med. Chem. 12, 498 (2969),
9. Brockman. R.W.; Schabel. F.M. Jr.: Montgomery, J.A. Blochem. Pharmacol. 26, 2193 (1977).
10. Fox, J.J.; Lopez, C., Watanabe, K.A. in Antiviral Chemotherapy. Design of Inhibitors of Yiral Functions. Gauri, K.K. (ed.). Academic Préss, p. 219 (1981).
11. Hä̈anabe; K.A., Su, T., L.; Reichwan, U.; Greenberg, N.; Lop.ez, C.: Fox, J.J. J. Med. Chem. 27. 91 (1984).
12. Mannur1, M.M.; Ghazzouli. L.; Chen, M.S.; Howell, H.G.; Brodfuehrer, P.R.; Benlgni, D.A.; Martin, J.C. J. Med. Chem. 30, 867 (1987).
13. Rabins, M.J.; Fouron, Y.; Mengel, $\bar{R}$. J.Org. Chem. 39, 1564 (1974).
14. Miyai, K.; Robins R.K.; Tulman R.L. J. Med. Chem. 15, 1092 (1972).
15. Kowollik, G.; Langen, P. Z. Chem, 15, 147 (1975).
16. Sharma, R.K.; Firy, J.L. J. org. Chem. 48, 2112 (1983).
17. Misra, H.K.; Gati, W.P.; Knaug. E.R.; Wiebe, L.I. J. Heterocyclic Chex. 21. 773 (1984).
18. Cushley, R.J.; Codington, J.f.1 Fox, J.J. Can. J. Chem. 46, 1131 (1968).
19. Wright, J.A.; Taylor, N.P. Carbohyd, Res. 6, 347 (1968).
20. Wright, J.A.; Taylor, N.F. Carbohyd. Res. 3, 333 (1967).
21. Wright, J.A.; Wilson, D.P.; Fox, J.J. J. Med. Chem. 13, 269 (1970).
22. Wright J.A.; Fox, J.J. Carbohyd. Res. 13,297 (1970).
23. Wright, J.A.; Taylor N. F., Fox J.J. J. Org. Chém. 34, 2632 (1969).
24. Hirschamen, R.F.; Niller, R.; Hood, J.; Jones, R.E. J. An. Chem. Soc. 78, 4956 ( 1956 ).
25. Herrmann, C.; Cech, D.; Kowollik, G.; Langen, P. 2. Chem. 19r 376 (1979).
26. Ajmera, S.; Danenberg, P.V. J. Med. Chem. 25, 999 (1982).
27. Kowollik, O.; Gaertner, K.; Etzold, $\overline{0 . ;}$ Langen, P. Carbohyd. Res. 12, 301 (1970).
28. Langen, P.; Kowollik, G. Eur. J. Blochem. 6, 344 (1968).
29. Langen, P.; Etzold, G.; Kowollik, G. Acta biol. med. gem. $28, \mathrm{~B}, \mathrm{~K}$ (1972).
30. Schutt, M.; Kowollik, G.; Ëtzold, G.; Langen, P. J. prakt. Chemie 314, 251 (1972).
31. TIn, T.-S. : Gao, Y.-S., Mancin1. W.R. J. Med. Chem. 26, 1691 (1983).
32. Rowollik G., Etzold, G.; von Janta-Eipinaki, M.; Gaertner, R.; Langen, P. J. prakt. Chemie 315, 895 (1973).
33. Langen, P.; Etzold, G.; Hintsche, R.; Kowollik, G. Acta biol. med. germ. 23, 759 (1969).
34. Etzold, G.; von Janta-Lipinski, M.; Langen, P. j. prakt. Chemie'318. 79 (1976).
35. Langen, P.; Kowollik, G. Acta Riol. Med. Germ. 20, 417 (1968).
36. Kowollik, G.; Langen, P. Ger. (East) 78 244. Chem. Abstr. 76, 72 752p (1972).
37. Hermann, G.; Cech, D.; Kowollik, G.; Langen, P. Z. Chem. 19; 376 (1979).
38. Langen, P.: Kowollik. G. Brit. 1161 586. Chem. Abstr. 72. 3724m (1970).: Ger (East) 65 935. Chem. Abstri. 72, 3728 r (1970). Er.M. 6966. Chem. Abstr. 74, 100360 p (1971).
39. Shen, T.-Y. Ruyle, W.V.; Neilison, T. U.S. 3. 575 .959. Chem. Abstr. 75, 98 780a (1971).
40. Schuert, M.; Von Janta-Liplnski. M.; Etzold. G.; Langen, P. Ger. (East) 83 144. Chem. Abstr. 78. 43 944p (1973).
41. Ranganathan, R. Tetrahedron Eete. 1291 (1977).
42. Ikehara, K.; Hasegawa, A.; Imura, J. J. Carbohyd. Nucl. Nuc1: 7. 131 (1980).
43. Vesugl, S.; Xaneyasu, T.; Katsugi, J.; Ikehara, M. Nucleosides 6 Nucleotides 2, 373 (1983).
44. Tkehara, M; Miki, H. Chew. Phamm, Bull. 26, 2449. (1978).
45. Ikehara, M. Keterocycles 31,75 (1984).
46. Uesugl, S.; Katbug1, J.; Kaneyasu, T.; Ikehara, M. Heterocycles 11. 285 (1982).
47. Ikehara, M. ; Imura, J. Cham. Phalm. Bull. 29, 1034 (1981) and Chem. Pharn. Büll. 29, 3281 (1981).
48. Hakoshima, T.; Omori, H.; Tomita, K.-I.; Hiki, H.; Ikehara, M. Nuclelc Acids Res. 9, 711 (1981).
49. (a) Ikehara, M.; Kakluchi, N.; Fukui, T. Nucleic Acids Res, 5, 3315 (1978); (b) Stoeckler, J.D.; Bell, C.A.; Parks, R.E.; Chu, C.K.; Fox, J.J.; Ikehara. M. Biochem. Pharmacol. 31, 1723 (1982).
50. Pankiewicz, K.U.; Nawrut. B.; Sochackg, E..; Watanabe, K.A. Nucleic Acids Res. Symp. Series 18, 257 (1987). Pankiewicz, X.R.; Nawrot., B.; Gadler, H.; Price, R.W.; Watanabe, K.A. J. Med. Chem. 30, 2314 (1987).
51. Doboszewski, B.; Hay, G.W.; Szarek, W.A. Can. J. Chem. 65, 412 (1987).
52. Reichman, U.; Watanabe, K.A.; Fox J.J. Carbohyd. Res. 42, 233 (1975).
53. Griengl, H.; Wanek, E.; Schwart. W.; Streicher. H.; Rosenwirth, B.; De Clercq, E. J. Med. Chem. 30, 1199 (1987).
54. Chou, T.C.i Kongi X.B. F Fanucchi, M.P.; Cheng. Y.-C.; Takahashi, K.; Watanabe, R.A.; Fox. J.J. Antimicrob, Agents Chemother, 31, 1355 (1987).
55. Chun, M.W. Arch. Pharm. Res. 6, 79 (1983),
56. Lopez, C.; Watanabe, R.A.; Reīchoan. D.; Fox, J.J. U.S. US 4594339. Chem. Abstr. 106, 113 538g (1987).
57. (a) Iopez, C.; Chou, T.C.; Watonabe. K.A.; Fox. J.J. Dey. Mol. Virol. 4, 105 (l9n4). (b) Svigor, J.E.: Pittman, K.A. J. Labell. Comp. Radiopharm. 22, 931 (1985).
S8. Sloan-Kettering Institute lor Cancer Research. Jpn. Kokai Tokkyo Koho 8049 395. Chem. Abstr. 93. 95 5978 (1980).
58. Watanabe, K.A.; Chu, C.K.; Fox, J.J. Eur. Par. Appl. EP 219829. Chem. Abstr. 107. 59 409u (1987).
59. Watanabe, X.A.; Reichman, U.; Hirota, K, ; Lopez, C.; Fox, J.J. J. Med. Chem. 2े2, 21 (1979).
60. Watanabe. K.A.; Su. I.-L., Klein, K.S.; Chu, C.K.; Matsuda, A.; Chun, M.W.; Loper, C'; Fox, J.J. J. Med. Chem. 26,152 (1983).
61. Su, T.-L., Watanabe, K.A.; Schinari, R.F.; Fox, J.J. J. Med. Chem. 29, 151 (1986).
62. Huang, J.-T.; Schinazi, R.F.; Gadler, H. : Price, R,W. Su, T.-L., Watanabe, K.A.; Nucleic Acids Res. Symp. Series 18. 261 (1987).
63. Montgomery, J.A.; Shortnacy, A.T.; Carson, D.A.i. Sécrist Ill, J.A. J. Med. Chem. 29, 2389 (1986).
64. Matulic-Adamic, J.; Watanabe, K.A. Chemica Scripta 26, 127 (1986).
65. Sharma, R,A.; Kavai, I.; Hughes, R.G., Jr.i Bobek M. J. Med. Chem. 27. 410 (1984).
66. Suzuki, S.: Migra, H.K.; Wlebe. L.I.; Knaus, E.E.; Tyrrell, D.L.J. Mol. Pharmacol. 31, 301 (1987).
68̣. Periman. M.E.; Watanabe, K.A.i Nchinazi, R.F.; Fox, J.J. J. Med. Chem. 28, 741 (1985).
67. Perlaian, M.E.; Conti, P.S.; Sclmall, B.; Watanabe, K.A. Int. J. Nuclelc Med. Biol. 11, 215 (1984).
68. a) Mista. H.K.; Knauss. E.E.; Wlebe, L.I.; Lorne, T.D. Appl. Kadiat. Isot. 37, 901 (1986). b) Misra, H.K.; Wiebe, L. I. ; Knaus, E.E. J. Labe11. Comp. Radiopharm. 24, 1107 (1987).
69. Harada, K.; Katulic-Adamlc, J.; Price, R.W.; Schinazi, R.P.; Watanabe, K.A.: Fox, J.J. J. Med. Chem. 30, 226 (1987).
70. a) Tann, C.K.; Brodfuehrer, $\bar{P}, \vec{R}$, Brundidge, S.P.; Sapino, C., Jr.i Howell, H.G. J. Orig. Chem. 50, 3644 (1985). b) Hovell, H.G.; Brodfuehrer, P.R.; Brundidge, S.F.; Benigni, D.A.: Sapino, C. Jr. J. Otg. Chem. 53, 85 (1988).
71. Brundidge, S.P.; Howell, H.G.; Supino, C. Jr.; Tann, C.H. Eur. Pat. Appl. EP. 145978. Chem. Abytr. 103, 179 579d (1985).
72. Brodiuefirer, P.R.; Sapinn, C. Jt.; Howell, H.G. J. Org. Chem. 50, 2597 (1985).
73. Manusisian, S.; Vatèle, J.-M. Tetrahedron Lett. 22, 3579 (1981).
74. Codingron. J.F.; Doerr, 1.L.; Fox, J.J. J. Org. Chem. 29, 558 (1964).
75. Polazzi, J.O.; Leland, D.L.; Kotick, M.P, J. Org. Chem. 39, 3114 (1974).
76. Abrans, D.N.; Knaus, E.E.: Mercer, J.R.; Wiebe, L.I. J. Label. Comp. Radiopharm. 16, 12 (1979).
77. Codington, J.F.; Doerr, I.: Van Praag, D.; Bondich, A.; Fox, J.J. J. Am. Chem. Soc. 83, S030 (1961).
78. Mercer, J.R.; Knaus..E.E.; Wiehe, L.I. J. Med. Chem. 30, 670. (1987).

81, a) Blandin, M.; Jankowski. K. Buli. Acād. Pol. Sci. Ser. Sci. Chim. 27. 563 (1979). b) Byandin, M. Jankoveki, K. Eur. J. Mass. Spectrom. Biochém. . Med. Environ. Res. 1. 129 (1980).
82. Abrams, D.N.; Mercer; 'J.R.; Knaus. E.E.; Uiebe; L.I. Int. J. Appl. , Radiat. [sot. 36. 233 (1985).
83. Kanal. T. Iching, 'M. ': Nakamura, T. Japan. Kokai 7216 483. Chem. Abstr. 77. $1404780^{\circ}(1972)$.
84. von Janta-fiptnski. M. ; Etzold, G.; Langen, P. J. prakt. Chemie 320, 157 (1978).
85. Mengel, R.: Guschlbaver, W. Angew. Chem. 90, 557 (1978).
86. Shannahoff, D.H.; Sancheqx. R.A. J. Org. Chem. 38, 593 (1973).
87. Kowollik, G.; Gaertner, K.; Langea, P. J. Carbohyd. Nucl. Nucl. 2, 191 (1975).
88, von Janta-Lipinski, M.; Langen, P.; Cech, D. 2. Chem. 23, 335 (1983).
89. Etzold, G.; Hintsche, R.; Laagen, P. Ger. Offen. 1913 384. Chem. Abstr. 73 , 48536 p ( 1970 ) ; Brit. 1 189 973. Chem. Abstr: $73,45794 \mathrm{k}$

90. Etzold, G.; Gintsche, R.; Kowollik, G.; Langen, P. Tetrahedron 27, 2463 (1971).
91. Afmera, S., Bapat, A.R.; Dumenterg, K.; Danenberg, P; V. J. Med; Chem: 27. 11 . (1984).
92. Joecke, A.; Köppel, H.; Schleinitz, K.D.; Cech, D. J. Prakt. Chem. 325, 881 (1983).
93. Etzold, G.; Kowollik, G.; voa Janta-Lipinski, M.; Gaertner. K.; Langen, P. Ger. (East) 103 241. Chem. Abstr ; 81; 25907 m (1974).
94. Kowollik, G.; Langen, P. in Nucleic Acid Chemistry part l. L.B. Townsend, R.S. T1pson Ed, J. Wlley, New York, p 299 (1978).
95. Kowollik: G.; Dewiruw, G.: Schitt, M.; Langen, P. 2. Chem. 12, 106 (1972).
96. von Janta-lipinski, M.; Etzold, G.; Langen, P. Z. Chem. 19. 106 (1979).
97. Kissman, H. M.; Weise, M.J. J. Am. Chem. Soc 80, 5559 (1958).
98. Kowollik, C.; Gaertner, K.; Langen, P. Tetrahedron Lert., 1737 (1971).
99. Doerr, I.L.; Fox, J.J. J. Org. Chem. 32, 1462 (1967).
100. Herrmann, G.; Staske, R.; Cech, D. 2. Chem. 18, 258 (1978).
101. Cech, D.: Meinert, H.; Etzold, G.; Langen, P: j.. Prake. Chemie 315, 149 (1973).
102. Cech,' D.; Herman, G.; Staske, R.; Langen, P.; Preussel, B. J. Prake. Chemie 321, 488 (1979):
103. Stockler, J.D.; Cambor, C.; Kuhns, V.; Chu, S.-H.; Parks, K.E. Blochem. Pharmacol: 3 ii, 163 (1982).
104. Hermann, G.; Cech; 'D.; Kowollik, G.: Langen, P. Z. Chem. 19. 422 (1979).
105. Rowollik, G.; Gaertner, K.; Langon, P. Z. Chew. 10, 141 (1970).
106. Herrmant, G.; Cech, D.; Kowollik, C.; Langen, P. 2. Chem. 20, 20 (1980).
107. Kotick, M.P.; Polazzi, J.O. U.S. 3870 700. Chem. 'Abstr. 82, 140453 t (1975).
108. Kowollik, G.; Langen, P.; Rosenthal, R.A.; Reefschlaeger, J. Ger. (East) 1.37 109. Chem. Abotr. 92, 147 151h (1980).
109. Cech, D.; Koitzsch, H.-मु.; Kō̃1g, J.; Morsel, T. Z. Chem. 21, 449 (1981).
110. (a) Rovollik, G.; Langed. P.; Kvasyuk, E.I.; Mikhailopulo, I.A. Ger. (East) DD 158 903. Chem. Abstr. 99. 158 785p (1983); (b) Zaitgeva, C.Y.; Kowollik, G.; Langen, P.: Mikhailopule, I.A.; Kvasyuk, E.I. Ger. (East) DD 109 197. Chem. Abstr. 101, 171660 y (1984).
111. Dyackina, N. B.; Alexandrova, L.A.; von.Janta-Lipinski, M.; Langen, p. Z. Chem. 25, 180 (1985).
112. Brink, A.J.; De Villiers, O.G.; Jordaan, A. Carbohyd. Res, 54. 285 (1977).
113. An, S.-H.; Bobek, M. Tetrahedron Lett. 27, 3219. (1986).
114. Bobek, M.; An, S.-H. ( De Clercq, E.; Berdacki, R.J. Nucletc Acids Res. Symp. Series 18. 5 (1987).
115. Bergstrom, D.; Romo, E.; Shum, P. Nucleosides \& Nucleotides 6, 53 (1987).
116. Hertel, L.W. Brit. UR Pat. Appl. CB 2136 425. Chem. Abstr. 102,113 894 (1985). Grindey, G.B.; Hertel, L.W. Eur. Pat. Appl. EP 184365. Chem. Abstr. 105, 91 327n (1986).
117. Kerrell Dow Pharmaceuticals Inc. Jpn. Kokal Tokkyo Koho JP 6229527. Chem. Absir. 107, 134 63ús (198i).
118. Owen, G.R.; Verheyden, J.P.H.; Moffatt, J.G. J. Org. Chem. 4l. 3010 (1976).
119. Jenkins, I.: Moffatt, J.G.; Verheyden, J.P. Ger. Offen: 2 228 750. Chem. Abaer: 78; 111 702k (1973).
120. Hough, L.; Kahn, R.; Otter, B.A. In Advances in Chemistry. Serie 74. Washingron. D.C. American Chemical Society, p. 120 (1968).
121. Verheyden, J.P.H.; Kattin, J.G.; Kadhavon, C.V.B.i KcGce., D.P.G.; Prisbe, E.J. (Syntex). U.S. US 4605 659. Chem. Abstr. 106, 84 997y (1987).
122. von Halasz, S.P.; Glemiser, O. Chem. Ber'. 103, 594 (1970).
123. Middleton, W.J.; Bingham, E.K. Organic Synth. 57, $50^{\circ}$ (1977).
124. Markovskif, L.N.: Pashinnlk, V.E.; Kirsanov, A.V. Synthesis, 787 (1973).
125. Markovskij, L.N.; Pighinnik, V.E. Synthesis; 801 (1975).
126. Middleton, H.J. J. Org. Chem. 40, 574 (1975).
127. Posner, G.H:; Haines, S.R. Tetrahedron lett. 26, S (1985).
128. Rosenbrook, W. Jr.; Riley, D.A.; Lartey, P.A. Tetrahedron Lect. 26. 3 (1985).
129. Yang, 5.S.: Dorn. C.P.; Jones, H. Tetrahedron Lett., 2315 (1977).
130. Van Robays. M.; Busson, R.; Vanderhaeghe, H. J. Chem. Soc. Perkin Trans. I, 251 (1986).
131. Card, P.J. J. Carbohydrate Chem. 4; 451 (1985).
132. Tewson, T:J.; Welch, M.J.J. Org. Chem. 43, 1090 (1978).
133. (a) Knox, L.H.i Velarde, E.; Berger, S.; Cuadricllo, D.; Cross, A.D. J. Org. Chem. 29, 2187 (1964). (b) Pruett, R.L.; Barr, J.T.; Rapp, $\bar{K} . E$; Bahner, C.T.; Gibsan, J.D.; Lafferty Jr., R.H. J. Am. Chem. Soc: 72,3646 (1950).
134. (a) Kbbayashi, Y.; Akashi, C.; Morinaga. K. Chem. Pharm. Bull. 16, 1784 (1968); (b) Kohayashi. Y.; Akash1, C. Chem. Pharm. BuI1. 16, 1009 (1968).
135. (a) Earl, R.A.; Townsend, L.B. J. Carbohydr. Nucl. Nucl. 7, 35 (1980). (b) Kowollik, G.; Gaertner, K.; Langen, P. Tetrahedron Lete., 3863 (1969).
136. Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. I. Med. Chew. 30, 1270 (1987).
137. Herdewijn, P.; Pauwels, R,; Baba, M.; Balzarini, J.; De Clercq, E. J. Med. Chem. 30, 2131 (1987).
138. Herdewijn, $\bar{P}$.; Balzarini, J.; Baba, M.; Pauwels, R.; Van Aerschot, A.; Janssen, G.; De Clercq, E. J. Med. Chem., submitced (1988).
139. Marquez, V.E.; Tseng, C.K.-H.; Kelley, J.A.; Mitsuya, H.; Broder, S.; Roth, J.S.; Driscoll, J.S. Biochem. Pharpacol. 36, 2719 (1987).
140. Colonna, S.; Re. A.: Gelbird, G.; Cesarotti, E. J. Chem. Soc. Perkin I, 2248 (1979).
141. Foster, A.B.; Hems, R.; Webber, J.M. Carbohyd. Res. 5, 292 (1967):
142. Szarek, W.A.; Hay, G.W.; Doboszewski, B. J. Chew. Soc. Chew. Comun. 663 (1985).
143. Gosselín, G. Personal Compunication.
144. Roberts, S.M. Personal Commication.
145. Tewson, T.J. J. Org. Chem. 48, 3507 (1983).
146. Tewson. T.J. J. Nucl. Med. 24, 718 (1983).
147. Jones, A.S.; Walker, R.T. Wyatic, P.G.; Balzarini, J.; De Clercq, E. J. Chem. Kes (s), 336 (19,85).
148. Jones, A.S.; McClean, M.J.; Tanaka, H.; Walker, R.T.; Balzarinf, J.; De Clercq, E. Terrahedron 41, 5965 (1985).

Recelved February 10, 1988,

# Synthesis of 4-Substituted Carbocyclic 2,3-Dideoxy-3.C-hydroxymethyl Nucleoside Analogues as Potential Anti-viral Agents 

Johanna Wachtmeister, Anna Mühlman, Björn Classon and Bertil Samuelsson**

Department of Organic Chemistry, Arrheñius Lahoratory, Stockholm University, S-106 91 Stockholm,

## Sweden.

\#Address also: Astra Hässle AB. Medicinal Chemistry, S-4.31 8.3 Mölndal. Sweden.
Received 11 February 1999; revised 16 June 1999; accepted 1 July 1999
Abstract: The synthesis of two carbecyclic guanosine analogues with an electronegative fluoro or hydroxy substituent in the 4 -position is described. The cyclopentanols 17 a and 18 were synthesized from enantiomerically pure $\mathbf{3 S}, 4 \mathrm{~S}$-bis(hydroxymelhyl)cyclopentanone ethylene glycol ketal (7) via a number of key steps involving stereospecific riduction of the keto function and a dihydroxylation of the C. 4 methylene. Substitution of the teniary C-4 hydroxyl group in 16 with fluorine using bis-(2methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor ${ }^{\text {TH }}$ ) and coupling of the cyclopentanol-moiety with 2 -amina-6-chloropurine using the Mitsunobu procedure gave compounds 3 and 4 which have been evaluated as porential anti-viral agents. 1999 Published by Elsevier Science Lid. All rights reserved.

Keywords: nucleosides, reduction, hydroxylation, halogenation, Mitsunobu reaction

## INTRODUCTION

Carbocyclic nucleoside analogues belong to a class of compounds that has attracted major interest in identifying effective drugs against human immunodeficiency virus (HIV) and other viruses. ${ }^{1-4}$ One potential therapeutic advantage of cartrocyclic nucleosides compared with the furanose nucleoside analogues is their increased metabolic stability to phosphorylase and hydrolase enzymes, which cleave the glycosidic linkage of nucleosides. We and others have previously described the synthesis and discovery of the potent broad spectrum anii-viral agent 2,3-dideoxy-3-C-hydroxymethyl cytidine (1) (Figure 1). ${ }^{5-8}$ The carbocyclic guanosine analogue (2) was subsequently synthesized but notably showed no anti-viral activity. ${ }^{9}$ In the present work the syntheses and anti-viral evaluation of C-3 hydroxymethyl substituted carbocyclic nucleoside analogues 3 and 4, having a C-4 hydroxyl (3) or a C-4 fluorine substituent (4), are described.


1


2


3


4

Figure 1
Electronegative substituents in the $\mathrm{C}-4$ position of carbocyclic nucleoside analogues have been shown to promote anti-viral activity (Figure 2). ${ }^{10}$ Notably, Borthwick et al. have shown that compounds 5 and- 6 have good activity against HSV-1 and HSV-2.


5


6

Figure 2

## RESULTS AND DISCUSSION

Chemistry. $\quad 3 S, 4 S$-Bis(hydroxyınethyl)cyclupentanone ethylene glycol metal (7) ${ }^{11}$, was monobenzylated using phase transfer conditions with benzyl bromide, $5 \%$ aqueous NaOH , tetrabutylammonium hydrogen sulphate and trethylamine in refluxing dichloromethane. ${ }^{12}$ The crude product was hydrolyzed in dioxane-water containing $p$-toluene sulphonic acid at $70^{\circ} \mathrm{C}$ to give ketone 8 in $74 \%$ yield (Scheme 11. Stereoselective reduction of the ketone with tetramethylammonium triacetoxyborohydride ( 15 equiv.) in acetone-acetonitrale $1: 1$ containing acetic acid ( 60 equiv:) gave dion 9 in $81 \%$ yield after 2 days. ${ }^{13,14}$ The other isomer could nor be detected. The use of other solvents such as 2-propanol or THF gave lower yields and longer reaction times, but without affecting the stereoselectivity.


Scheme 1: (a) $\mathrm{BnBr}, \mathrm{QHSO}_{4}, \mathrm{NaOH}, \mathrm{Et}_{3} \mathrm{~N}_{1} \mathrm{CH}_{2} \mathrm{Cl}_{2}$, reflux; (b) pTsOH , dioxane, $\mathrm{H}_{2} \mathrm{O}, 50^{\circ} \mathrm{C}$; (c) $\mathrm{Me}_{4} \mathrm{NBH}(\mathrm{OAc})_{3}$, acetone, $\mathrm{CH}_{3} \mathrm{CN}, \mathrm{HOAc}$; (d) $\mathrm{ICH}_{2} \mathrm{CH}_{2} \mathrm{I}$, PPh3. THF: (e) DBU, toluene. $95^{\circ} \mathrm{C}$; ( $\left(\right.$ ) MMJ「Cl, DMAP, E! $3 \mathrm{~N}, \mathrm{CH}_{2} \mathrm{Cl}_{2}$, reflux; (g)K $\mathrm{K}_{2} \mathrm{OsO}_{4}$ $\times 2 \mathrm{H}_{2} \mathrm{O}, \mathrm{N}$-methylmorpholine- N -oxide. $\mathrm{THF}_{v} \mathrm{H}_{2} \mathrm{O}$; (h) $\mathrm{NaH}, \mathrm{BnBr}, \mathrm{DMF},-78^{\circ} \mathrm{C}$.

Selective iodination of compound 9 was initially attempted using iodine, triphenylphosphine and imidazole in toluene-acetonitrile 2:1.15-17 This method, however, gave a mixture of 10 and the diiodinated compound. Using other solvents, temperatures and equivalents of reagents failed to provide only the monoiodinated product 10 , indicating an exceptionally $\mathrm{S}_{\mathrm{N}} 2$ reactive secondary hydroxyl at C -1. Selective replacement of the primary hydroxyl group in compound 9 by iodine was, however, accomplished using 1.2-
diiculoethane and triphenylphosphine in THF, which after a 6 days reaction time gave iodide 10 in $91 \%$ yield. ${ }^{18}$

Elimination of Hl from 10 using 1,8 -diazabicyclo(5.4.0)undec-7-ene (DBU) in toluene at $95{ }^{\circ} \mathrm{C}$ for 18 hours gave the olefin 13 in $76 \%$ yield. ${ }^{19}$ Higher reaction temperature or the use of silver fluoride in pyridine gave Inwer yields of the olefin 11. Tritylation of 11 using monomethoxytrityl chloride, 4. (dimethylamino)pyridine (DMAP) and triethylamine in refluxing dichloromethane gave 12 in $90 \%$ yield. ${ }^{20}$

Dihydroxylation of the olefinic bond using potassium osmate dihydrate and $N$-methylmorpholine- N oxide in THF-water 3:1 gave two diastereomers which were separated by column chromatography to furnish 13 and 14 in $12 \%$ and $66 \%$ yield respectively (see Configuration Assignment). 21.22 The product distribution reflects the preferential approach of the osmium oxidant from the sterically less hindered $\beta$-face. The primary hydroxyls in 13 and 14 were selectively benzylated using benzyl bromide and sodium hydride in DMF to give 15 and 16 in $76 \%$ and $87 \%$ yield, respectively. ${ }^{23}$

Detritylation of 15 using $p$-toluenesulfonic acid in aqueous dichloromethane gave the diol 17a in quantitative yield (Scheme 2). Fluorination of 16 using diethylaminosulphur trifluoride (DAST) and pyridine in dichloromethane gave a mixture of products, ${ }^{10.24-26}$ which was detritylated, as described above, to give fluoride 18 in $25 \%$ yield. The fluorination of 16 could be improved using bis-(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor ${ }^{\text {M }}$ ) giving 18 in $\mathbf{4 3 \%}$ yield. ${ }^{27.28}$

 $\mathrm{NH}_{4} \mathrm{OH}, \mathrm{MeOH}$; (d) $\mathrm{H}_{2}$, PJ-black, MeOH. $\mathrm{H}_{2} \mathrm{O}$ : (e) Deoxonuor ${ }^{\text {TM }}$. pyridine, $\mathrm{CH}_{2} \mathrm{Cl}_{2}$.

The carbocyclic nucleoside analogues were synthesized by coupling 17a and 18 with 2-amino-6chloropurine using the Mitsunobu reaction (triphenylphosphine-diisopropyl azodicarboxylate (DIAD)] to give 19 and 20 in $25 \%$ and $82 \%$ yield respectively. ${ }^{29}$ The low yield ( $25 \%$ ) in the coupling of the purine base with 17a is attributed to competing side reactions of the tertiary hydroxyl group. Treatment of 19 and 20 with $80 \%$ formic acid at $80^{\circ} \mathrm{C}$ followed by $25 \%$ ammonium hydroxide in methanol, ${ }^{30}$ and hydrogenation of the benzyl groups using Pd-black in methanol-water $10: 1$ gave the final products 3 and 4 in $53 \%$ and $52 \%$ yield, respectively.

Configuration Assignments. The configurations of 9, 17a and 17b were determined on the basis on COSY and NOESY experiments (Figure 3). In 9 the chemical shifts for $\mathrm{H}-2 \alpha$ and $\mathrm{H}-2 \beta$ were well resolved and significant nOes were found between $\mathrm{H} \cdot 1$ and $\mathrm{H} \cdot 2 \beta$ as well as between $\mathrm{H}-3$ and $\mathrm{H}-2 \beta$. Weaker nOes were also found between the $\mathrm{C}-3$ benzyloxymethyl protons and $\mathrm{H}-2 \alpha$. This indicates a cis-relationship between the $\mathrm{C}-1$ hydroxyl group and the $\mathrm{C}-3$ benzyloxymethyl, confirming the ( $S$ )-stereochemistry at $\mathrm{C}-1$.

In 17b the chemical shifts for $\mathrm{H}_{5 \alpha}$ and $\mathrm{H}_{5 \beta}$ were also well resolved and significant nOes were found between $\mathrm{H}-1$ and $\mathrm{H}-5_{\beta}$ and also between the $\mathrm{C}-4$ benzyloxymethyl protons and $\mathrm{H}-5_{\alpha}$, indicating a $4(\mathrm{~S})$-; stereochemistry. The $\mathrm{H}-5_{\alpha}$ and $\mathrm{H}-5_{\beta}$ chemical shifts were less well resolved in 1.7 a . In spite of this fact, significian noes were found between $\mathrm{H}-\mathrm{I}$ and $\mathrm{H}-\mathrm{S}_{\beta}$ and also between $\mathrm{H}-5 \beta$ and the $\mathrm{C}-4$ benzyloxymethyl. protons. This indicates a cis-relationship between the C-4 benzyloxymethyl and the C-1 hydroxyl group in 17b and a trans-relationship in 17a.

The 'H NMR spectrum of 18 resembles that of 17 a , but in a NOESY experiment no nOes were detected. However in 20, by selective irradiation of $\mathrm{H}_{3}$, nOe was found to the $\mathrm{C}-4$ benzyloxymethyl protons indicating a cis-relationship, and thus ihat the fluorine substitution had occurred via inversion of configuration al C-4. No nOes weré found between ihe C-3- and C-4-benzyloxymethyl'protons in compound 20.


9



Figure 3

Biological Results. Compounds 3 and 4 were tested in an XTT assay for anti HIV-1 activity and cytopathic effects ${ }^{31}$ (and in a similar assay for anti HSV-1 effect) ${ }^{32}$ but were found to be inactive in these assays.

## EXPERIMENTAL SECTION

General procedures. All solvents were distilled prior to use. Thin layer čthromatography was performed using silica gel $60 \mathrm{f}-254$ (Merck) plates with detection by UV, charring with $8 \%$ sulphuric acid or a mixture of 4 -methoxybenzaldehyde-sulphưric acid-acetic acid-EtOH (5:7:2:186). Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35-70 $\mu \mathrm{m}$, Amicon). Organic phases were dried over anhydrous sodium sulphate. Concentrations were performed iunder reduced pressure. NMR spectra were recorded on a

JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $\mathrm{CDCl}_{3}$ and DMSOD6. Accurate mass measurements were recorded on a JEOL SX 102 Mass Spectrometer / MS-MP7000 Data system.
( 35,4 ) )-3-(Benzyloxymethyi)-4-(hydroxymethyl)cyclopentanone (8). To a stirred solution of ( $3 \mathrm{~S}, 45$ )-bis (hydroxymethyl)cyclopentanone ethyleneglycol metal (7) ${ }^{\circ}(6.05 \mathrm{~g}, 32.1 \mathrm{mmol})$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(400$ mL ) was added triethylamine ( 0.3 mL ), followed by tetrabutylammonium hydrogen sulphate ( $2.18 \mathrm{~g}, 6.42$ mine and $5 \%$ aqueous $\mathrm{NaOH}(40 \mathrm{~mL}$ ). The mixture was heated to reflux and benzyl bromide ( $11.4 \mathrm{~mL}, 96.3$ mol) was added. After 40 h the aqueous phase was removed and the organic layer was washed with water ( $2 x$ ). The water phase was extracted with. $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 2 x ) and the combined organic layer was dried and concentrated. The crude ( $3 S, 4 S$ )-3-(benzyloxy)methyl-4-(hydroxymethyl)cyclopentanone ethyleneglycolketal was dissolved in dioxane ( 400 mL ) and water ( 40 mL ), p-toluene sulphonic acid ( 1.0 g ) was added and the mixture was heated to $70^{\circ} \mathrm{C}$. After 1.3 h saturated aqueous $\mathrm{NaHCO}_{3}$ was added and the mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \mathrm{x})$. The combined organic layer was dried concentrated and purified by column chromatography (toluene-EtOAc $2: 1,1: 1$ ) to give $8(5.58 \mathrm{~g}, 23.8 \mathrm{mmol})$ as a light yellow oil in $74 \% ;[\alpha]_{\mathrm{D}}$ $+50.5\left(\mathrm{c}_{1.16} \mathrm{CHCl}_{3}\right)$. NMR $\left(\mathrm{CDCl}_{3}\right) \delta_{\mathrm{H}}: 1.95-2.09(2 \mathrm{H}, \mathrm{m}), 2.24-2.47(4 \mathrm{H}, \mathrm{m}), 3.14(1 \mathrm{H}, \mathrm{s}), 3.44-3.73$ $(4 \mathrm{H}, \mathrm{m}), 4.55(2 \mathrm{H}, \mathrm{s}), 7.13-7.44(5 \mathrm{H}, \mathrm{m}) ; \delta_{\mathrm{C}}: 40.9,41.9,42.0,43.8,65.3,72.8,73.6,127.9,128.0$. 128.6, 137.3, 216.3. Anal. Calcd. for $\mathrm{C}_{14} \mathrm{H}_{18} \mathrm{O}_{3}$ : $\mathrm{C}, 71.77$; $\mathrm{H}, 7.74$. Found: $\mathrm{C}, 71.73 ; \mathrm{H}, 7.70$.
(1S,3S,4S)-3.(Benzyloxymethyl)-4-(hydroxymethyl)cyclopentanol (9). To a stirred solution of $8(5.86 \mathrm{~g}, 25.0 \mathrm{mmol})$ in acetone-acutonitrile $1: 1(600 \mathrm{~mL})$ under argon, HOAc ( $90 \mathrm{~mL}, 1.5 \mathrm{~mol}$ ) was added dropwise. Tetramethylammonium triacetoxyborohydride ( $98.7 \mathrm{~g}, 375 \mathrm{mmol}$ ) was added in one portion and the mixture was stirred at ambient temperature for 2 days, before successive addition of saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(250 \mathrm{~mL}), 1 \mathrm{M}$ potassium tartrate $(200 \mathrm{~mL})$, saturated aqueous $\mathrm{NaHCO}_{3}(200 \mathrm{~mL})$ and ErOAc ( 250 mL ). The mixture was stirred for 1 h before the phases were separated and the aqueous layer was extracted with EIOAc ( 3 x ). The combined organic layer was dried concentrated and purified by column chromatography (toluene-EtOAc 1:2, $1: 3,1: 4)$ to give $9(4.80 \mathrm{~g}, 20.3 \mathrm{mmol})$ as a white solid in $81 \%$ yield. A small portion was recrystallized from $\mathrm{CH}_{2} \mathrm{Cl}_{2}$-hexane to give white needle shaped crystals; melting point 77 ${ }^{\circ} \mathrm{C} ;[\alpha]_{\mathrm{D}}-6.5\left(c 1.27, \mathrm{CHCl}_{3}\right) . \mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta_{\mathrm{H}}: 1.36-1.47(2 \mathrm{H}, \mathrm{m}), 1.75-1.84(1 \mathrm{H}, \mathrm{m}), 1.99-2.15(2 \mathrm{H}$, $\mathrm{m})$, 2.16-2.35 ( $1 \mathrm{H}, \mathrm{m}$ ), 3.02 ( $2 \mathrm{H}, \mathrm{s}$ ), 3.35-3.44 $(2 \mathrm{H}, \mathrm{m}), 3.53-3.64(2 \mathrm{H}, \mathrm{m}), 4.18-4.26(1 \mathrm{H}, \mathrm{m}), 4.56(2 \mathrm{H}$, s), 7.22-7.40 (5H, m); $\delta_{\mathrm{C}}: 38.8,39.6,42.6,44.6,66.5,72.2,73.5,74.3,127.8,127.9,128.5,137.4$. Anal. Calcd. for $\mathrm{C}_{14} \mathrm{H}_{20} \mathrm{O}_{3}$ : C. 71.16; $\mathrm{H}, 8.53$. Found: $\mathrm{C}, 71.12 ; \mathrm{H}, 8.51$.
(1R,3S,4S)-3-(Benzyloxymethyl)-4-(iodomethyl)cyclopentanol (10). To a stirred solution of triphenylphosphine ( $31.9 \mathrm{~g}, 121.8 \mathrm{mmol}$ ) and 1,2 -diiodoethane ( $29.2 \mathrm{~g}, 103.5 \mathrm{mmol}$ ) in THF ( 250 mL ) under an argon atmosphere was added $9(4.80 \mathrm{~g}, 20.3 \mathrm{mmol})$. After 6 days the successive addition of saturated aqueous $\mathrm{NaHCO}_{3}$, ( 300 mL ), $0.1 \mathrm{M} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(100 \mathrm{~mL}$ ) and toluene ( 250 mL ) was followed by stirring for an additional how, separation of the phases and extraction of the aqueous layer with toluene ( 3 x ). The combined organic layer was dried, concentrated and immediately purified by column chromatography (toluene-EIOAc 10:1) to give $10(6.37 \mathrm{~g}, 18.4 \mathrm{mmol})$ as a yellow oil in $91 \%$ yield; $\{\alpha\}_{\mathrm{D}}+26.3$ (c 0.90 ,
$\left.\mathrm{CHCl}_{3}\right)$. NMR $\left(\mathrm{CDCl}_{3}\right): \delta_{\mathrm{H}}: 1.47(1 \mathrm{H}$, dd, $\mathrm{j}=4.3,10.4$ and 13.3 Hz$), 1.63(1 \mathrm{H}$, dad, $\mathrm{J}=1.9,3.7$ and 13.9 $\mathrm{Hz}), 1.92-2.03(2 \mathrm{H}, \mathrm{m}), 2.15(1 \mathrm{H}, \mathrm{ddd}, \mathrm{J}=4.9,10.8$ and 13.9 Hz$), 2.24-2.29(1 \mathrm{H}, \mathrm{m}), 3.02(1 \mathrm{H}, \mathrm{s}), 3.27$ ( $1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=6.4$ and 9.7 Hz ), $3.36(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=5.4$ and 9.7 Hz$), 3.41(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=4.2$ and 9.0 Hz$), 3.56(1 \mathrm{H}$, $\mathrm{dd}, \mathrm{J}=3.7$ and 9.0 Hz$), 4.18-4.26(1 \mathrm{H}, \mathrm{m}), 4.56(2 \mathrm{H}, \mathrm{s}), 7.22-7.40(5 \mathrm{H}, \mathrm{m}) ; \delta_{\mathrm{C}}: 14.8,39.2,41.7,44.0$, 44.4, 72.4, 72.8, $73.3,127.6,127.8,128.4,137.6$. Anal. Calcd. for $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{O}_{2} \mathrm{I}$ : C, 48.57; H, 5.53. Found: C, 48.57; H, 5.43.
(1R,3S)-3-(Benzyloxymethyl)-4-methylenecyclopentanol (11). To a stirred solution of 10 $(2.73 \mathrm{~g}, 7.89 \mathrm{mmol})$ in dry toluene $(250 \mathrm{~mL})$ under an argon atmosphere was added $1,8-$ diazabicyclo[5.4.0]undec-7-ene (DBU) ( $2.36 \mathrm{~mL}, 15.8 \mathrm{mmol}$ ). The mixture was heated to $95^{\circ} \mathrm{C}$ for 18 h , before it was washed with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The aqueous layer was extracted with ErOAc ( 2 x ) and the combined organic layer was dried and concentrated to give 11 ( $1.3 \mathrm{lg}, 5.98 \mathrm{mmol}$ ) as a yellow oil in $76 \%$ yield. No further purification was made due to instability of the product. [ $\alpha]_{\mathrm{D}}+33.9$ ( $c 0.81, \mathrm{CHCl}_{3}$ ). NMR $\left(\mathrm{CDCl}_{3}\right): \delta_{\mathrm{H}}: 1.74(1 \mathrm{H}, \mathrm{ddt}, \mathrm{J}=3.0,3.1$ and 14.4 Hz$), 2.20(1 \mathrm{H}, \mathrm{ddd}, \mathrm{J}=5.3,9.7$ and 14.4 Hz$), 2.41(1 \mathrm{H}$, $\mathrm{dd}, \mathrm{J}=2.8$ and 16.9 Hz ), $2.54\left(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=3.4\right.$ and 16.9 Hz ), $2.66-2.87(1 \mathrm{H}, \mathrm{m}), 3.32^{(1 \mathrm{H}, \mathrm{s})} 3.58(2 \mathrm{H}, \mathrm{d}$, $\mathrm{J}=4.4 \mathrm{~Hz}), 4.18-4.20(1 \mathrm{H}, \mathrm{m}), 4.54(2 \mathrm{H}, \mathrm{s}), 5.01(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=28.6 \mathrm{~Hz}) ; 7.20-7.40(5 \mathrm{H}, \mathrm{m}) ; \delta_{\mathrm{C}}: 39.4,41.7$, 44.5, 71.4, 73.5 (2 C), 107.6, 127.6, 127.8, 128.4, 137.6, 151.3.
( $1 R, 3 S$ )-3-(Benzyloxymethyl)-1-(4-methoxyphenyIdiphenylmethoxy)-4-
methylenecyclopentane (12). To a stirred solution of 11 ( $1.30 \mathrm{~g}, .5 .96 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 200 mL ) under an argon atmosphere was added monomethoxytrityl chloride ( $2.53 \mathrm{~g}, 8.19 \mathrm{mmol}$ ). 4-dimethylaminopyridine ( $30 \mathrm{mg}, 0.24 \mathrm{mmol}$ ) and triethylamine ( $1.24 \mathrm{~mL}, 8.90 \mathrm{mmol}$ ). The mixture was refluxed for 3 days, before it was washed with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ ( 3 x ). The aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 1 x ) and the organic layer was dried, concentrated and purified by column chromatography (toluene) to give 12 ( 2.63 g , 5.36 mmol ) as a colorless syrup in $90 \%$ yield: $[\alpha]_{\mathrm{D}}+20.7$ (c $0.92, \mathrm{CHCl}_{3}$ ). NMR ( $\mathrm{CDCl}_{3}$ ): $\delta_{\mathrm{H}}: 1.40-1.52$ ( $\mathrm{IH}, \mathrm{dt}, \mathrm{J}=8.2$ and 13.0 Hz ), $1.77(1 \mathrm{H}, \mathrm{dt}, \mathrm{J}=6.6$ and 13.0 Hz ), $1.91(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=6.2$ and 16.3 Hz ), 2.09 ( 1 H, ddt, $\mathrm{J}=2.2,7.4$ and 16.3 Hz ), $2.42-2.60(1 \mathrm{H}, \mathrm{m}), 3.40(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=6.1$ and 8.9 Hz$), 3.55(1 \mathrm{H}, \mathrm{dd}$, $\mathrm{J}=8.0$ and 8.9 Hz ), $3.76(3 \mathrm{H}, \mathrm{s}) ; 4.02(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=7.0 \mathrm{~Hz}), 4.48(2 \mathrm{H}, \mathrm{s}), 4.75(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=11.0 \mathrm{~Hz}), 6.81(2 \mathrm{H}$, d, J=9.0 (z). 7.14:7.50 (17H, m); $\delta \mathrm{c}: 37.7,41.0,41.4,55.1,73.0,73.8,74.2,86.6,106.8,113.0,126.7$, 127.4, 127.5, 127.7, 128.2, 128.4, 130.3, 136.8, 138.5, 145.6, 150.3, 158.5. Anal. Calcd. for $\mathrm{C}_{34} \mathrm{H}_{34} \mathrm{O}_{3} \times$ $1 \mathrm{H}_{2} \mathrm{O}: \mathrm{C}, 80.28 ; \mathrm{H}, 7.13$. Found: C, $80.51 ; \mathrm{H}, 6.89$.
(1R,3R,4R)-3-(Benzyloxymethyl)-4-(hydroxymethyl)-1-(4-methoxyphenyldiphenyl-methoxy)-4-cyclopentanol. (13) and ( $1 R, 3 R, 4 S$ )-3-(Benzyloxymethyi)-4-(hydroxymethyl)-1-(4-methoxyphenyldiphenyimethoxy)-4-cyclopentanoi (14): To a cold, stirred solution of 12 $(3.20 \mathrm{~g}, 6.52 \mathrm{mmol})$ and 4-methylmoipholine- N -oxide ( $1.52 \mathrm{~g}, 13.0 \mathrm{mmol}$ ) in THF- $\mathrm{H}_{2} \mathrm{O} 3: 1$ ( 30 mL ) under an argon atmosphere, was added potassium osmate dihydrate ( $239 \mathrm{mg}, 0.65 \mathrm{mmol}$ ). The mixture was stirred at ambient temperature for 24 h , before the reaction was quenched by the addition of $\mathrm{NaHSO}_{3}$ (s) ( 0.9 g ) and the stirring was continued for 15 min . The mixture was concentrated, dissolved and extracted in $\mathrm{EtOAc}-\mathrm{H}_{2} \mathrm{O}$. The organic layer was dried. concentrated and purified by column chromatography (oluene-EtOAc 3:1) to give
the two alcohols 13 ( $413 \mathrm{mg}, 0.79 \mathrm{mmol}, 12 \%$ ), 14 ( $2.25 \mathrm{~g}, 4.28 \mathrm{mmol}, 66 \%$ ) as colorless syrups and unreacted 12 ( $430 \mathrm{mg}, 0.88 \mathrm{mmol}, 13 \%$ ). 13: $\left.[\alpha]_{\mathrm{D}}-2.4(c] .1, \mathrm{CHCl}_{3}\right) . \mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta_{\mathrm{H}}: 1.40-1.6(4 \mathrm{H}$, m), $1.65-1.80(1 \mathrm{H}, \mathrm{m}), 3.12(1 \mathrm{H}, \mathrm{s}) ; 3.25-3.55(4 \mathrm{H}, \mathrm{m}), 3.60(1 \mathrm{H}, \mathrm{t}, \mathrm{J}=4.5 \mathrm{~Hz}), 3.73(3 \mathrm{H}, \mathrm{s}), 3.98(1 \mathrm{H}$, p. $J=6.4 \mathrm{~Hz}), 4.47(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=3.0 \mathrm{~Hz}), 6.80(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.1 \mathrm{~Hz}), 7.14 .7 .50(17 \mathrm{H}, \mathrm{m}) ; \delta \mathrm{C}: 36.1 .44 .7,45.5$, 55.1, 68.9, 09.1, 72.7, 73.4, 79.9, 87.0, 113.1, 126.8, 127.8, 127.9, 128.4, 128.5, 130.4, 136.6, 137.2, 145.3, 158.5 . HRMS calcd. For $\mathrm{C}_{34} \mathrm{H}_{36} \mathrm{O}_{5}+\mathrm{Na}: 547.2460$. Found 547.2507. 14: $[\alpha]_{\mathrm{D}}+5.7\left(c \quad 1.2, \mathrm{CHCl}_{3}\right)$. NMR $\left(\mathrm{CDCl}_{3}\right): \delta_{\mathrm{H}}: 1.03(\mathrm{lll}, \mathrm{dt}, \mathrm{J}=5.8$ and 14.0 Hz$), 1.42(2 \mathrm{H}, \mathrm{dq}, \mathrm{J}=4.1$ and 8.5 Hz$), 1.73-1.91(1 \mathrm{H}, \mathrm{m})$, $1.91-2.05(\mathrm{IH}, \mathrm{m}), 2.70(\mathrm{JH}, \mathrm{s}), 3.30-3.39(3 \mathrm{H}, \mathrm{m}), 3.48(1 \mathrm{H}, \mathrm{t}, \mathrm{J}=4.5 \mathrm{~Hz}), 3.63(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}-5.4$ and 11.3 $\mathrm{Hz}), 3.75(3 \mathrm{H}, \mathrm{s}), 4.24(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=6.0 \mathrm{~Hz}), 4.48(2 \mathrm{H}, \mathrm{s}), 6.80(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.1 \mathrm{~Hz}), 7.14-7.50(17 \mathrm{H}, \mathrm{m}) ; \delta_{\mathrm{C}}$ : 35.7. 42.6, 47.5, 55.1, 66.3, 71.9, 72.8, 73.6. 81.3, 86.8, 113.1, 126.8, 127.8, 128.0, 128.1, 128.4, 128.6, 130.4, 136.7, 137.1, 145.4, 158.S. HRMS cajled. For $\mathrm{C}_{34} \mathrm{H}_{36} \mathrm{O}_{5}+\mathrm{Na}$ : 547.2460 . Found 547.2467. Due to instability of the alcohols 13 and 14 , no elemental analysis of these compounds gave satisfying results.
( $1 R, 3 R, 4 R$ )-3,4-Bis(benzyloxymethyl)-1-(4-methoxyphenyldiphenylmethoxy)-4cyclopentanol (15). To a stirred suspension of NaH ( $95 \%$ ) ( $28 \mathrm{mg}, 1.11 \mathrm{mmol}$ ) in DMF ( 2 mL ) under an. argon atmosphere was added 13 ( $291 \mathrm{mg}, 0.55 \mathrm{mmol}$ ) in DMF ( 4 mL ). The mixture was cooled to $-70^{\circ} \mathrm{C}$ and benzyl bromide ( $67 \mu \mathrm{~L}, 0.58 \mathrm{mmol}$ ) in DMF ( 2 mL ) was added dropwise during 10 min . After 1 h the ice bath was removed and stirting continued at ambient temperature for 19 h before $\mathrm{MeOH}(0.5 \mathrm{~mL})$ and $\mathrm{H}_{2} \mathrm{O}(10 \mathrm{~mL})$ were added. The mixture was extracted with EIOAc ( $3 x$ ), dried, concentrated and purified by column chromatography (toluene-EIOAc 20:1) to give $15(258 \mathrm{mg}, 0.42 \mathrm{mmol}$ ) as a colorless syrup in $76 \%$ yield; $[\alpha]_{\mathrm{D}}+3.2\left(c 0.6, \mathrm{CHCl}_{3}\right)$. $\mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta_{\mathrm{H}}: 1.42-1.69(4 \mathrm{H}, \mathrm{m}), 1.84-1.97(1 \mathrm{H}, \mathrm{m}), 3.15(1 \mathrm{H}, \mathrm{s}), 3.19$ $(1 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.1 \mathrm{~Hz}), 3.32(1 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.1 \mathrm{~Hz}), 3.46(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=6.2$ and 9.9 Hz$), 3.66(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=6.0$ and 9.9 $\mathrm{Hz}), 3.75(3 \mathrm{H}, \mathrm{s}), 4.02(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=7.1 \mathrm{~Hz}), 4.41(4 \mathrm{H}, \mathrm{s}), 6.80(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.0 \mathrm{~Hz}), 7.14-7.50(21 \mathrm{H}, \mathrm{m}) ; \delta \mathrm{C}:$ 36.4, 42.9, 45.2, 55.1, 70.5, 73.1, 73.2, 73.4, 75.7, 80.0, 87.0, 113.1, 126.7, 127.3, 127.5, 127.8, 128.3, 128.5, 130.4, 136.6, 138.2, 138.4, 145.3. 158.5. HRMS calcd. For $\mathrm{C}_{41} \mathrm{H}_{42} \mathrm{O}_{5}+\mathrm{Na}: 637.2930$. Found 637.2933.
(1R,3R,4S)-3,4-Bis(benzyloxymethyl)-1-(4-methoxyphenyldiphenylmethoxy)-4cyclopentanol (16). Compound 16 was prepared from $14(1.94 \mathrm{~g}, 3.69 \mathrm{mmol})$ in the same manner as described for compound 15 to afford the title compound as a colorless syrup in $87 \%$ yield ( $1.97 \mathrm{~g}, 3.20$ mmol); $[\alpha]_{\mathrm{U}}+8.2\left(c 0.9, \mathrm{CHCl}_{3}\right)$. NMR ( $\mathrm{CDCl}_{3}$ ): $\delta_{\mathrm{H}:} 1.37(1 \mathrm{H}, \mathrm{ddd}, \mathrm{J}=5.8,8.3$ and 13.5 Hz ), 1.45-1.61 $(2 \mathrm{H}, \mathrm{m}), 1.81(1 \mathrm{H}, \mathrm{dt}, \mathrm{J}=7.9$ and 13.5 Hz$), 1.98(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=7.3 \mathrm{~Hz}), 2.56(1 \mathrm{H}, \mathrm{s}) ; 3.31-3.56(4 \mathrm{H}, \mathrm{m}), 3.77$ $(3 \mathrm{H}, \mathrm{s}), 4.22$ ( $1 \mathrm{H}, \mathrm{p}, \mathrm{J}=7.0 \mathrm{~Hz}$ ), $4.48(2 \mathrm{H}, \mathrm{s}), 4.50(2 \mathrm{H}, \mathrm{s}), 6.80(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.0 \mathrm{~Hz}), 7.14-7.50(17 \mathrm{H}, \mathrm{m}) ;$ $\delta_{\text {C: }}$ 36.2, 44.4, 47.1, 55.2, 70.7, 72.7, 73.0, 73.6, 74.2, 80.1, 86.7, 113.0, 126.7, 127.5, 127.5, 127.6, 127.8, 128.3, 128.5, 130.4, 136.9, 138.1, 138.4, 145.6, 158.5. HRMS calcd. For $\mathrm{C}_{41} \mathrm{H}_{42} \mathrm{O}_{5}+\mathrm{Na}$ : 637.2930 . Found 637.2900.
( $1 R, 3 R, 4 R$ )-3,4-Bis(benzyloxymethyl)-1,4-cyclopentanedial (17a). To a stirred solution of 15 ( $258 \mathrm{mg}, 0.42 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 13 mL ) was added $p$-toluenesulfonic acid ( 32 mg ) and. $\mathrm{H}_{2} \mathrm{O}$ ( 3 drops). After 2.5 h at ambient temperature the mixture was washed with saturated aqueous $\mathrm{NaHCO}_{3}$, the
aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{x})$ and the combined organic layer was dried, concentrated and purified by column chromatography (toluene-EIOAc 2:1) to give 17a as a colorless syrup( $146 \mathrm{mg}, 0.42$ mmol) in quantitative yield; $[\alpha]_{D}+4.1\left(c 0.7, \mathrm{CHCl}_{3}\right)$. NMR $\left(\mathrm{CDCl}_{3}\right): \delta_{\mathrm{H}}: 1.72(1 \mathrm{H}$, ddd, $\mathrm{J}=2.2,8.0$ and 14.4 Hz , 1.91-1.94 ( $2 \mathrm{H}, \mathrm{m}$ ); 2.04-2.34 ( $2 \mathrm{H}, \mathrm{m}$ ), $2.90(1 \mathrm{H}, \mathrm{s}, \mathrm{br}), 3.40(1 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.2 \mathrm{~Hz}), 3.50(1 \mathrm{H}, \mathrm{s}$, br), $3.57(1 \mathrm{H}, \mathrm{d}, \mathrm{J}=9.2 \mathrm{~Hz}), 3.63-3.75(2 \mathrm{H}, \mathrm{m}), 4.20-4.31(1 \mathrm{H}, \mathrm{m}), 4.49(2 \mathrm{H}, \mathrm{s}), 4.54(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=4.0 \mathrm{~Hz})$, 7.17-7.40 (10H, m); $\delta_{\mathrm{C}}{ }^{\prime} 38.5,43.6,46.6,70.3,71.9,73.2,73.3,75.1,82.1,127.5,127.6,128.2,128.3$, 137.9, 138.I. Anal. Calcd. For $\mathrm{C}_{2} \mathrm{H}_{26} \mathrm{O}_{4}: \mathrm{C}, 73.66 ; \mathrm{H}, 7.65$. Found: $\mathrm{C}, 73.42 ; \mathrm{H}, 7.49$. Due to the gradual decomposition of compounds $13-16$ a small portion of 16 was detritylared as above to give 17 b , to be able to compare it with 17a in the configurational assignments. [ $\alpha]_{\mathrm{D}}+14.5\left(c \quad 1.0, \mathrm{CHCl}_{3}\right)$. NMR ( $\mathrm{CDCl}_{3}$ ): $\delta_{\mathrm{H}}: 1.50$ ( 1 H, ddd, $\mathrm{J}=1.9,3.8$ and 13.9 Hz ), 1.60 (1 H. dd, $\mathrm{J}=3.5$ and $14.5-\mathrm{Hz}), 2,12-2.23-(2 \mathrm{H}-\mathrm{m}), 2.15(\mathrm{IH} ; \mathrm{dt}$; $\mathrm{J}=7.7$ and 13.9 Hz , $2.72(1 \mathrm{H}, \mathrm{s}, \mathrm{br}), 3.13(1 \mathrm{H}, \mathrm{s}, \mathrm{br}), 3.41-3.56(4 \mathrm{H}, \mathrm{m}), 4.37(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=1.83 \mathrm{~Hz}), 4.43$ $(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=1.83 \mathrm{~Hz}), 7.23-7.34(10 \mathrm{H}, \mathrm{m}) ; \delta \mathrm{C}: 38.8,48.0,48.3,70.7,71.1,73.6,73.7,74.2,81.6,128.1$, 128.2, 128.6, 137.5, 137.7. Anal. Calcd. For $\mathrm{C}_{2}{ }_{1} \mathrm{H}_{26} \mathrm{O}_{4}: \mathrm{C}, 73.66 ; \mathrm{H}, 7.65$. Found: C, 73.39; H, 7.51.
( $1 R, 3 R, 4 R$ )-3,4-Bis(benzyloxymethyl)-4-fluoro-1-cyclopentanol (18). To a stirred solution of bis-(2-methoxyethyl)aminosulphur trifluoride ( $140 \mathrm{mg}, 0.68 \mathrm{mmol}$ ) and pyridine ( $60 \mu \mathrm{~L}, 0.73$ mmol ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(9 \mathrm{~mL})$ under an argon atınosphere at $-78{ }^{\circ} \mathrm{C} .16$ ( $346 \mathrm{mg}, 0.56 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(6 \mathrm{~mL}$ ) was added dropwise during 10 min . The mixture was allowed to reach room temperature and after 18 h saturated aqueous $\mathrm{NaHCO}_{3}(10 \mathrm{~mL}$ ) was added. TLC indicated the formation of 1 main product and 4 byproducts. The mixture was washed with $\mathrm{H}_{2} \mathrm{O}(2 x)$, the aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 3 x ), the combined organic layer was dried and concentrated. The crude mixture was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(17 \mathrm{~mL})$ and $p$-toluensulfonic acid ( 100 mg ) and $\mathrm{H}_{2} \mathrm{O}$ ( 10 drops) was added. After stirring for 2 days at ambient temperature the mixture was washed with saturated uqueous $\mathrm{NaHCO}_{3}$, the aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 x)$ and the combined organic ldyer was dried, concentrated and purified by column chromatography (toluene-EiOAc 3:1) to give 18 as a light yellow syrup ( $83 \mathrm{mg}, 0.24 \mathrm{mmol}$ ) in $43 \%$ yield; [ $\alpha]_{\mathrm{D}}+5.5$ (c 1.0, $\left.\mathrm{CHCl}_{3}\right)$. NMR ( $\mathrm{CDCl}_{3}$ ): $\delta_{\mathrm{H}}$ : $1.55-1.76(\mathrm{H}, \mathrm{m}), 2.00(1 \mathrm{H}, \mathrm{s}, \mathrm{br}), 2.07-2.38(4 \mathrm{H}, \mathrm{m}) ; 3.43-3.79(4 \mathrm{H}, \mathrm{m})$, $4.20-4.31(1 \mathrm{H}, \mathrm{m}), 4.48^{\prime}(2 \mathrm{H}, \mathrm{s}), 4.56(2 \mathrm{H}, \mathrm{d}, \mathrm{J}=7.0 \mathrm{~Hz}), 7.20-7.40(10 \mathrm{H}, \mathrm{m}) ; \delta_{\mathrm{C}}: 38.6,44.0(\mathrm{~d}$, $\left.\mathrm{J}_{\mathrm{C}, F}=20.2 \mathrm{~Hz}\right), 45.1\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, F}=22.0 \mathrm{~Hz}\right), 69.2\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, F}=9.1 \mathrm{~Hz}\right), 71.0,72.8\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=29.4 \mathrm{~Hz}\right), 73.2,73.5$, 104.9 (d, J $\mathrm{C}, \mathrm{F}=179.7 \mathrm{~Hz}$ ); 127.5, 127.6, 128.3, 138.0, 138.1. Anal. Calcd. for $\mathrm{C}_{21} \mathrm{H}_{25} \mathrm{O}_{3} \mathrm{~F}: \mathrm{C}, 73.23 ; \mathrm{H}$, 7.32. Found: C, 73.07; H, 7.44.
(IS,3R,4R)-2-Amino-9-[3,4-bis(hydroxymethyl)-4-hydroxycyclopentyl]-9H-purine$6(1 H)$-one (3). To a stirred solution of triphenylphosphine ( $165 \mathrm{mg}, 0.63 \mathrm{mmol}$ ) in THF ( 4 mL ) under an argon atmosphere at $0^{\circ} \mathrm{C}$, diisopropylqzodicarboxylate (DIAD) was added dropwise during 5 min . The mixture was stirred for 30 min to yield a white precipitate of thiphenylphosphine-DIAD complex. A suspension of 2-amino-6-chloropurine ( $107 \mathrm{mg}, 0.63 \mathrm{mmol}$ ) and 17 a ( $146 \mathrm{mg}, 0.42 \mathrm{mmol}$ ) in THF ( 6 mL ) was added and the mixture was stirred for 15 h at ambient temperature, concentrated and purified by column chromatography (toluene-EtOAc 2:1, 2:3, l:2) to give 19 as a light yellow syrup ( $53 \mathrm{mg}, 0.107 \mathrm{mmol}$ ) in $\mathbf{2 5 \%}$ yield. NMR ( $\mathrm{CDCl}_{3}$ ): $\delta_{\mathrm{H}}$ : 2.08-2.25 ( $1 \mathrm{H}, \mathrm{m}$ ), 2.30-2.55 ( $3 \mathrm{H}, \mathrm{m}$ ). 2.60-2.80 ( $\mathrm{lH}, \mathrm{m}$ ), 3.45-3.72 ( $5 \mathrm{H}, \mathrm{m}$ ), $5.05(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=6.8 \mathrm{~Hz}), 5.15(2 \mathrm{H}, \mathrm{s}), 7.20-7.40(10 \mathrm{H}, \mathrm{m}), 7.81(1 \mathrm{H}, \mathrm{s}) ; \delta \mathrm{C}: 33.8,42.9,43.9,53.3,69.2$,
73.5. 74.6. $81.1,125.8,127.6,127.8 ; 127.9,128.4,137.6,137.9,141.3,151.2,153.6,158.7$. Unreacted 17 a ( $31 \mathrm{mg}, 0.091 \mathrm{mmol}, 22 \%$ ) was also recovered. A solution of 19 ( 53 mg .0 .107 mmol ) in $80 \%$ formic acid ( 3 mL ) was stirred at $80^{\circ} \mathrm{C}$ for 2 h . The mixture was concentrated and dissolved in $\mathrm{MeOH}(3 \mathrm{~mL})$ and $25 \% \mathrm{NH}_{4} \mathrm{OH}(0.4 \mathrm{~mL})$ and stirred ovemight before it was concentrated. A suspension of the crude product and a catalytic amount of Pd -black in $\mathrm{MeOH}-\mathrm{H}_{2} \mathrm{O} 10: 1$ was hydrogenated at ambient pressure overnight, filtered through a pad of celite and concentrated. The mixture was purified by column chromatography (ErOAc-$\mathrm{MeOH}-\mathrm{H}_{2} \mathrm{O} 7: 2: 1$ ) and on a BioGel ${ }^{18} \mathrm{P}-2$ column to give 3 as a white hygroscopic solid ( $18 \mathrm{mg}, 0.057 \mathrm{mmol}$ ) in $53 \%$ y ield; $[\alpha]_{D}+5.0\left(c 0.4, \mathrm{H}_{2} \mathrm{O}\right)$.NMR ( $\mathrm{DMSO}-\mathrm{D}_{6}$ ): $\delta \mathrm{H}: 1.86-2: 23(4 \mathrm{H}, \mathrm{m}), 2.31(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=6.2 \mathrm{~Hz})$, 3.30-3.68 ( $4 \mathrm{H}, \mathrm{m}$ ), $4.47,(1 \mathrm{H}, \mathrm{s}), 4.55(\mathrm{lH}, \mathrm{s}), 4.89(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=6.8 \mathrm{~Hz}), 4.99(1 \mathrm{H}, \mathrm{s}), 6.45(2 \mathrm{H}, \mathrm{s}) 7.81$ $(1 \mathrm{H}, \mathrm{s}) ; \delta_{\mathrm{C}}: 35.0,43.9,44.8,51.2,60.4,65.9,80.8,116.6,135.3,150.9,153.2,156.8$. Anal. Calcd. for $\left(\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{~N}_{5} \mathrm{O}_{4} \times 4 \mathrm{H}_{2} \mathrm{O}\right) \mathrm{C}, 39.23 ; \mathrm{H}, 6.86 ; \mathrm{N}, 19.23$. Found: C, 39.42; H, 6.57; N, 19.06.
(1S,3R,4R)-2-Amino:9-[3,4-bis(hydroxymethyl)-4-fluorocyclopentyl]-9H-purine$6(1 H)$.one (4). Compound 4 was prepared from $18(113 \mathrm{mg}, 0.33 \mathrm{mmol})$ in the same manner as described for compound 3 (above) via compound 20 which was isolated in $82 \%$ yield as a light yellow syrup ( 132 mg , $0.27 \mathrm{mmol})$. NMR ( $\mathrm{CDCl}_{3}$ ): $\delta_{\mathrm{H}}: 2.20-2.33(2 \mathrm{H}, \mathrm{m}), 2.54-2.72(2 \mathrm{H}, \mathrm{m}), 2.91$ ( $\mathrm{H}, \mathrm{dtt}, \mathrm{J}=7.1,9.5$ and 27.5 Hz ): $3.50(1 \mathrm{H}, \mathrm{ddd}, \mathrm{J}=2.0,6.8$ and 8.8 Hz ), $3.69-3.77(2 \mathrm{H}, \mathrm{m}), 3.84(1 \mathrm{H}, \mathrm{dd}, \mathrm{J}=10.5$ and 11.1 Hz$), 4.50$ $(2 \mathrm{H}, \mathrm{dd}, \mathrm{J}=11.9$ and 19.3 Hz$), 4.59(2 \mathrm{H}, \mathrm{dd}, \mathrm{J}=12.0$ and 23.2 Hz$), 4.99(2 \mathrm{H}, \mathrm{s}, \mathrm{br}), 4.98-5.07(1 \mathrm{H}, \mathrm{m})$, 7.27-7.37 ( $10 \mathrm{H}, \mathrm{m}$ ), $7.83(1 \mathrm{H}, \mathrm{s}) ; \delta_{\mathrm{C}}: 34.5,41.7\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, F}=22.0 \mathrm{~Hz}\right), 43.5\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=18.3 \mathrm{~Hz}\right), 53.0,68.5$ (d. $\mathrm{J}_{\mathrm{C}, \mathrm{F}}=9.2 \mathrm{~Hz}$ ), 71.6; (d, $\mathrm{J}_{\mathrm{C}, \mathrm{F}}=29.3 \mathrm{~Hz}$ ), 73.2, 73.5, $104.0\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C} .}=179.7 \mathrm{~Hz}\right), 125.7,127.5,127.6$. $127.8,128.3,128.4,137.6,138.0,141.1,151.2,153.4,158: 7$. Unreacted 18 (20 mg, $0.058 \mathrm{mmol}, 17 \%$ ) was also recovered. The title compound was afforded in $52 \%$ yield as a white hygroscopic solid ( 44 mg , $0.139 \mathrm{mmol}) ;[\alpha]_{\mathrm{D}}+12.0\left(c 0.5, \mathrm{H}_{2} \mathrm{O}\right)$. NMR (DMSO-D $)_{6}$ : $\delta_{\mathrm{H}}: 1.98-2.20(2 \mathrm{H}, \mathrm{m}), 2.26-2.49(2 \mathrm{H}, \mathrm{m}), 2.61$ ( $1 \mathrm{H}, \mathrm{p}, \mathrm{J}=6.4 \mathrm{~Hz}$ ), 3.17-3.72 ( $4 \mathrm{H}, \mathrm{m}$ ), $4.70(1 \mathrm{H}, \mathrm{s}), 4.86(1 \mathrm{H}, \mathrm{p}, \mathrm{J}=6.9 \mathrm{~Hz}), 5.24(1 \mathrm{H}, \mathrm{s}), 6.50(2 \mathrm{H}, \mathrm{s})$ $7.83(1 \mathrm{H}, \mathrm{s}) ; \delta_{\mathrm{C}}: 34.5,41.6\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, F}=22.0 \mathrm{~Hz}\right), 45.0\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=18.4 \mathrm{~Hz}\right), 51.0,59.5\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=12.8 \mathrm{~Hz}\right)$, 63.8. (d, $\mathrm{J}_{\mathrm{C}, \mathrm{F}}=27.4 \mathrm{~Hz}$ ), 105.4 (d, $\mathrm{J}_{\mathrm{C}, \mathrm{F}}=179.6 \mathrm{~Hz}$ ), 116.8. 135.4, 150.9, 153.3, 156.8. Anal. Calcd. for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{5} \mathrm{O}_{4} \mathrm{~F} \times 4 \mathrm{H}_{2} \mathrm{O}: \mathrm{C}, 39.42 ; \mathrm{H}, 6.80 ; \mathrm{N}, 18.91$. Found: $\mathrm{C}, 39.41 ; \mathrm{H}, 6.45 ; \mathrm{N}, 18.93$.

Acknowledgments. We gratefully acknowledge the Swedish National Board for Industrial and Technical Development:(NUTEK) and Medivir AB for financial support, Medivir AB for biological testings. and Dr. Marie Landergren, Astra Hässle AB, for NMR-assistance with compound 20.

## REFERENCES AND NOTES

1. Marquez, V. E.; Lim, M.-I. Medicinal Research Reviews 1986, $6,1-40$
2. Borthwick, A. D.; Biggadike, K. Tetrahedron 1992, 48, 571-623.
3. Niitsuma, S.: Ichikawa, Y.-I.; Takita, T. Studies in Natural Products Chemistry: Elsevier Science Publishers: New York, 1992, 10, 585-627.
4. Agrofoglio, L.; Suhas, E.; Farese, A.: Condom, R.; Challaṇd, S. R.; Earl, R. A.; Guedj, R. Tetrahedron 1994, 50, 10611-10670.
5. Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. J. Org. Chem. 1991, 56, 2993-2997.
J. Wachtmeister et al. / Tetrahedron 55 (1999) 10761-I0770
6. Sterzycki, R. Z.; Martin, J. C.; Wittman, M.; Brankovan, V.; Yang, H.; Hichcock, M. J.; Mansuri, M. M. Nucleosides \& Nucleorides 1991, 10, 291-294.
7. Mann. J.; Weymouth-Wilson, A. C. J. Chem. Soc.. Perkin Trans. 1 1994, 3141-3148.
8. Bölliger. D.; Johansson, N.-G.; Samuelsson, B.; Zhang, H.; Putkonen, L.; Wrang, L.; Öberg, B. AIDS 1997, II, 157-162.
9. Jansson, M.; Svansson, L.; Sveñsson, S. C. T.; Kvarnström, I.; Classon, B.; Samuelsson, B. Nucleosides \& Nucleotides 1992, II, 1739-1747.
10. Borthwick, A. D.; Biggadike, K.; Paternoster, I. L.; Coates, J. A. V. Bioorg: \& Med. Chem. Lett. 1993, 3, 2577-2580.
11. Rosenquist, Å.: Kvamström, I.; Sivensson, S. C. T.; Classon, B.; Samuelsson, B. Acta Chem. Scand. 1992, 46, 1127-1129.
12. Garegg, P. J.; Jversen, T.; Oscarson, S. Carbohydr. Res. 1976, 50, C12-CI4.
13. Solladié, G.; Lohse, O. J. Org. Chem. 1993, 58, 4555-4563.
14. Evans, D. A.; Chapman, K. T.; Carreira, E. M. J. Am. Chem. Soc. 1988, 110, 3560-3578.
15. Garegg, P. J.; Samuelsson, B. J. Chem. Soc, Chem. Commun. 1979, 978-980.
16. Garegg. P. J.; Samuelsson, B. J. Chem. Soc. Perkin Trans. / 1980, 2866-2869.
17. Garegg, P. J.; Samuelsson, B. J. Chem. Soc. Perkin Trans. / 1982, 681-683.
18. Bringmann, G.; Schneider, S. Synthē̄is 1983, 139-141.
19. Jäger, V.; Günther, H. J. Tetrahedron Lett. 1977, 2543-2546.
20. Chaudhary, S. K.; Hernandez, O. Tetrahedron Lett. 1979, 95-98.
21. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. Tetrahedron Lett. 1976, 1973-1976.
22. Schröder, M. Chem. Rev. 1980, 187-213.
23. Fukozowa, A.; Masamune, T. Tetrahedron Lett. 1987, 28, 4303-4306.
24. Barros, M. T.; Santos, A. G.; Godinho, L.! S.; Mayçock, C. D. Tetrahedron Lett. 1994, 35, 3999. 4002.
25. Pankiewicz, K. W.; Krezeminski, J.; Wataṇabe, K. A. J. Org. Chem. 1992, 57, 7315-7321.
26. Middleton, W. J. J. Org. Chem. 1975, 40, 574-578.
27. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Syvret, R. G.; Prozonic, F. M. In 21 bih ACS National Meeting, Organic Chemistry Boston, 1998.
28. The reagent Bis(2-methoxyethyl)aminosulfur trinluoride (Deoxo-Fluor ${ }^{T M}$ ) was purchased from Air Products and Chemicals, Inc., 7201 Hamilton Boulevard, Allentown, PA 18195-1501
29. Mitsunobú, O. Synthesis 1981, 1-28.
30. Duckworth, D. M.; Harnden, M. R.; Perkins, R. M.; Planterose, D. N. Antiviral Chemistry and Chematherapy 1991, 2, 229-24I.
31. Weislow, O. S.; Kiser, R.; Fine, D. L.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. Joumal of the National Cancer Institute 1989, 81, 577-586.
32. Unpublished test methods by Medivir AB, E-mail: Medivir@Medivir.se.

# Nucleosides. 139. Synthesis and Anticytomegalovirus and Antiherpes Simplex Virus Activity of $\mathbf{5}^{\prime}$-Modified Analogues of $\mathbf{2 '}^{\prime}$-Fluoroarabinosylpyrimidine Nucleosides 

Kazuho Harada, ${ }^{\dagger}$ Jasenka Matulic-Adamic. ${ }^{\dagger}$ Richard W. Price, ${ }^{\dagger}$ Raymond F. Schinazi, ${ }^{\dagger}$ Kyoichi A. Watanabe, ${ }^{\dagger \dagger}$ and Jack J. Fox ${ }^{\text {t }}$<br>Sloan-Kettering Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, Stoan-Kettering Division, Graduate School of Medical Sciences, Cornell University, New York, New York 10021, and Veterans Administration Medical Center and Department of Pediatrics, Emory University School of Medicine,.Atlanta, Georgia 30303. Received July 1, 1986


#### Abstract

In order to determine if modification of the $5^{\prime}$-position reduces or abolishes the antiviral activity of $2^{\prime}$-fluor- 5 -iodo-ara-C (FISC), $2^{\prime}$-fluoro-5-iodo-ara-U (FLAU), or $2^{\prime}$-flioro-5-methyl-ara-U (FMAU) against human cytomegalovirus (HCMV) and herpes simplex virus (HSV), the $5^{\prime}$-doxy, $6^{\prime}$-mercapto, and $5^{\prime}$-amino analogues of these nucleosides were prepared. $5^{\prime}$-Deoxy-FIAC and $5^{\prime}$-deoxy-FIAU were prepared by catalytic hydrogenation of $5^{\prime}$-iodo-FIAC and $5^{\prime}$-iodo-FIAU to $5^{\prime}$ deoxy-FAC and $5^{\prime}$-deoxy-FAU, respectively, followed by reiodination at $\mathrm{C}-5$. Reduction of $5^{\prime}$-iodo-FMAU afforded $5^{\prime}$ deoxy-FMAU. These $5^{\prime}$-deary nucleosides were found to be inactive against HCMV, indicating that the conversion to $5^{\prime}$-phosphate by the cellular enzyme (s) is a requirement for antiviral activity against this virus. Other $5^{\prime}$-modified ( $\mathrm{NH}_{2}$ and SH ) analogues were also prepared from $5^{\prime}-0$-tosyl-FIAC and $5^{\prime}-0$-tosyl-FMAU. Treatment of these tosylates with $\mathrm{LiN}_{3}$ in DMF afforded the corresponding $5^{\prime}-\mathrm{N}_{3}$ products. Catalytic hydrogenation of $5^{\prime} \cdot \mathrm{N}_{3}-\mathrm{FMAU}$ afforded $5^{\prime} \cdot \mathrm{NH}_{2}-\mathrm{FMAU}$, whereas $5^{\prime}-\mathrm{NH}_{2}$-FIAC was obtained by treatment of $5^{\prime}-\mathrm{N}_{3}-$ FIAC with $\mathrm{Ph}_{3}$ P in pyridine. $5^{\prime}$ - Mercapto analogues were prepared by treatment of $5^{\prime} \cdot 0$-tosyl $\cdot 3^{\prime}$ - 0 -acetyl nucleosides with KSAc followed by deacetylation. $5^{\prime} \cdot \mathrm{NH}_{2}-$ FMAU was the only compound that showed good activity against HSV-1 and HSV-2 in vito. However, this compound was less potent and had a lower therapeutic index than-FMAU.


Among many $2^{\prime}$-fluoro- $\beta$-D-arabinosylpyrimidines synthesized in our laboratory ${ }^{14}$ as potential antitumor and/or antiviral agents, $2^{\prime}$-fluoro-5-iodo-ara-C (FIAC, la, Scheme I) ${ }^{1,5,6}$ and $2^{\prime}$-fuoro-5-methyl-ara-U (FMAU, Ic) ${ }^{2.6}$ have shown most potent and selective inhibitory activity against herpes simplex viruses types 1 and 2 (HSV-1 and -2$)^{1,2,5-8}$ and Varicella zoster virus (VZV). ${ }^{8.6,8,9}$ These nucleosides are phosphorylated preferentially by a vlrus-specified thymidine kinase (TK), ${ }^{5,6,10,11}$ which appears to account, in significant measure, for their selective antiherpetic activity.
Recently, these nucleosides were found to exhibit selective activity against human cytomegalovirus (HCMV), ${ }^{12,13}$ a virus that does not specify an HCMV-TK. for its replication. ${ }^{14,16}$ It was suggested ${ }^{12,13}$ therefore that the mechanism of action of these nucleosides against HCMV may be different qualitatively from that found for HSV.
In order to determine if phosphorylation to the $5^{\prime}$-nucleotide is a prerequisite for inhibition of HCMV by these nucleosides, we synthesized $5^{\prime}$-doxy analogues of FIAC, FIAU, and FMAU (Fa, 7b, and Tc, respectively). We also prepared several other $5^{\prime}$-modified analogues of FIAC and FMAU as potential antiviral agents on the basis of the rationale that certain $5^{\prime}$-amino- $2^{\prime}, 5^{\prime}$-dideoxypyrimidine nucleosides are phosphorylated selectively by virus-encoded TK ${ }^{18,17}$ and exhibit antiherpesvirus activity. ${ }^{18-20}$ They are also incorporated into the DNA of HSV-1. ${ }^{21,22}$ The $5^{\prime}$-amino analogues 6 might also serve as substrates for the virus-coded TK and, on the basis of our previous studies, ${ }^{1,6}$ the $2^{\prime}$-fluor substituent may enhance the antiviral potency of 6 . Should the $5^{\prime}$-amino- $2^{\prime}$ - $l$ uoro nucleosides 6 be incorporated (with the phosphoramidate linkage) into viral DNA, they might provide a unique basis for antiviral activity. It would also be of interest to determine if the $5^{\prime}$-thiol of 9 acts by a similar mechanism.
Selective tosylation ${ }^{23}$ of FIAC, FIAU, or FMAU at the 5 '-position afforded the corresponding 5 '-tosylates 2 , which were converted into their respective 5 -iodides 4 by treatment with MaI in dimethylformamide (DMF). The same nucleosides 4 were also prepared in one step by direct

[^12]Scheme I

treatment of 1 with methyltriphenoxyphosphonium iodide in DMF. ${ }^{24}$ Catalytic hydrogenolysis of 4 c afforded $5^{\prime}$ -
(1) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. J. Med. Chem. 1979, 22, 21.

Table I. Anti-HSV Activity of 5'-Modified 1-(2-Deoxy-2-nuoro- $\beta$-D-arabinofuranosyl)pyrimidine Nucleosides ${ }^{\circ}$

| compround | HSV. 1 (strain F) |  | HSV-2 (strain G) |  | $\begin{gathered} \text { cytotoxicity } \\ I D_{60} \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\mathrm{ED}_{50}$ | $E D^{90}$ | $\mathrm{ED}_{50}$. | $\mathrm{ED}_{80}$ |  |
| 6a ( $5^{\prime} \cdot \mathrm{NH}_{2}$ - FlAC ) | 202 | 480 | $>400$ | $>409$ | $>400$ |
| 6 b ( $5^{\prime} \cdot \mathrm{NH}_{2} \mathrm{FIAU}$ ) | 108 | >200 | $>200$ | $>200$ | $>200$ |
| 6c ( $5^{\prime} \cdot \mathrm{NH}_{2} \cdot \mathrm{FMAU}$ ) | 0.78 | 3.0 | 5.6 | 14.0 | 6.7 |
| 7a (5'-deury-FIAC) | >400 | $>400$ | >400 | $>400$ | $>400$ |
| 7b (5'-deuxy-FIAU) | 220 | 384 . | 135 | 290 | $>400$ |
| 7 c ( $5^{\prime}$-deoxy-FMAU) | 31.1 | 298 | 173 | 493 | 214 |
| 7d ( $6^{\prime}$-dooxy-FAC) | 13.3 | 35.0 | 17.1 | 45.6 | 325 |
| 7 P ( $5^{\prime} \cdot \mathrm{deoxy} \cdot \mathrm{FAU}$ ) | 346 | 538 | 224 | 379 | 333 |
| 9 a ( $5^{\prime}$ SH-FIAC) | 216 | 444 | >200 | >200 | 337 |
| 9 c ( $5^{\prime}$-SH-FMAU) | $>200$ | >200 | $>200$. | $>200$ | 314 |
| la (FLAC) | 0.023 | 0.048 | 0.03 | 0.08 | 21.7 |
| lb (FIAU) | 0.012 | 0.041 | 0.01 | 0.045 | 10.3 |
| - lc (FMAU) | 0.018. | 0.047 | 0.023 | 0.09 | 2.8 |
| $5^{\prime}-\mathrm{NH}_{2}$-IddUrd | 1.86 | 26.6 | $>400$ | $>400$ | $>400$ |
| 5 - $\mathrm{NH}_{2}$-dd'l'hd | 7.7 | 153 | $>400$ | >400 | $>400$ |

${ }^{a}$ Tested in Vero cells by a plaque reduction assay. $E D_{60}$ and $E D_{90}$ are effective concentrations ( $\mu \mathrm{M}$ ) required to inhibit replication of HSV by $50 \%$ and $90 \%$, respectively. $\mathrm{ID}_{50}$ is concentration necessary for $50 \%$ inhibition of growth of rapidly dividing Vero cells.
deoxy-FMAU (7c) in high yield. Reduction of $4 a$ and $4 b$, however, gave the correspondins completely deiodinated products (7d and 7e, respectively), which were reiodinated to give $5^{\prime}$-deoxy-FIAC (7a) and $5^{\prime}$-deoxy-FIAU (7b).
The $5^{\prime}$-tosylate of FIAC and FMAU ( $2 a$ and 2 c ) were
(2) Watanabe, K. A.; Su, T-L.; Klein, R. S.; Chu, C. K.; Matsuda, A.; Chun, M-W.; Lopez, C.; Fox, J. J. J. Med. Chem. 1983, 26, 152.
(3) Watariabe, K. A.; Su, T-L.; Reichman, U.; Greenberg, N.; Lopez, C.: Fox, J. J. J. Med. Chem. 1984, 27, 91.
(4) Perlman, M. E.; Watanabe, K. A:; Schinazi, R. F.; Fox, J. J. J. Med. Chem. 1985, 28, 741.
(5) Lopez, C.; Watanabe, K. A.; Fox, J. J. Antimicrob. Agents Chemother 1980, 17, 803.
(6) Fox, J. J.: Lupez, C.; Watanabe, K. A. Medicinal Chemistry Aduances; De Las Heras, F. G., Ed.; Pergamon: Now York; 1981; p 27.
(7) Schinazi, R. F.; Peters, J.; Sokol, M. K.; Nahmias, A. J. Antimicrob. Agents Chemother. 1983, 24, 95.
(8) Fox, J. J.; Watanabe, K. A.; Lopez, C.; Philips, F. S.; Ley-land-Jones, H. Herpesvirus: Clinical, Pharmacological and Basic Aspects; Shiota, H., Cheng, Y-C., Prusoff, W. H., Eds.; Excerpta Modica: Amstordam, 1982; pp 135-147.
(9) Fox, J. J.; Watanabe, K. A.; Schinazi, R. F.; Lopez, C. Herpes Viruses and Virus Chemotherapy. Pharmacological and Clinical Approaches; Kono, R., Nakajima, A., Eds.; Excerpta Medica: Amsterdam, 1985; pp 53-56.
(10) Cheng, Y-C.; Dutchman. G.; Fox. J. J.; Watagabe, K. A.; Ma- chida, H. Antimicrob. Agents Chemother. 1982, 20, 420.
(11) Kreis, W.; Demin, L.; Colacino, J.; Lopez, C. Biochem. Pharmacol. 1982, 31, 767 .'
(12) Colacino, J. M.; Lopez, C. Antimicrob. Agento Chemother. 1983, 24, 508.
(13) Mar, E-C.; Patel, P. C.; Cheng, Y-C.; Fox, J. J.; Watanabe, K. A.; Huang, E.S.J. Gen. Virol. 1984, 65, 47.
(14) Zavada, V.; Erban, V.; Rezacova, D.; Vonka, V. Arch. Virol. 1976, 52, 333.
(15) Esters, J. E.; Huang, E-S. J. Virol. 1977, 24, 13. •
(16) Chen, M-S.; Shiau, G. T.; Prusolf, W. H. Antimicrob. Agents Chemother. 1980, 18, 433.
(17) Chen, M-S.; Prusoff, W. H. J. Biol. Chem. 1979, ${ }^{\text {2 }} 254,10449$.
(18) Lin, T-S.: Prusoff, W. H. J. Med. Chem. 1978, 21, 106.
(19) Lin, T-S.; Prusoff, W. H. J. Med. Chem. 1978, 21, 109.
(20) Iltis, J. P.; Lin, T-S.; Prusoff, W. H.; Rapp, F..Anlimicrob. Agents Chemother. 1979, 16, 82.
(21) Chen, M-S.; Ward, D. C.; Prusoff, W. H. J. Biol. Chem. 1976, - 251, 4833.
(22) Fischer, P. J.; Chen, M-S.; Prusoff, W. H. Biochim. Biophys. Acta 1980, 606, 236.
(23) Reist, R. J.; Benitez, A.; Goodman, L. J. Org. Chem. 1964, 29, 554.
(24) Verheyden, J. P. H.; Muffatt, J. G. J. Org. Chem. 1970, 35. 2319.
converted into the $5^{\prime}$-azido nucleosides (3a and 3c) by treatment with $\mathrm{LiN}_{3}$ in DMF. Catalytic reduction of 3c afforded $5^{\prime}$-amino-5 $5^{\prime}$-deoxy-FMAU (6c). $5^{\prime}$-Amino-5'-deoxy-FIAC (6a) was obtained from 3a by treatment with triphenylphosphine in pyridine. 25 Treatment of $2 a$ or $2 c$ directly with KSAc in various solvents led to formation of intractable mixtures. However, ufter acetylation of 2 to 5 , the latter was found to undergo smooth conversion to the corresponding $5^{\prime}$-SAc derivatives 8 , which were deacetylated to FLAC-5'-thiol (9a) and FMAU-5'-thiol (9c).

The 5'-deoxynucleosides 7a-c were inactive against HCMV in vitro at the highest concentration tested ( 1 mM ). They are about 1000 times less active than the corresponding parent antivirals 1 against HSV-1 and HSV-2 (Table I). These results establish the importance of phosphorylation at the C-5' hydroxyl group for FIAC and FMAU to exert anti-HCMV activity. They are also consistent with a more recent report by Colacino and Lopez, ${ }^{26}$ which indicated that the HCMV viral DNA polymerase may use available FIAC triphosphate (product of cellular kinases) more efficiently as an alternative substrate for incorporation into DNA and may be more susceptible to analogue inhibition than the cellular enzyme.

It is also interesting to note that $5^{\prime}$-amino- $5^{\prime}$-deoxyFMAU (6c) showed activity against HSV-1 and -2 and was also quite cytotoxic, although the FIAC and FIAU ana-. logues ( $6 a$ and $6 b$ ) were practically inactive. This antiviral characteristic of 6 c is interesting since $5^{\prime}$-amino-IddUrd and $5^{\prime}$-amino-ddThd are noncytotoxic at $400 \mu \mathrm{M}$ concentration, and the thymine nucleoside is less active than 5 '-amino-IddUdR against.HSV-1 (Table I). Replacement of the 5 '-hydroxy function of FIAC and FMAU by a hydrogen or SH group reduced or eliminated the antiviral. activity..

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on silica gel G60 (70-230 mesh, ASTM, Merck). Elementary analyses were performed by M-H-W Laboratories, Phoenix, AZ, and Spang Microanalytical Laboratory, Eagle Harbor, MI, and all the new compounds were analyzed correctly (Table II). ${ }^{1} \mathrm{H}$ NMR spectra are recorded on a JEOL PFT-100 or JEOL FX90Q spectrometerwith $\mathrm{Me}_{4} \mathrm{Si}$ as the internal standard (Table III). $5^{\prime}$-Amino- $2^{\prime}, 5^{\prime}$-dideoxy-5-iodouridine (5'- $\mathrm{NH}_{2}$ IddUrd)
(25) Mungall, W. S.; Greene, G. L.; Heavner, G. A.; Letsinger, R. J. Org. Chem. 1975, 40, 1695.
(26) Colacino, J. M.; Lopez, C. Antimicrob. Agents Chemother. 1985, 28, 252.

Table II. New Compounds.


Table III. ${ }^{1} \mathrm{H}$ NMR Parameters of $5^{\prime}$-Modified 1-(2-Deoxy-2-fluoro- $\beta$-D-arabinofuranosyl)pyrimidines ${ }^{a}$

|  | chemical shifts, $\delta$ |  |  |  |  |  |  | coupling constants, Hz |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| no. | H.1 | H-2' | H. ${ }^{\prime}$ | H-4' | H-5' | H.6 | others | $J_{1^{\prime}, 2^{\prime}}$ | $J_{1 ; ~}$ | $J_{2,3^{\prime}}$ | $J_{2 ;}$; | $J_{3}{ }^{\prime}{ }^{\prime}$ | $J_{3 ; 5}$ |
| 2a | 6.09dd | 4.09ddd | 4.01-4 | 4.15 m | 4.29 d | 7.798 | 2.438 ( MePh ) | 3.67 | 18.9 | 3.67 | 57.3 |  |  |
| 2b | 6.09dd | 5.01 ddd |  | 385-444m |  | 7.82d | 2.42s(MePh) | 4.11. | 17.3 | 2.47 | 52.6 |  |  |
| 2c | 6.16dd | 5.08ddd | 3.82-4 | 4.17m | 4.32 d | 7.338 | 1.79s(5-Me), $2.42 \mathrm{~s}(\mathrm{MePh})$ | 4.27 | 16.5 | 4.27 | 49.1 |  |  |
| 3a | 6.10dd | 5.01 ddd | 4.18 m | 4.06 m | 3.65 m | 7.838 |  | 3.66 | 18.6 | 3.66 | 54.6 |  | 20.0 |
| 3b | 6.11 dd | 5.05 ddd | 4.45-3 | 3.97m | 3.68 m | 7.90d |  | 3.84 | 17.2 | 2.47 | 52.4 |  |  |
| 3 c | 6.17d | 5.06 ddd | 4.20 dm | 3.95 m | 3.65 m | 7.39s | $1.80 \mathrm{~s}(5-\mathrm{Me})$ | 4.12 | 17.9 | 4.12 | 52.5 |  | 20.1 |
| $4{ }^{\circ}$ | 6.16dd | 5.06 dd | 4.13 dd | 3.87dd | 3.58 m | 7.96 s |  | 3.66 | 19.1 | 0 | 52.2 | 2.0 | 15.0 |
| 4b. | 6.14 dd | 5.07 ddd . | 4.13 dm | 3.83 m . | 3.53m | 7.97d |  | 3.98 | 18.0 | 2.47 | 52.9 |  | 19.5 |
| 4 c | 6.19dd | 5.08 ddd | 4.16 dd | 3.33-3 | 3.97m | 7.47s | $1.82 \mathrm{~s}(5-\mathrm{Me})$ | - 4.12 | 17.8 | 4.12 | 55.5 | 4.8 | 20.0 |
| 5 E | 6.09dd | 5.24 dd | 5.19dd | 4.37 m | 4.21 d | 7.798 | 2.09s(OAc), $2,43 \mathrm{~s}(\mathrm{MePh}$ ) | 3.82 | 18.8 | 0 | 50.8 | 4.0 | 18.5 |
| 5 c | 6.15dd | 5.33 m | 5.21 dm | 4.39 m | 4.24 d | 7.36s | $1.78 \mathrm{~s}(5-\mathrm{Me}), 2.78 \mathrm{~s}(\mathrm{OAc}), 2.41 \mathrm{~s}(\mathrm{MePh})$ | 3.82 | 17.2 | 3.82 | 51.8 | 4.0 | .26.4 ${ }^{\text {' }}$ |
| 6 a | 6.03dd | 4.96 ddd | 4.18dd | 3.73 m | 2.78 d | 7.998 |  | 3.51 | 18.5 | 3.51 | 52.5 | 6.0 | 19.4 |
| 6b | 6.05dd | 5.01 ddd | 4.22dd | 3.72 m | 2.81 m | 8.18d |  | 4.12 | 15.9 | 3.02 | 52.7 | 4.9 | 19.8 |
| 6 c | 6.07 dd | 5.00 ddd . | 4.10 dd | 3.69 m | 2.81d | 7.55s | 1.868(5-Me) | 4.13 | 17.3 | 4.13 | 53.1 | 5.0 | 21.3 |
| 7 a | 6.01 dd | 4.44 dd . | 3.97 dd | 3.90m | 1.34 d | 7.758 |  | 3.35 | 19.5 | 0 | 50.3 | 2.0 | 15.0 |
| 7b | 6.02dd | 4.97 ddd | 4.19-3 | 3.70 m | 1.35d | 7.82d |  | . 3.66 | . 18.3 | 3.66 | 52.6 | 2.0 |  |
| 7 c | 6.07dd | 4.95 ddd | 3.98 dd | 3.83 m | 1.32d | 7.36 s | 1.808(5-Me) | 4.28 | 17.4 | 4.0 | 53.0 | 4.0 | 18.0 |
| .7d | 6.06dd | 4.93 dd | 4.03dd | 3.87 m | 1.36d | 7.53d | $5.79 \mathrm{~d}\left(\mathrm{H} \cdot 5, J_{5.8}=7.3 \mathrm{~Hz}\right)$ | 3.50 | 19.0 | 0 | 49.2 | 2.4 | 14.0 |
| 7 e | 5.92dd | 4.99 ddd | 3.95-3 | 3.49 m | 1.18d | 7.39 dd | $5.49 \mathrm{~d}\left(\mathrm{H}-5, J_{5,6}=8.2 \mathrm{~Hz}\right)$ | 4.27 | 17.4 | 4.27 | 52.9 | 2.75 |  |
| 8 a | 6.07 dd | 5.26dd | 5.18dd | 4.20 m | 3.35 d | 7.80 s | $2.119(\mathrm{SAc}), 2.40 \mathrm{~s}(\mathrm{OAc})$ : | 3.51 | 19.7 | 0 | 50.8 | 4.0 | 18.5 |
| 8 c | 6.12 dd | 5.30 dm | 5.17 dm | 4.10 m | 3.35 d | 7.448 | 1.82s(5-Me), 2,12s(SAc), 2.38 s (OAc) | 4.0 | 18.9 | 4.0 | 49.4 | 4.0 | 17.7 |
| 9 a | 6.07 dd | 5.00 ddd | 4.21 dm | 3.87 m | 2.52 d | 7.9 HB |  | 3.56 | 19.2 | 3.56 | 52.1 |  | 18.9 |
| 9 c | 6.13dd | 5.03 ddd | 4.24 dm | 3.87 m | 2.84d | 7.468 | $1.81 \mathrm{~s}(5 . \mathrm{Me})$ | 4.10 | 17.2 | 4.10 | 52.0 | 4.0 | 19.9 |

${ }^{-}$The spectra were recorded in $\mathrm{Me}_{2} \mathrm{SO} \cdot d_{8}$ solutions. Signals are quoted as s (singlet), d (doublet), dd (double doublet), ddd (double double-doublet), m (multiplet), dm (double multiplet), and coupling constants reported are first order.
and $5^{\prime}$-amino- $5^{\prime}$-deoxythymidine ( $5^{\prime} \cdot \mathrm{NH}_{2}$-ddThd) were:prepared by the method of Lin et al. ${ }^{18,19}$

1-(2-Deoxy-2-fluoro-5-O-tosyl- $\theta$-D-arabinofuranosyl)thymine (2c). To an ice-cooled solution of FMAU ( $1.04 \mathrm{~g}, 4 \mathrm{mmol}$ ) in pyridine ( 20 mL ) was added $\mathrm{TsCl}(0.92 \mathrm{~g}, 4.8 \mathrm{mmol})$. After stirring at $4^{\circ} \mathrm{C}$ for 24 h , the mixture was poured onto an ice-water mixture ( 20 mL ) and then extracted with $\mathrm{CHCl}_{3}(20 \mathrm{~mL} \times 2)$. The combined extracts were washed with aqueous $\mathrm{NaHCO}_{3}$ (20 $\mathrm{mL} \times 3$ ) and water $(20 \mathrm{~mL} \times 3)$, dried $\left(\mathrm{MgSO}_{4}\right)$, and concentrated in vacuo. Recrustallization of the residue from $95 \% \mathrm{EtOH}$ af-
forded $2 \mathrm{c}\left(1.06 \mathrm{~g}, 64 \%\right.$ ), mp 206-207 ${ }^{\circ} \mathrm{C}$. The ${ }^{1} \mathrm{H}$ NMR spectral data are reported in Table III.

In a similar manner, FIAC and FIAU were cōnverted into the corresponding $5^{\prime}$-O-tosylates $2 \mathrm{a}, \mathrm{mp} 199^{\circ} \mathrm{C}$ dec, and $2 \mathrm{~b}, \mathrm{mp}$ $220-221^{\circ} \mathrm{C}$. The ${ }^{1} \mathrm{H}$ NMR characteristics of these nucleosides are listed in Table III.

1-(2,5-Dideoxy-2-fluoro-5-iodo- $\beta$-D-arabinofuranosyl)-5iodocytosine (4a). A mixture of FIAC ( $1.30 \mathrm{~g}, 3.5 \mathrm{mmol}$ ) and methyltriphenoxyphosphonium iodide ( $1.82 \mathrm{~g}, 4.0 \mathrm{mmol}$ ) in DMF $(12 \mathrm{~mL}$ ) was stirred for 30 min at room temperature and then
diluted with MeOH ( 6 mL ). The mixture was concentrated in vacuo and the solid residue was dissolved in $\mathrm{CHCl}_{3}$. The solution was washed with $5 \% \quad \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ and water, dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, and then concentrated in varuo. The residue was recrystallized from MeOH to give 4 a ( $1.10 \mathrm{~g}, 60 \%$ ), $\mathrm{mp} 225-227^{\circ} \mathrm{C}$.
$5^{\prime}$-Deoxy-5'-iodo-FIAU (4b), mp $245^{\circ} \mathrm{C} \mathrm{dec} ,\mathrm{and} 5^{\prime}$-deoxy- $5^{\prime}$. iodo-FMAU (4c), $\mathrm{mp} 231-232^{\circ} \mathrm{C}$, were also prepared in a'similar manner with FIAU or FMAU as the starting material. See Table III for the ${ }^{1} \mathrm{H}$ NMR parameters of sa-c.

1-(2,5-Dideoxy-2-fluoro- $\beta$-D-arabinofuránosyl)thymine ( $5^{\prime}$-Deoxy-FMAU, 7c). A solution of 4 c ( $200 \mathrm{mg}, 0.55 \mathrm{mmol}$ ) in a mixture of water ( 10 mL ) and EtOH ( 20 mL ) was adjusted to pH 10 with concentrated $\mathrm{NH}_{4} \mathrm{OH}$. The solution was hydrogenated at room temperature, at atmospheric pressure in the presence of $5 \% \mathrm{Pd} / \mathrm{BaSO}_{4}(800 \mathrm{mg})$ for 4 h . The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo. Recrystallization of the residue from $\mathrm{EtOH}-\mathrm{Et}_{2} \mathrm{O}$ gave 7 c ( $105 \mathrm{mg}, 83 \%$ ), mp $200-202{ }^{\circ} \mathrm{C}$ :

Reduction of $4 a$ and $4 b$ in a similar manner afforded 1-(2,5-dideoxy-2-fluoro- $B$-D-arabinofuranosyl) cytosine ( $5^{\prime}$-deoxy-FAC, 7 d ), mp 117-119 ${ }^{\circ} \mathrm{C}$, and 1 -(2,5-dideoxy-2-fluoro- $\dot{\beta}$-D-arabinofuranosyl)uracil ( $5^{\prime}$-deoxy-FAU, 7e), mp 218-219 ${ }^{\circ} \mathrm{C}$, respecitively. The 'H NMR parameters of these 5 '-deoxynucleosides $7 \mathrm{c}-\mathrm{e}$ are reported'in Table III.

1-(2,5-Dideoxy-2-fluoro- $\beta$-d-arabinofuranosyl)-5-iodocytosine ( $5^{\prime}$-Deoxy-FIAC, 7a). A mixture of 7d ( $110 \mathrm{mg}, 0.5$ mmol), $\mathrm{HIO}_{3}$ ( $45 \mathrm{mg}, 0.25 \mathrm{mmol}$ ), $\mathrm{I}_{2}(75 \mathrm{mg}, 0.30 \mathrm{mmol}$ ), water $(0.2 \mathrm{~mL}), \mathrm{HOAc}(0.4 \mathrm{~mL})$, and $\mathrm{CCl}_{4}(0.1 \mathrm{~mL})$ was stirred at $45-55$ ${ }^{\circ} \mathrm{C}$ for 2 h . After cooling to room temperature, the reaction mixture was passed through a column of'Amberlite IR-45 ( $\mathrm{OH}^{-}$) resin, and the resin was washed with water and EtOH. The combined filtrate and washings were concentrated in vacuo, and the residue was recrystallized from EtOH-water to give 7a (143 $\mathrm{mg}, 81 \%$ ), mp $220-225^{\circ} \mathrm{C}$ dec. The ${ }^{1} \mathrm{H}$ NMR spectral data for 7 a are given in Table III.

1-(2,5-Dideoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-5-iodouracil (5'-Deoxy-FIAU, 7b). To a mixture of 7 e ( $172 \mathrm{mg}, 0.75 \mathrm{mmol}$ ) and $\mathrm{I}_{2}(95 \mathrm{mg}, 0.38 \mathrm{mmol})$ in $\mathrm{HOAc}(5.0 \mathrm{~mL})$ was added fuming $\mathrm{HNO}_{3}$ gradually until the color of $\mathrm{I}_{2}$ disappeared ( $\sim 2 \mathrm{~h}$ ). Water ( 50 mL ) was added and the mixturo was concentrated in vacuo. Recrystallization of the residue from MeOH -water afforded $\mathbf{7 b}$ ( $240 \mathrm{mg}, 90 \%$ ) as colorless needles, $\mathrm{mp} 230^{\circ} \mathrm{C}$. See Table III for the ${ }^{1} \mathrm{H}$ NMR parameters of 7 b .

1-(5-Azido-2,5-dideoxy-2-fluoro- $\beta$-D-arabinofuranosyl)-5iodocytosine (3a). A mixture of $2 \mathrm{a}(1.00 \mathrm{~g}, 1.90 \mathrm{mmol})$ and $\mathrm{LiN}_{3}$ $(1.86 \mathrm{~g}, 3.80 \mathrm{mmol})$ in DMF ( 15 mL ) was heated at $70-75^{\circ} \mathrm{C}$ fot 3 h and then concentrated in vacuo. The residue was triturated with a small amount of cold water and then recrystallized from EtOH to give $3 \mathrm{a}\left(603 \mathrm{mg}, 80 \%\right.$ ) as çolorless crystals; $\mathrm{mp} 229^{\circ} \mathrm{C}$ dec.

In a similar manner, 2c ( $628 \mathrm{mg}, 1.5 \mathrm{mmol}$ ) was converted into 1 -(5-azido-2, $\mathrm{\sigma}$-dideoxy- 2 -fluono- $\beta$-D-arabinofuranosyl)thymine (3c) (348 mg, 80\%), mp 192-193 ${ }^{\circ} \mathrm{C}$.
The ${ }^{1} H$ NMR spectral characteristics of $3 \mathrm{a}-\mathrm{c}$ are reported in Table III.

1-(5-Amino-2,5-dideoxy-2-fluoro- $\beta$-D-arabinofuranosyl)5 -iodocytosine ( $5^{\prime}$-Amino-5'-deoxy-FIAC, 6a). Mixture of 3a ( $396 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) and $\mathrm{Ph}_{3} \mathrm{P}$ ( $420 \mathrm{mg}, 1.6 \mathrm{mmol}$ ) in pyridine ( 10 mL ) was stirred at room temperature for 4 h . After dilution with concentrated $\mathrm{NH}_{4} \mathrm{OH}(1 \mathrm{~mL})$, the mixture was stirred for an additional 3 h and then concentrated in vacuo. The residue was triturated with $\mathrm{Et} \mathbf{1}$ O to give a crystalline mass, which was collected by fitration and recryntallized from FtOH-water to afford 6a (301 $\mathrm{mg}, 83 \%$ ), $\mathrm{mp} 2155-213^{\circ} \mathrm{C}$ dec. T'able III list the 'H NMR parameters of 6

1-(3-O-Acetyl-2-deoxy-2-fluaro-5-O-tosyl- $\beta$-D-arabinoPuranosyl).5.iodocytosine (5a). A mixture of $2 \mathrm{a}(\mathbf{5 . 3 0 \mathrm { g } , 1 0 . 0}$ $\mathrm{mmol})$ and $\mathrm{Ac}_{2} \mathrm{O}(4.0 \mathrm{~mL})$ in dry pyridine ( 1.00 mL ) was stirred at roum temperature for 3 h and then the reaction was quenched by addition of $\mathrm{EtOH}(10 \mathrm{~mL})$. After concentration of the mixture
in vacuo, the residue was crystallized from EtOH to afford $5 \mathrm{5a}$ (4.85 g. $85 \%$ ), mp $157-159^{\circ} \mathrm{C}$.

In a similar manner $2 \mathrm{c}(2.0 \mathrm{~g}, 4.83 \mathrm{mmol})$ was acetylated to give 1.78 g ( $82 \%$ ) of 1-(3-O-acetyl-2-deoxy-2-fluoro-5-O-to-syl- $\beta$-D-arabinofuranosyl)thymine ( 5 c ), mp $120-125^{\circ} \mathrm{C}$ dec. The ${ }^{1} \mathrm{H}$ NMR parameters of 5 a and 5 c are listed in Table III.

1-(3-O-Acetyl-5-S-acetyl-2,5-dideoxy-2-fluoro-5-thio- $\beta$-Darabinofuranosyl)thymine (8c). A suspension of $5 \mathrm{c}(640 \mathrm{mg}$, 1.42 mmol ) and KSAc ( $640 \mathrm{mg}, 5.60 \mathrm{mmol}$ ) in $\mathrm{Me}_{2} \mathrm{CO}(15 \mathrm{~mL})$ was stirred at room temperature for 16 h . The mixture was cooled to $0^{\circ} \mathrm{C}$ und filtered. The filtered cake was washed with $\mathrm{Me}_{2} \mathrm{CO}$ $(10 \mathrm{~mL})$. The combined filtrate and washings were concentrated in vacuo, and the residue was chromatographed on a silica gel column using $\mathrm{CHCl}_{3}-\mathrm{MeOH}(10: 1, v / v)$ as the eluent. The major fraction containing the nucleosides was evaporated in vacuo, and the residue was crystallized from EtOH to afford 8 c ( $396 \mathrm{mg}, 78 \%$ ) as colorless crystals, $\mathrm{mp} 114-116^{\circ} \mathrm{C}$.

1-(3-O-Acetyl-3-S-acetyl-2,5-dideoxy-2-flunro-5-thin- $\beta$-n-arabinofuranosyl)-5-iodocytosine (8a), mp $118-125^{\circ} \mathrm{C}$ dec, was obtained from 5 a in a similar manner. The ${ }^{1} \mathrm{H}$ NMR data for 5 a and 5 c are reported in Table III.

1-(2,5-Dideoxy-2-fluoro-5-thio- $\beta$-D-arabinofuranosyl)thymine (9c). A mixture of $8 \mathrm{c}(718 \mathrm{mg}, 2.0 \mathrm{mmol})$ in $1 \mathrm{M} \mathrm{HCl} /$ $\mathrm{MeOH}(20 \mathrm{~mL})$ was heated at $45^{\circ} \mathrm{C}$ for 3 h under $\mathrm{N}_{2}$. A small amount of insoluble materials was removed by filtration, and the filtrate was concentrated in vacuo. Recrystallization of the residue from $\mathrm{CHCl}_{3}$-petroleum ether afforded $9 \mathrm{c}(398 \mathrm{mg}, 72 \%$ ) mp $202-204^{\circ} \mathrm{C}$.

By following the same procedure but using $8 \mathrm{a}, 1$ - $2,5-\mathrm{d}$ - . deoxy-2-fluoro-5-thio- $\beta$-D-arabinofuranosyl)-5-iodocytosine (9a), mp 223-225 ${ }^{\circ} \mathrm{C}$ dec, was obtained. The ${ }^{1} \mathrm{H}$ NMR spectral data for 9 a and 9 c are listed in Table III.

Anti-HCMV Evaluation. Nucleosides were assessed for anti-HCMV activity by using a previously described microtiter assay ${ }^{27}$ in which antiviral efficacy was determined by inhibition of the development and spread of cytopathology induced by HCMV (strain AD169) in human foreskin fibroblasts. Each drug was evaluated at 10 -fold dilutions ranging from $10^{-3}$ to $10^{-9} \mathrm{M}$ at both a high and low virus inoculum. Medium with fresh drug was replenished every 2-3 days, and plates were read-at-days 8-12 after viral inoculation. Drug-induced cytopathology was screened morphologically by evaluation of the thinning or loss of the cell monolayers in uninfected control wells. With each of the nucleosides, no appreciable viral inhibition was detected at $\cdot 10^{-4} \mathrm{M}$ concentration, while direct cell cytotoxicity was present at $10^{-3}$ M.

Anti-HSV Evaluation. The newly synthesized nucleosides 6, 7, and 9 were screened for activity against HSV-1 (strain F) and HSV-2 (strain G) by a plaque reduction assay in Vero cells, using the methodologies previously described. ${ }^{28}$ Cytotoxicity assays were conducted in rapidly dividing Vero cells, as previously. described. ${ }^{28}$
Acknowledgment. This investigation was supported by funds from the National Cancer Institute, USDHHS (Grant No. CA-08748, 18601, and 18856) and a Veterans Administration Merit Award (R.F.S.).

Registry No. 1á, 69123-90-6; 1b, 69123-98-4; 1c, 69256-17-3; 2a, 105281-00-3; 2b, 105281-01-4; 2c, 105281-02-5; 3a, 105281-10-5; 3b, 105281-12-7; 3c, 105281-11-6; 4a, 105281-03-6; 4b, 105281-04-7; 4c, 105281:05-8; 5a, 105281-15-0; 5c, 105281-16-1; 6a, 105281-13-8; 6b, 105281-14-9; 6c, 105281-14-9; 7a, 105309-31-7; 7b, 105281-09-2; 7c, 105281-06-9; 7d, 105281-07-0; 7e, 105281-08-1; 8a, 105281-18-3; 8c, 105281-1才-2; 9a, 105281-20-7; 9c, 105281-19-4.
(27) Matulic-Adamic, J.; Price, R. W.; Watanabe, K. A. Chem. Scrip. 1986, 26, 127.
(28) Schinazi, R. F.; Peters, J.; Williams, C. C.; Chance, D.; Nahmias, A. J. Antimicrob. Agents Chemother. 1982, 22, 499.
 :elate (3). $\mathrm{C}_{2} \mathrm{j}^{1}{ }_{38} \mathrm{O}_{6}$,
d but was hyitrolyaed i, , debencoyletind compound
rathe aid of ${ }^{1} H^{-1} H_{\text {and }} \mathrm{I}_{\mathrm{H}}$. l maybe a daterpenc acid measured under various $s$ In the molecule. $A_{5}$ :He coupled ${ }^{13} \mathrm{C}$ - ${ }^{13} \mathrm{C}$ pairs I. Therefore u labdanc.
on spectrum of 1 in order che methylencearbion at $f$

3-113). In turn, the anat at 642.9 (C-5) are - $1.48\left(20-\mathrm{H}_{3}\right), 1.61(2-11)$, $35\left(19-\mathrm{H}_{3}\right), 1.48\left(20-\mathrm{H}_{3}\right)$,
 uluin Fig. 3. Thus, the s determined by nuclear of the 19 - and 20~nethyls 1 the 19 -and 2 ', $6^{\prime}$-protons aged the signal intensity) eel stand 6-proions and ton of scoparic acid 1
ill be reported elsouhcre.
from Japan International to T.K. (Ho.61470148) (rat
:1979). Also. several , M.C.Das and N.P.Sabu. ublising Co.. Dordrectit. Int, Ed. Engr., 22. 3>0 rn was supposed lobe $0^{n}$ (Received July 8, 1987 )


RADTCAL DEOXYGENATYON OF TERT'.ALCOHOLS !H 2'. -BRANCHED CHAJN SUGAR PYRIMIDINE NUCLEOSIDES: SYNTHESIS AND ANIILEUKEMIC ACTIVITY OF $2^{\prime}-$ DHOXY-2'(S)-METHYLGYTTDTNF: $\left.{ }^{\prime}\right)$

Akita Matsuda, ${ }^{*}$, a Kanji Takenuki, ${ }^{\text {a Bioko Itch, }}$,

Takuma Sasaki, b and Thru Veda ${ }^{\circ}$

Faculty of Pharmaceutical Sciences, Hokkaido University, ${ }^{\text {a }}$ Kita-12, Nishl-G, Kita-ku, Sapuco ob o ant Cancer Research institute, Kanazawa University, ${ }^{\text {b }}$ Takaramachi, Kanazawa 920, Japan

We have synthesized $2^{\prime}-$ deoxy-2'(S)-methylcytidine ( $\underline{\text { I }}$ ), a ne y antileukemic nucleoside. The carbonyl methylation of $\mathbf{2}^{\prime}$ ketonucleoside (1) with Mali, He $3^{A l}$ and MeMgX was examined. Only. LII the reaction with Mong, did the more hindered s-attack | afford the 2 -methyl-t-a')cohol (Lb). Compound $2 b$ was converted into the methyl oxalate (4), which was subjected to radical deoxygenation lin give the $2^{\prime}-d e o x y-2^{\prime}(\underline{S})$-methyl derivative ( $\underline{S}$ ). The deprotection of 5 followed by substitution, with $\mathrm{NH}_{3}$ furnished 2. The sifucture-activity relationships of $\underline{y}$ and some other 2'-branched-chain sugar cytidines against L12l0 cells are also described.

KEYNORDS - Carbonyl methxtation; radial deoxygenation; nucleoside; branched-ihain nucleoside: 2'-deoxy-2'(S)methylcytidine; antileukemic activity .

Introducing of a substituent into the $C \cdot ?^{\prime}$ position with the arabino confiquration from a natwraliy-oceurring pyrimidine ribonucleoside is extremely ditficult, because the $\mathrm{C}-2$ carbonyl group of the pyrimidine base is so close to the C-2' leaving group in the filo configuration of the sugar residue that $0^{2}, 2^{\prime}-$ sycfonnmeosiles is formed instead. ${ }^{2)}$ Although several 2'-substituted-arabinufutanowy pyrimidine moleosides have been found to be potent antimetabolites, ${ }^{31}$ all. of , these nucleosides have been synthesized by the condensation of the nutleobasen with appropriately substituted sugar previously obtained by multi-step manipulation f. This method usually gives an anomeric mixture and requires tedious separation processes. Although certain branched-chain sugar nucleo. sties ${ }^{4}$ lave shown futaresting biological activities, they have also been synthesized by the classical condensation methods. Here, we clescribe a new method for the synthesis of $2^{\prime}$-deoxy-2'branched-chain sugar pyrimidine nucleosides with the carbon chain of the sugar branches in the arabino configuration, from the naturally occurifug pyrimidine ribonucteoside wridine. 'This method consists Of the carbonyl alkylation of the 2'-ketonncleosides and subsequent radical deoxygenation of the methyl oxalyl ester of the tert-alcolools.


JPO DELHI 25-06-2015 16:02


IPO DELHI 23-06-201.5 15:02





 keton!rleoside is leas minherad. while investigating the introduction of a neth'] substituent to the more hindered $\beta$-position, we found that the treatment of impound 1 with Memes for Hent, 5 eq. in Et, 0 at $-50^{\circ} \mathrm{C}$, gave the desired

 fidel, 6) which might form a stable complex with the carbonyl oxygen at the 2 ' position, was employed with MeMgn $H_{\text {. }}$ However, inverse selectivity afforded the undesired nucleoside (Zn) instead. Also, the use of br 3 . oft 2 did not iniprove the stercuscleulivjity,

The $C-2$ configuration of these nucleosides $(\underline{2 a}, \underline{b}$ was determined as follows. Removal of. the si ty protecting group by fluoride ions in the gave the free nucleosides ( $3 \mathrm{a} \boldsymbol{\mathrm { a }} \mathrm{b})$, ${ }^{\prime}$ ) respectively. The free nucleoside (db) bearing the jo configuration shown a positive periodate-benzidine spray test. Compound 3 h formed o 2', ${ }^{\prime}-$-cyclic bromate complex and migrated on paper electrophoresis, but. Ba did not.

The tertwalcohol it 2 b wis deoxygenate by the method developed by Dolman and Macmillan. ${ }^{\text {a }}$ (he $\boldsymbol{z}^{\prime}(\underline{R})$ methyl-tertialcohol (Lb) was treated with methyl oxilyl chloride in the presence of dimethylaminopyridine (DNAP) to afford the ester (1), which was then subjected to radical deoxygenation. with BugSnH and Albi in hot toluene. The reaction proceeded smoothly to give exclusively the desired $2^{\prime}$-deoxy-2'(S)-muthylnumleoside ( $\underline{5}$ ). However, $2^{\prime}-(\underline{s})$-tiert-alcohol (aa) resisted reacting with methyl oxalyl chloride even under vigorous conditions, probably due to the steric hindrance of the $3^{\prime}, 5^{\prime}$-protecting group. Therefore, compound 3 a was converted to its di-O-acetate ( $\underline{B}$ ) by treatment with Ac 20 and
 easily obtained from 8 . The aster 9 was deoxygenate under similar conditions giving a product which show nd a single spot on thin layer chromatography. However, the ${ }^{1} H-N H R$ spectrum of the product indicated that this was a mixture of $2^{\prime}$-deoxy- $2^{\prime}(\underline{R})$ - and (S )-isomers (10,12) in a ratio of 1:3. It is obvious that Buy ShH as a reductarit reacts preferably from the less hindered a-face of the tert-alkyl radical intermediate. This epimeric mixture was separated, after duprotection by treatment with $\mathrm{NH}_{3} / H \in O H$ at room temperature, by semi-preparative rovers phase high pressure liquid chromatography to give 6 and 11 , respective dy. The sternochenistry at the $2^{\prime}$-position was determined by NoE experiments in Which the NOI: (5.4. 1 are observed between the $1-6$ and $2^{\prime}(\underline{S})-m e t h y l$ protons in 6 . $r$ The title compound $2^{\prime}-$ d roxy $^{\prime} 2^{\prime}(\underline{S})$-methylcytidine ( $\boldsymbol{I}^{10}$ ) was obtained by treatment of $\underline{6}$ with ${ }^{\circ} \mathrm{NH}_{3} / \mathrm{MeOH}$ in a sealed tube at $100^{\circ} \mathrm{C}$. Other $2^{\prime}$-branched-chain sugar nucleosides ware also converted to the corresponding cytosine derivatives (13-15) ${ }^{11)}$ in ásmilat manner.

Among these $2^{\prime}-b r a n c h e d-c h a i n$ sugar cytosine nucleosides, compound 2 was the most active against mouse leukemic cell line 11210 cells $1 C_{50}=0.26$ ug/mll. The order of the inhibitory activity against the cells in vito. war ?,


3907, 109. 7914. stry; Shiba, r.
. 1. 1985, 2247.
; Plattner, J.J.; ylation of sodium nytalandue methy] mide, THF' or LDA, ldol condensation
h L-serine methyl
a to afford 3 a in aci with phthalic romide and dilisoand 85\%). L and
-jogren, E.B.;
iment with N .
1 and 3 e ( $68 \%$ and
ibition, 1989, 2,

# synthesis of a potential inhibitor 

## of udp.glucuronosylirandirerase

1). Nonrt ${ }^{\text {.h }}$, N.C.J. van Straten', G.J.P.H. Boons', G.A. van der Marel', X. Bossuyt, N. Blanckaert, G.J. Muldert, J.J. van Boom'

- Ciorlacus Lahornories, P.O. Box 9502, 2300 RA Leiden; 'Division of Toxicology, Center for BioPharmacemical Sciences, P.O. Box 9503, 2300 RA Leiden, The Netherlands; 'Laboratory of Biological Chemistry, Uhiversity of Lemen, ì $\cdot 3000$ Leaven, Belgimm
(Recclucd 3 March 1992)

Absiract: A convenient synthesis of phosplonomethyl 1-0-(2,2,2-riphenyl)ethyl-a-D-ghuco-2heplulopyramosiduronate (2) is presented. The target compound proved to be an inhibitor of UDP. glucuronosyluansferase in vilro.

Glucuronidation of hydroxyl, thiol, anino or carboxylate functions in xenobiotics and endogenous compounds [e.g. $\mathrm{RXH} ; \mathrm{X}=\mathrm{O}, \mathrm{S}$. NH or $\mathrm{C}(\mathrm{O}) \mathrm{O}$ ] is a mijur detoxification pathway catalyzed by UDPglucuronosyluansferases (UDP $\left.{ }^{-} \mathrm{Ci}^{\prime}\right)^{\prime}$. It has been propused ${ }^{2}$ that the glucuronidation reaction proceeds via transition-state $A$ (see Figure 1) ressuting from the atack of an aglycon RXIH on the anomeric centre of

the sugar nuclcotide UDP-glucuronic acid. Collapse of the transition state (TS) will yield uridine $5^{\circ}$ diptosphate (UID') and the B-glucuronide 13 , which is readily excreted due to the hydrophilicity of the gluiuronic acid .moicty.

Glucuronidaion also plays a pivonal role in drug metabolism and it may thus be anticipated that UIPFG'S inhibition could improve the theripeutic efficiency of a drug. For example, the anti-Human

- phosphor stercospi ioduhepr

$$
\Lambda 1
$$ introduce condemns trilyl-D. reagent ${ }^{10}$ replace abortive

$$
\mathrm{Scl}
$$

$$
\because p
$$

We here report the synthesis of phosphamomethy' 1 -O-(2,2,2-iriphenyl)ethyl- $\alpha$-D-ghtico- 2 . hepmopyranosiduronate (2) which ewers a distima inhibitory effect on UDPG' activity in vito.

The design and. synthesis wo te the new rS analogue 2 is based on the following heuristic considerations. Thins, in view of the strong inhibitory effect of 1 on UDPGT activity, it would be reasonable to incorporate the triphenyletiyl (TPE) moiety. Further, replacement of the UDP unit by a more stable


I via glucuronidation
hyl-UDP (1), which IMit activity in the -o (ie. isolated rat


Nan isl- $\alpha$-D-glico-2.
biro.
following heuristic would be reasonable by a more stable
$\cdot 1$

phasphonomethylenes function will shotten the synthetic route. In addition, the recently repined ${ }^{\text {s }}$ sterospecific ioslunimm ion promote reaction of exocyctic glycals (egg. S) with alcohols resulting in 1 . iadohepthlosides enables the consinution of the requisite configuration at the anomeric centre.

A first attempt to assemble target compound 2 is outlined in Selene 1 and commences with the introduction of the phosphonomethylene function. Thus, iodoniuin sym-dicollidine perchlorate' (IDCP) assisted condensation of diethyl(h)'droxymechyl)phosphonate' (6) with 2,6-anhydro-3,4,5-ni-O-benzyl-1-deoxy-7.0. erityl-D-gluco-hepy-l-enitol (5), prepared by methylemation of readily accessible lactone $3^{9}$ with Table's reagent ${ }^{10}(4)$, gave the expected $a$ ketoside ${ }^{11} 7^{14}\left(m . p .135^{\circ} \mathrm{C}_{;} \alpha_{6}{ }^{23}+54.4^{\circ}\right.$ ) in $84 \%$ yield. Unfortunately, direct replacement of the iodine atom in 7 by lithium 2,2,2-triphenylethoxide, giving fully protected 8 , was abonive ${ }^{3}$.

Scheme $2^{\text {: }}$



a key: $\quad{ }^{\text {ai }} 16 \quad R^{\prime}=\mathrm{H}$
i) $\mathrm{ICl}_{2} \mathrm{SnBu}_{3} / \mathrm{KH}, \mathrm{THF}$. ii) $n$-BuLL, THF. iii) 11, THF. iv) DAST,

THF. v) $6, \mathrm{SnCl}_{2} / \mathrm{AgClO}_{4}$, diethyl ether, 48 h . vi) ( $n$ - Bu$)_{4} \mathrm{~F}, \mathrm{THF}$, ,
vii) $\mathrm{K}_{2} \mathrm{Cr}_{2} \mathrm{O}_{7} / \mathrm{H}_{2} \mathrm{SO}_{4}$, acetone: villi) $\mathrm{CH}_{2} \mathrm{~N}_{2}$; MeOH :-
ix) $\mathrm{Pd}(\mathrm{OH})_{2} / \mathrm{H}_{2}$, ethanol. x) Ac 2 O /pyridine. xi) a) TMSBr ,
$\mathrm{CH}_{2} \mathrm{Cl}_{2}$, b) $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$ xii) $\mathrm{LiOH}\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$.

An alternative pathway to compound 2 is presented in Scheme $2 . A$ key clement of this pathway is the introduction, at an early stage of the synthesis, of the TPE unit dia'the organolithinm reagent 11. The latter was readily accessible by tighthitum exchange" of the corresponding tributylstannane derivative 10 which, in tum, was prepared by the reaction of 9 with iodomethyl ributylammane according to Seyfert'. Addition of the properly protected D-gluconolatione $12^{16}$ to 11 . generated in sim by quenching 10 with $n$-butyllithium, led to the exclusive formation of the anomerically pure" 1 -O-(2,2,2-triphenyl)ethyl- $\alpha$-D -gheco-heptulopyranose 13 in $86 \%$ yield $\left(\alpha_{0}{ }^{m n}+40 . r^{\circ}\right)$.

The phosphorate function was now introstused by the following two -sep procedure. Treatment of 13 with diethylaminosulfur trifluoride (I) $\wedge S T)^{\prime \prime}$ furnished the stable ketoglycosyl fluoride 14 ( $\alpha / B$ mixture) in a quantitative yield. Glycosylation of diethyl(hydroxymethyl)phosphonate (6) by the ketopyranosyl fluoride
 Hhosphonomethyl derivative $15\left({ }_{\left(C_{0}\right)}{ }^{n}+34.2^{\circ}\right)$ in $52 \dot{\%}$ yield.

At this sage, the sibyl protecting group of HO. 7 in 15 was removed nad the resulting hydroxyl was converted but the required carboxylate methyl ester. Thus, removal of the tert-butyldiphenytsilyl group with Hluoride ions afforded homogeneous 16 (yield $92 \% ; a_{0}{ }^{2 n}+29.3^{\circ}$ ). Oxidation of 16 could be realized most effectively ${ }^{18}$ will Jones reagem ${ }^{2 n}$ to give, after methylation of the carboxylate group with diazomethane, fully protected 17 (overall yield $6\left(0 \% ; \alpha_{0}{ }^{20}+18.7^{\circ}\right.$ )

Complete dehlocking of 17 to give the beget compound 2 was executed as follows. Hydrogenolysis of the benzyl groups followed by acetylation of 18 yielded homogeneous 19 . Hydrolysis of the phosphorate dieilyl ester by trimethylsilyl bromide ( TMSBr$)^{31}$ and subsequent addition of $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$ afforded 20 . Finally, deesterifation of 20 resulted, after purification and conversion (Dower $50 \mathrm{~W}, \mathrm{Na}^{+}$-form) into the trisodium salt, in the isolation of homogeneous $2\left[\alpha_{0}{ }^{20}+59.3^{\circ}\right.$ ( $\left.\left.\mathrm{c} 1, \mathrm{H}_{2} \mathrm{O}\right)\right]$.

Preliminary biological studies indicated that the " S-analogue 2 , in a 20 -fold excess with respect to UDPglucuronic acid, acis as an inhibitor of 1 -melhylumbelliferone ( $78 \%$ inhibition) and bilirubin ( $41 \%$ inhibition) glucuronidation in a rat liver, microsomal fraction. A detailed study on the inhibitory effect of 2 will be published in due course.

Acknowledgencut. This work was supported by a grant from the Foundation for Medical Researelt MEDIGON.

## References and-Noles

1. Mulder, G.J.; Coughtrie, M.W. II; Burchell, B. Conjugation Reactions in Drug Metabolism. An Integrated Approach; Mulder G.J., Ed.; Taylor and Francis: London, pp 51-106, 1990.
2. Noorı, D.; Coughtrie, M.W.H.; Burchell, B.; Van der Mare, G.A.; Van Boom, J.H.; Van der Gen, A.; Mulder, G.J. Ear., J. Bionhem. 1990, 188, 309. .
3. Reschar, A.; Spector, T. Biochem. Pharmucol. 1989, 38, 1389.
4. Noorı, D.; Mcijer, E.A.; Visser, T.J.; Mecmman, J.H.N.; Van der Marcel, G.A.; Van Boom, J.H.; Milder, G.J. Molec. Pharmac. 1991, 40, 316.
of this pathway is the eagent 11. The lilter derivative 10 which. , Seyferth's. Addition ) with 1 -butyllithium, huco-heptulopyranose
ure. Ireatment of 13 14. ( $\alpha / \beta$ mixture) in elopyranosyl flugride protected $\alpha$-linked"
sulting hydroxy! was henylsilyl group with uld be reatized most ith diazomethane.
ows. Hydrogenolysis ss of the phospilionate ' afforded 20. Finkilly, $n$ ) into the trisolium
with respect to UDPabin ( $41 \%$ inhibition) , effect of 2 will be
or Medical Research

- holismi. An Integroted A.; Van der Gen, A.:

Hoom, J.H.; Mulder,
5. Holy', A. Nuclcosides and Nuclenides 1987, 6; 147.
(3. Noort, D.: Vecneman, G.H.; Bexns, G.J.P.H.: Vnn der Marel, G.A.; Mulder, G.J.; Van Bowm, J.H. Synlet, 1990. 205.
Recently, similar iodoniun-ion medated glyeosylation reactions were reponed by olters. Sce for instance. Handrechy, A.; Smay, P. Tetrahedron Lell. 1990, 31, 576.5. Thiem, J.; Kleeberg, M. Carbohydrate Res, 1490, 205, 333.
7. L.cmicux, R.U.; Morgan, A.R. Cidn. J. Chem. 1965, 4.3, 2190.
8. Kluge, A.F. Org. Synth. 1.986, $64,80$.
9. Lactonc 3 was prepared by regióselective tritylation (Irityl chloride/pyridine) of 2,3,4-ari-O-benayl-o/B. D-glueopyranose followed by Swern oxidation.
10. Camizzo, L.F., Grubbs, R.H. J. Org. Chem. 1985, j0, 2386.
11. Hice $\alpha$-configimation of compounds 7,13 and 15 was iner alion assigned on the basis of the characteristic chemical shift ( 3.9 .4 .1 ppm ) and patten (dd, $\mathrm{J}_{3,4}=\mathrm{J}_{4}=9.0-9.5 \mathrm{~Hz}$ ) of the proton at the C 4 position. Sac also: Nicom, ’ł; Panza, L.; Russo, G. Tetralledron Lell. 1991, 32, 4035.
12. Satisfactory elemental analytieal data were obtained for compounds $2,5,7,10,12,13,14,15,16,17$ and 19. Ofmical rotations wefo measured in $\mathrm{CHCl}_{\text {, ( }}$ ( 1 ) unless stated otherwise.
Relevant 'H NMR data ( $300 \mathrm{MHz} ; \delta$ in $\mathrm{p} \mu \mathrm{m}$ ) of compounds 2, 5, 7, 13, 17 and 19:
2: $\delta$ 4.9-4.5 ( $\mathrm{AB}, 2 \mathrm{H},-\mathrm{CH}, \mathrm{CPh} ; \mathrm{J}=9.7 \mathrm{~Hz}$ ); $3.95-3.75\left(\wedge \mathrm{~B}, 2 \mathrm{H}, \mathrm{H},+\mathrm{H}_{1} ; \mathrm{J}=11.2 \mathrm{~Hz}\right.$ ), 3.55-3.35.(m, $\left.2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{P}\right) .5: \delta 6.95\left(\mathrm{~m}, 2 \mathrm{H},=\mathrm{CH}_{2}\right) .7: \delta 4.1\left(\mathrm{~m}, 4 \mathrm{H}, 2 \times \mathrm{CH}_{2} \mathrm{CH}_{3}\right), 3.9\left(\mathrm{dd}, 1 \mathrm{H}, \mathrm{H}_{4}\right) ; 3.8-3.7(\mathrm{~m}, 2 \mathrm{H}$, $\left.\mathrm{CH}_{2} \mathrm{P}\right), 13.6 .3 .4\left(\mathrm{AH}, 2 \mathrm{H}, \mathrm{CH}_{2} ; \mathrm{J}=10.9 \mathrm{~Hz}\right), 1.2\left(\mathrm{t}, 6 \mathrm{H}, 2 \times \mathrm{CH}_{3}\right) .13: \delta 4.5\left(\mathrm{AB}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CPH}_{3}\right), 4.0$ (dd, 1H, $\mathrm{H}_{4}$ ), 3.5 ( $\mathrm{AB}, 2 \mathrm{H}, \mathrm{H}_{1}+\mathrm{H}_{1}: \mathrm{J}=11 \mathrm{~Hz}$ ). $1.0(\mathrm{~s}, 9 \mathrm{H}, 3 \times \mathrm{CH}$, -TBDPS). $15: \delta 4.1(\mathrm{~m}, 4 \mathrm{H}, 2 \mathrm{x}$ $\mathrm{CH}_{2} \mathrm{CH}_{3}$ ), $3.95\left(\mathrm{dd}, \mathrm{H}, \mathrm{H}_{4}\right), 3.9-3.6\left(\mathrm{AB}, 2 \mathrm{H}, \mathrm{H}_{1}+\mathrm{H}_{1} ; \mathrm{J}=11.0 \mathrm{~Hz}\right), 1.2\left(\mathrm{~m}, 6 \mathrm{H} ; 2 \mathrm{XCH}_{3} \mathrm{CH}_{3}\right) .17: 3.32$ $\left(\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}\right.$ ) . 19: $\delta 4.6-4.3\left(\mathrm{AB}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CPh}_{3} ; \mathrm{J}=9.6 \mathrm{~Hz}\right), 4.1-4.2\left(\mathrm{n}, 4 \mathrm{H}_{1}, \mathrm{OCH}_{2} \mathrm{CH}_{3}\right), 3.7(\mathrm{~s}, \mathrm{H} \mathrm{H}$, $\mathrm{OCH}_{3}$ ), 3.7-3.2 (m, $\left.4 \mathrm{H}_{1} \mathrm{H}_{1}+\mathrm{H}_{1} ., \mathrm{CH}_{2} \mathrm{P}\right), 2.0 .1 .8\left(3 \mathrm{x}, 9 \mathrm{H}, 3 \times \mathrm{CH}_{3}\right.$, acctyl), $1.2\left(\mathrm{~m}, 6 \mathrm{HI}, 2 \mathrm{CCH}_{2} \mathrm{CH}_{3}\right)$. Relevant ${ }^{\text {³ }} \mathrm{C}$ ('H\} NMR data ( $50.1 \mathrm{MHz} ; 8$ in ppin) of compounds $2,5,7,13,14,15$ and 17:
2: $\delta 177.5(\mathrm{C}=\mathrm{O}), 146.2\left(\mathrm{C}_{8}, \mathrm{CH}_{3}\right), 101.0\left(\mathrm{~d}_{1} \mathrm{C}_{2}: \mathrm{J}_{\text {Coc.p}}=10.0 \mathrm{~Hz}\right), 79.3\left(\mathrm{CH}_{2} \mathrm{CPH}_{3}\right), 70.2\left(\mathrm{C}_{1}\right), 59.8$ -
 $\left.+\mathrm{C}_{7}\right), 56.8 .53 .4\left(\mathrm{~d}, \mathrm{CH}_{\mathrm{d}} \mathrm{P} ; \mathrm{J}_{\mathrm{C}, \mathrm{p}}: 172 \mathrm{~Hz}\right), 16.1\left(\mathrm{~d}, \mathrm{CH}_{3} ; \mathrm{J}_{\mathrm{p} .0 \mathrm{cc}}=6.0 \mathrm{~Hz}\right), 13 ; 8145.5\left(\mathrm{C}_{\mathrm{q}}, \mathrm{CPH}_{3}\right), 97.6\left(\mathrm{C}_{2}\right)$; $79.4\left(\mathrm{CH}_{2}(\mathrm{CPh}), 72.1\left(\mathrm{C}_{1}\right), 57.6\left(\mathrm{C}_{4}, \mathrm{CPH}_{3}\right) .14: \delta 115.5-111.0\left(\mathrm{~d}, \mathrm{C}_{2} \mathrm{~J}_{\mathrm{c} \cdot \mathrm{r}}=226 \mathrm{~Hz}\right) .15: \delta 101.6\left(\mathrm{~d}, \mathrm{C}_{2}\right.\right.$;
 $\left.\mathrm{CH}_{2} \mathrm{CH}_{3} ; \mathrm{J}_{\text {r.oc. }-}=5.9 \mathrm{~Hz}\right) .17: 8169.5(\mathrm{C}=\mathrm{O}), 102.4\left(\mathrm{~d}, \mathrm{C}_{2} ; \mathrm{J}_{\mathrm{coc-r}}=10.3 \mathrm{~Hz}\right), 69.8\left(\mathrm{C}_{1}\right), 52.3(\mathrm{OCH})$. Relevant " P NMR data ( $\delta$ jin ppun) of compounds 2, 7, 15, 16 and 17:
2: $\delta 18: 1 ; 7: \delta 20.5 ; 15 ; \delta 20.4 ; 16: \delta 20.4 ; 17: \delta 20.9$.
13. It was also established that nucleqphilic substitution could not be effected, in contrast with expectation, by cesium acctate in HMPA. See ref. 6 (laudrechy et al.).
14. Still, W.C. J. Am. Chem. Soc. 1978, 100, 1481.
15. Seyferh, D.; Andrews, S.B. J. Organomet. Chem. 1971, 30, 151.
16. Lactone 12 was prepared by regioselective silyiation (reat-butyldiphenylsilyl chloride/pyridine) of 2,3,4-

1ri-()-benzyl-o/B-3-glucopyramose followed by Swern uxidation.
17. Rosenbront, Win, Jr.; Riles, D.A.; I.arte;, P.A. Temahedron Lect. 1985, 26. 3.
18. Mukaiyama, T.: Murai, Y.; Shoha, S. Chem. l.ctl. 1981, 43]
 McDonald et al. (i.c. Swern oxidation of $1 \mathrm{O} \cdot 7$ and stibsequent NIS/MCOII mediated conversion of ithe resulting aldeliyde function) weic not successtul. Sec: MeDonald, C.; Holcomb, H:; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vancmion, P. J. Org. Chem. 1989, 54, 1213.
20. Fugedi, P. J. Carbohydr. Chem. 1987, 6, 377.
21. McKenna, C.E.; Higa, M.T.; Cheung, N.H.; McKenma, M.C. Tcirahedron l.ett. 1977, 15.5.

Prepara
[. innias*.] plammaceul

The scosi:
heart faile ventions. e.g. Suls
mainly a

Luring $G^{i}$
acyi-!etra
Ansong 1
1,3,4 this
:ism of:
inhibis: 1
were nee

# BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI 

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND

IN THE MATTER OF:

Indian Patent Application 6087/DELNP/2005 filed on $27^{\text {th }}$ December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 30 May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).
AND
IN THE MATTER OF:
INDIA CARES
S 323, Panchsheel Park, New Delhi 110017, India
... PETITIONER/OPPONENT
VS.
Pharmasset, Inc.
A Corporation organized and existing under and by virtue of the laws of the state of Delaware. 303A, College Road East, Princeton New Jersey 08540, United States of America.

## AFFIDAVITT $5 T O Z-90-\Sigma Z$ IHTJa OdI

I, Otto Orlean Yang MD, aged about 50 years and residing at 12544 Woodgreen Street, Los Angeles, California, 90066, United States of America, do hereby solemnly affirm and sincerely state as follows:

1. I, Otto Orlean Yan an US citizen, residing at 12544 Woodgreen Street, Los Angeles, California, 90066, United States of America, do hereby solemnly affirm and declare as under -
2. That, I graduated from Brown University Medical School. I have been engaged in virology medical research since 1994 and as such I am competent to execute this affidavit.
3. That, I understand that INDIA CARES is filing a pre-grant opposition against the Indian Patent Application No. 6087/DELNP/2005 (hereinafter ‘6087). The relevant records in respect of the above matter being the impugned patent and the corresponding applications, the prior art, the documents attached thereto, have been made available to me.
4. That, in the light of the aforesaid documents, I have been asked to opine as to whether the claims of the impugned application No. 6087/DELNP/2005 are obvious to a person skilled in the art.
5. That, I submit that the Indian Patent Application No. 6087/DELNP/2005 is drawn to a compound being represented by a chemical structure and its pharmaceutically salts or prodrugs, depicted by a general chemical structure represented here below at Figure 1.


Figure 1: Chemical structure of the impugned specification
6. Thereafter, the specification proceeds to provide various substitutions as possible embodiments represented generally by $\mathrm{R}^{1}, \mathrm{R}^{2}, \mathrm{R}^{2}, \mathrm{R}^{6}, \mathrm{X}$ and Base. The nitrogenous base may be naturally occurring or modified purine or pyrimidine base and may be depicted in Figure 2.

(a)
(b)

Figure 2: Structure of Bases
7. From the above figure, it appears that substituted thymine, uracil, adenine, guanine and cytosine base may also be arrived from the structures represented at Figure 2 (a) and (b) by suitable substitutions of various embodiments disclosed.
8. Additionally, ' 6087 further proceeds to list phosphate ester derivatives of the compound of chemical structure of Figure 1.
9. The application also provides various general disclosures pertaining to dosage, compositions, administrations and use of the said compounds as set out in
 antiviral compounds.
10. That, ' 6087 provides a process for preparation of the compounds disclosed therein. The process is a general process which is purportedly applicable to the million of compounds encompassed in the said general chemical structure and even such a process is admitted as prior art process.
11. That, ' 6087 relates to nucleoside analogues with modifications on 2 ' positions of the sugar. That, I note that methyl is present above the plane in the 2 ' position and is referred to as methyl ("up") and fluorine is present below the plane in the 2' position and is referred to as fluoro ("down"). This configuration of methyl ("up") and fluor ("down") has been achieved by inversion of configuration.
12. That, nucleoside analogues are nucleosides which contain a nucleic acid analogue and a sugar. Nucleoside analogues are used for the treatment of cancer and viral infections.
13. That, nucleoside analogues are used as inhibitors of HIV, hepatitis B and herpes viruses. Their antitumor and antiviral uses were known long before the date of priority of the impugned application. It was also known that nucleoside analogues are converted to monophosphate prodrugs that facilitate in drug delivery. It was also known that nucleoside analogues are also administered as compositions, in combination with other pharmaceutical active agents. Various types of nucleosides were known and active compounds were synthesized and
 Emtricitabine are such examples of nucleoside analogues.
14. That, even before 2003, various strategies for treating HCV that were being pursued for treating HCV were known, including the use of nucleoside analogues to inhibit NS5B enzymatic activity. For instance $R$ De Francesco et al, "New therapies on the horizon for hepatitis C: Are we close? Clan Liver Dis. 2003 Feb;7(1):211-42, XI", confirms that NS5B had been identified as a target for the development of anti-HCV therapies by early 2003 and suggested that inhibition of this pivotal enzyme would lead to the suppression of HCV replication in infected cells (see page 225 paragraph 3). It further identified novel series of nucleosides that are candidates such as $\beta$-D- 2'-methyl-ribofuranosyl-guanosine for the treatment of HCV .
15. That, from the 1980s or before, it was well known that nucleoside analogue synthesis might be performed by making a modification to an existing nucleoside that is sugar with the desired base already attached (often known as the "nucleoside route"), or by first preparing a sugar with the desired modifications before attaching the base by glycosylation (often known as the "sugar route"). The sugar route itself might involve either modifying a sugar which was already readily available, or starting with small molecules which could be used to build up the sugar with the desired modifications in place.
16. That, the structure-activity relationship at the 2 ' position of sugar attached to a nucleoside was also known before the priority date. For instance, Eldrup et al.

Conference on Antiviral Research (April 27, 2003, Savannah, Ga) disclosed that RNA dependent RNA polymerase NS5B is an obvious target for intervention by design of specific inhibitors. It stated that $2^{\prime}$ modified ribs nucleosides had been identified as potent inhibitors of HCV RNA replication in vitro. It also disclosed that 2 ' modified ribonucleosides included introduction of modified bases, various substitutions and change of stereo- and region-chemistry on the sugar moieties.
17. That, 2' modification on the ribose ring are a very well known technique in the art and have been practiced by medicinal chemists for many years. For instance, WO 2001/90121 and WO 2001/92282 disclosed biologically active $1^{\prime}, 2^{\prime}, 3^{\prime}$, or $4^{\prime}$-branched $\beta$-D or $\beta$-L nucleosides or a pharmaceutically acceptable salt or derivative thereof for the treatment of Hepatitis C Virus.
18. That, it has been well known since 1990 and before that such 2' modification on the ribose ring can include addition of fluorine, which was known to increase biological activity of the nucleoside analogue compounds. Examples of nucleoside analogues with fluorine modifications at the ribose ring included gemcitabine and mericitabine.
19. That, before the priority it was well known that inclusion of a fluorine atom in a drug molecule can influence both the disposition of the drug and the interaction of the drug with its pharmacological target. It was also known that fluorine when attached to a reaction centre, can act as good leaving group and
 reactivity at that centre with it strong inductive effect. Fluorine substitution has been extensively investigated in drug research and biochemistry as a useful strategy to increase metabolic stability. B. K. Park and N. R. Kitteringham, "Effects of fluorine substitution on drug Metabolism: Pharmacological and Toxicological Implications "Drug Meta. Rev., 1994, 26, 605 disclosed that fluorine substitution can also have a profound effect on drug disposition, in terms of distribution, drug clearance, routes and extent of drug metabolism. It also stated that fluorination could affect the pharmacokinetics of the drug. Further substitution of fluorine can reduce toxicity by blocking the formation of toxic metabolite.
20. That, it is well known that isosteres are frequently used in drug design to increase bioavailability. It has been common chemical strategy to use isoteric substitution to a lead compound, to synthesise compounds that have less undesirable characteristics, for instance, low bioavailability, inadequate halflife and potential to reform metabolites. It has been well known that one of the classical isoteric substitutions is the incorporation of fluorine into a compound in replacement of a hydroxyl group. That, the rationale for such replacement is based on the fact that the size of the fluorine atom is intermediate between that of hydrogen and oxygen, and the substitution of the hydroxy group with fluorine is particularly favoured when the presence of an electronegative atom is necessary for the interaction of the ligand with the target protein. Fluorine has the strongest electronegativity in the periodic table, both fluorine and

Adamic, R. W. Price,R. F. Schinazi,K. Watanabe and J. J. Fox, J. Med. Chem., 1987, 30, 226]
21. That, Pankiewicz "Fluorinate Nucleosides", Carbohydrate Research, 327 (2000) 87-105, discussed the development in the field of fluorinated nucleosides and stated that more than $77 \%$ of fluorinate nucleosides synthesized to date contain fluorine at C-2' of the sugar. It also emphasizes that since fluorine is good mimic of a proton or a hydroxyl group, it is able to form hydrogen bonding increasing the activity of many compounds. It also suggested that fluorination at the C-2 position of the sugar enhanced therapeutic activity in anti-cancer and anti-viral agents.
22. That, several reagents used to conduct fluorination reactions were known. For instance, P. Herdewijn, et al, Synthesis of nucleosides fluorinate in the sugar moiety. The Application of diethylaminosulfur trifluoride to the synthesis of fluorinate nucleosides, Nucleosides and Nucleotides, (1989), 8(1), 65-96, disclosed that three different methods were used to synthesise nucleosides fluorinate in the sugar moiety using DAST and illustrated that all reactions resulted in the inversion of the configuration. Several other authors also documented that fluorination with DAST could result in the inversion of the configuration. For instance, Van Aerschnt et al, disclosed that the reaction of arabinouridine with DAST to prepare $2^{\prime}$ F-ribouridine in a single step transformation could result in simultaneous inversion of the stereochemistry at the 2 '-carbon of arabinouridine.
23. That, before 2003, nucleosides with methyl (up) and fluorine (down) at ${ }^{2} 3 \mathrm{Ba}$ OdI position of the ribose ring were known to be used for the treatment of HCV infection. For instance, WO 2002/057425 (hereinafter WO '425) titled "Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase" published on 25 July 2002, disclosed nucleoside derivatives used as inhibitors of NS5B polymerase thereby inhibiting HCV replication and useful for the Hepatitis C infection. Further, WO ' 425 Application disclosed a compound of general formula:

(I)

Figure 3: General Chemical Structure in WO ' 425
24. That, this disclosure included a sugar attached to a nitrogenous base, and also encompassed various substitutions for the nitrogenous base which could include either purine or pyrimidine bases and several substituents for $\mathrm{R}^{1}, \mathrm{R}^{2}$, $R^{3}$ and $Y$. This also suggested that $R^{1}$ could be $C_{1}-C_{4}$ alkyl that includes methyl and $\mathrm{R}^{2}$ as fluorine, and that Y could be $\mathrm{H}, \mathrm{C}_{1-10}$ alkylcarbonyl, $\mathrm{P}_{3} \mathrm{O}_{9} \mathrm{H}_{4}, \mathrm{P}_{2} \mathrm{O}_{6} \mathrm{H}_{3}$ or $\mathrm{P}(\mathrm{O}) \mathrm{R}^{9} \mathrm{R}^{10}$. Furthermore, specific examples of uridine derivatives and 5'methyluridine were provided in Examples 46-51 (pages 8895) and Examples 102 and 103 (pages 134-138). Furthermore, WO ' 425 also
described the pharmaceutical compositions of the claimed compounds (pages Furthermore, WO '425 described the claimed compounds could occur as racemates, racemic mixtures, single enantiomers, diasteromeric mixtures and individual diasteriomers (pages 51-52). WO '425 disclosed the process for preparation of these nucleosides whether by alkylation of the appropriately modified sugar, followed by glycosylation or glycosylation followed by alkylation of nucleosides. Further, the stereochemistry of substituents at C-2 and C-3 position of the furanose ring was already contemplated in WO '425.
25. That, moreover another example of nucleoside derivatives with methyl (up) and fluorine (down) substitutions at 2' position of the ribose ring was disclosed in WO 2002/057287 (hereinafter referred to as WO '287) published on 25 July 2002. The nucleosides disclosed in WO'287 were used as inhibitors of NS5B polymerase to inhibit HCV replication. WO ' 287 disclosed a chemical structure of a nucleoside, in which a sugar is attached to a nitrogenous base, and various substitutions on the sugar ring. WO '287 discloses Compound II wherein $\mathrm{R}^{1}$ is Cl-4 alkyl or methyl and $\mathrm{R}^{2}$ is fluorine [pages 8 and 9 of WO '287]. It is pertinent to note that for $R^{1}$ and $R^{2}$ only limited substituents were provided in WO '287. The Compounds III, IV and V of WO '287 disclosed 5'-monophosphate, 5'-diphosphate and 5'triphosphate ester derivatives as well as pharmaceutically acceptable salts [pages 13 and 14 of WO '287]. Thus possible prodrugs of the compounds were also disclosed. WO ' 287 disclosed the pharmaceutical compositions for use as medications for the inhibition of RNA-dependent RNA polymerase, a critical step in HCV replication, to use in treatment of HCV infection.
26. That, a skilled person in light of WO ' 425 and WO ' 287 and the disclosures in the prior art, would find methyl "up" and fluorine "down" modification on the 2' position obvious.
27. That, I note therefore that the application 6087/DELNP/2005 is drawn to compounds that are derivatives of already known prior art compounds. Also the Applicant has not clearly demonstrated and compared the therapeutic efficacy of the compounds claimed with the closest prior art compounds. In the light of the prior documents discussed above, the alleged invention is an obvious modification which could be derived by a person skilled in the art.
28. That, based on the above, I opine that the claims of the impugned application 6087/DELNP/2005 are not inventive in view of the prior art documents under the principles set forth by Indian law.

## DEPONENT VERIFICATION

I, the Deponent above named, do hereby verify that the contents of my above affidavit at para 1 to 28 are true, correct, and complete to the best of my knowledge and available information.

Verified on this: 19 th day of June, 2015.

A notary public or other officer completing this certificate verifies only the identity of the individual who signed the document to which this certificate is attached, and not the truthfulness, accuracy, or validity of that document.

State of California
County of Los Angeles
Subscribed and sworn to (or affirmed) before me on this 19th day of June 2015, by Otto 0. 4 lng
proved to me on the basis of satisfactory evidence to be the persons) who appeared before me.


[^0]:    * Corresponding author.

    E-muil address: rallacle_defrancesco(igmerck.com (R. De Francesco).

[^1]:    IPO DELHI 23-06-2015 15: 65

[^2]:    * cilcd by examiner

[^3]:    

[^4]:    *This paper was refereed by Bernard Testa, Ph.D., University of Lausanne, CH-1015 Lausanne. Switzerland; and by Frederick J. Di Carlo, Ph.D., Environmental Protection Agency, HERD TS796, Washington ${ }_{\text {r }}$ DC.
    ${ }^{\dagger}$ To whom correspondence should be sent at the Department of Pharmacology and Therapeutics, University of Liverpool, PO Box 147, Liverpool, Merseyside L69 3BX, England.

[^5]:    IPO Studies to date have shown only modest inorganic fluoride serum levels

[^6]:    † The University of Georgia.
    t Emory University School of Medicine/Veterans Affairs Medical Center.
    (I) Zidovudine ( AZT ), didanosine (ddt), zalcitabine (AdC), stavudine (daT), lamivudine (3TC), and abacavir (1596U89).
    (2) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehman, S. N.; Gallo, R. C.; Bolognesi, D.: Barry, D. W.: Breeder, S. Proc. Natl. Accad. Sci. U.S.4. 1985, 82, 7096-7100.
    (3) (a) Owen, G. K.; Verheyden, J. P. H.; Moffall, J. (i. J. Min. Chem. 1976, 41, 3010-3017. (b) Marquez, V. E ; Tseng, C. K.-H.; Mitstyn, 11.; Aoki, S.; Kelley. J. A.; Ford, H., Jr.; Driscoll. J. S. J. Med. Chum. 1990, 33, 978-985. (c) Pul, S. B.; Lu, S.-H.; /Lu, Y.-L.; Chub, C. K.; Chang, Y.-C. Antimicrob. Anoints Chemother: 1996, 40, 380-386. (d) Lee. K.; Choli, Y.; Gulleñ, E.; Schlucter-Wirtz, S.; Schinaai, R. F.: Chang, Y'.-C.: Chur, C. K. J. Med. Chem. 1984, 7, 1320-1328. (e) Lev, K.; Choi, Y.; Sclinazi, R. F.; Chang, Y.-C.: Chi, C. K. Abstracts of Papers, Part 1, 2181 ib National Meeting of the American Chemical Society; American Chemical Society: Washington, DC. 1949; MEDI 9. (1) Chum, B. K.; Schinazi, R. F.; Chang, Y.-C.; Chu, C. K. Curbolycdr. Res. 2000. 328. 49-59.
    10.102 1/010.168059 CCC: $\$ 20.00$ - 2001 American Chemical Society Published on Web 12104/2001

[^7]:    (4) (a) Koshida, K . Cox, S.; Harmenhorg. H.; (iilljan, (i.; IM, hen, 8. Antimisrob. Agems (hemother. 1949, 3.1. 2083-2088. (b) Van derschos, A.; Herdewijn, P.; Balzarini, J.; Puuwels, K.; De C'lerq, I: J Mud, Chem. 1989, 32, 1743-1744.
    (5) (a) Ma, T.; Pul. S. B.; Zhu, Y. L.; Lin, J. S.; Shaumugunathin, K.; Du, J., Wang, C.: Kim, H.; Newton, M. (i.; Chang, Y.C.; Chur, C. K. J. Med . Chem. 1996. 19, 2835-2843. (b) Coopenvood, I. S.; Boyd, V.; Gumina, G.; Cha, C. K. Nucleosides Nucleotides 2000, 19. 219 -. 236.
    (6) Binkley, R. W. Modern Cullbohydrate Chemistry; Marcel Dekker Inc.: New York, 1488; pp 53-60.
    (7) Korma, P.; Christian, R.; Schulz, G.; Unger, F. M. Carbohydr. Res: 1985, 141, 239-253.

[^8]:    (8) Yellow oil: $[\alpha]^{23}{ }_{D} 40.78^{\circ}\left(c 4.28, \mathrm{CHCl}_{3}\right)$; ${ }^{1} \mathrm{H}$ NMR ( $\mathrm{CDCl}_{3}, 400$ MHz $\delta 8.08(\mathrm{~m}, 2 \mathrm{H}), 7.57(\mathrm{~m}, 1 \mathrm{H}), 7.45(\mathrm{~m}, 2 \mathrm{H}), 5.15\left(\mathrm{dt}, 1 \mathrm{H}, \mathrm{H}_{1}, J=\right.$. 5.7, 1.7 Hz ), 4.63-4.41 ( $\mathrm{m}, 3 \mathrm{H}, \mathrm{H}_{4}, \mathrm{H}_{\mathrm{s}}$ ), $3.40(\mathrm{~s}, 3 \mathrm{H}), 2.67\left(\mathrm{tdd}, \mathrm{IH}, \mathrm{H}_{2 \mathrm{a}}\right.$. $J=16.6,15.0 .55 .7 \mathrm{~Hz}$ ), 2.49 (tdd, $1 \mathrm{H}, \mathrm{H}_{2 \rho}, J=15.0,9.0,2.0 \mathrm{~Hz}$ ); ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}, 100 \mathrm{MHz}\right) \delta 166.05,133.14,129.71,128.38,128.32\left(1, J_{r-\mathrm{F}}\right.$ $=252.8 \mathrm{~Hz}), 103.70\left(\mathrm{dd}, J_{\mathrm{C}-\mathrm{F}}=7.1,4.2 \mathrm{~Hz}\right), 79.46\left(\mathrm{dd}, J_{\mathrm{C}-\mathrm{F}}=32.1\right.$, 24.9 Hz ) $62.94\left(\mathrm{dd}, J_{C-F}=7.5,4.5 \mathrm{~Hz}\right), 55.38,42.26\left(\mathrm{t}, J_{\mathrm{C}-\mathrm{F}}=24.3 \mathrm{~Hz}\right.$ ); HRMS (FAB) mi found 273.0950. called for $\mathrm{C}_{13} \mathrm{H}_{15} \mathrm{~F}_{2} \mathrm{O}_{4} 273.0938\left(\mathrm{MH}^{+}\right)$. Anal. Calcd for $\mathrm{C}_{13} \mathrm{H}_{44} \mathrm{~F}_{2} \mathrm{O}_{4}$ : C, 57.35; H, 5.18. Found: C, 57.64; H, 5.30.
    (9) Mikhailopulo, I. A.; Poopeiko, N. E.; Pricota, T. I.; Sivets, G. G.; Kvasyuk, E. I.; Balzarini. J.; De Clercq, E. J. Med. Chem. 1991, 34, 21952202.
    (10) White solid: $\mathrm{mp} 194-196{ }^{\circ} \mathrm{C}(\mathrm{dec})$; $[\mathrm{C}]^{24} \mathrm{D}-51.89^{\circ}$ ( $c \quad 1.15$, McOH); UV (MeSH) $\lambda_{\text {max }} 276.5(\mathrm{\epsilon} \cdot 18160)(\mathrm{pH} 2), 268.0(\epsilon 13280)(\mathrm{pH}$ 7). 268.5 ( +13580 ) ( pH II); 'H NMR (CD3OD, 400 MHz ) $\delta 7.97$ (d, IH, $\left.\mathrm{H}_{0,}, J=7.3 \mathrm{~Hz}\right), 6.27\left(\mathrm{~L}, 1 \mathrm{H}, H_{1}, J=6.8 \mathrm{~Hz}\right), 5.93\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{H}_{5}, J=7.3\right.$ $\mathrm{H} . \mathrm{R}), 4.17\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}_{4}\right), 3.83\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}_{5^{\prime}}\right), 2.90\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}_{2^{\prime}}\right), 2.51(\mathrm{~m}, 1 \mathrm{H}$, $\left.I_{2}\right)$ ); ${ }^{13} \mathrm{C}$ NMR (DMSO- $\alpha_{6}, 100 \mathrm{MHz}$ ) $\delta 168.19,158.46,142.62,128.71$ $\left(\mathrm{dd} . \mathrm{I}_{\mathrm{c}-\mathrm{F}}=255.1,247.4 \mathrm{~Hz}\right), 97.04 .84 .73\left(\mathrm{dd} . J_{\mathrm{C}-\mathrm{F}}=6.7 .4 .9 \mathrm{~Hz}\right), 83.74$

[^9]:    (14) Yellow oil: 'H NMR ( $\left.\mathrm{CDCl}_{3}, 400 \mathrm{MHz}\right) \delta 8.75(\mathrm{bs}, 2 \mathrm{H}), 8.06-$ $7.45(\mathrm{~m}, 24 \mathrm{H}), 6.14-6.10(\mathrm{~m}, 2 \mathrm{H}) .7 .57(\mathrm{~m} .2 \mathrm{H}) .4 .56(\mathrm{dd}, 1 \mathrm{H} . J=11.5$. $3.2 \mathrm{~Hz}), 4.51(\mathrm{dd}, 1 \mathrm{H}, J=11.7,4.2 \mathrm{~Hz}), 4.37(\mathrm{~m}, 2 \mathrm{H}), 4.27(\mathrm{~m}, 2 \mathrm{H}), 3.40$ $(\mathrm{s}, 3 \mathrm{H}), 3.38(\mathrm{~s}, 3 \mathrm{H}), 2.57(\mathrm{~m} .2 \mathrm{H}), 2.42(\mathrm{~m}, 2 \mathrm{H}), 0.17(\mathrm{~s}, 9 \mathrm{H}), 0.16(\mathrm{~s}$, 911); ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}, 100 \mathrm{MHz}\right) \delta 166.13,166.07,154.90,154.81,143.12$, $133.20,133.16,129.60,129.56,128.97,128.45,128.41,127.60,121.33$ ( 1, $J_{C-F}=248.2 \mathrm{~Hz}$ ), $121.10\left(\mathrm{t}, J_{C-F}=248.2 \mathrm{~Hz}\right.$ ), 97.69, $97.53,83.91$, (dd, $\left.J_{C-F}=5.1,3^{\circ} 1\right), 83.76\left(\mathrm{dd}, J_{(C-F}=7.1,3.1\right), 72.13\left(1, J_{C-F}=29.3 \mathrm{~Hz}\right)$, $72.08\left(1, J_{\mathrm{C}-\mathrm{F}}=28.0 \mathrm{~Hz}\right), 64.20,64.16,57.08,57.01,37.92\left(1, J_{\mathrm{C}-\mathrm{F}}=\right.$ 23.5 Hz ). $37.81\left(\mathrm{t}, J_{\mathrm{C}-\mathrm{F}}=23.6 \mathrm{~Hz}\right), 0.11 ; \mathrm{MS}(\mathrm{PAB}) \mathrm{m} / 2560\left(\mathrm{MH}^{+}\right)$.
    (15) Bergstrom, D.; Romo, E.; Shum, P. Nucleosides Nucleotides 1987, 6. 53-63.

[^10]:    * Tel.: + 1-678-395()027; fax: + 1-678-3950030.

    Email address: kpankiewicz@pharmasset.com (K.W. Pankiewicz).

[^11]:    ' Extensive studies on the influence of intramolecular stereoelectronic gauche and anomeric effects on the conformation of the sugar moiety in modified nucleosides have been published recently by Chattopadhyaya and co-workers. See one of the last articles in the series.
    ${ }^{2}$ Constructive conformational studies of mono- and difluorodideoxy nucleosides and discussion of the relationship between conformation of their fluorosugars and anti-HIV activity has been published.

[^12]:    ${ }^{\dagger}$ Cornell University.
    ${ }^{1}$ Emory University School of Medicine.

