2	Transmittal Letter	039560538003_iDSTransmittal.pdf	81982 10bc52d1fe4810fe267cb6fe1058044e4fe	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	694472	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/013,237

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	28 minus 20 =	* 8			OR	x 80 =	640
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						4000
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	6240

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/013,237	08/29/2013	1623	6240	03956.053800.3	28	2

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

FILING RECEIPT



Date Mailed: 09/26/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jinfa Du, Redwood City, CA;
Dhanapalan Nagarathnam, Bethany, CT;
Michael Joseph Sofia, Doylestown, PA;
Peiyuan Wang, Totowa, NJ;

Applicant(s)

Gilead Pharmasset LLC, Foster City, CA

Assignment For Published Patent Application

GILEAD PHARMASSET LLC, Foster City, CA

Power of Attorney: The patent practitioners associated with Customer Number 104538

Domestic Priority data as claimed by applicant

This application is a CON of 13/609,614 09/11/2012
which is a CON of 13/099,671 05/03/2011 PAT 8334270
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/19/2013

Gilead Exhibit 2018
PGR2023-00046 - Page 00865

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/013,237**

Projected Publication Date: To Be Determined - pending completion of Sequence Disclosures

Non-Publication Request: No

Early Publication Request: No

Title

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

FORMALITIES LETTER

OC000000063907248

Date Mailed: 09/26/2013

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Filing Date Granted

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to comply with the sequence rules, 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136.

- This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c) Applicant must provide an initial paper or compact disc copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application** and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000).
- A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the U.S. Patent and Trademark Office, such request in accordance with 37 CFR 1.821(e) may be submitted in lieu of a new CRF.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to these requirements, please contact:

- **For Rules interpretation, call (571) 270-5300**
- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**

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- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A surcharge (for late submission of the basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ **140** for an undiscounted entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $ **140** for an undiscounted entity
- $ **140** Surcharge.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Jinfa Du
  Dhanapalan Nagarathnam
  Michael Joseph Sofia
  Peiyuan Wang

  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/ipetros/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

POA ACCEPTANCE LETTER

OC000000063907298

Date Mailed: 09/26/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/29/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/nmohammed/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No. 14/013,237	)	Examiner: Not Yet Known
First Named Inventor: Jinfa DU	)	Group Art Unit: 1623
Filed: August 29, 2013	)	Confirmation No. 7005
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	November 22, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND PRELIMINARY AMENDMENT,
RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR
PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE
AND/OR AMINO ACID SEQUENCE DISCLOSURES, AND
REQUEST TO TRANSFER SEQUENCE INFORMATION UNDER 37 C.F.R. § 1.821(e)

Commissioner:

Preliminary to examination on the merits, and in response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, please amend the above-identified application as follows.

- Amendments to the Specification begin on page 2;
- Response to Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures is on page 4;
- Request to Transfer Sequence Information under 37 C.F.R. § 1.821(e) is on page 5; and
- Remarks are on page 6.

AMENDMENTS TO THE SPECIFICATION

Please add, after the paragraph reciting the priority claim added by the Preliminary Amendment filed August 30, 2013 and before the subheading "Field of the Invention" at page 1, the following subheading and paragraph:

INCORPORATION OF SEQUENCE LISTING

The Sequence Listing filed on October 10, 2012 (in U.S. Patent Application No. 13/609,614, filed September 11, 2012), created on September 30, 2012, named 039560538002_ST25.txt, having a size in bytes of 1,091 B, is hereby incorporated by reference herein in its entirety.

Please replace the paragraph beginning at line 3 and ending at line 17 on page 675 of the original specification submitted on August 29, 2013 (i.e., the paragraph immediately following the "EXAMPLE 82" heading), with the following paragraph (with markings to show all changes as per 37 C.F.R. § 1.121(b)(1)(ii)):

HCV replicon assay. HCV replicon RNA-containing Huh7 cells (clone A cells; Apath, LLC, St. Louis, Mo.) were kept at exponential growth in Dulbecco's modified Eagle's medium (high glucose) containing 10% fetal bovine serum, 4 mM L-glutamine and 1 mM

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sodium pyruvate, 1× nonessential amino acids, and G418 (1,000 μg/ml). Antiviral assays were performed in the same medium without G418. Cells were seeded in a 96-well plate at 1,500 cells per well, and test compounds were added immediately after seeding. Incubation time 4 days. At the end of the incubation step, total cellular RNA was isolated (RNeasy 96 kit; Qiagen). Replicon RNA and an internal control (TaqMan rRNA control reagents; Applied Biosystems) were amplified in a single-step multiplex RT-PCR protocol as recommended by the manufacturer. The HCV primers and probe were designed with Primer Express software (Applied Biosystems) and covered highly conserved 5'-untranslated region (UTR) sequences (sense[[,]] primer: 5'-AGCCATGGCGTTAGTA(T)GAGTGT-3' (SEQ ID NO:1)[[, and]]; antisense[[,]] primer: 5'-TTCCGCAGACCACTATGG-3' (SEQ ID NO:2); and probe[[,]]: 5'-FAM-CCTCCAGGACCCCCCCTCCC-TAMRA-3' (SEQ ID NO:3)).

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RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, mailed September 26, 2013, Applicant has requested transfer of the sequence information from the parent application, and amended the specification to include (1) the required incorporation-by-reference of the electronically filed Sequence Listing and (2) notation of the sequences by the required sequence identifiers.

As required in the Notice to Comply, the late-declaration surcharge of $140.00 has been paid herewith. The Commissioner is authorized to charge any additional fee associated with the present submission, or to credit any overpayment, to Deposit Account No. 50-3939.

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REQUEST TO TRANSFER SEQUENCE INFORMATION UNDER 37 C.F.R. § 1.821(e)

Further to the Notice to Comply, and subsequent conference calls with the USPTO (Ms. Barbara N. O'Bryen), Applicant states as follows.

Pursuant to 37 C.F.R. § 1.821(e), the electronically filed copy of the Sequence Listing in the instant application is identical to the electronically filed copy of the Sequence Listing filed in application No. 13/609,614, filed September 11, 2012. In accordance with 37 C.F.R. § 1.821(e), please use the electronically filed copy of the Sequence Listing in that application as the electronically filed copy of the Sequence Listing for the instant application. It is understood that the Patent and Trademark Office will make the necessary changes in application number and filing date for the instant application.

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REMARKS

In response to the Notice to Comply, Applicant has amended the specification to include the required paragraph to incorporate-by-reference the Sequence Listing filed in the parent application. The present amendment hereby specifically directs the entry of the Sequence Listing into the application, as required by 37 C.F.R. § 1.821. Applicant also has amended the specification to include the required sequence identifiers, as previously included in the parent application. Accordingly, no new matter has been added by way of these amendments. Therefore, entry of the present amendment is respectfully requested.

Applicant respectfully submits that the Notice to Comply has been responded to in full. An early and favorable action on the merits is respectfully requested.

Applicant's undersigned attorney may be reached in our New York office by telephone at 212.218.2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

/Joseph P. Pieroni/
Joseph P. Pieroni
Attorney for Applicant
Registration No. 53,469

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, NY 10104-3800
Facsimile: (212) 218-2200

Gilead Exhibit 2018
PGR2023-00046 - Page 00876

Electronic Patent Application Fee Transmittal

Application Number:	14013237
Filing Date:	29-Aug-2013
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Filer:	Joseph P. Pieroni
Attorney Docket Number:	03956.053800.3

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	140

Electronic Acknowledgement Receipt	
EFS ID:	17477592
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Joseph P. Pieroni/DAVID NGUY
Filer Authorized By:	Joseph P. Pieroni
Attorney Docket Number:	03956.053800.3
Receipt Date:	22-NOV-2013
Filing Date:	29-AUG-2013
Time Stamp:	13:41:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$140
RAM confirmation Number	11769
Deposit Account	503939
Authorized User	NGUY, DAVID

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		SECONDPRELAMD0395605380003.pdf	149286 24baaf6fdec61a5b9fab127e2dfbf86aa1f7117139	yes	6

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	3
Applicant Response to Pre-Exam Formalities Notice	4	5
Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30079 1f00a6d4e739948bc7bc8e0dda06080e1690c79f	no	2

Warnings:

Information:

Total Files Size (in bytes):	179365

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	DU, Jinfa
Art Unit	1623
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8580765	B2	2013-11-12	SOFIA,Michael Joseph	
	2	8415322	B2	2013-04-29	CLARK, Jeremy	
	3	8551973	B2	2013-10-08	BAO, Donghui	
	4	7754699	B2	2010-07-13	CHUN, Byoung-Kwon	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20120245335	A1	2012-09-27	CLARK, Jeremy	
	2	20130109647	A1	2013-05-02	BERREY, Miriam Michelle	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	3	20130136776	A1	2013-05-30	CLEARY, Darryl G.		

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Yuodka et al., Bioorganicheskaya Khimiya, 2(11), 1513-1519 (1976) (translated from Russian)	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-12-09
Name/Print	Alicia A. Russo	Registration Number	46,192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	17599012
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.3
Receipt Date:	09-DEC-2013
Filing Date:	29-AUG-2013
Time Stamp:	11:43:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	03956053800-3IDSTransmittal.pdf	77009 035586920a4e4e7ea0f249ea8f6088d7c259c899df	no	3

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	03956053800-3-IDS-SB08.PDF	612778 8a65f6d7e06e42c1d7a07d973e5ac808ee9f4f	no	4
Warnings:					
Information:					
			Total Files Size (in bytes):	689787	

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03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/013,237	)	
	:	Examiner: Not yet assigned
First Named Inventor:	)	
	:	Group Art Unit: 1623
JINFA DU	)	
	:	Confirmation No.: 7005
Filed: August 29, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	
	:	
	)	December 9, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the documents listed on the attached PTO/SB/08a Form.

A copy of the listed non-U.S. patent document can be found in the file wrapper of grandparent application U.S. Patent Application No. 12/053,015, filed March 21, 2008, from which the present application claims priority under 35 U.S.C. §120. The Examiner is respectfully directed to the file of this application in the U.S. Patent and Trademark Office for review of this document. (*See* 37 C.F.R. § 1.98(d) and MPEP § 609.)

The Examiner's attention is also directed to the following U.S. Application, which is electronically viewable:

Appln. No.	Filing Date	Group Art Unit	Examiner's Initials
14/057,675	2013-10-18	1621	

In accordance with 37 C.F.R. §1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether these references are, or are considered to be, material to patentability.

It is respectfully requested that the above information be considered by the Examiner and that a copy of the attached PTO/SB/08a form be returned indicating that such information has been considered.

Pursuant to 37 C.F.R. § 1.97(b), it is believed that no fees are due in connection with this submission. However, should the U.S. Patent and Trademark Office determine that fees are due, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-3939.

Gilead Exhibit 2018
PGR2023-00046 - Page 00888

Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
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Filing Date	2013-08-29
First Named Inventor	DU, Jinfa
Art Unit	1623
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2006/067606	WO	A1	2006-06-29	INSERM, CNRS		☐
	2	2002/008241	WO	A2	2002-01-31	GILEAD SCIENCES, INC.		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Gilead Exhibit 2018
PGR2023-00046 - Page 00890

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	MCGUIGAN, CHRISTOPHER, et al., Certain Phosphoramidate Derivatives of Dideoxy Uridine (ddU) Are Active Against HIV and Successfully By-pass Thymidine Kinase, FEBS Letters (1994), 351, 11-14.	☐
	2	CAHARD, DOMINIQUE, et al., Aryloxy Phosphoramidate Triesters as Pro-Tides, Mini-Reviews in Medicinal Chemistry (2004), 4, 371-381.	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-12-12
Name/Print	Alicia A. Russo	Registration Number	46,192

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 June 2006 (29.06.2006)

PCT

(10) International Publication Number
WO 2006/067606 A1

(51) International Patent Classification:
A61K 31/70 (2006.01) *A61P 31/12* (2006.01)

(21) International Application Number:
PCT/IB2005/003882

(22) International Filing Date:
22 December 2005 (22.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04356207.3 24 December 2004 (24.12.2004) EP

(71) Applicants *(for all designated States except US)*: **INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)** [FR/FR]; 101 Rue De Tolbiac, F-75654 Paris Cedex 13 (FR). **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (C.N.R.S.)** [FR/FR]; 3 Rue Michel Ange, F-75016 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AUCAGNE, Vincent** [FR/FR]; 5 Rue De La Ruette, F-28300 Amilly (FR). **ESCURET, Vanessa** [FR/FR]; 5 Rue Saint Philippe, F-69003 Lyon (FR). **ZOULIM, Fabien** [FR/FR]; 5 Rue Du Paillet, F-69570 Dardilly (FR). **DURANTEL, David** [FR/FR]; 26 Rue Du Bonnand, F-69003 Lyon (FR). **TREPO, Christian** [FR/FR]; 4 Passage Du Verdier Sud, F-69500 Bron (FR). **AGROFOGLIO, Luigi** [FR/FR]; 23 Avenue Du Chateau De L'espée, F-06600 Antibes (FR). **JOUBERT, Nicolas** [FR/FR]; 23 rue des Varennes, Bât 5 - Appt 266, F-45650 Saint Jean Le Blanc (FR). **AMBLARD, Franck** [FR/FR]; 9 Impasse Des Chasseurs, F-36330 Le Poinconnet (FR).

(74) Agent: **COLOMBET, Alain**; Cabinet Lavoix, 62 Rue De Bonnel, F-69448 Lyon Cedex 03 (FR).

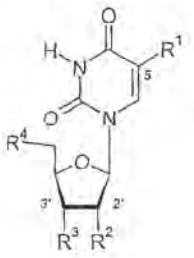
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(54) Title: URIDINE DERIVATIVES AS ANTIVIRAL DRUGS AGAINST A FLAVIVIRIDAE, ESPECIALLY HCV



(I)

(57) Abstract: The invention relates to the use of an uridine derivative of formula (I) : wherein - R^1 represents monohalogenated alkynyl or dihalogenated alkenyl; - R^2 is chosen from among hydrogen, hydroxyl, O-alkyl, O-CO alkyl and halogen; - R^3 is chosen from among hydrogen, hydroxyl, O-alkyl, O-CO alkyl, halogen, SH, S-alkyl and N_3; and - R^4 is chosen from among hydroxyl, O-alkyl, O-CO alkyl, O-phosphate, O-diphosphate, O-triphosphate and O phosphonate, as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms, for the preparation of a drug having antiviral activity against a Flaviviridae.

WO 2006/067606 A1

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URIDINE DERIVATIVES AS ANTIVIRAL DRUGS AGAINST A FLAVIVIRIDAE, ESPECIALLY HCV

The present invention relates to the use of uridine derivative(s) for the preparation of a drug having antiviral activity against a Flaviviridae, e.g. against hepatitis C virus (HCV). It also relates to new compounds having such antiviral activity, to drugs incorporating them and to a method of treating a subject (a human or an animal) with such a drug.

Hepatitis C Virus (HCV) infection remains a main public health preoccupation with 175 million people infected in the world. Currently, the best treatment available consists in the association of pegylated interferon (IFN) alpha 2b and ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). 20% of patients infected with HCV genotype 2 or 3 and 50% of patients infected with HCV genotype 1 are responders to this treatment. Therefore new treatment regimens based on more potent and specific inhibitors of HCV replication are required to improve the current antiviral strategies against chronic HCV infection.

The absence of a cellular system able to allow a complete multiplication cycle of HCV *in vitro* is a limiting factor for the search of new drugs. Recently, major knowledge has been gained about the mechanism of HCV replication. Study models have been developed such as the replicon system described in Ju-Tao Guo et al. (J. Virol. 2001, 75, 18: 8516-8523), allowing replication of HCV subgenome in cell culture.

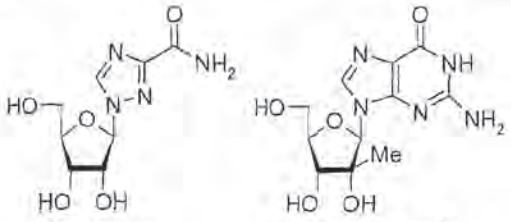
The recent developments of the replicon system has promoted the study of new inhibitors of HCV replication. The NS3 serine protease and NTPase/helicase and the RNA-dependent RNA polymerase NS5B are key enzymes for the replication of HCV. To date, several inhibitors of NS3 were discovered. The NS5B has also been studied because of its central role in viral replication (Behrens, S.E. et al. *EMBO J.*, **1996**, *15*, 12; Ferrari, E. et al. *J. Virol.*, **1999**, *73*, 1649 ; Ishii, K. et al. *Hepatology* **1999**, *29*, 1227; Lohmann, V. et al. *J. Virol.*, **1997**, *71*, 8416; Oh, J.W. et al. *J. Virol.*, **1999**, *73*, 7694; Yamashita, T. et al. *J. Biol. Chem.*, **1998**, *273*, 15479 ; Walker, M.P.; Hong, Z., *Curr. Opinion Pharmacol.* **2002**, *2*, 1). Recently Bressanelli *et al.* reported a first co-crystallization of HCV NS5B with ribonucleotides, which lead to the identification of a specific and unique GTP-binding pocket outside the active site (Bressanelli, S. et al. *J. Virol.* **2002**, *76*, 3482). Specific inhibitors of this virus-encoded RNA-dependent RNA polymerase (RdRP) may represent potent antiviral agents (De Francesco, R. et al. *Antiviral Res.* **2003**, 58, 1-16.

The pharmaceutical importance of nucleoside analogues against viral DNA polymerases such as HIV-RT, HBV and HSV polymerases, has prompted the design and synthesis of analogous viral RNA polymerase. While numerous of non-nucleoside inhibitors of NS5B-

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mediated HCV RNA replication have been reported (Chan, L. et al. *J. Med. Chem.* **2003**, *46*, 1283-1285; Wang, M. et al. *J. Biol. Chem.* **2003**, *278*, 9489-9495; Dhanak, D. et al. *J. Biol. Chem.* **2002**, *277*, 38322-38327), only a few nucleoside inhibitors have been identified so far (Carroll, S. S. et al *J. Biol. Chem.* **2003**, *278*, 11979-11984; Shim, J. et al. *Antiviral Res.* **2003**, 243-251; Eldrup, A. B. et al. *J. Med. Chem.* **2004**, 47- 2283-2295). An example of nucleoside inhibitor is the 2'-*C*-methylarabinoguanosine (2'-C-methylara*G*), recently reported in WO 01/190121, which is phosphorylated in cultured, uninfected cells and orally bioavailable in primates.



1, Ribavirin

2, 2'-*C*-methyl*ara*G
Idenix Pharmaceuticals

Many nucleoside analogues substituted at the 5-position of the heterocycle, and especially in the 2'-deoxyuridine series (*e.g.* BVDU, IDU, FIAU), are known to have potent biological properties and have been developed as antiviral and anticancer agents. The 5-(2-substitutedvinyl)-2'-deoxyuridines have emerged as potent and selective inhibitors of herpes viruses (HSV-1 & HSV-2) (De Clercq, E. *Exp. Clin. Pharmacol.* **1980**, *2*, 253 ; De Clercq, E. *Biochem. Pharmacol.* **1984**, *33*, 2159). In general, 5-alkynyl-2'-deoxyuridines has been also evaluated as potential antiviral agents (De Clercq, E. et al *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947 ; De Clercq, E.et al. *J. Infect. Dis.* **1980**, *141*, 563; Kundu, N. G.; Dasgupta, S. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2657). The structure activity relationship studies seem to indicate that the type of C-5 substituents likely to confer activity are those which are electron withdrawing and conjugated to the heterocycle (Goodchild, J. et al. *J. Med. Chem.* **1983**, *26*, 1252). Recently, McGuigan *et al.* reported that analogous furanopyridine by-product in the preparation of the parent 5-alkynyl-2'-deoxyuridine displayed important potency and exclusive selectivity for varicella zooster virus (VZV) (McGuigan C. et al. *J. Med. Chem.* **1999**, *42*, 4479; McGuigan, C. et al. *J. Med. Chem.* **2000**, *43*, 4993; Srinivasan, S. et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 391; McGuigan, C.et al. *Drugs Future* **2000**, *25*, 1151; Carangio, A. et al. *Antivir. Chem. Chemother.* **2001**, *12*, 187), meanwhile imidazo[1,2-c]pyrimidin-5(6H)-one heterosubstituted nucleoside analogues were discovered by Mansour *et al.* (*Bioorg. Med. Chem. Lett.* **1997**, *7*, 303) to have anti-HBV (hepatitis B virus) activity. The chemistry involves the Pd-catalyzed coupling of arylacetylenes or terminal alkynes with 5-iodonucleosides.

Providing the art with new efficient and acceptable anti-Flaviridae, in particular anti-HCV, drugs or treatments would be of great benefit.

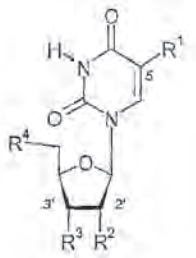
An objective of the invention is to provide the art with new treatments effective against a Flaviviridae infection, e.g. against FCV, say new treatments having a strong antiviral activity with no or acceptable side effects.

Another objective of the invention is to provide a treatment that is efficient against the major HCV genotypes, including genotypes 1, 2 and 3.

Another objective of the invention is to provide a treatment that is efficient against any HCV genotype.

These objectives are attained by the use of some uridine derivatives that will be described in details below.

A first object of the invention is the use of a uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms,
for the preparation of a drug having antiviral activity against a Flaviviridae.

In the above formula (I):

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"monohalogenated alkynyl" is –C ≡C-X or –C ≡C-Ak(X), where Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;

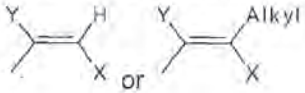
"dihalogenated alkenyl" is -C(Y)=CH(X), -C(Y)=C(X)alkyl or -C(Y)=C-Ak(X), where Y is halogen and Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;

"alkyl", unless otherwise indicated, represents a linear or branched C_1-C_{10} alkyl radical;

"halogen" is fluorine, chlorine, bromine or iodine, preferably chlorine, bromine or iodine.

The dihalogenated alkenyl may present a *Z* or *E* configuration, the *E* configuration being preferred, i.e. the two halogen atoms X and Y are not on the same side of the planar double bond.

Preferred configuration for -C(Y)=CH(X) or -C(Y)=C(X)alkyl is therefore respectively :



According to a first embodiment, a preferred uridine derivative of formula (I) useful for the preparation of a drug having antiviral activity against a Flaviviridae, presents the following characteristics:

- R^1 represents –C ≡C-X or -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen ;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -phosphate, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Preferred compounds of formula (I) are those where

- R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R^2, R^3 and R^4 being as defined above,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

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Compounds where R^2 and R^3 do not simultaneously represent hydrogen form another sub-group of even more preferred compounds.

Particularly preferred compounds for the intended above-mentioned use are those wherein

- R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl; and
- R^2 and R^3 not simultaneously being each hydrogen ; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

A most preferred uridine derivative of formula (I) is chosen from among the following compounds:

- (*E*)-5-(1-Chloro-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Diiodovinyl)-2'-deoxyuridine,
- 5-(2-Iodoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Dibromovinyl)-2'-deoxyuridine,
- 5-(2-Bromoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Chloro-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Diiodovinyl)-uridine,
- 5-(2-Iodoethynyl)-uridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Dibromovinyl)-uridine, and
- 5-(2-bromoethynyl)-uridine,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Compounds of formula (I) wherein R^4 represents -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate are deemed to represents pro-drugs of the corresponding compounds wherein R^4 represents -OH. Other pro-drugs leading to compounds wherein R^4 is -OH are also encompassed within the present invention. Such other pro-drugs include for instance esters, such as aminoacid esters, e.g. alanine esters and glycine esters, quaternary salts of phosphate, and the like.

Acids that may be used to form pharmaceutically acceptable addition salts of the compound of formula (I) are organic or inorganic acids. Such salts include for example hydrochlorides, hydrobromides, sulfates, hydrogensulfates, dihydrogene-phosphates, citrates, maleates, fumarates, trifluoroacetates, 2-naphthalenesulfonate and *para*-toluenesulfonate.

Similarly, bases that may be used to form pharmaceutically acceptable addition salts of the compound of formula (I) are organic or inorganic bases. Such salts include for example metallic salts from alkali metals, alkaline-earth metals or transition metals, such as sodium, potassium, calcium, magnesium, aluminum. Other suitable bases include ammoniac or secondary or tertiary amines (diethylamine, triethylamine, piperidine, piperazine, morpholine) or basic amino-acids, or alternatively osamines (such as meglumine), or aminoalcools (such as 3-aminobutanol and 2-aminoéthanol).

The present invention also encompasses salts that are useful for suitable separation or crystallization of the compounds of formula (I), such as salts obtained from chiral amines or acids.

Example of chiral amines include for example quinine, brucine, (*S*)-1-(benzyloxy-methyl)propylamine, (-)-ephedrine, (4*S*,5*R*)-(+)-1,2,2,3,4-tetramethyl-5-phenyl-1,3-oxazolidine, (*R*)-1-phenyl-2-*p*-tolylethylamine, (*S*)-phenylglycinol, (-)-N-methylephedrine, (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol, (*S*)-phenylglycinol, (*S*)-α-methylbenzylamine, alone or in mixtures.

Example of chiral acids include for example (+)-d-di-O-benzoyltartaric acid, (-)-l-di-O-benzoyltartaric acid, (-)-di-O,O'-p-toluyl-l-tartaric acid, (+)-di-O,O'-p-toluyl-d-tartaric acid, (*R*)-(+)-malic acid, (*S*)-(-)-malic acid, (+)-camphanic acid, (-)-camphanic acid, (+)-camphoric acid, (-)-camphoric acid, (*S*)-(+)-2-phenylpropionic acid, (*R*)-(-)-2-phenylpropionic acid, d-(-)-mandelic acid, l-(+)-mandélic acid, d-tartaric acid, l-tartaric acid, alone or mixtures.

In an embodiment, the invention more specifically relates to the use of such an uridine derivative and an efficient amount of an interferon (IFN), for the preparation of a drug having antiviral activity against a Flaviviridae. It also relates to the use of such an uridine derivative for the preparation of a drug having antiviral activity against a Flaviviridae, that is intended to be used in an recipient that is treated with an efficient amount of IFN. The recipient may have been treated recently with the IFN (for instance less than 30 days before), or received IFN at

approximatively the same time or later, for instance less than 30 days. The IFN may be chosen among those that are described *infra*.

In another embodiment, the IFN is replaced or accompanied (concomitant or successive administration) by the use of another drug such as one of those described *infra*

According to a preferred aspect, the Flaviviridae is HCV and the use of a uridine derivative of formula (I) is for the preparation of a drug having antiviral activity against HCV. There exists up to 6 HCV genotypes classified 1-6. Any of them is included in the present invention. The major genotypes are genotypes 1, 2 and 3, and a "use" according to the invention may be, for example, directed against HCV genotype 1, HCV genotype 2, HCV genotype 3, HCV genotypes 1 and 2, HCV genotypes 2 and 3, HCV genotypes 1 and 3, HCV genotypes 1, 2 and 3. The use may also be against any and all HCV genotypes, including quasispecies.

In another aspect of the invention, the Flaviviridae member may be a member of the Japanese encephalitis virus group, including Japanese encephalitis virus and West Nile Virus.

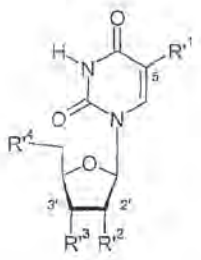
Alternatively it may be a member of the Yellow fever virus group.

Alternatively it may be a member of the Pestivirus group, such as Bovine viral diarrhea virus (BVDV-1 and/or BVDV-2), Classical swine fever virus, Border disease virus.

It may be appreciated that the recipient may be a human or an animal, depending on the Flaviviridae concerned.

Among the compounds of formula (I), 5-bromoethynyl-2'-deoxyuridine is known and reported by Eger K. *et al.* (*Tetrahedron*, **1994**, *50*, 8371-8380), whereas compounds of formula (I), wherein R^1 represents dihalogenated alkenyl are new.

Therefore, a further object of the present invention is a compound of formula (I'):



(I')

wherein

- R'^1 represents dihalogenated alkenyl;
- R'^2, R'^3 and R'^4 have the same definitions as R^2, R^3 and R^4, respectively, in the above formula (I);

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Compounds of formula (I') may be used for the preparation of a drug having an antiviral activity against a Flaviviridae.

In the above formula (I'), "dihalogenated alkenyl" has the same meaning as defined above, i.e. -C(Y)=CH(X), -C(Y)=C(X)alkyl or -C(Y)=C-Ak(X), where Y is halogen and Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;

All definitions and preferred embodiments described hereinbefore for compounds of formula (I) also apply to compounds of formula (I'), R'^1 not possibly representing however a monohalogenated alkynyl radical.

Accordingly, a preferred compound of formula (I') presents the following characteristics:

- R'^1 represents -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R'^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

Preferred compounds of formula (I') are those where:

- R'^1 represents -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R'^2, R'^3 and R'^4 being as defined above,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

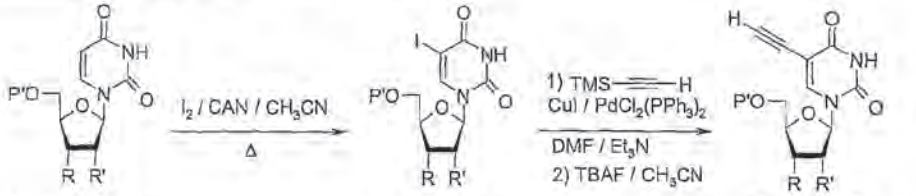
Particularly preferred compounds for the intended above-mentioned use are those wherein

- R'^1 represents -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R'^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl; and
- R'^2 and R'^3 not simultaneously being each hydrogen; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as their possible tautomers, their possible pharmaceutically acceptable additions salts with an acid or a base, and their N-oxide forms.

The present invention is further related to the process for the preparation of compounds of formula (I) and formula (I').

Halogenated pyrimidine **4a-c** in Scheme 1 below are prepared by direct reaction with halogens following the procedure reported by Asakura et al. (*J. Org. Chem.*, **1990**, *55*, 4928-4933) *via* a cerium(IV)-mediated halogenation at the C-5 of uracil derivatives. Thus, treatment of the known acetylated nucleosides **3a-c**, according to a process well known by the one skilled in the art, with elemental iodine and ceric ammonium nitrate (CAN) at 80°C, gives the corresponding protected 5-iodouracil nucleosides 4a-c in excellent yields. This CAN-mediated halogenation has advantages over other available methods as mild reaction conditions are employed with short reaction times.



3a R = OPc, R' = H
3b R = R' = OP
3c R = H, R' = OP

4a R = OP, R' = H
4b R = R' = OP
4c R = H, R' = OP

5a R = OP, R' = H
5b R = R' = OP
5c R = H, R' = OP

Scheme 1

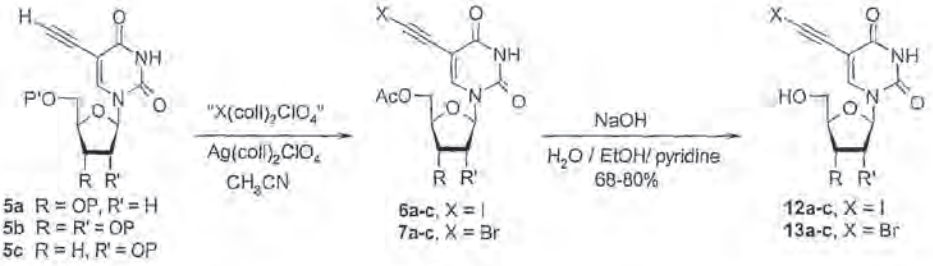
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In the above scheme 1, P and P', which may be identical or different, stand for protective groups of hydroxyl groups, and are well-known to the person skilled in the art.
Preferably, protective groups P and P' are chosen from among acyl groups such as $CH_3C=O$, trityl, monomethoxytrityl, mesyl, and the like.
In scheme 1 above, protective groups P and P' each preferably an acyl group, specifically $CH_3C=O$.

The introduction of a C-5-alkynyl group is performed by a Pd(0)-mediated reaction, using the *Sonogashira conditions* (Sonogashira K., *Comprehensive Organic Synthesis*, Trost/Fleming (Eds), Pergamon Press, New York, **1991**, vol 3, p. 521;. Sonogashira K. et al.; *Tetrahedron Lett.*, **1975**, *16*, 4467; Takahashi S. et al., *Synthesis*, **1980**, 627; Ratovelomana V. et al., *Synth. Commun.*, **1981**, *11*, 917). Thus, reaction of the resulting pure acetylated 5-iodouracil **4a-c** with trimethylsilylacetylene in the presence of triethylamine (Et_3N, base), cuprous iodide (CuI, co-catalyst) and $PdCl_2(PPh_3)_2$ (catalyst) in anhydrous dimethyl formamide (DMF) at room temperature, followed by a removal of the trimethylsilyl (TMS) group with TBAF (tetrabutyl ammonium fluoride) affords the corresponding 5-ethynyluracil nucleosides **5a-c**. In most cases, it is observed that slight elevations in the reaction temperature lead to increase in the rate of coupling. In all cases, a by-product, furanopyrimidine derivatives is either isolated with a < 7% yield, or just detected by TLC; nevertheless, the using of DMF reduces the amount of this cyclic by-product; this base-catalyzed cyclization was previously reported by Bleackley *et al.* (*Tetrahedron*, **1976**, 32, 2795) by base treatment of (E)-5-(2-bromovinyl)uracil.

The halogenation of alkynes **5a-c** is realized using halogenating agents (such as iodonium di-syn-collidine perchlorate (IDCP), N-iodosuccinimide (NIS) or chloroiodine (ICL) for iodination, bromonium di-syn-collidine perchlorate ($Br(coll)_2ClO_4$) for bromination, or, for chlorination, sulfuryl chloride, Cl_2, CCl_4, N-chlorophtalimide, dichlorine monoxide or PCl_5, in anhydrous polar solvent, for example methane nitrile (CH_3CN) according to reaction Scheme 2, where P and P' are as defined above for Scheme 1. These halogenating reagents are known to act as very reactive electrophiles (such as I^+ and Br^+, respectively).

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5a R = OP, R' = H
5b R = R' = OP
5c R = H, R' = OP

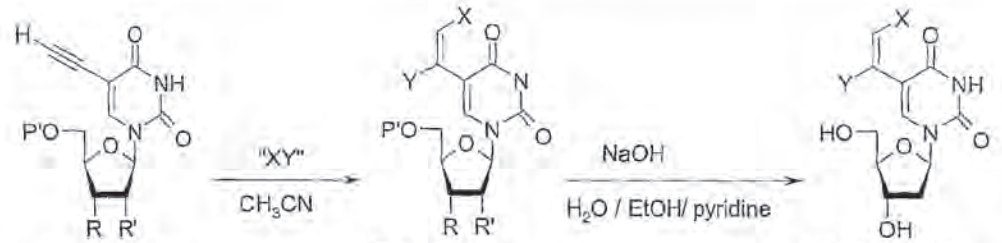
6a-c, X = I
7a-c, X = Br

12a-c, X = I
13a-c, X = Br

Scheme 2

The final deprotection of protected nucleosides **6a-c** and **7a-c** is realized under smooth basic conditions (for example 1M sodium hydroxide in a mixture of H_2O/EtOH/pyridine) when P = P' = Ac) to afford final 5-haloethynyluracil nucleosides **12a-c** and **13a-c**, respectively, in good to moderate yield.

Dihalogenation of the above 5-ethynyl nucleosides (Scheme 3) leads to hitherto unknown 5-(1,2-dihalogenated)ethenyluracil nucleosides **14a-c** to **17a-c**. Several halogenating reagents (i.e. I_2, IBr, ICl or Br_2) are used to reach the corresponding 1,2-dihaloderivatives. In all cases of halo-iodination, the formation of vicinal halo-iodoalkenes (**8a-c to 10a-c**) occurs with high anti-stereospecificity, implicating the intermediary of an iodonium ion in the reaction sequence, and a high and unique regioselectivity, implicating a predominantly Markovnikov addition. The formation of **11a-c** using Br_2 occurs also with a *E*-stereochemistry.



5a R = OP, R' = H
5b R = R' = OP
5c R = H, R' = OP

8a-c, X = Y = I
9a-c, X = I, Y = Br
10a-c, X = I, Y = Cl
11a-c, X = Y = Br

14a-c, X = Y = I
15a-c, X = I, Y = Br
16a-c, X = I, Y = Cl
17a-c, X = Y = Br

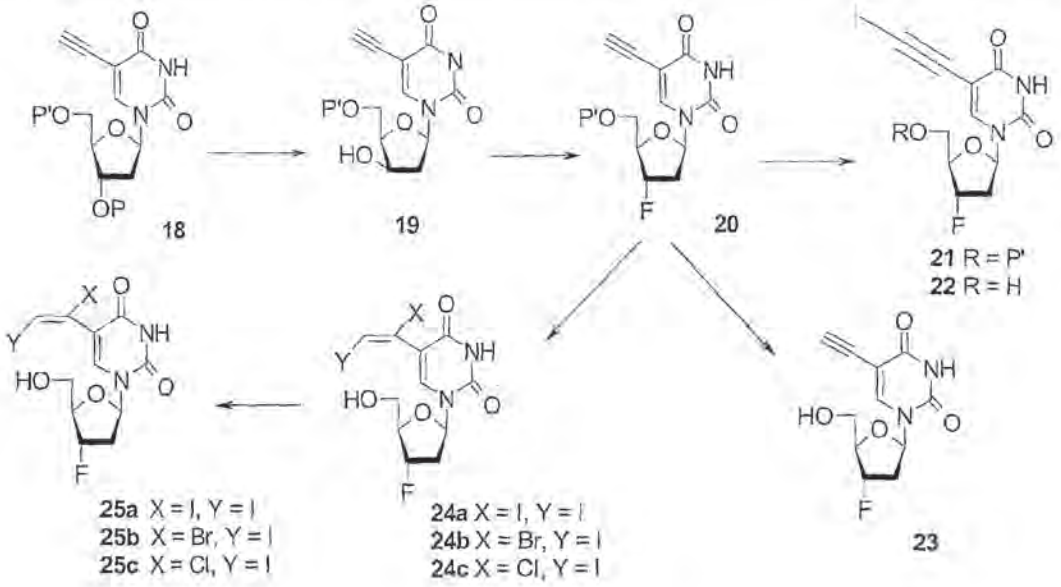
Scheme 3

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The final deprotection of protected nucleosides **8a-c** to **11a-c** is realized as previously reported (for example 1M NaOH in a mixture of H_2O/EtOH/pyridine when P = P'Ac) and final 5-(1,2-dihaloethenyl)uracil nucleosides **14a-c** (for X = Y = I), **15a-c** (for X = I, Y = Br), **16a-c** (for X = I, Y = Cl), **17a-c** (for X = Y = Br) are obtained, respectively.

All other compounds encompassed by formulae (I) and (I') are easily prepared from the above described synthetic route with easily conceivable modifications and/or adaptations well known by the one skilled in the art.

For illustrative purposes only, compounds of formula (I) or of formula (I') may be obtained according to scheme 4 below, wherein P preferably represents mesyl and P' preferably represents monomethoxytrityl.



Scheme 4

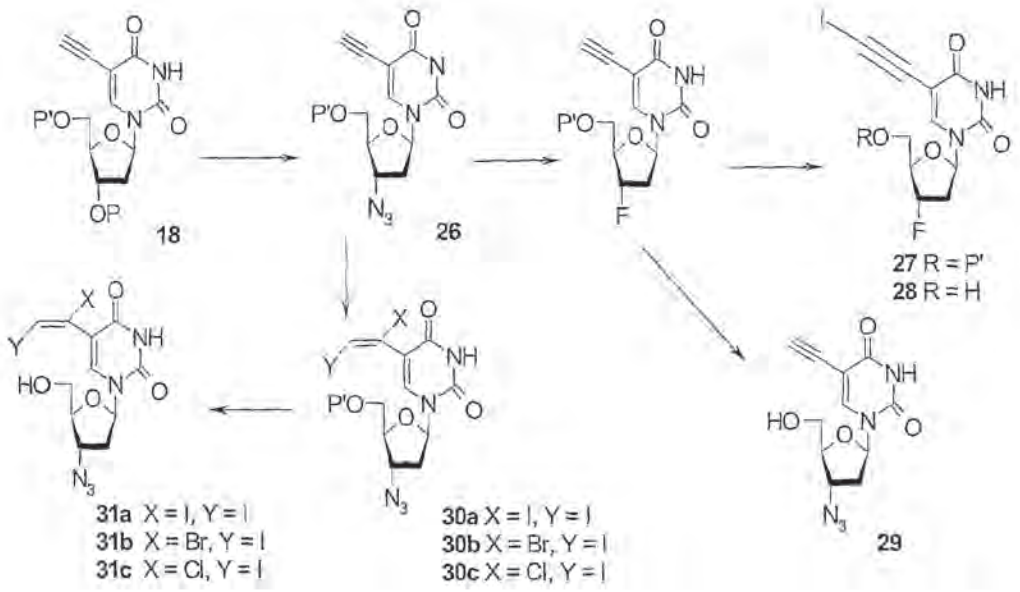
In scheme 4 above, coumpound **19** is obtained after specific deprotection, in mild basic conditions, the free resulting hydroxyl group being substituted by methods well known in the art, for example using diethylaminosulfur trifluoride, affordinf compound 21.

Compounds 21 and 22 are obtained from compound **20** under conditions similar as those described above for the preparation of compounds **12** and **13.**

Compound 23 results from the deprotection of the P' protecting group of compound 20.

Compounds **24a-c** and **25a-c** are respectively obtained using a similar process as the one disclosed above for the preparation of compounds **8-11a-c** and **14-17a-c**.

As further illustrative purpose only, compounds of formula (I) and of formula (I') wherein R^3 (and R^{13} respectively) represents N_3 may be obtained according the following scheme 5.



Scheme 5

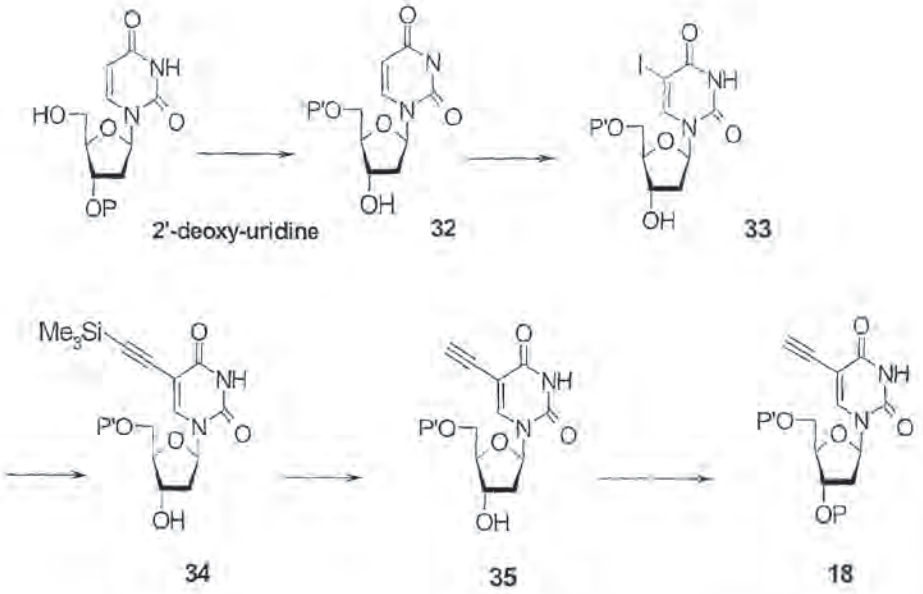
In the above scheme 5, P and P' each denote protective groups defined as defined above and advantageously P represents mesyl and P' represents monomethoxytrityl.

Azidation of compound **18** may be carried out using conventional techniques of azidation and for example using sodium azide in polar aprotic solvent, such as for example dimethylformamide under reflux, resulting in compound 26.

Compounds **27-31** are obtained through similar methods as those disclosed above for the preparation of compounds **21-25** respectively.

Compound **18** in scheme 4 and scheme 5 above may be obtained according to a process similar to the process for the preparation of compound 5 in the above scheme 1.

Alternatively, compound of formula 18 may advantageously be obtained according to the preparation process of scheme 6 below :



In scheme 6 above, P and P' are preferably different, each representing a protective group as defined above. Particularly preferred are compounds wherein P' represents monomethoxytrityl and P represents mesyl.

The introduction of the P' protective group is carried out using conventional techniques, and for example, where P' represents monomethoxytrityl using para-anisylchlorodiphenyl-methane in mild basic conditions, such as dry pyridine at reflux.

The selective introduction of protective group I is also achieved using conventional techniques, and, for example, when P represents mesyl, using methanelsulfonychloride in mild basic conditions, such as for example dry pyridine at 0° C.

In scheme 6 above, the introduction of a C-5-alkynyl group is performed as stated above in scheme 1 for the preparation of compound **5**.

Compounds **14-31 a-c** are purified, when necessary, using conventional methods known in the art.

Compounds of formulae (I) and (I') may be obtained in pure enantiomeric form and/or isomeric form, or in mixture, in all proportions, of enantiomers and/or isomers. Separations of such enantiomers and/or isomers is run according to techniques well known in the art.

The above compounds are also optionally converted into pharmaceutically acceptable addition salts with an acid or a base, and optionally into their N-oxide form, using appropriate and suitable methods as known by the one skilled in the art.

All starting materials are known and either commercially available or prepared, directly or with slight variations easily conceivable by the one skilled in the art, from one or more processes disclosed in the scientific literature, patents and patents application, the "Chemical Abstracts", on-line data bases and the Internet.

Another object of the invention is a drug or drug formulation having an antiviral activity against a Flaviviridae, in particular HCV, comprising at least one compound of formulae (I) (the active ingredient) with a pharmaceutically acceptable vehicle, carrier or excipient. "Acceptable" means that this further ingredient is compatible with the active ingredient included in the formulation and is not deleterious to the recipient thereof. The pharmaceutically acceptable vehicle, carrier or excipient are well known to the one skilled in the art. For example, for parenteral administration, it can be a 0.9 % NaCl saline solution for a phosphate buffer. The pharmaceutical acceptable vehicles, carriers or excipients also cover any compound or combination of compounds facilitating the administration of the active ingredient and/or improving preservation.

In the whole specification and Claims, the words "comprise/comprising" are synonymous with (means the same thing as) "include/including", "contain/containing", are inclusive or open-ended and do not exclude additional, unrecited elements.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal or sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. These various formulations are well known, as well as their methods of preparation. The choice of the formulation may vary depending upon the identity of the recipient, and will generally be chosen according to the best practice for a human or for the animal considered. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Formulations for oral administration may be presented as discrete units such as, for example: capsules, cachets or tablets each containing a predetermined amount of active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or an emulsion, e.g. a water-in-oil or an oil-in-water emulsion. The active ingredient may also be presented as a bolus, electuary or paste. The solid forms may optionally be coated and may be formulated so as to provide slow or controlled release of the

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active ingredient. For infections of the eye or other external tissues (e.g. skin or mouth), the formulations are preferably presented as ointment or cream for topical application, containing an efficient amount of active ingredient. Formulations suitable for administration to the eye also include eye drops where the active ingredient is dissolved or suspended in a suitable carrier, such as an aqueous solvent. Formulations for rectal administration may be presented as a suppository with a suitable base. Liquid or solid carriers may be used for nasal administration. Pessaries, tampons, creams, gels, pastes, foams or spray formulations may be used for vaginal administration. Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions, suspensions or emulsions.

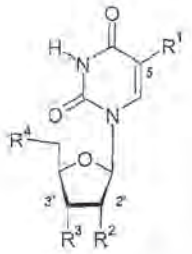
The amount of active ingredient in a single dosage form will depend upon a number of factors including the identity of the recipient and the condition to be treated. In general, however, for a human, the amount of active ingredient in a single dose form will be in the range, for example, of 1 mg to 10 g, preferably in the range of 100 mg to 5 g, most preferably in the range of 500 to 2000 mg.

For multiple dosage form, for example a cream or ointment, the concentration of active ingredient will depend upon a number of factors including the identity of the recipient and the condition to be treated. In general, however, for a human, the concentration of active ingredient in a multiple dose form will be in the range, for example, of 0.01 to 200 mg of active ingredient per g of formulation, preferably in the range of 0.1 to 100 mg/g, most preferably in the range of 1 to 50 mg/g.

In one embodiment, the drug formulation according to the invention further comprises an additional compound having an antiviral activity against a Flaviviridae or that is useful in the treatment of the infection or its symptoms. The use according to the invention thus encompasses the use of at least two different active ingredients, at least one of them being an uridine derivative as described herein.

In a first aspect, this additional compound is at least one formula (I) compound. Thus the invention formulation does comprise at least two formula (I) compounds or derivatives.

In a second aspect, the drug formulation having an antiviral activity against a Flaviviridae comprises an additional compound which is not an uridine derivative according to the invention. The drug formulation may be then represented as comprising :
(1) an uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms,

(2) an immunomodulator or another active ingredient having an antiviral activity against a Flaviviridae or being useful in treating the infection by a Flaviviridae, and

(3) a pharmaceutically acceptable vehicule, carrier or excipient.

The additional compound is advantageously an immunomodulator, especially an interferon (IFN) or a derivative of an interferon such as the so-called pegylated forms of interferon (pegylated interferon), such as any those currently used in the medical field. It may be in particular IFN-α, e.g. IFN-α 2b, such as pegylated IFN-α 2b Peg-Intron® (Schering Plough), IFN-α 2a, such as pegylated IFN-α 2a Pegasis® (Roche), Albuferon-a® (Human Genome Sciences), Multiferon® (Viragen) ; IFN-β, e.g. IFN β 1a, such as Rebif® IFN-β 1a (Serono) ; IFN-γ, e.g. IFN-γ 1b, such as IFN-γ 1b (from Interimmune Pharmaceuticals ; IFN-ω, e.g. IFN-ω from Biomedines.

Other immunomodulators may be associated to the invention compounds, such as histamine dihydrochloride (e.g. Ceplene®, Maxim Pharmaceuticals), Thymosine-a (SciClone Pharmaceuticals), Interleukines such as IL-12 and IL-10, therapeutical vaccines (e.g. based on the E1 protein), preparation for passive immunity transfer (e.g. Cicavir®, NABI).

More generally, the invention compounds may find an interest in the association to any available drug used in the treatment of the infection by a Flaviviridae, especially HCV. Thus, the drug formulation may include in addition an active principle chosen among antisens

molecules, protease inhibitors, helicase inhibitors, polymerase inhibitors, nucleoside or nucleotide analogs (chain terminators, ribonucleoside analogs, sugar modified nucleoside analogs), ribavirine or ribavirine pro-drug, inosine monophosphate dehydrogenase inhibitors.

The invention encompasses of course combinations of at least two different additional compounds with an uridine derivative according to the invention.

In a third aspect, the drug or drug formulation according to the invention comprises at least two formula (I) compounds and at least one additional compound as described above, in particular an IFN or derivative thereof.

Another object of the invention is thus a drug formulation comprising at least one formula (I) compound, at least one additional compound as described *supra*, in particular an IFN or derivative thereof, and a pharmaceutically acceptable vehicle, carrier or excipient, as described *supra*.

Another object of the invention is a method for antiviral treatment of a recipient (a human or an animal), wherein the recipient is administered with an efficient amount of a drug or drug formulation according to the invention.

In an embodiment, the method includes the administration of an efficient amount of uridine derivative(s) and an efficient amount of interferon(s) (IFN). The uridine derivative and the IFN may be in admixture, or may be separately formulated and are either co-injected after extemporaneous mixture, or administered separately to the recipient. As an alternative, the method provides for the administration of an efficient amount of uridine derivative(s), where this administration is intended to be made in a recipient that is treated with an efficient amount of IFN(s). The recipient may have been treated recently with the IFN(s) (for instance less than 30 days before), or he receives IFN(s) at approximately the same time or later, for instance less than 30 days. In another embodiment, the IFN is replaced or accompanied (concomitant or successive administration) by the administration of another drug such as one of those described *supra*. Any and all characteristics recited with respect to the use according to the invention apply to the method.

As mentioned above, the compounds or derivatives, and the formulations or compositions comprising them may be administered by any route appropriate to the condition to be treated. Suitable routes including oral, rectal, nasal, topical (including buccal or sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal,

intrathecal and epidural). It will be appreciated that the preferred route may vary with, for example, the condition of the recipient. Various suitable formulation types have been described earlier and may be used in the method.

For each of the above-indicated infectious events or indications the amount required of the active ingredient will depend upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician. In general, however, for each of these indications, a suitable, effective dose will be in the range 0.01 to 200 mg per kilogram body weight of recipient per day, preferably in the range of 2 to 100 mg, most preferably 10 to 40 mg per kilogram body weight of recipient per day. The dose may if desired be presented as two, three, four or more sub-doses administered at appropriate intervals throughout the day.

The invention is described further in details with the following description of non-limitative examples.

EXAMPLES

Commercially available chemicals and solvents are reagent grade and used as received. Dry tetrahydrofuran, pyridine and dichloromethane are obtained from distillation over calcium hydride (CaH_2) or sodium (Na), *N,N*-dimethylformamide and ethanol over barium oxide (BaO) over calcium hydride (CaH_2). Triethylamine is dried over potassium hydroxide (KOH). The reactions are monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 F_{254}, E. Merck). Compounds are visualized by UV irradiation and/or spraying with 20% sulphuric acid (H_2SO_4) in ethanol (EtOH), followed by charring at 150 °C. Column chromatography is performed on Silica Gel 60 M (0.040-0.063 mm, E. Merck). Melting points (mp) are recorded on a Büchi (Dr. Tottoli) and are uncorrected. ^1H and ^{13}C NMR spectra are recorded on a Bruker AVANCE DPX 250 Fourier Transform spectrometer at 250 MHz for ^1H and 62.9 MHz for ^{13}C, respectively, in (D)-chloroform, (D_4)-methanol and (D_6)-DMSO, shift values in ppm relative to $SiMe_4$ as internal reference, unless otherwise stated ; signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), J in Hz. $[\alpha]_D$ were performed with a Perkin-Elmer (model 41) polarimeter. UV spectra were recorded on a Beckman DU-640 spectrophotometer. Mass spectra are recorded on a Perkin-Elmer SCIEX API-300 (heated nebullizer) spectrometer. High-resolution Mass spectra (HRMS) were performed by the Centre Regional de Mesures Physiques de l'Ouest, University of Rennes 1 (France) using the FAB (Fast Atom Bombardment) or ESI (Electron Spray Ionization) mode. The nomenclature of the obtained compounds is in accordance with the IUPAC rules. The

numbering and assignment of the chemical shifts for all described compounds are related to the corresponding ribose derivatives.

Preparation of compounds of formula (I)

General procedure for iodination of acetylated nucleosides

A solution of acetylated nucleoside **3a-c** (synthetic route described by L. B. Townsend and R. S. Tipson in "Nucleic acid chemistry", Wiley Eds., 1978) (15 mmol) in dry methane nitrile (CH_3CN, 150 mL), ceric ammonium nitrate (CAN, 4.94 g, 0.6 eq.) and iodine (I_2, 2.28 g; 0.6 eq.) is refluxed until completion (typically 1 h, checked by TLC). After cooling to room temperature (rt), solvents are evaporated under reduced pressure and the dark oily residue is dissolved in ethyl acetate (AcOEt, 300 mL) and water (H_2O, 50 mL). The biphasic mixture is cooled in an ice bath and a saturated $Na_2S_2O_3$ solution is smoothly added until complete decolouration. The organic layer is washed with water (2 x 50 mL) and brine (50 mL), dried over magnesium sulfate ($MgSO_4$) and concentrated under reduced pressure. The white foam is triturated with pentane (50 mL), filtrated and dried under reduced pressure to afford pure iodinated compounds **4a-c**, respectively.

General procedure for Sonogashira cross-coupling and subsequent desilylation

Iodinated nucleoside **4a-c** (5 mmol) was dissolved in a mixture of dry dimethyl formamide (DMF; 15 mL), dry triethyl amine (Et_3N; 2.06 mL, 3 eq.) and trimethyl silyl acetylene (2.06 mL, 3 eq.). Cuprous iodide (CuI; 190 mg, 0.2 eq.) and $PdCl_2(PPh_3)_2$ (350 mg, 0.1 eq.) were then added and the reaction mixture was stirred at room temperature until completion (typically 5-20 h, checked by TLC). Solvents were evaporated under reduced pressure. The oily residue was dissolved in AcOEt (250 mL) then washed with water (5 x 40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to a dark oil. A first purification using a short path flash chromatography (eluent: methylene chloride (CH_2Cl_2) then MeOH/CH_2Cl_2 5 %) afforded the desired compound contaminated with coloured reaction co-products. Pure silylated alkynes (2 mmol), obtained after a second flash chromatography (eluent: hexanes/AcOEt 7/3 then 1/1), were dissolved in dry CH_3CN (20 mL). Tetrabutyl ammonium fluoride (TBAF) monohydrate (583 mg, 1.05 eq.) was added and the resulting solution was stirred at room temperature until completion (typically 30 min. to 2 h, checked by TLC). Solvents were evaporated under reduced pressure at room temperature and the oily residue was submitted to a flash column chromatography (eluent: hexanes/AcOEt 1/1 then AcOEt then MeOH/AcOEt 2% then 5%) to afford pure 5-ethynyl nucleosides **5a-c**, respectively.

General procedure for mono-halogenation of 5-ethynyl nucleosides

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5-Ethynyl nucleoside **5a-c** (0.5 mmol) is dissolved in 5 mL dry CH_3CN and the mixture is cooled in an ice bath. 0.7 mmol (1.4 eq.) of the halogenating reagent (i.e. IDCP (iodonium di-syn-collidine perchlorate) or $Br(coll)_2ClO_4$) and 11 mg $Ag(coll)_2ClO_4$ (0.05 eq.) are added and the mixture is stirred in the dark at rt (typically 2 h-20 h, checked by TLC). The reaction mixture is cooled to 0°C then quenched by a saturated $Na_2S_2O_3$ solution (2 mL) and extracted with AcOEt (4 x 10 mL). The organic layer is washed with water (10 mL), a 1M HCl (hydrochloric acid) solution (3 x 5 mL), water (2 x 5 mL) and brine (10 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. The solid residue is purified by flash chromatography (eluent : hexanes/AcOEt, 1/1, v/v) to yield the desired mono-halogenated compound **6-7a-c**.

Example 1: **3',5'-Di-*O*-acetyl-5-(2-iodoethynyl)-2'-deoxyuridine (6a)**

The title compound is obtained according to the above described general procedures from 3',5'-Di-*O*-acetyl-2'-deoxy-5-iodouridine (4a) (see Asakura, J. et al., *J. Org. Chem.*, **1990**, *55*, 4928-4933; and Asakura, J. et al., *Tetrahedron Lett.*, **1988**, *29*, 2855-2858) or from 3',5'-di-*O*-acetyl-2'-deoxy-5-ethynyluridine (5a) (see US 5,028,596).

Yield: 93%.

mp: 175-177 (dec) °C

$[\alpha]_D^{20}$ -32 (c 0.5, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 11.68 (br s, 1H, NH), 8.02 (s, 1H, H-6), 6.12 (t, J = 7.1 Hz, 1H, H-1'), 5.20 (m, 1H, H-3'), 4.33-4.15 (m, 3H, H-4',5'), 2.55 (m, 1H, H-2'a), 2.31 (m, 1H, H-2'b), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc).

HRMS m/z 486.1982 calculated for $C_{15}H_{15}IN_2O_7Na$, found m/z 486.1986.

Example 2: **3',5'-Di-*O*-acetyl-5-(2-bromoethynyl)-2'-deoxyuridine (7a)**

According to a procedure similar to that of Example 1, the title compound is obtained as an oil.

Yield: 21%

$[\alpha]_D^{20}$ -68 (c 1.0, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 8.88 (br s, 1H, NH), 7.95 (s, 1H, H-6), 6.31 (dd, J = 7.3, 6.4 Hz, 1H, H-1'), 5.25 (m, 1H, H-3'), 4.38-4.30 (m, 3H, H-4',5'), 2.55 (m, 1H, H-2'a), 2.31 (m, 1H, H-2'b), 2.18 (s, 3H, OAc), 2.12 (s, 3H, OAc).

HRMS m/z 439.1978 calculated for $C_{15}H_{15}BrN_2O_7Na$, found m/z 439.1981.

Examples 3 to 6 below are obtained according to similar processes.

Example 3: **2',3',5'-Tri-*O*-acetyl-5-(2-iodoethynyl)-uridine (6b)**

Yield: 68%

mp: 100-102 °C

$[\alpha]_D^{20}$ -71 (c 1.0, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 9.41 (br s, 1H, NH), 7.91 (s, 1H, H-6), 6.07 (d, J = 4.6 Hz, 1H, H-1'), 5.35 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.25 (s, 3H, OAc), 2.12 (s, 2 x 3H, 2 x OAc).

HRMS m/z 544.2352 calculated for $C_{17}H_{17}IN_2O_9Na$, found m/z 544.2349.

Example 4: 2',3',5'-Tri-*O*-acetyl-5-(2-bromoethynyl)-uridine (7b)

Yield: 58% as a colorless oil

$[\alpha]_D^{20}$ -59 (c 0.4, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 9.75 (br s, 1H, NH), 7.92 (s, 1H, H-6), 6.07 (d, J = 4.4 Hz, 1H, H-1'), 5.35 (m, 2H, H-2',3'), 4.37 (m, 3H, H-4',5'), 2.22 (s, 3H, OAc), 2.12 (s, 2 x 3H, 2 x OAc).

HRMS m/z 497.2348 calculated for $C_{17}H_{17}BrN_2O_9Na$, found m/z 497.2351.

Example 5: 2',5'-Di-*O*-acetyl-5-(2-iodoethynyl)-3'-deoxyuridine (6c)

Step a): 2',5'-Di-*O*-acetyl-3'-deoxy-5-iodouridine (4c)

^1H NMR ($CDCl_3$) δ 9.53 (br s, 1H, NH), 7.93 (s, 1H, H-6), 5.82 (d, J = 1.6 Hz, 1H, H-1'), 5.30 (m, 1H, H-2'), 4.55 (m, 1H, H-4'), 4.41 (dd, J = 12.8, 2.8 Hz, 1H, H-5'a), 4.33 (dd, J = 12.8, 3.8 Hz, 1H, H-5'b), 2.31-1.95 (m, 2H, H-3'), 2.23 (s, 3H, OAc), 2.13 (s, 3H, OAc).

Step b): 2',5'-Di-*O*-acetyl-3'-deoxy-5-ethynyluridine (5c)

^1H NMR ($CDCl_3$) δ 9.8 (br s, 1H, NH), 7.88 (s, 1H, H-6), 5.78 (s, 1H, H-1'), 5.31 (d, J = 7.5 Hz, 1H, H-2'), 4.48 (m, 1H, H-4'), 4.35 (dd, J = 12.5, 1.8 Hz, 1H, H-5'a), 4.25 (dd, J = 12.5, 3.4 Hz, 1H, H-5'b), 3.1 (s, 1H, H-Csp), 2.31-1.95 (m, 2H, H-3'), 2.12 (s, 3H, OAc), 2.05 (s, 3H, OAc)

HRMS m/z 360.2968 calculated for $C_{15}H_{16}N_2O_7Na$, found m/z 360.2971.

Step c): 2',5'-Di-*O*-acetyl-5-(2-iodoethynyl)-3'-deoxyuridine (6c)

Yield: 76% as an oil

$[\alpha]_D^{20}$ -49 (c 0.8, $CHCl_3$)

^1H NMR ($CDCl_3$) δ 11.68 (br s, 1H, NH), 7.98 (s, 1H, H-6), 5.74 (s, 1H, H-1'), 5.30 (d, J = 7.5 Hz, 1H, H-2'), 4.43 (m, 1H, H-4'), 4.28 (br s, 2H, H-5'), 2.31-1.95 (m, 2H, H-3'), 2.09 (s, 3H, OAc), 2.05 (s, 3H, OAc).

HRMS m/z 486.1982 calculated for $C_{15}H_{15}IN_2O_7Na$, found m/z 486.1986.

Example 6: 2',5'-Di-*O*-acetyl-5-(2-bromoethynyl)-3'-deoxyuridine (7c)

Yield: 25% as an oil

$[\alpha]_D^{20}$ -52 (c 0.4, $CHCl_3$)

^{1}H NMR (DMSO-d_6) δ 11.75 (br s, 1H, NH), 8.07 (s, 1H, H-6), 5.85 (s, 1H, H-1'), 5.31 (d, J = 7.5 Hz, 1H, H-2'), 4.43 (m, 1H, H-4'), 4.28 (br s, 2H, H-5'), 2.31-1.95 (m, 2H, H-3'), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc).

HRMS m/z 439.1978 calculated for $C_{15}H_{15}BrN_2O_7Na$, found m/z 439.1975.

General procedure for di-halogenation of 5-ethynyl nucleosides

5-ethynyl nucleoside **5a-c** (0.5 mmol) is dissolved in 5 mL dry CH_3CN and the mixture is cooled in an ice bath. 0.6 mmol (1.2 eq.) of a solution of the halogenating reagent (i.e. I_2, IBr, ICl or Br_2) in 1 mL dry CH_3CN is added dropwise and the mixture is stirred at 0°C until completion (typically 15 min.-2 h, checked by TLC). The reaction mixture is quenched at 0°C by a saturated $Na_2S_2O_3$ solution (2 mL) then extracted with AcOEt (3 x 10 mL). The organic layer is washed with water (2 x 5 mL) and brine (10 mL) then dried over $MgSO_4$ and concentrated *in vacuo* to yield the desired di-halogenated compounds of examples 7-18 (**8-11a-c**) in a reasonably pure form. Pure analytical samples were obtained using flash chromatography (eluent: hexanes/AcOEt, 1/1, v/v).

Example 7: **(*E*)-3',5'-Di-*O*-acetyl-5-(1,2-diiodovinyl)-2'-deoxyuridine (8a)**

94% yield; mp 76-78 °C; $[\alpha]_D^{20}$ -19 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.72 (br s, 1H, NH), 7.67 (s, 1H, H-6), 7.45 (s, 1H, =CHI), 6.36 (dd, J = 8.1, 5.6 Hz, 1H, H-1'), 5.25 (m, 1H, H-3'), 4.50-4.28 (m, 3H, H-4',5'), 2.60 (m, 1H, H-2'a), 2.30 (m, 1H, H-2'b), 2.17 (s, 3H, OAc), 2.08 (s, 3H, OAc). HRMS m/z 614.1106 calculated for $C_{15}H_{16}I_2N_2O_7Na$, found m/z 614.1110.

Example 8: **(*E*)-2',3',5'-Tri-*O*-acetyl-5-(1,2-diiodovinyl)-uridine (8b)**

98% yield; mp 83-85 °C; $[\alpha]_D^{20}$ -41 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.56 (br s, 1H, NH), 7.58 (s, 1H, H-6), 7.40 (s, 1H, =CHI), 6.15 (d, J = 4.6 Hz, 1H, H-1'), 5.36 (m, 2H, H-2',3'), 4.38 (br s, 3H, H-4',5'), 2.19 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.11 (s, 3H, OAc). HRMS m/z 672.1476 calculated for $C_{17}H_{18}I_2N_2O_9Na$, found m/z 672.1480.

Example 9: **(*E*)-2',5'-Di-*O*-acetyl-5-(1,2-diiodovinyl)-3'-deoxyuridine (8c)**

87% yield; mp 75-77 °C; $[\alpha]_D^{20}$ -23 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.38 (br s, 1H, NH), 7.64 (s, 1H, H-6), 7.39 (s, 1H, =CHI), 5.92 (d, J = 1.6 Hz, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.44 (dd, J = 12.5, 4.4 Hz, 1H, H-5'a), 4.33 (dd, 1H, H-5'b), 2.31-1.95 (m, 2H, H-3'), 2.14 (s, 3H, OAc), 2.12 (s, 3H, OAc). HRMS m/z 614.1106 calculated for $C_{15}H_{16}I_2N_2O_7Na$, found m/z 614.1101.

Example 10: **(*E*)-3',5'-Di-*O*-acetyl-5-(1-bromo-2-iodovinyl)-2'-deoxyuridine (9a)**

96% yield; mp 82-84 °C; $[\alpha]_D^{20}$ -14 (c 4.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.78 (br s, 1H, NH), 7.71 (s, 1H, H-6), 7.08 (s, 1H, =CHI), 6.25 (dd, J = 8.1, 5.6 Hz, 1H, H-1'), 5.28 (m, 1H, H-3'), 4.50-4.05 (m, 3H, H4', 5'), 2.58 (m, 1H, H-2'a), 2.20 (m, 1H, H-2'b), 2.12 (s, 3H, OAc), 1.96 (s, 3H, OAc). HRMS m/z 567.1102 calculated for $C_{15}H_{15}BrIN_2O_7Na$, found m/z 567.1107.

Example 11: (*E*)-2',3',5'-Tri-*O*-acetyl-5-(1-bromo-2-iodovinyl)-uridine (9b)

92% yield; mp 86-88 °C; $[\alpha]_D^{20}$ -39 (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.57 (br s, 1H, NH), 7.66 (s, 1H, H-6), 7.15 (s, 1H, =CHI), 6.15 (d, J = 4.7 Hz, 1H, H-1'), 5.38 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.18 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.13 (s, 3H, OAc). HRMS m/z 625.1469 calculated for $C_{17}H_{18}BrIN_2O_9Na$, found m/z 625.1473.

Example 12: (*E*)-2',5'-Di-*O*-acetyl-5-(1-bromo-2-iodovinyl)-3'-deoxyuridine (9c)

89% yield as an oil; $[\alpha]_D^{20}$ -19 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.63 (br s, 1H, NH), 7.61 (s, 1H, H-6), 7.13 (s, 1H, =CHI), 5.92 (s, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.44 (dd, J = 12.4, 2.6 Hz, 1H, H-5'a), 4.33 (dd, J = 12.4, 4.4 Hz, 1H, H-5'b), 2.31-1.95 (m, 2H, H-3'), 2.16 (s, 3H, OAc), 2.14 (s, 3H, OAc). HRMS m/z 567.1102 calculated for $C_{15}H_{16}BrIN_2O_7Na$, found m/z 567.1105.

Example 13: (*E*)-3',5'-Di-*O*-acetyl-5-(1-chloro-2-iodovinyl)-2'-deoxyuridine (10a)

91% yield; mp 81-83 °C; $[\alpha]_D^{20}$ -14 (c 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.28 (br s, 1H, NH), 7.75 (s, 1H, H-6), 6.91 (s, 1H, =CHI), 6.32 (m, 1H, H-1'), 5.24 (m, 1H, H-3'), 4.50-4.30 (m, 3H, H-4',5'), 2.75 (m, 1H, H-2'a), 2.18 (m, 1H, H-2'b), 2.13 (s, 2 x 3H, 2 x OAc). HRMS m/z 522.6592 calculated for $C_{15}H_{16}ClIN_2O_7Na$, found m/z 522.6597.

Example 14: (*E*)-2',3',5'-Tri-*O*-acetyl-5-(1-chloro-2-iodovinyl)-uridine (10b)

97% yield; mp 85-87 °C; $[\alpha]_D^{20}$ -27 (c 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.43 (br s, 1H, NH), 7.68 (s, 1H, H-6), 6.92 (s, 1H, =CHI), 6.15 (br s, 1H, H-1'), 5.36 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.17 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.12 (s, 3H, OAc). HRMS m/z 580.6962 calculated for $C_{17}H_{18}ClIN_2O_9Na$, found m/z 580.6958.

Example 15: (*E*)-2',5'-Di-*O*-acetyl-5-(1-chloro-2-iodovinyl)-3'-deoxyuridine (10c)

83% yield; mp 87-89 °C; $[\alpha]_D^{20}$ -13 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.75 (br s, 1H, NH), 7.74 (s, 1H, H-6), 6.90 (s, 1H, =CHI), 5.91 (d, J = 1.7 Hz, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.43 (dd, J = 12.5, 2.8 Hz, 1H, H-5'a), 4.33 (dd, J = 12.5, 4.1 Hz, 1H, H-5'b), 2.35-1.95 (m, 2H, H-3'), 2.14 (s, 2 x 3H, 2 x OAc). HRMS m/z 522.6592 calculated for $C_{15}H_{16}ClIN_2O_7Na$, found m/z 522.6593.

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Example 16: **3',5'-Di-*O*-acetyl-5-(1,2-dibromovinyl)-2'-deoxyuridine (11a)**

97% yield; mp 79-81 °C; $[\alpha]_D^{20}$ -15 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.85 (br s, 1H, NH), 7.75 (s, 1H, H-6), 6.89 (s, 1H, =CHBr), 6.33 (dd, J = 8.1, 5.6 Hz, 1H, H-1'), 5.24 (m, 1H, H-3'), 4.45-4.25 (m, 3H, H-4',5'), 2.65 (m, 1H, H-2'a), 2.18 (m, 1H, H-2'b), 2.14 (s, 2 x 3H, 2 x OAc). HRMS m/z 520.1098 calculated for $C_{16}H_{16}Br_2N_2O_7Na$, found m/z 520.1099.

Example 17: **(*E*)-2',3',5'-Tri-*O*-acetyl-5-(1,2-dibromovinyl)-uridine (11b)**

92% yield; mp 83-85 °C; $[\alpha]_D^{20}$ -43 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.38 (br s, 1H, NH), 7.66 (s, 1H, H-6), 6.90 (s, 1H, =CHBr), 6.12 (d, J = 4.8 Hz, 1H, H-1'), 5.36 (m, 2H, H-2',3'), 4.38 (m, 3H, H-4',5'), 2.17 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.12 (s, 3H, OAc). HRMS m/z 578.1468 calculated for $C_{17}H_{18}Br_2N_2O_9Na$, found m/z 578.1473.

Example 18: **2',5'-Di-*O*-acetyl-5-(1,2-dibromovinyl)-3'-deoxyuridine (11c)**

82% yield; mp 78-80 °C; $[\alpha]_D^{20}$ -16 (c 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.61 (br s, 1H, NH), 7.72 (s, 1H, H-6), 6.88 (s, 1H, =CHI), 5.88 (d, J = 1.5 Hz, 1H, H-1'), 5.38 (m, 1H, H-4'), 4.58 (m, 1H, H-2'), 4.43 (dd, J = 12.5, 2.8 Hz, 1H, H-5'a), 4.33 (dd, J = 12.5, 4.1 Hz, 1H, H-5'b), 2.35-1.95 (m, 2H, H-3'), 2.15 (s, 3H, OAc), 2.14 (s, 3H, OAc). HRMS m/z 520.1098 calculated for $C_{15}H_{16}Br_2N_2O_7Na$, found m/z 520.1103.

General procedure for deacetylation

Acetylated nucleoside analogue **6-11a-c** (1 mmol) is dissolved in 10 mL pyridine and 5 mL EtOH. The reaction mixture is cooled to -10°C and 5 mL of a 1M NaOH (sodium hydroxide) aqueous solution is added. The resulting solution is stirred at this temperature until completion (typically 1-4 h, checked by TLC). The reaction mixture is neutralized with Dowex then filtered through a fritted glass funnel. Solvents are evaporated *in vacuo* and the oily residue is submitted to a flash column chromatography using an appropriate eluent (typically hexanes/AcOEt 25/75 then AcOEt then MeOH/AcOEt 1%) to yield pure compounds **12-17a-c** (Examples 19-36).

Example 19: **5-(2-Iodoethynyl)-2'-deoxyuridine (12a)**

68% yield; mp 135-137 °C; $[\alpha]_D^{20}$ +14 (c 0.8, MeOH); ^1H NMR (CD_3OD) δ 8.32 (s, 1H, H-6), 6.22 (t, J = 6.6 Hz, 1H, H-1'), 4.41 (m, 1H, H-3'), 3.95 (m, 1H, H-4'), 3.83 (dd, J = 12.1, 3.0 Hz, 1H, H-5'a), 3.73 (dd, J = 12.1, 3.4 Hz, 1H, H-5'b), 2.40-2.12 (m, 2H, H-2'). HRMS m/z 402.1229 calculated for $C_{11}H_{11}IN_2O_5Na$, found m/z 402.1231.

Example 20: **5-(2-Iodoethynyl)-uridine (12b)**

70% yield as an oil; $[\alpha]_D^{20}$ -12 (c 0.2, MeOH); ^{1}H NMR (DMSO-*d6*) δ 11.65 (br s, 1H, NH), 8.29 (s, 1H, H-6), 5.72 (m, 1H, H-1'), 5.05-5.12 (3 x br s, 3 x OH), 4.05-3.95 (m, 2H, H-2',3'), 3.85 (m, 1H, H-4'), 3.70-355 (m, 2H, H-5'). HRMS m/z 418.1223 calculated for $C_{11}H_{11}IN_2O_6Na$, found m/z 418.1219.

Example 21: 5-(2-Iodoethynyl)-3'-deoxyuridine (12c)

66% yield as an oil; $[\alpha]_D^{20}$ +6 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 11.65 (s, 1H, NH), 8.48 (s, 1H, H-6), 5.59 (s, 1H, H-1'), 5.54 (d, J = 4.1 Hz, 1H, OH), 5.23 (t, J = 5.1 Hz, 1H, OH), 4.32 (m, 1H, H-4'), 4.21 (m, 1H, H-2'), 3.75 (m, 1H, H-5'a), 3.52 (m, 1H, H-5'b), 1.98 (m, 1H, H-3'a), 1.76 (m, 1H, H-3'b). HRMS m/z 402.1229 calculated for $C_{11}H_{11}IN_2O_5Na$, found m/z 402.1233.

Example 22: 5-(2-Bromoethynyl)-2'-deoxyuridine (13a)

80% yield as an oil; $[\alpha]_D^{20}$ +3 (c 0.3, MeOH); ^{1}H NMR (CD_3OD) δ 8.30 (s, 1H, H-6), 6.05 (t, J = 6.3 Hz, 1H, H-1'), 4.21 (m, 1H, H-3'), 3.78 (m, 1H, H-4'), 3.65-3.50 (m, 2H, H-5'), 2.15 (dd, J = 5.6, 5.0 Hz, 2H, H-2'). HRMS m/z 355.1225 calculated for $C_{11}H_{11}BrN_2O_5Na$, found m/z 355.1227.

Example 23: 5-(2-bromoethynyl)-uridine (13b)

74% yield as an oil; $[\alpha]_D^{20}$ -23 (c 0.5, MeOH); ^{1}H NMR (DMSO-*d6*) δ 11.69 (br s, 1H, NH), 8.39 (s, 1H, H-6), 5.73 (d, J = 4.7 Hz, 1H, H-1'), 5.41 (d, J = 5.3 Hz, OH), 5.24 (t, J = 4.7 Hz, OH), 5.08 (d, J = 5.3 Hz, OH), 4.10-3.91 (m, 2H, H-2',3'), 3.85 (m, 1H, H-4'), 3.75-350 (m, 2H, H-5'). HRMS m/z 371.1219 calculated for $C_{11}H_{11}BrN_2O_6Na$, found m/z 371.1224.

Example 24: 5-(2-Bromoethynyl)-3'-deoxyuridine (13c)

72% yield as an oil; $[\alpha]_D^{20}$ -29 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 11.63 (s, 1H, NH), 8.53 (s, 1H, H-6), 5.59 (s, 1H, H-1'), 5.56 (d, J = 4.1 Hz, 1H, OH), 5.26 (t, J = 5.1 Hz, 1H, OH), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.81 (m, 1H, H-5'a), 3.61 (m, 1H, H-5'b), 1.95 (m, 1H, H-3'a), 1.72 (m, 1H, H-3'b). HRMS m/z 355.1225 calculated for $C_{11}H_{11}BrN_2O_5Na$, found m/z 355.1223.

Example 25: (*E*)-5-(1,2-Diiodovinyl)-2'-deoxyuridine (14a)

72% yield; mp 103-105 °C; $[\alpha]_D^{20}$ +28 (c 0.3, MeOH); ^{1}H NMR (CD_3OD) δ 8.27 (s, 1H, H-6), 7.52 (s, 1H, =CHI), 6.28 (t, J = 6.3 Hz, 1H, H-1'), 4.43 (m, 1H, H-3'), 3.97 (m, 1H, H-4'), 3.83 (dd, J = 11.9, 3.2 Hz, 1H, H-5'a), 3.73 (m, J = 11.9, 3.4 Hz, 1H, H-5'b), 2.43-2.12 (m, 2H, H-2'). HRMS m/z 530.0353 calculated for $C_{11}H_{12}I_2N_2O_5Na$, found m/z 530.0558.

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Example 26: **(*E*)-5-(1,2-Diiodovinyl)-uridine (14b)**

82% yield; mp 107-109 °C; $[\alpha]_D^{20}$ +5 (c 1.0, MeOH); ^{1}H NMR (DMSO-*d6*) δ 11.65 (br s, 1H, NH), 8.05 (s, 1H, H-6), 7.05 (s, IH, =CHI), 5.80 (d, *J* = 4.7 Hz, 1H, H-1'), 5.50-5.10 (3 x br s, 3 x OH), 4.12-3.95 (m, 2H, H-2',3'), 3.87 (m, 1H, H-4'), 3.75-355 (m, 2H, H-5'). HRMS m/z 546.0347 calculated for $C_{11}H_{12}I_2N_2O_6Na$, found m/z 546.0351.

Example 27: **(*E*)-5-(1,2-Diiodovinyl)-3'-deoxyuridine (14c)**

76% yield as an oil; $[\alpha]_D^{20}$ +1.0 (c 0.8, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.21 (s, 1H, H-6), 7.55 (s, 1H, =CHI), 5.61 (s, 1H, H-1'), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.81 (m, 1H, H-5'a), 3.52 (m, 1H, H-5'b), 1.97 (m, 1H, H-3'a), 1.74 (m, 1H, H-3'b). HRMS m/z 530.0553 calculated for $C_{11}H_{12}I_2N_2O_5Na$, found m/z 530.0554.

Example 28: **(*E*)-5-(1-Bromo-2-iodovinyl)-2'-deoxyuridine (15a)**

78% yield as an oil; $[\alpha]_D^{20}$ +26 (c 2.0, MeOH); ^{1}H NMR (CD_3OD) δ 8.35 (s, 1H, H-6), 7.39 (s, 1H, =CHI), 6.25 (t, *J* = 6.5 Hz, 1H, H-1'), 4.45 (m, 1H, H-3'), 3.94 (m, 1H, H-4'), 3.86 (dd, *J* = 11.9, 3.2 Hz, 1H, H-5'a), 3.72 (dd, *J* = 11.9, 3.4 Hz, 1H, H-5'b), 2.45-2.15 (m, 2H, H-2'). HRMS m/z 483.0349 calculated for $C_{11}H_{12}BrIN_2O_5Na$, found m/z 483.0352.

Example 29: **(*E*)-5-(1-Bromo-2-iodovinyl)-uridine (15b)**

76% yield as an oil; $[\alpha]_D^{20}$ -1 (c 0.3, MeOH); ^{1}H NMR (D_2O) δ 8.27 (s, 1H, H-6), 7.45 (s, IH, =CHI), 5.79 (d, *J* = 4.7 Hz, 1H, H-1'), 4.15-3.92 (m, 2H, H-2',3'), 3.88 (m, 1H, H-4'), 3.67 (dd, *J* = 11.8, 2.5 Hz, 1H, H-5'a), 3.56 (dd, 1H, H-5'b). HRMS m/z 499.0343 calculated for $C_{11}H_{12}BrIN_2O_6Na$, found m/z 499.0348.

Example 30: **(*E*)-5-(1-Bromo-2-iodovinyl)-3'-deoxyuridine (15c)**

68% yield as an oil; $[\alpha]_D^{20}$ +3 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.35 (s, 1H, H-6), 7.39 (s, 1H, =CHI), 5.61 (d, *J* = 1.3 Hz, 1H, H-1'), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.76 (dd, *J* = 12.2, 2.4 Hz, 1H, H-5'a), 3.52 (dd, J = 12.2, 2.8 Hz, 1H, H-5'b), 1.97 (m, 1H, H-3'a), 1.75 (m, 1H, H-3'b). HRMS m/z 483.0349 calculated for $C_{11}H_{12}BrIN_2O_5Na$, found m/z 483.0344.

Example 31: **(*E*)-5-(1-Chloro-2-iodovinyl)-2'-deoxyuridine (16a)**

71% yield; mp 109-111 °C; $[\alpha]_D^{20}$ +34 (c 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 8.38 (s, 1H, H-6), 7.06 (s, 1H, =CHI), 6.30 (t, *J* = 6.5 Hz, 1H, H-1'), 4.43 (ddd, *J* = 6.5, 3.8, 3.6 Hz, 1H, H-3'), 3.96 (ddd, *J* = 3.6, 3.4, 3.0 Hz, 1H, H-4'), 3.83 (dd, *J* = 11.9, 3.1 Hz, 1H, H-5'a), 3.73 (dd, *J* = 11.9, 3.4 Hz, 1H, H-5'b), 2.45-2.10 (m, 2H, H-2'). HRMS m/z 438.5839 calculated for $C_{11}H_{12}ClIN_2O_5Na$, found m/z 438.5843.

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Example 32: **(*E*)-5-(1-Chloro-2-iodovinyl)-uridine (16b)**

78% yield; mp 109-111 °C; $[\alpha]_D^{20}$ +5 (c 0.4, MeOH); ^{1}H NMR (D_2O) δ 8.45 (s, 1H, H-6), 7.05 (s, IH, =CHI), 5.89 (br s, 1H, H-1'), 4.30 (br s, 2H, H-2',3'), 4.10 (m, 1H, H-4'), 3.85 (dd, J = 11.5, 2.2 Hz, 1H, H-5'a), 3.75 (dd, 1H, H-5'b). HRMS m/z 454.5833 calculated for $C_{11}H_{12}ICIN_2O_6Na$, found m/z 545.5835.

Example 33: **(*E*)-5-(1-Chloro-2-iodovinyl)-3'-deoxyuridine (16c)**

70% yield as an oil; $[\alpha]_D^{20}$ +2 (c 2.0, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.38 (s, 1H, H-6), 7.18 (s, 1H, =CHI), 5.65 (d, J = 1.2 Hz, 1H, H-1'), 4.32 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.76 (dd, J = 12.3, 2.6 Hz, 1H, H-5'a), 3.52 (dd, J = 12.3, 2.8 Hz, 1H, H-5'b), 2.01 (m, 1H, H-3'a), 1.75 (m, 1H, H-3'b). HRMS m/z 438.5839 calculated for $C_{11}H_{12}ClIN_2O_5Na$, found m/z 438.5837.

Example 34: **(*E*)-5-(1,2-Dibromovinyl)-2'-deoxyuridine (17a)**

85% yield as an oil; $[\alpha]_D^{20}$ +26 (c 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 8.39 (s, 1H, H-6), 7.06 (s, 1H, =CHBr), 6.28 (t, J = 6.5 Hz, 1H, H-1'), 4.41 (m, 1H, H-3'), 3.95 (m, 1H, H-4'), 3.82 (dd, J = 11.9, 2.9 Hz, 1H, H-5'a), 3.73 (dd, J = 11.9, 3.4 Hz, 1H, H-5'b), 2.45-2.10 (m, 2H, H-2'). HRMS m/z 436.0345 calculated for $C_{11}H_{12}Br_2N_2O_5Na$, found m/z 436.0348.

Example 35: **(*E*)-5-(1,2-Dibromovinyl)-uridine (17b)**

72% yield as an oil; $[\alpha]_D^{20}$ -14 (c 0.5, MeOH); ^{1}H NMR (D_2O) δ 8.45 (s, 1H, H-6), 7.07 (s, 1H, =CHBr), 5.93 (d, J = 5.2 Hz, 1H, H-1'), 4.18 (m, 2H, H-2',3'), 4.05 (m, 1H, H-4'), 3.88 (dd, J = 12.5, 2.5 Hz, 1H, H-5'a), 3.74 (dd, J = 12.5, 2.8 Hz, 1H, H-5'b). HRMS m/z 452.0339 calculated for $C_{11}H_{12}Br_2N_2O_6Na$, found m/z 452.0342.

Example 36: **(*E*)-5-(1,2-Dibromovinyl)-3'-deoxyuridine (17c)**

74% yield as an oil; $[\alpha]_D^{20}$ +5 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.42 (s, 1H, H-6), 7.25 (s, 1H, =CHI), 5.64 (br s, 1H, H-1'), 4.35 (m, 1H, H-4'), 4.25 (m, 1H, H-2'), 3.78 (m, H-5'a), 3.54 (m, H-5'b), 1.95 (m, 1H, H-3'a), 1.75 (m, 1H, H-3'b). HRMS m/z 436.0345 calculated for $C_{11}H_{12}Br_2N_2O_5Na$, found m/z 436.0340.

Preparation of the key intermediate 18 (for both 3'-F and 3'-N_3 series)

1-(4-Hydroxy-5-trityloxymethyl-tetrahydro-furan-2-yl)-1H-pyrimidine-2,4-dione (32)

A solution of 2'-deoxyuridine (10.0 g, 43.9 mmol) and para-anisylchlorodiphenylmethane (16.3 g, 52.6 mmol) in dry pyridine (235 mL) is refluxed for 2 hours. After cooling at room

temperature (rt), pyridine is evaporated under reduced pressure, then dichloromethane (400mL) is added and the solution is washed with water (50 mL x3), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5 to EtOAc/MeOH: 9/1) to give the pure protected nucleoside **32** (21.9 g, 99 %) as a white solid. The physico-chemical data of the compound are fully related with those previously published.

1-(4-Hydroxy-5-trityloxymethyltetrahydrofuran-2-yl)-5-iodo-1*H*-pyrimidine-2,4-dione(33)

A solution of **32** (21.9 g, 43.8 mmol), I_2 (17.0 g, 66.9 mmol), CAN (17.7 g, 32.3 mmol), $NaHCO_3$ (1.0 g) in dry acetonitrile (480 mL) is refluxed for 4 days. After cooling at rt, a solution of saturated Na_2SO_3 (800 mL) and EtOAc (200 mL) are added: aqueous layer is extracted with EtOAc (300 mL x2), then organic layer is washed with saturated Na_2SO_3 (300mL), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 6/4 to EtOAc) to give the pure iodinated nucleoside **33** (12.8 g, 57 %) as a white solid. The physico-chemical data of the compound are fully related with those previously published.

1-(4-Hydroxy-5-trityloxymethyl-tetrahydro-furan-2-yl)-5-trimethylsilanylethynyl-1*H*-pyrimidine-2,4-dione (34)

33 (5.00 g, 8.0mmol) is dissolved in a mixture of dry DMF (62.5 mL), dry Et_3N (3.3 mL, 24.0mmol), and trimethylsilylacetylene (3.4 mL, 24.0 mmol). CuI (300.0 mg, 1.6 mmol) and $PdCl_2(PPh_3)_2$ (563 mg) are then added and the reaction mixture is stirred at rt under argon for 16 hours. Solvents are evaporated under reduced pressure. The crude product is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5 to 2/8) to give **34** (4.10 g, 86 %) as a pale yellow solid. $[\alpha]_D^{20}$ +27.5 (c 0.5, $CHCl_3$); mp 104 °C; ^{1}H NMR ($CDCl_3$) δ : 2.08-2.33 (m, 1H, H-2'a), 2.42-2.64 (m, 1H, H-2'b), 3.20-3.52 (m, 2H, H-5'), 3.78 (s, 3H, OCH3), 4.05-4.25 (m, 1H, H-4'), 4.40-4.53 (m, 1H, H-3'), 6.31 (dd, J = 5.6 Hz, 8.1 Hz, 1H, H-1'), 6.78-7.55 (m, 14H, trityl), 8.05 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ : 41.5 (C-2'), 55.3 (OCH3), 63.7 (C-5'), 72.5 (C-3'), 85.9 (C-1'), 86.6 (C-4'), 87.3 (C), 94.9 (C), 99.9 (C), 100.7 (C), 113.5 (CH), 127.2 (CH), 128.2 (CH), 128.3 (C), 130.5 (CH), 135.1 (C), 142.8 (C-6), 144.0 (C), 144.1 (C), 149.5 (C=O), 158.8 (C), 161.5 (C);

5-Ethynyl-1-(4-hydroxy-5-trityloxymethyl-tetra hydro-furan-2-yl)-1*H*-pyrimidine-2,4-dione (35)

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A solution of **34** (616.3 mg, 1.03mmol), TBAF (303.4 mg, 1.16 mmol) in dry acetonitrile (24.0mL) is stirred at rt for 2 hours. Solvent is removed under reduced pressure, the crude product is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5 to 2/8) to give **35** (516.8 mg, 95 %) as a pale yellow solid. $[\alpha]_D^{20}$ +14.5 (c 1.0, $CHCl_3$); mp 110°C ; ^1H NMR ($CDCl_3$) δ : 2.22-2.40 (m, 1H, H-2'a), 2.45-2.60 (m, 1H, H-2'b), 2.90 (s, 1H, CH alkyne), 3.41 (t, J = 3.6 Hz, 2H, H-5'), 3.81 (s, 3H, OCH3), 4.15-4.20 (m, 1H, H-4'), 4.51-4.62 (m, 1H, H-3'), 6.30 (t, J = 8.2 Hz, 1H, H-1'), 6.70-7.50 (m, 14H, trityl), 8.10 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ : 41.6 (C-2'), 55.4 (OCH3), 63.7 (C-5'), 72.4 (C-3'), 74.2 (C), 82.2 (C), 85.9 (C-1'), 86.6 (C-4'), 87.5 (C), 99.4 (C), 113.5 (CH), 127.3 (CH), 128.2 (CH), 128.3 (C), 128.4 (C), 130.5 (CH), 135.1 (C), 143.8 (C-6), 143.9 (C), 144.1 (C), 149.4 (C=O), 158.9 (C), 161.7 (C);

Methanesulfonic acid 5-(5-ethynyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-2-trityloxy-methyltetrahydrofuran-3-yl ester (18)

A solution of **35** (500.0 mg, 0.95 mmol) and methanesulfonylchloride (0.73 mL, 9.50 mmol) in dry pyridine at 0°C is allowed to warm to rt and is stirred for 16 hours. After cooling at 0°C, ice, water (100 mL) and EtOAc (100 mL) are added, the aqueous layer is extracted with EtOAc (50 mL x3), the organic layers are washed with water (50 mL x3), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5) to give **18** (587.0 mg, 99 %) as an orange solid. $[\alpha]_D^{20}$ +28.5 (c 1.0, $CHCl_3$); mp 99 °C; ^1H NMR ($CDCl_3$) δ : 2.30-2.50 (m, 1H, H-2'a), 2.70-2.82 (m, 1H, H-2'b), 2.91 (s, 1H, CH alkyne), 3.02 (s, 3H, SCH_3), 3.33-3.57 (m, 2H, H-5'), 3.80 (s, 3H, OCH_3), 4.35 (se, 1H, H-4'), 5.31 (se, 1H, H-3'), 6.29 (t, J = 8.2 Hz, 1H, H-1'), 6.75-7.50 (m, 14H, trityl), 8.07 (s, 1H, H-6), 8.58 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 38.8 (SCH_3), 39.3 (C-2'), 55.4 (OCH_3), 63.0 (C-5'), 74.0 (C-3'), 79.8 (C), 82.4 (C), 84.5 (C-1'), 85.4 (C-4'), 88.0 (C), 99.9 (C), 113.6 (CH), 127.5 (CH), 128.3 (CH), 128.3 (CH), 129.2 (C), 130.5 (CH), 134.6 (C), 143.2 (C-6), 143.6 (C), 143.7 (C), 149.2 (C=O), 159.0 (C), 161.2 (C);

Example 37 : 5-(1,2-Di-iodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2.4-dione (25a)

Step a):5-Ethynyl-1-(4-hydroxy-5-trityloxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (**19**)

A solution of **18** (50.0 mg, 0.08 mmol) in dioxanne (2.0 mL) and aqueous 1M NaOH (168 µL, 0.16 mmol) is refluxed for 2 hours. After cooling at rt, solvents are removed in vaccuo and the crude product is submitted to a flash silica gel column chromatography (eluent:

hexanes/EtOAc: 5/5 to EtOAc) to give **19** (41.0 mg, 93 %) as a pale yellow solid. $[\alpha]_D^{20}$ –13.0 (c1.0, $CHCl_3$); mp 124 °C ; ^1H NMR ($CDCl_3$) δ: 2.08-2.25 (m, 1H, H-2'a), 2.47-2.66 (m, 1H, H-2'b), 3.07 (s, 1H, CH alkyne), 3.43-3.72 (m, 2H, H-5'), 3.79 (s, 3H, OCH_3), 4.00-4.12 (m, 1H, H-4'), 4.38-4.50 (m, 1H, H-3'), 6.15 (t, J = 6.1 Hz, 1H, H-1'), 6.80-7.55 (m, 14H, trityl), 8.15 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 41.1 (C-2'), 55.4 (OCH_3), 61.9 (C-5'), 70.9 (C-3'), 75.0 (C), 81.7 (CH alkyne), 83.4 (C-1'), 85.9 (C-4'), 87.5 (C), 98.5 (C), 113.6 (CH), 127.4 (CH), 128.2 (CH), 130.4 (CH), 134.9 (C), 143.8 (C), 143.8 (C), 145.3 (C-6), 149.5 (C=O), 159.0 (C), 161.8 (C);

Step b): 5-Ethynyl-1-(4-fluoro-5-trityloxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (**20**)

To a solution of the product Step (a) (1.26 g, 2.4 mmol) in dry dichloromethane (77.0 mL) at 0°C is added dropwise diethylaminosulfur trifluoride (0.6mL, 4.8mmol), and the reaction mixture is stirred for 15 minutes. Then a saturated $NaHCO_3$ solution (50.0 mL) is added, the aqueous layer is extracted with CH_2Cl_2 (50 mL x3), the organic layers are washed with water (50 mL), dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 5/5) to give **20** (805.0 mg, 64 %) as a pale yellow solid. $[\alpha]_D^{20}$ +12.0 (c 1.0, $CHCl_3$); mp 54 °C; ^1H NMR ($CDCl_3$) δ: 2.12-2.46 (m, 1H, H-2'a), 2.68-2.90 (m, 1H, H-2'b), 2.88 (s, 1H, CH alkyne), 3.35-3.48 (m, 2H, H-5'), 3.80 (s, 3H, OCH_3), 4.37 (d, J = 27.4 Hz, 1H, H-4'), 5.28 (dd, J = 4.6 Hz, 53.6 Hz, 1H, H-3'), 6.34 (dd, J = 5.3 Hz, 9.0 Hz, 1H, H-1'), 6.80-7.50 (m, 14H, trityl), 8.10 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 39.7 (d, J = 84.2 Hz, C-2'), 55.4 (OCH_3), 63.4 (d, J = 40.9 Hz, C-5'), 82.2 (CH alkyne), 84.8 (d, J = 101.1 Hz, C-4'), 85.7 (C-1'), 87.8 (C), 94.5 (d, J = 710.0 Hz, C-3'), 99.7 (C), 113.6 (CH), 127.4 (CH), 128.3 (CH), 128.4 (CH), 130.5 (CH), 134.6 (C), 143.4 (C-6), 143.6 (C), 143.7 (C), 149.2 (C=O), 159.0 (C x2);

General procedure for di-halogenation of 5- ethynyl compound

5-ethynyl nucleoside of example 37, Step b) (0.5 mmol) is dissolved in dry acetonitrile (5.0 mL) and the reaction mixture is cooled to an ice bath. A solution of the halogenating reagent (i.e. I_2, Ibr or ICl; 0.6 mmol) in dry CH_3CN (1.0 mL) is added dropwise at 0°C and the reaction mixture is stirred until completion (typically 15 min.-2 hours, checked by TLC). The reaction mixture is quenched at 0°C by a saturated Na_2SO_3 solution (2 mL) then extracted with EtOAc (10 mL x 3). The organic layer is washed with water (5 mL x2) and brine (10 mL), then dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure

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to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 8/2 to 3/7) to give the desired di-halogenated compound.

Step c): 5-(1,2-Diiodovinyl)-1-(4-fluoro-5-trityloxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (**24a**)

Prepared from compound **20** of step b) using I_2 with the typical procedure described before to give **24a** (32 %) as an orange solid. $[\alpha]_D^{20}$ +4.5 (c 1.0, $CHCl_3$); mp 58 °C; ^1H NMR ($CDCl_3$) δ: 2.05-2.35 (m, 1H, H-2'a), 2.67-2.86 (m, 1H, H-2'b), 3.43 (d, J = 3.8 Hz, 2H, H-5'), 3.81 (s, 3H, OCH_3), 4.34 (td, J = 3.5 Hz, 27.0 Hz, 1H, H-4'), 5.23 (dd, J = 4.7 Hz, 53.7 Hz, 1H, H-3'), 6.33 (dd, J = 5.0 Hz, 9.1 Hz, 1H, H-1'), 6.75-7.50 (m, 15H, CH alkene, trityl), 7.63 (s, 1H, H-6), 9.00 (se, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 39.4 (d, J = 84.2 Hz, C-2'), 55.5 (OCH_3), 63.1 (d, J = 38.5 Hz, C-5'), 84.5 (d, J = 101.0 Hz, C-4'), 85.3 (C), 85.5 (CH alkene), 87.5 (C), 87.7 (C-1'), 94.1 (d, J = 710.0 Hz, C-3'), 113.6 (CH), 118.1 (C), 127.4 (CH), 128.3 (CH), 128.4 (CH), 130.5 (CH), 134.8 (C), 139.2 (C-6), 143.7 (C), 143.8 (C), 149.5 (C=O), 158.9 (C), 159.0 (C);

Step d): 5-(1,2-Diiodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (**25a**)

Prepared from compound **24a**, using the typical procedure described before to give **25a** (51%) as a yellow solid. $[\alpha]_D^{20}$ +16.0 (c 1.0, CH_3OH); mp 112 °C; UV (MeOH) λ_{max} 232 nm, 274 nm; ^1H NMR (CD_3OD) δ : 2.13-2.47 (m, 1H, H-2'a), 2.50-2.77 (m, 1H, H-2'b), 3.80 (d, J = 2.8 Hz, 2H, H-5'), 4.32 (td, J = 2.9 Hz, 27.0 Hz, 1H, H-4'), 5.30 (dd, J = 4.6 Hz, 53.7 Hz, 1H, H-3'), 6.36 (dd, J = 5.6 Hz, 9.0 Hz, 1H, H-1'), 7.53 (s, 1H, CH alkene), 8.28 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 40.3 (d, J = 81.9 Hz, C-2'), 62.7 (d, J = 43.3 Hz, C-5'), 87.0 (C-1'), 87.3 (d, J = 96.3 Hz, C-4'), 87.3 (C), 88.1 (CH alkene), 96.0 (d, J = 698.0 Hz, C-3'), 119.2 (C), 142.2 (C-6), 151.5 (C=O), 161.8 (C=O);

Compounds of examples 38 and 39 are obtained in a similar way starting from compounds **24b** and **24c** respectively.

Example 38 : 5-(1-Bromo-2-Iodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (25b).

Prepared from compound **24b**, using the typical procedure described before to give the title compound (52 %) as a pale yellow solid. $[\alpha]_D^{20}$ +13.0 (c 0.6, CH_3OH); mp 107 °C; UV (MeOH) λ_{max} 296 nm; ^1H NMR (CD_3OD) δ: 2.14-2.47 (m, 1H, H-2'a), 2.52-2.78 (m, 1H, H-2'b), 3.80 (d, J = 3.0 Hz, 2H, H-5'), 4.31 (td, J = 2.9 Hz, 27.0 Hz, 1H, H-4'), 5.30 (dd, J = 4.7 Hz, 53.7 Hz, 1H, H-3'), 6.36 (dd, J = 5.6 Hz, 9.0 Hz, 1H, H-1'), 7.30 (s, 1H, CH alkene), 8.36 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 40.3 (d,C-2'), 62.7 (d, C-5'), 83.2 (CH alkene), 87.0 (C-1'),

87.3 (d, C-4'), 87.3 (C), 96.0 (d, C-3'), 115.5 (C), 116.0 (C), 143.9 (C-6), 151.5 (C=O), 161.8 (C=O);

Example 39 :5-(1-Chloro-2-iodovinyl)-1-(4-fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (25c)

Prepared from compound **24c**, using the typical procedure described before to give the title compound (76 %) as an orange solid. $[\alpha]_D^{20}$ +17.0 (c 0.7, CH_3OH); mp 87 °C; UV (MeOH) λ_{max} 274 nm; ^1H NMR (CD_3OD) δ : 2.13-2.48 (m, 1H, H-2'a), 2.52-2.75 (m, 1H, H-2'b), 3.80 (d, J = 2.8 Hz, 2H, H-5'), 4.30 (td, J = 2.8 Hz, 26.8 Hz, 1H, H-4'), 5.30 (dd, J = 4.6 Hz, 53.5 Hz, 1H, H-3'), 6.37 (dd, J = 5.7 Hz, 8.8 Hz, 1H, H-1'), 7.06 (s, 1H, CH alkene), 8.38 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 40.2 (d, J = 84.2 Hz, C-2'), 62.7 (d, J = 43.3 Hz, C-5'), 81.1 (CH alkene), 87.0 (C-1'), 87.4 (d, J = 93.9 Hz, C-4'), 96.2 (d, J = 698.0 Hz, C-3'), 114.5 (C) , 128.9 (C), 146.0 (C-6), 151.2 (C=O), 164.2 (C=O);

Example 40 : 1-(4-Fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (22)

Step a): 1-(4-Fluoro-5-trityloxymethyl-tetrahydro-furan-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (**21**)

5-ethynyl nucleoside **20** (0.5 mmol) was dissolved in dry acetonitrile (5.0 mL) and the reaction mixture is cooled to an ice bath. A solution of the halogenating reagent (i.e. IDCP; 0.7 mmol) and $Ag(coll)_2ClO_4$ (11.0mg) are added and the reaction mixture is stirred in the dark at rt (typically 2 h-20 h, checked by TLC). The reaction mixture is quenched at 0°C by a saturated Na_2SO_3 solution (2 mL) then extracted with EtOAc (10 mL x4). The organic layer is washed with water (10 mL), a 1M HCl solution (5 mL x3), water (5 mL x2), and brine (10 mL), then dried over $MgSO_4$, filtered through a fritted glass funnel and concentrated under reduced pressure to afford the crude product, which is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 8/2 to 3/7) to give **21** (26 %) as yellow solid. $[\alpha]_D^{20}$ +122.0 (c 1.0, $CHCl_3$); mp 73 °C; ^1H NMR ($CDCl_3$) δ: 2.15-2.48 (m, 1H, H-2'a), 2.68-2.93 (m, 1H, H-2'b), 3.30-3.56 (m, 2H, H-5'), 3.81 (s, 3H, OCH_3), 4.38 (d, J = 27.0 Hz, 1H, H-4'), 5.32 (dd, J = 4.4 Hz, 53.4 Hz, 1H, H-3'), 6.33 (dd, J = 5.3 Hz, 9.1 Hz, 1H, H-1'), 6.75-7.50 (m, 14H, trityl), 8.01 (s, 1H, H-6), 9.20 (se, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 12.1 (CCl), 39.8 (d, J = 86.6 Hz, C-2'), 55.4 (OCH_3), 63.4 (d, J = 40.9 Hz, C-5'), 84.2 (C), 84.9 (d, J = 101.1 Hz, C-4'), 86.0 (C-1'), 87.8 (C), 94.5 (d, J = 707.6 Hz, C-3'), 101.0 (C), 113.6 (CH), 127.5 (CH), 127.9 (C), 128.1 (CH), 128.2 (CH), 130.4 (CH), 134.6 (C), 143.5 (C), 143.7 (C-6), 143.8 (C), 149.2 (C=O), 159.0 (C), 161.6 (C);

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Step b): 1-(4-Fluoro-5-hydroxymethyltetrahydrofuran-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (**22**)

A solution of the protected nucleoside **21** (0.3 mmol) in acetic acid 80 % (30 mL) is stirred until completion (checked by TLC, typically 18 hours). After evaporation of the solvent, the crude product was submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 2/8) to give **22** (47 %) as a yellow solid. $[\alpha]_D^{20}$ –1.5 (c 1.0, CH_3OH); mp 140°C; UV (MeOH) λ_{max} 233 nm, 298 nm; ^1H NMR (CD_3OD) δ: 2.11-2.45 (m, 1H, H-2'a), 2.46-2.75 (m, 1H, H-2'b), 3.79 (d, J = 3.2 Hz, 2H, H-5'), 4.29 (td, J = 2.9 Hz, 27.0 Hz, 1H, H-4'), 5.27 (dd, J = 4.9 Hz, 53.9 Hz, 1H, H-3'), 6.28 (dd, J = 5.5 Hz, 8.9 Hz, 1H, H-1'), 8.30 (s, 1H, H-6); ^{13}C NMR (CD_3OD) δ: 15.8 (C<u>C</u>I), 39.8 (d, J = 81.8 Hz, C-2'), 62.5 (d, J = 43.3 Hz, C-5'), 85.2 (C), 87.0 (C-1'), 87.3 (d, J = 96.3 Hz, C-4'), 96.0 (d, J = 700.4 Hz, C-3'), 101.5 (C) , 146.0 (C-6), 151.1 (C=O), 164.4 (C=O).

<u>Example 41:</u> 1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1,2-diiodovinyl)-1*H*-pyrimidine-2,4-dione (31a)

Step a): 1-(4-Azido-5-trityloxymethyltetrahydrofuran-2-yl)-5-ethynyl-1*H*-pyrimidine-2,4-dione (**26**)

A solution of **18** (100 mg, 0.16 mmol) and NaN_3 (35 mg, 0.54 mmol) in DMF (5 mL) is refluxed overnight. After evaporation of volatiles, the crude product is submitted to a flash silica gel column chromatography (eluent: hexanes/EtOAc: 2/8) to give **26** (61.0 mg, 70%) as a pale yellow solid. $[\alpha]_D^{20}$ +13 (c 0.8, CH_3OH); mp 110°C; ^1H NMR ($CDCl_3$) δ : 2.35-2.46 (m, 1H, H-2'a), 2.52-2.62 (m, 1H, H-2'b), 2.89 (s, 1H, CH alkyne), 3.37-3.52 (m, 2H, H-5'), 3.82 (s, 3H, O<u>C</u>H_3), 4.00-4.04 (m, 1H, H-4'), 4.28-4.34 (m, 1H, H-3'), 6.15 (t, J = 6.1 Hz, 1H, H-1'), 6.88 (d, J = 8.9 Hz, 2H, trityl), 7.21-7.51 (m, 14H, trityl), 8.08 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 38.6 (C-2'), 55.3 (O<u>C</u>H_3), 60.4 (C-3'), 62.7 (C-5'), 82.3 (CH alkyne), 84.0 (C-4'), 85.5 (C-1'), 87.6 (C), 99.4 (C), 113.6 (CH x2), 127 .3 (CH), 128.1 (CH), 128.2 (CH), 130.4 (CH), 134.7 (C), 143.7 (C), 149.2 (C), 158.9 (C), 161.6 (C);

Step b):1-(4-Azido-5-trityloxymethyl-tetrahydro-furan-2-yl)-5-(1,2-diiodo-vinyl)-1*H*-pyrimidine-2,4-dione (**30a**)

Prepared from compound of Step a), using I_2 with the typical procedure described before for the preparation of **24a** to give **30a** (52 %) as a pale yellow solid. $[\alpha]_D^{20}$ +16 (c 1.0, CH_3OH); mp 139°C; ^1H NMR ($CDCl_3$) δ: 2.23-2.34 (m, 1H, H-2'a), 2.51-2.61 (m, 1H, H-2'b); 3.36-3.49 (m, 2H, H-5'), 3.81 (s, 3H, O<u>C</u>H_3), 3.98-4.05 (m, 1H, H-4'), 4.16-4.26 (m, 1H, H-3'), 6.16 (t, J = 6.6 Hz, 1H, H-1'), 6.87 (d, J = 8.8 Hz, 2H, trityl), 7.21-7.43 (m, 13H, trityl, CH alkene), 7.58 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 38.1 (C-2'), 55.2 (O<u>C</u>H_3), 60.4 (C-3'), 62.8 (C-5'), 83.5 (C-

4'), 85.1 (C-1'), 87.1 (C), 87.2 (CH alkene), 113.3 (CH), 117.6 (C), 127.1 (CH), 128.0 (CH), 128.1 (CH), 130.2 (CH), 135.6 (C), 139.0 (C-6), 143.5 (C), 143.6 (C), 149.1 (C=O), 158.6 (C), 158.7 (C);

Step c):1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1,2-diiodo-vinyl)-1*H*-pyrimidine-2,4-dione (**31a**)

Prepared from compound **30a** using the typical procedure described before for the preparation of **24a** to give **31a** (78%) as a pale yellow gum. $[\alpha]_D^{20}$ +17 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 225 nm, 284 nm; ^1H NMR (DMSO-d_6) δ : 2.34-2.43 (m, 2H, H-2'), 3.56-3.71 (m, 2H, H-5'), 3.85-3.90 (m, 1H, H-4'), 4.35-4.41 (m, 1H, H-3'), 5.26 (t, J = 4.9 Hz, 1H, OH), 6.09 (t, J = 6.3 Hz, 1H, H-1'), 7.61 (s, 1H, CH alkene), 8.06 (s, 1H, H-6'), 11.68 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 37.5 (C-2'), 60.4 (C-3'), 61.4 (C-5'), 85.0 (C-1', C-4'), 88.9 (C-I), 90.2 (CH alkene), 117.7 (C-5), 140.5 (C-6), 150.1 (C=O), 159.9 (C=O).

Compounds of examples 42 and 43 are obtained in a similar way, starting from compounds **30b** and **30c** respectively.

Example 42: 1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1-bromo-2-iodo-vinyl)-1H-pyrimidine-2,4-dione (31b)

Prepared from compound **30b** using the typical procedure described before to give **31b** (53%) as a pale yellow gum. $[\alpha]_D^{20}$ +11 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 229 nm, 276 nm; ^1H NMR (DMSO-d_6) δ: 2.36-2.43 (m, 2H, H-2'), 3.57-3.69 (m, 2H, H-5'); 3.86-3.91 (m, 1H, H-4'), 4.35-4.42 (m, H-3'), 5.28 (brs, 1H, OH), 6.09 (t, J = 5.9 Hz, 1H, H-1'), 7.45 (s, 1H, CH alkene), 8.18 (s, 1H, H-6'), 11.7 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 37.0 (C-2'), 60.0 (C-3'), 60.7 (C-5'), 84.6 (C-1', C-4'), 85.6 (CH alkene), 113.9 (C), 114.2 (C), 141.9 (C-6), 149.6 (C=O), 159.4 (C=O);

Example 43: 1-(4-Azido-5-hydroxymethyltetrahydrofuran-2-yl)-5-(1-chloro-2-iodo-vinyl)-1*H*-pyrimidine-2,4-dione (31c)

Prepared from compound **30c** using the typical procedure described before to give **31c** (57%) as a pale yellow gum. $[\alpha]_D^{20}$ +28 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 214 nm, 273 nm; ^1H NMR (DMSO-d_6) δ: 2.33-2.44 (m, 2H, H-2'), 3.33-3.71 (m, 1H, H-5'), 3.86-3.91 (m, 1H, H-4'), 4.35-4.42 (m, 1H, H-3'), 5.28 (t, J = 4.9 Hz, 1H, OH), 6.09 (t, J = 6.2 Hz, 1H, H-1'), 7.23 (s, 1H, CH alkene), 8.22 (s, 1H, H-6), 11.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 37.7 (C-2'), 60.7 (C-3'), 61.3 (C-5'), 84.5 (CH), 85.2 (CH x2), 113.0 (C), 127.4 (C), 143.1 (C-6), 150.3 (C=O), 160.1 (C=O);

Example 44: 1-(4-Azido-5-hydroxymethyl-tetrahydro-furan-2-yl)-5-iodoethynyl-1*H*-pyrimidine-2,4-dione (28)

Prepared from compound **26** using a similar procedure as the one disclose above for Example 40, to give the title compound 60 % as a pale yellow gum, $[\alpha]_D^{20}$ +15 (c 1.0, CH_3OH); UV (MeOH) λ_{max} 236 nm, 295 nm; ^1H NMR (DMSO-d_6) δ : 2.24-2.34 (m, 1H, H-2'a), 2.39-2.46 (m, 1H, H-2'b), 3.54-3.72 (m, 2H, H-5'), 3.79-3.84 (m, 1H, H-4'), 4.34-4.41 (m, 1H, H-3'), 5.30 (t, *J* = 5.3 Hz, 1H, OH), 6.01 (t, *J* = 6.0 Hz, 1H, H-1'), 8.22 (s, 1H, H-6), 11.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ : 19.8 (C), 36.8 (C-2'), 59.2 (C-3'), 60.2 (C-5'), 84.3 (C-1', C-4'), 84.8 (C), 99.0 (C), 144.6 (C-6), 149.3 (C=O), 161.7 (C=O).

Biological evaluation

Antiviral and Cytotoxicity assays for HCV. Huh7 cells harbouring the subgenomic HCV replicon BM4-5 (J.T. Guo et al., J. Virol. 2001, 75 : 8516-8523) were used in this study. Cells were maintained in Dulbecco's modified Eagle's medium high glucose 4.5 g/l (LifeTechnlogies) supplemented with 10% fetal bovine serum, 1% L-glutamine, 1% penicillin and streptomycin, 1% L-Pyruvate and 500 µg/ml of geneticien (G418, Invitrogen). Geneticin was used to select cells permitting the HCV RNA replication. Cells were passaged every four days with a 1:4 ratio.

Cells were seeded in 6-wells plates at a density of 2.5 x 10^5 cells per well, sixteen hours before the beginning of treatment. Cells were treated with the molecules administered at different concentrations in complete medium that did not contain geneticin. The administration of each drug was renewed every day for three consecutive days. Ribarivin (ICN Pharmaceuticals), mycophenolic acid (MPA, Sigma), and interferon alpha-2b (IntronA®) were used in the same conditions as positive controls. The concentrations used for these drugs were respectively: 0; 0.5; 1; 2; 4; 8; 16; 32; 64; 128; 256 and 512 µM for ribavirin, 0; 2.5; 5; 10; 20; 40 µM for mycophenolic acid, and 0; 0.1; 1; 10; 100 and 1000 UI/mL for IFN alpha-2b. Total RNA was extracted at the end of treatment (24 hours after the last day of treatment) with the « Extract all » reagent (Eurobio), which is a mix of phenol and guanidium thiocyanate. Northern blot analysis was then performed using the NorthernMax™-Gly kit (Ambion), following manufacturer's instructions. Five micrograms of total RNA were denaturated in glyoxal buffer at 50°C for 30 minutes, separated by 1.1% agarose gel electrophoresis, and then transferred for 12 hours onto a charged nylon membrane (HybondN+, Amersham). Hybridization was carried out with three different [^{32}P]CTP-labelled riboprobes obtained by *in vitro* transcription (Riboprobe *in vitro* transcription system, Promega). Two probes were complementary to the NS5A region of the HCV genome of

negative polarity and positive polarity. A third probe was complementary to the beta-actin mRNA and obtained by *in vitro* transcription from a specific plasmid (pTRI beta actin human, reference 7424, Ambion). First, the blot was hybridized with the riboprobes directed against the negative strand of HCV RNA and beta-actin mRNA, respectively. After one night of hybridization at 68°C, the membrane was washed, then exposed to X-ray film and a phosphor screen (phosphorimager). This screen was then scanned and quantitative analysis was achieved using ImageQuant software. The amount of beta-actin mRNA was used as an internal loading control to standardize the amount of HCV RNA detected. The same membrane was subsequently hybridized with the negative sense riboprobe to determine the level of positive strand HCV RNA, suing the same approach.

For cell viability assays, cells were seeded in 96-well plates at a density of 12,500 cells per well. They were treated by the different molecules with the same concentrations and conditions than those used for the antiviral assays. Then, cell viability was measured by neutral red assay. Neutral red specifically colors lysosomes and its accumulation depends on cellular membrane integrity. The yield of neutral red incorporated in cells is proportional to the number of living cells. At the end of treatment, culture medium was removed; cells were washed by PBS, then coloured with neutral red at 0.005% for 3 hours at 37°C. Cells were then fixed 1 minute by formol calcium and lysed by atreatment with a vol/vol mixture of acetic acid and ethanol. After 15 minutes incubation, absorbance was read at 490nm.

Antiviral and cytotoxicity assays for BVDV. Noncytopathic-BVDV-free MDBK cells (European Collection of Animal Cell Cultures, Porton Down, U.K.) were kindly provided by Dr N. Zitzmann (Oxford University). Cells were propagated in DMEM F12 (Eurobio) supplemented with 10% horse serum (Life Technologies), 1% L-glutamin (Gibco), 1% penicillin ansd streptomycin (Gibco). The NADL cytopathic (CP) BVDV strain was obtained from ATCC: VR-504.

MDBK cells were seeded in microwell plates (96 wells) at a density of 1.10^5 cells per well, then infected with BVDV (strain NADL) (at dilution inducing 100% cytopathic effect three days post inoculation, *i.e* approximately 10 plaque forming units (pfu) per well at three days post infection) for one hour, at 37°C. After a wash with DMEM, infected cells were incubated for three days in the presence of absence of drug; each concentration of drug was added in 12 consecutive wells. The appearance of CPE was visually checked the third day post inoculation to evaluate the IC50 on BVDV (strain NADL), according to the different conditions of treatment. By definition, the IC50 is the concentration of drug that inhibits 50% of the CPE in comparison to cells inoculated but untreated presenting 100% of CPE.

Uninfected MDBK cells were grown in the absence or presence of varying concentrations of drug tested. After 3 days, toxicity was evaluated by neutral red coloration as described above.

	Compound #	Anti-HCV activity and cytotoxicity on Replicon System (+)-RNA				Cytotoxicity (CC_{50})		
		CC_{50}	IC_{50}	IC_{90}	SI	PBM	CEM	VERO
	IFNα-2b	> 1000	19	760	52			
	Ribavirin	110	170	> 512	< 1			
	MPA	7	40		< 1			
2'-deoxyribosyl moiety	12a	>182	57.1	> 239	> 3.2	7.5	15.8	> 100
	13a	>200	> 200	> 200	≥1	>100	> 100	> 100
	14a	76.7	> 161	> 263	< 1	14.7	19.5	19.5
	15a	43	> 100	> 100	< 1	13.3	0.13	6.6
	16a	213	79.8	> 207	2.7	3.2	14.8	1.4
	17a	> 200	< 200	> 200	≥1	>100	43.9	> 100
ribosyl moiety	12b	147.5	> 200	> 200	< 1	> 100	> 100	> 100
	13b	188.3	58	> 200	3.2	> 100	> 100	> 100
	14b	> 250	161.7	> 250	> 1.5	> 100	41.7	49.5
	15b	> 100	> 100	> 100	≤1	> 100	93.6	> 100
	16b	> 200	74.9	> 250	> 2.8	> 100	> 100	> 100
	17b	> 200	> 200	> 200	≤1	> 100	> 100	59.8
3'-deoxyribosyl moiety	12c	> 200	> 200	> 200	≤1	> 100	> 100	3.2
	13c	> 300	> 300	> 300	≤1	> 100	> 100	6.4
	14c	> 200	> 200	> 200	≤1	87.2	> 100	42.6
	15c	> 200	> 200	> 200	≤1	71.5	79.3	> 100
	16c	> 200	> 200	> 200	≤1	94.4	66.6	15.3
	17c	> 200	≥200	> 200	≤1	> 100	79.3	7.8

Table 1 : Evaluation of the antiviral activity and cells viability (obtained with neutral red test) against Hepatitis C Virus (HCV) replication using cell line harboring HCV subgenomic replicon, of the antiviral activity against HIV-1 in PBM cells and of the cytotoxicity against PBM, CEM and VERO cells *in vitro*. Results are expressed in *µM*, except for IFN which is expressed as International Units/ml. Selectivity Index (SI) is the ratio between CC_{50} and IC_{50}.

Compound #	**CC_{50} (Neutral Red)**	**EC_{50} ECP inhibition (3rd day p.i.)**	**SI**
Ribavirin	> 100	36 µM	> 2.77
12a-c, 13b, 14a-c, 15c, 16a-c	> 100	> 100	< 1

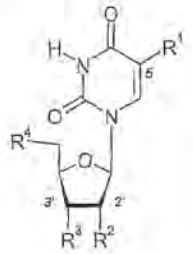
Table 2 :Neutral red testing and antiviral assay on BVDV strain NADL expressed in µM.

It should be clearly understood that the invention defined by the attached claims is not limited to the particular embodiments indicated in the above description, but encompasses the variants which depart neither from the context nor from the spirit of the present invention.

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CLAIMS

1. Use of an uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms,

for the preparation of a drug having antiviral activity against a Flaviviridae.

2. The use according to claim 1, wherein the uridine derivative of formula (I) presents the following characteristics:

- R^1 represents $-C\equiv C-X$ or -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen ;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -phosphate, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

3. The use according to claim 2, wherein R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or –C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.

4. The use according to claim 2, wherein

- R^1 represents chloroethynyl, bromoethynyl, iodoethynyl or -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine;
- R^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl;
- R^2 and R^3 not simultaneously being each hydrogen ; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as their possible tautomers, their possible pharmaceutically acceptable addition salts with an acid or a base, and their N-oxide forms

5. The use according to claim 1, wherein the uridine derivatives is chosen from among the following compounds:

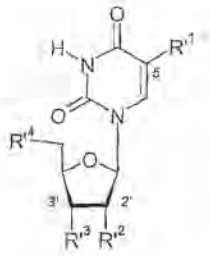
- (*E*)-5-(1-Chloro-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Diiodovinyl)-2'-deoxyuridine,
- 5-(2-Iodoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-2'-deoxyuridine,
- (*E*)-5-(1,2-Dibromovinyl)-2'-deoxyuridine,
- 5-(2-Bromoethynyl)-2'-deoxyuridine,
- (*E*)-5-(1-Chloro-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Diiodovinyl)-uridine,
- 5-(2-Iodoethynyl)-uridine,
- (*E*)-5-(1-Bromo-2-iodovinyl)-uridine,
- (*E*)-5-(1,2-Dibromovinyl)-uridine, and
- 5-(2-bromoethynyl)-uridine,

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

6. The use according to any one of claims 1 to 5, wherein an uridine derivative of formula (I) as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms, and an interferon are used for the preparation of a drug having antiviral activity against a Flavividdae.

7. The use according to any one of claims 1 to 6, for the preparation of a drug having antiviral activity against hepatitis C virus (HCV).

8. A compound of formula (I') :



(I')

wherein

- R'^1 represents -C(Y)=CH(X), -C(Y)=C(X)alkyl or -C(Y)=C-Ak(X), where Y is halogen and Ak(X) denotes a linear or branched C_1-C_{10} alkyl radical, one hydrogen atom of which being substituted by one halogen atom X;
- R'^2, R'^3 and R'^4 have the same definitions as R^2, R^3 and R^4, respectively, in the above formula (I);

as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms.

9. The compound according to claim 8, wherein :

- R'^1 represents -C(Y)=CH(X);
- X and Y each independently represents halogen;
- R'^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms.

10. The compound according to claim 9, wherein R^1 represents –C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.

11. The compound according to claim 9, wherein

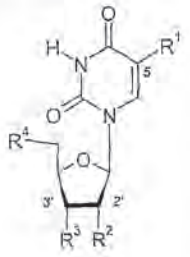
- R'^1 represents -C(Y)=CH(X), where Y is chosen from among chlorine, bromine and iodine, and X is bromine or iodine.
- R'^2 is chosen from among hydrogen, hydroxyl, and -O-alkyl;
- R'^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -SH, and -S-alkyl; and

- R'^2 and R'^3 not simultaneously being each hydrogen; and
- R'^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms.

12. A drug formulation having an antiviral activity against a Flaviviridae comprising

(1) an uridine derivative of formula (I) :



(I)

wherein

- R^1 represents monohalogenated alkynyl or dihalogenated alkenyl;
- R^2 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl and halogen;
- R^3 is chosen from among hydrogen, hydroxyl, -O-alkyl, -O-CO-alkyl, halogen, -SH, -S-alkyl and N^3; and
- R^4 is chosen from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate,

as well as its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or a base, and its N-oxide forms,

(2) an immunomodulator or another active ingredient having an antiviral activity against a Flaviviridae, and

(3) a pharmaceutically acceptable vehicule, carrier or excipient.

13. The drug formulation according to claim 12, wherein ingredient (2) comprises an interferon.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003882

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/70 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GOODCHILD ET AL: "Structural requirements of olefinic 5 substituted deoyuridines for antiherpes activity" J.MED.CHEM, vol. 26, 1983, pages 1252-1257, XP002329924 cited in the application compound 5	8-11
A	CLERCQ: "HAMAO UMEZAWA MEMORILA AWARD LECTURE" INTERN.J.ANTIMICROB AGENTS, vol. 18, 2001, - 2001 pages 309-328, XP002329925 paragraph [02.5]	1-12

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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2006	25/04/2006

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003882

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MENDIRATTA ET AL: "Structure Activity Study on Antiviral 5-vinylpyrimidine Nucleoside Analogs Using Wiener's Topological Index" J.CHEM.INF.COMPUT.SCI, vol. 34, 1994, - 1994 pages 867-871, XP002371658 compound 30	8-11

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(54) Title: PRODRUGS OF PHOSPHONATE NUCLEOTIDE ANALOGUES AND METHODS FOR SELECTING AND MAKING SAME

(57) Abstract: A novel method is provided for screening prodrugs of methoxyphosphonate nucleotide analogues to identify prodrugs selectively targeting desired tissues with antiviral or antitumor activity. This method has led to the identification of novel mixed ester-amidates of PMPA for retroviral or hepadnaviral therapy, including compounds of structure (5a) having substituent groups as defined herein. Compositions of these novel compounds in pharmaceutically acceptable excipients and their use in therapy and prophylaxis are provided. Also provided is an improved method for the use of magnesium alkoxide for the preparation of starting materials and compounds for use herein.

Prodrugs of Phosphonate Nucleotide Analogues and Methods for Selecting and Making Same

This application relates to prodrugs of methoxyphosphonate nucleotide analogues. In particular it relates to improved methods for making and identifying such prodrugs.

Many methoxyphosphonate nucleotide analogues are known. In general, such compounds have the structure A-$OCH_2P(O)(OR)_2$ where A is the residue of a nucleoside analogue and R independently is hydrogen or various protecting or prodrug functionalities. See U.S. Patent Nos. 5,663,159, 5,977,061 and 5,798,340, Oliyai et al, "Pharmaceutical Research" 16(11):1687-1693 (1999), Stella et al., "J. Med. Chem." 23(12):1275-1282 (1980), Aarons, L., Boddy, A. and Petrak, K. (1989) *Novel Drug Delivery and Its Therapeutic Application* (Prescott, L. F. and Nimmo, W. S., ed.), pp. 121–126; Bundgaard, H. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 70–74 and 79-92; Banerjee, P. K. and Amidon, G. L. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 118-121; Notari, R. E. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 135-156; Stella, V. J. and Himmelstein, K. J. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 177-198; Jones, G. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 199-241; Connors, T. A. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 291–316. All literature and patent citations herein are expressly incorporated by reference.

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Summary of the Invention

Prodrugs of methoxyphosphonate nucleotide analogues intended for antiviral or antitumor therapy, while known, traditionally have been selected for their systemic effect. For example, such prodrugs have been selected for enhanced bioavailability, i.e., ability to be absorbed from the gastrointestinal tract and converted rapidly to parent drug to ensure that the parent drug is available to all tissues. However, applicants now have found that it is possible to select prodrugs that become enriched at therapeutic sites, as illustrated by the studies described herein where the analogues are enriched at localized focal sites of HIV infection. The objective of this invention is, among other advantages, to produce less toxicity to bystander tissues and greater potency of the parental drug in tissues which are the targets of therapy with the parent methoxyphosphonate nucleotide analogue.

Accordingly, pursuant to these observations, a screening method is provided for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue;

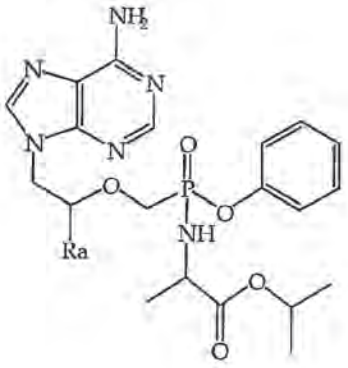
(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and

(d) determining the relative antiviral activity conferred by the prodrug in the tissues in step (c).

In preferred embodiments, the target tissue are sites where HIV is actively replicated and/or which serve as an HIV reservoir, and the non-target tissue is an intact animal. Unexpectedly, we found that selecting lymphoid tissue as the target tissue for the practice of this method for HIV led to identification of prodrugs that enhance the delivery of active drug to such tissues.

A preferred compound of this invention, which has been identified by this method has the structure (1),

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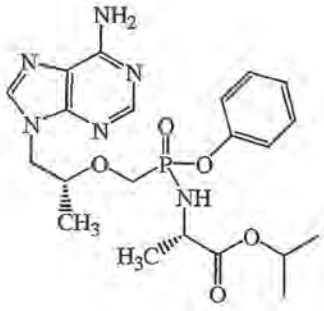


(1)

where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

A preferred compound of this invention has the structure (2)



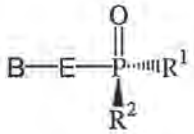
(2)

and its enriched diasteromers, salts, free base and solvates.

In addition, we unexpectedly found that the chirality of substituents on the phosphorous atom and/or the amidate substituent are influential in the enrichment observed in the practice of this invention. Thus, in another embodiment of this

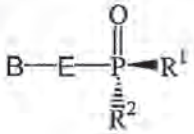
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invention, we provide diastereomerically enriched compounds of this invention having the structure (3)



(3)

which are substantially free of the diastereomer (4)



(4)

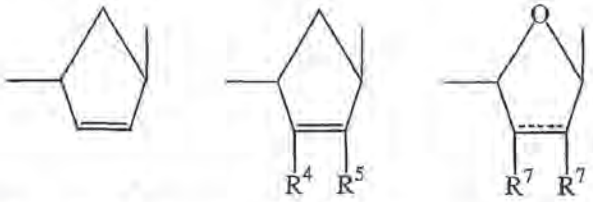
wherein

R^1 is an oxyester which is hydrolyzable *in vivo*, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $-(CH_2)2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2F)CH_2-$, $-CH(CH_2OH)CH_2-$, $-CH(CH=CH_2)CH_2-$, $-CH(C\equiv CH)CH_2-$, $-CH(CH_2N_3)CH_2-$,



$-CH(R^5)OCH(R^{6'})-$, $-CH(R^9)CH_2O-$ or $-CH(R^8)O-$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

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R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form -O- or $-CH_2-$;

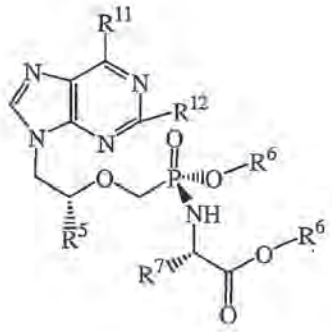
R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

R^9 is H, hydroxymethyl or acyloxymethyl;

and their salts, free base, and solvates.

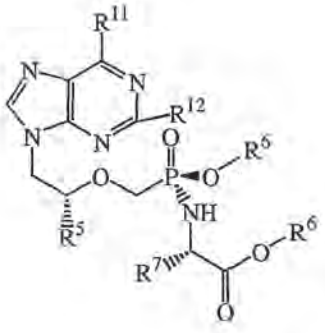
The diastereomers of structure (3) are designated the (*S*) isomers at the phosphorus chiral center.

Preferred embodiments of this invention are the diastereomerically enriched compounds having the structure (5a)



(5a)

which is substantially free of diastereomer (5b)



(5b)

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wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

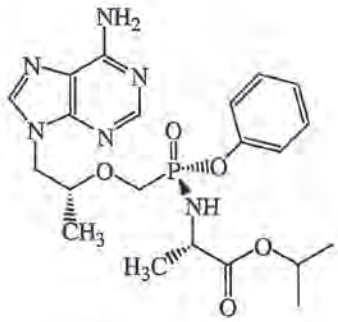
R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

and its salts, tautomers, free base and solvates.

A preferred embodiment of this invention is the compound of structure (6), 9-[(*R*)-2-[[(*S*)-[[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine, also designated herein GS-7340

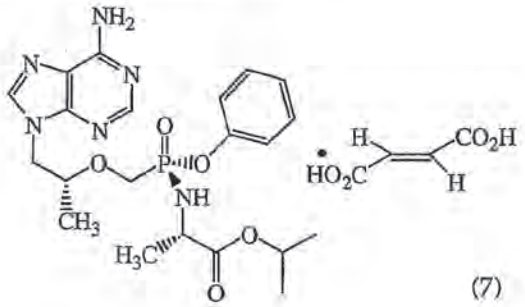


(6)

Another preferred embodiment of this invention is the fumarate salt of structure (5) (structure (7)), 9-[(*R*)-2-[[(*S*)-[[(*S*)-1-

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(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine fumarate (1:1), also designated herein GS-7340-2



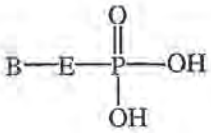
(7)

The compounds of structures (1)-(7) optionally are formulated into compositions containing pharmaceutically acceptable excipients. Such compositions are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.

In a further embodiment, a method is provided for the facile manufacture of 9-[2-(phosphonomethoxy)propyl]adenine (hereinafter "PMPA" or 9-[2-(phosphonomethoxy)ethyl] adenine (hereinafter "PMEA") using magnesium alkoxide, which comprises combining 9-(2-hydroxypropyl)adenine or 9-(2-hydroxyethyl)adenine, protected *p*-toluenesulfonyloxymethylphosphonate and magnesium alkoxide, and recovering PMPA or PMEA, respectively.

Detailed Description of the Invention

The methoxyphosphonate nucleotide analogue parent drugs for use in this screening method are compounds having the structure A-$OH_2P(O)(OH)_2$ wherein A is the residue of a nucleoside analogue. These compounds are known per se and are not part of this invention. More particularly, the parent compounds comprise a heterocyclic base B and an aglycon E, in general having the structure



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wherein the group B is defined below and group E is defined above. Examples are described in U.S. Patent Nos. 4,659,825, 4,808,716, 4,724,233, 5,142,051, 5,130,427, 5,650,510, 5,663,159, 5,302,585, 5,476,938, 5,696,263, 5,744,600, 5,688,778, 5,386,030, 5,733,896, 5,352,786, and 5,798,340, and EP 821,690 and 654,037.

The prodrugs for use in the screening method of this invention are covalently modified analogues of the parent methoxyphosphonate nucleotide analogues described in the preceding paragraph. In general, the phosphorus atom of the parent drug is the preferred site for prodrug modification, but other sites are found on the heterocyclic base B or the aglycon E. Many such prodrugs are already known. Primarily, they are esters or amidates of the phosphorus atom, but also include substitutions on the base and aglycon. None of these modifications per se is part of this invention and none are to be considered limiting on the scope of the invention herein.

The phosphorus atom of the methoxyphosphonate nucleotide analogues contains two valences for covalent modification such as amidation or esterification (unless one phosphoryl hydroxyl is esterified to an aglycon E hydroxyl substituent, whereupon only one phosphorus valence is free for substitution). The esters typically are aryloxy. The amidates ordinarily are naturally occurring monoamino acids having free carboxyl group(s) esterified with an alkyl or aryl group, usually phenyl, cycloalkyl, or t-, n- or s- alkyl groups. Suitable prodrugs for use in the screening method of this invention are disclosed for example in U.S. Patent No. 5,798,340. However, any prodrug which is potentially believed to be capable of being converted *in vivo* within target tissue cells to the free methoxyphosphonate nucleotide analogue parent drug, e.g., whether by hydrolysis, oxidation, or other covalent transformation resulting from exposure to biological tissues, is suitable for use in the method of this invention. Such prodrugs may not be known at this time but are identified in the future and thus become suitable candidates available for testing in the method of this invention. Since the prodrugs are simply candidates for screening in the methods their structures are not relevant to practicing or enabling the screening method, although of course their structures ultimately are dispositive of whether or not a prodrug will be shown to be selective in the assay.

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The pro-moieties bound to the parent drug may be the same or different. However, each prodrug to be used in the screening assay will differ structurally from the other prodrugs to be tested. Distinct, i.e. structurally different, prodrugs generally are selected on the basis of either their stereochemistry or their covalent structure, or these features are varied in combination. Each prodrug tested, however, desirably is structurally and stereochemically substantially pure, else the output of the screening assay will be less useful. It is of course within the scope of this invention to test only a single prodrug in an individual embodiment of the method of this invention, although typically then one would compare the results with prior studies with other prodrugs.

We have found that the stereochemistry of the prodrugs is capable of influencing the enrichment in target tissues. Chiral sites are at the phosphorus atom and are also found in its substituents. For example, amino acid used in preparing amidates may be D or L forms, and the phosphonate esters or the amino acid esters can contain chiral centers as well. Chiral sites also are found on the nucleoside analogue portion of the molecules, but these typically are already dictated by the stereochemistry of the parent drug and will not be varied as part of the screen. For example the R isomer of PMPA is preferred as it is more active than the corresponding S isomer. Typically these diasteromers or enantiomers will be chirally enriched if not pure at each site so that the results of the screen will be more meaningful. As noted, distinctiveness of stereoisomers is conferred by enriching or purifying the stereoisomer (typically this will be a diastereomer rather than an enantiomer in the case of most methoxyphosphonate nucleotide analogues) free of other stereoisomers at the chiral center in question, so that each test compound is substantially homogeneous. By substantially homogeneous or chirally enriched, we mean that the desired stereoisomer constitutes greater than about 60% by weight of the compound, ordinarily greater than about 80% and preferably greater than about 95%.

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Novel Screening Method

Once at least one candidate prodrug has been selected, the remaining steps of the screening method of this invention are used to identify a prodrug possessing the required selectivity for the target tissue. Most conveniently the prodrugs are labeled with a detectable group, e.g. radiolabeled, in order to facilitate detection later in tissues or cells. However, a label is not required since other suitable assays for the prodrug or its metabolites (including the parent drug) can also be employed. These assays could include mass spectrometry, HPLC, bioassays or immunoassays for instance. The assay may detect the prodrug and any one or more of its metabolites, but preferably the assay is conducted to detect only the generation of the parent drug. This is based on the assumption (which may not be warranted in all cases) that the degree and rate of conversion of prodrug to antivirally active parent diphosphate is the same across all tissues tested. Otherwise, one can test for the diphosphate.

The target tissue preferably will be lymphoid tissue when screening for prodrugs useful in the treatment of HIV infection. Lymphoid tissue will be known to the artisan and includes CD4 cells, lymphocytes, lymph nodes, macrophages and macrophage-like cells including monocytes such as peripheral blood monocytic cells (PBMCs) and glial cells. Lymphoid tissue also includes non-lymphoid tissues that are enriched in lymphoid tissues or cells, e.g. lung, skin and spleen. Other targets for other antiviral drugs of course will be the primary sites of replication or latency for the particular virus concerned, e.g., liver for hepatitis and peripheral nerves for HSV. Similarly, target tissues for tumors will in fact be the tumors themselves. These tissues are all well-known to the artisan and would not require undue experimentation to select. When screening for antiviral compounds, target tissue can be infected by the virus.

Non-target tissues or cells also are screened as part of the method herein. Any number or identity of such tissues or cells can be employed in this regard. In general, tissues for which the parent drug is expected to be toxic will be used as non-target tissues. The selection of a non-target tissue is entirely dependent upon

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the nature of the prodrug and the activity of the parent. For example, non-hepatic tissues would be selected for prodrugs against hepatitis, and untransformed cells of the same tissue as the tumor will suffice for the antitumor-selective prodrug screen.

It should be noted that the method of this invention is distinct from studies typically undertaken to determine oral bioavailability of prodrugs. In oral bioavailability studies, the objective is to identify a prodrug which passes into the systemic circulation substantially converted to parent drug. In the present invention, the objective is to find prodrugs that are not metabolized in the gastrointestinal tract or circulation. Thus, target tissues to be evaluated in the method of this invention generally do not include the small intestines or, if the intestines are included, then the tissues also include additional tissues other than the small intestines.

The target and non-target tissues used in the screening method of this invention typically will be in an intact living animal. Prodrugs containing esters are more desirably tested in dogs, monkeys or other animals than rodents; mice and rat plasma contains high circulating levels of esterases that may produce a misleading result if the desired therapeutic subject is a human or higher mammal.

It is not necessary to practice this method with intact animals. It also is within the scope of this invention to employ perfused organs, *in vitro* culture of organs (e.g. skin grafts) or cell lines maintained in various forms of cell culture, e.g. roller bottles or zero gravity suspension systems. For example, MT-2 cells can be used as a target tissue for selecting HIV prodrugs. Thus, the term "tissue" shall not be construed to require organized cellular structures, or the structures of tissues as they may be found in nature, although such would be preferred. Rather, the term "tissue" shall be construed to be synonymous with cells of a particular source, origin or differentiation stage.

The target and non-target tissue may in fact be the same tissue, but the tissues will be in different biological status. For example, the method herein could be used to select for prodrugs that confer activity in virally-infected tissue (target tissue) but which remain substantially inactive in virally-uninfected cells (corresponding non-target tissue). The same strategy would be employed to select

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prophylactic prodrugs, i.e., prodrugs metabolized to antivirally active forms incidental to viral infection but which remain substantially unmetabolized in uninfected cells. Similarly, prodrugs could be screened in transformed cells and the untransformed counterpart tissue. This would be particularly useful in comparative testing to select prodrugs for the treatment of hematological malignancies, e.g. leukemias.

Without being limited by any particular theory of operation, tissue selective prodrugs are thought to be selectively taken up by target cells and/or selectively metabolized within the cell, as compared to other tissues or cells. The unique advantage of the methoxyphosphonate prodrugs herein is that their metabolism to the dianion at physiological pH ensures that they will be unable to diffuse back out of the cell. They therefore remain effective for lengthy periods of time and are maintained at elevated intracellular concentrations, thereby exhibiting increased potency. The mechanisms for enhanced activity in the target tissue are believed to include enhanced uptake by the target cells, enhanced intracellular retention, or both mechanisms working together. However, the manner in which selectivity or enhanced delivery occurs in the target tissue is not important. It also is not important that all of the metabolic conversion of the prodrug to the parent compound occurs within the target tissue. Only the final drug activity-conferring conversion need occur in the target tissue; metabolism in other tissues may provide intermediates finally converted to antiviral forms in the target tissue.

The degree of selectivity or enhanced delivery that is desired will vary with the parent compound and the manner in which it is measured (% dose distribution or parent drug concentration). In general, if the parent drug already possess a generous therapeutic window, a low degree of selectivity may be sufficient for the desired prodrug. On the other hand, toxic compounds may require more extensive screening to identify selective prodrugs. The relative expense of the method of this invention can be reduced by screening only in the target tissue and tissues against which the parent compound is known to be relatively toxic, e.g. for PMEA, which is nephrotoxic at higher doses, the primary focus will be on kidney and lymphoid tissues.

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The step of determining the relative antiviral activity of a prodrug in the selected tissues ordinarily is accomplished by assaying target and non-target tissues for the relative presence or activity of a metabolite of the prodrug, which metabolite is known to have, or is converted to, a metabolite having antiviral or antitumor activity. Thus, typically one would determine the relative amount of the parent drug in the tissues over substantially the same time course in order to identify prodrugs that are preferentially metabolized in the target tissue to an antivirally or antitumor active metabolite or precursor thereof which in the target tissue ultimately produces the active metabolite. In the case of antiviral compounds, the active metabolite is the diphosphate of the phosphonate parent compounds. It is this metabolite that is incorporated into the viral nucleic acid, thereby truncating the elongating nucleic acid strand and halting viral replication. Metabolites of the prodrug can be anabolic metabolites, catabolic metabolites, or the product of anabolism and catabolism together. The manner in which the metabolite is produced is not important in the practice of the method of this invention.

The method of this invention is not limited to assaying a metabolite which per se possesses antiviral or antitumor activity. Instead, one can assay inactive precursors of the active metabolites. Precursors of the antivirally active diphosphate metabolite include the monophosphate of the parent drug, monophosphates of other metabolites of the parent drug (e.g., an intermediate modification of a substituent on the heterocyclic base), the parent itself and metabolites generated by the cell in converting the prodrug to the parent prior to phosphorylation. The precursor structures may vary considerably as they are the result of cellular metabolism. However, this information is already known or could be readily determined by one skilled in the art.

If the prodrug being assayed does not exhibit antitumor or antiviral activity per se then adjustments to the raw assay results may be required. For example, if the intracellular processing of the inactive metabolite to an active metabolite occurs at different rates among the tissues being tested, the raw assay results with the inactive metabolite would need to be adjusted to take account of the differences

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among the cell types because the relevant parameter is the generation of activity in the target tissue, not accumulation of inactive metabolites. However, determining the proper adjustments would be within the ordinary skill. Thus, when step (d) of the method herein calls for determining the activity, activity can be either measured directly or extrapolated. It does not mean that the method herein is limited to only assaying intermediates that are active per se. For instance, the absence or decline of the prodrug in the test tissues also could be assayed. Step (d) only requires assessment of the activity conferred by the prodrug as it interacts with the tissue concerned, and this may be based on extrapolation or other indirect measurement.

Step (d) of the method of this invention calls for determining the "relative" activity of the prodrug. It will be understood that this does not require that each and every assay or series of assays necessarily must also contain runs with the selected non-target tissue. On the contrary, it is within the scope of this invention to employ historical controls of the non-target tissue or tissues, or algorithms representing results to be expected from such non-target tissues, in order to provide the benchmark non-target activity.

The results obtained in step (d) are then used optimally to select or identify a prodrug which produces greater antiviral activity in the target tissue than in the non-target tissue. It is this prodrug that is selected for further development.

It will be appreciated that some preassessment of prodrug candidates can be undertaken before the practice of the method of this invention. For example, the prodrug will need to be capable of passing largely unmetabolized through the gastrointestinal tract, it will need to be substantially stable in blood, and it should be able to permeate cells at least to some degree. In most cases it also will need to complete a first pass of the hepatic circulation without substantial metabolism. Such prestudies are optional, and are well-known to those skilled in the art.

The same reasoning as is described above for antiviral activity is applicable to antitumor prodrugs of methoxyphosphonate nucleotide analogues as well. These include, for example, prodrugs of PMEG, the guanyl analogue of PMEA. In

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this case, cytotoxic phosphonates such as PMEG are worthwhile candidates to pursue as their cytotoxicity in fact confers their antitumor activity.

A compound identified by this novel screening method then can be entered into a traditional preclinical or clinical program to confirm that the desired objectives have been met. Typically, a prodrug is considered to be selective if the activity or concentration of parent drug in the target tissue (% dose distribution) is greater than 2x, and preferably 5x, that of the parent compound in non-target tissue. Alternatively, a prodrug candidate can be compared against a benchmark prodrug. In this case, selectivity is relative rather than absolute. Selective prodrugs will be those resulting in greater than about 10x concentration or activity in the target tissue as compared with the prototype, although the degree of selectivity is a matter of discretion.

Novel Method for Preparation of Starting Materials or Intermediates

Also included herein is an improved method for manufacture of preferred starting materials (parent drugs) of this invention, PMEA and (*R*)-PMPA. Typically, this method comprises reacting 9-(2-hydroxypropyl)adenine (HPA) or 9-(2-hydroxyethyl)adenine (HEA) with a magnesium alkoxide, thereafter adding the protected aglycon synthon *p*-toluene-sulfonyloxymethylphosphonate (tosylate) to the reaction mixture, and recovering PMPA or PMEA, respectively.

Preferably, HPA is the enriched or isolated R enantiomer. If a chiral HPA mixture is used, R-PMPA can be isolated from the chiral PMPA mixture after the synthesis is completed.

Typically the tosylate is protected by lower alkyl groups, but other suitable groups will be apparent to the artisan. It may be convenient to employ the tosylate presubstituted with the prodrug phosphonate substituents which are capable of acting as protecting groups in the tosylation reaction, thereby allowing one to bypass the deprotection step and directly recover prodrug or an intermediate therefore.

The alkyl group of the magnesium alkoxide is not critical and can be any C_1-C_6 branched or normal alkyl, but is preferably t-butyl (for PMPA) or isopropyl (for

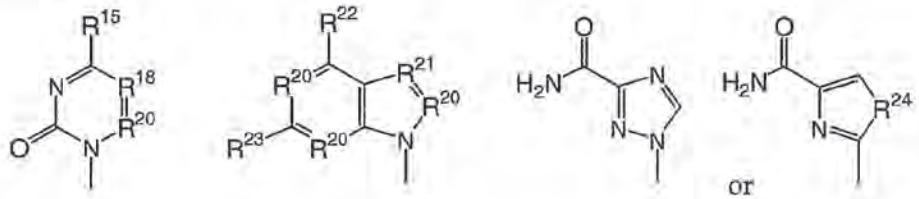
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PMEA). The reaction conditions also are not critical, but preferably comprise heating the reaction mixture at about 70-75°C with stirring or other moderate agitation.

If there is no interest in retaining the phosphonate substituents, the product is deprotected (usually with bromotrimethylsilane where the tosylate protecting group is alkyl), and the product then recovered by crystallization or other conventional method as will be apparent to the artisan.

Heterocyclic Base

In the compounds of this invention depicted in structures (3) and (4), the heterocyclic base B is selected from the structures



or

wherein

R^{15} is H, OH, F, Cl, Br, I, OR^{16}, SH, SR^{16}, NH_2, or NHR^{17};

R^{16} is C_1-C_6 alkyl or C_2-C_6 alkenyl including CH_3, CH_2CH_3, CH_2CCH, CH_2CHCH_2 and C_3H_7;

R^{17} is C_1-C_6 alkyl or C_2-C_6 alkenyl including CH_3, CH_2CH_3, CH_2CCH, CH_2CHCH_2, and C_3H_7;

R^{18} is N, CF, CCl, CBr, CI, CR^{19}, CSR^{19}, or COR^{19};

R^{19} is H, C_1-C9 alkyl, C_2-C9 alkenyl, C_2 - C9 alkynyl, C_1-C9 alkyl-C_1-C9 alkoxy, or C7-C9 aryl-alkyl unsubstituted or substituted by OH, F, Cl, Br or I, R^{19} therefore including -CH_3, -CH_2CH_3, -$CHCH_2$, -CHCHBr, -CH_2CH_2Cl, -CH_2CH_2F, -CH_2CCH, -CH_2CHCH_2, -C_3H_7, -CH_2OH, -CH_2OCH_3, -$CH_2OC_2H_5$, -CH_2OCCH, -$CH_2OCH_2CHCH_2$, -$CH_2C_3H_7$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$,

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$-CH_2CH_2OC_2H_5$, $-CH_2CH_2OCCH$, $-CH_2CH_2OCH_2CHCH_2$, and $-CH_2CH_2OC_3H_7$;

R^{20} is N or CH;

R^{21} is N, CH, CCN, CCF_3, CC≡CH or $CC(O)NH_2$;

R^{22} is H, OH, NH_2, SH, SCH_3, SCH_2CH_3, SCH_2CCH, SCH_2CHCH_2, SC_3H_7, $NH(CH_3)$, $N(CH_3)_2$, $NH(CH_2CH_3)$, $N(CH_2CH_3)_2$, $NH(CH_2CCH)$, $NH(CH_2CHCH_2)$, $NH(C_3H_7)$, halogen (F, Cl, Br or I) or X wherein X is $-(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein each m is independently 0-2, n is 0-1, and

R^{10} independently is

H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_{15} arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 heterocycloalkyl,

C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by –O-,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

or one of the foregoing R^{10} groups which is substituted with 1 to 3 halo, CN or N_3; but optionally at least one R^{10} group is not H;

R^{23} is H, OH, F, Cl, Br, I, SCH_3, SCH_2CH_3, SCH_2CCH, SCH_2CHCH_2, SC_3H_7, OR^{16}, NH_2, NHR^{17} or R^{22}; and

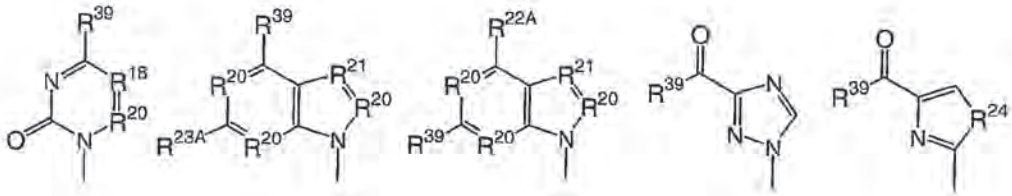
R^{24} is O, S or Se.

B also includes both protected and unprotected heterocyclic bases, particularly purine and pyrimidine bases. Protecting groups for exocyclic amines and other labile groups are known (Greene et al. "Protective Groups in Organic Synthesis") and include N-benzoyl, isobutyryl, 4,4'-dimethoxytrityl (DMT) and the

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like. The selection of protecting group will be apparent to the ordinary artisan and will depend upon the nature of the labile group and the chemistry which the protecting group is expected to encounter, e.g. acidic, basic, oxidative, reductive or other conditions. Exemplary protected species are N^4-benzoylcytosine, N^6-benzoyladenine, N^2-isobutyrylguanine and the like.

Protected bases have the formulas Xa.1, XIa.1, XIb.1, XIIa.1 or XIIIa.1



(Xa.1) (XIa.1) (XIb.1) (XIIa.1) (XIIIa.1)

wherein R^{18}, R^{20}, R^{21}, R^{24} have the meanings previously defined; R^{22A} is R^{39} or R^{22} provided that R^{22} is not NH_2; R^{23A} is R^{39} or R^{23} provided that R^{23} is not NH_2; R^{39} is NHR^{40}, $NHC(O)R^{36}$ or $CR^{41}N(R^{38})_2$ wherein R^{36} is C1-C19 alkyl, C1-C19 alkenyl, C3-C10 aryl, adamantoyl, alkylanyl, or C3-C10 aryl substituted with 1 or 2 atoms or groups selected from halogen, methyl, ethyl, methoxy, ethoxy, hydroxy and cyano; R^{38} is C1-C10 alkyl, or both R^{38} together are 1-morpholino, 1-piperidine or 1-pyrrolidine; R^{40} is C_1-C_{16} alkyl, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, octyl and decanyl; and R^{41} is hydrogen or CH_3.

For bases of structures XIa.1 and XIb.1, if R^{39} is present at R^{22A} or R^{23A}, both R^{39} groups on the same base will generally be the same. Exemplary R^{36} are phenyl, phenyl substituted with one of the foregoing R^{36} aryl substituents, $-C_{10}H_{15}$ (where $C_{10}H_{15}$ is 2-adamantoyl), $-CH_2-C_6H_5$, $-C_6H_5$, $-CH(CH_3)_2$, $-CH_2CH_3$, methyl, butyl, t-butyl, heptanyl, nonanyl, undecanyl, or undecenyl.

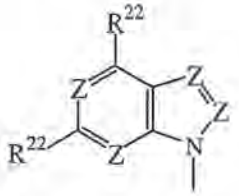
Specific bases include hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza

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derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

Preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-dezazadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B′ is a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(C_1-C_3-alkyl)cytosinyl.

Preferred B groups have the formula



wherein

R^{22} independently is halo, oxygen, NH_2, X or H, but optionally at least one R^{22} is X;

X is $-(CH_2)_m(O)_n(CH_2)_mN(R^{10})_2$ wherein m is 0-2, n is 0-1, and

R^{10} independently is

H,

C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_6-C_{15} arylalkynyl, C_2-C_{15} alkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroaralkyl, C_5-C_6 aryl, C_2-C_6 heterocycloalkyl,

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C_2-C_{15} alkyl, C_3-C_{15} alkenyl, C_6-C_{15} arylalkenyl, C_3-C_{15} alkynyl, C_7-C_{15} arylalkynyl, C_1-C_6-alkylamino-C_1-C_6 alkyl, C_5-C_{15} aralkyl, C_6-C_{15} heteroalkyl or C_3-C_6 heterocycloalkyl wherein methylene in the alkyl moiety not adjacent to N^6 has been replaced by –O-,

optionally both R^{10} are joined together with N to form a saturated or unsaturated C_2-C_5 heterocycle containing one or two N heteroatoms and optionally an additional O or S heteroatom,

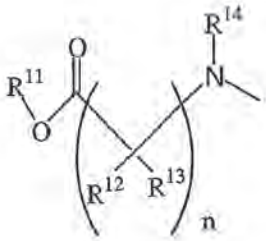
or one of the foregoing R^{10} groups is substituted with 1 to 3 halo, CN or N3; but optionally at least one R^{10} group is not H; and

Z is N or CH, provided that the heterocyclic nucleus varies from purine by no more than one Z.

E groups represent the aglycons employed in the methoxyphosphonate nucleotide analogues. Preferably, the E group is $-CH(CH_3)CH_2-$ or $-CH_2CH_2-$. Also, it is preferred that the side groups at chiral centers in the aglycon be substantially solely in the (*R*) configuration (except for hydroxymethyl, which is the enriched (*S*) enantiomer).

R^1 is an *in vivo* hydrolyzable oxyester having the structure $-OR^{35}$ or $-OR^6$ wherein R^{35} is defined in column 64, line 49 of U.S. Patent No. 5,798,340, herein incorporated by reference, and R^6 is defined above. Preferably R^1 is aryloxy, ordinarily unsubstituted or para-substituted (as defined in R^6) phenoxy.

R^2 is an amino acid residue, optionally provided that any carboxy group linked by less than about 5 atoms to the amidate N is esterified. R^2 typically has the structure



(8)

wherein

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n is 1 or 2;

R^{11} is R^6 or H; preferably R^6 = C_3-C_9 alkyl; C_3-C_9 alkyl substituted independently with OH, halogen, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, O or N; or C_3-C_6 arylalkyl which is independently substituted with OH, halogen, O or N;

R^{12} independently is H or C_1-C_9 alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; C_3-C_6 aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen; or C_3-C_9 aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, $COOR^{11}$ and halogen;

R^{13} independently is C(O)-OR^{11}; amino; amide; guanidinyl; imidazolyl; indolyl; sulfoxide; phosphoryl; C_1-C_3 alkylamino; C_1-C_3 alkyldiamino; C_1-C_6 alkenylamino; hydroxy; thiol; C_1-C_3 alkoxy; C_1-C_3 alkthiol; $(CH_2)_nCOOR^{11}$; C_1-C_6 alkyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; C_2-C_6 alkenyl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and C_6-C_{12} aryl which is unsubstituted or substituted with OH, halogen, SH, NH_2, phenyl, hydroxyphenyl or C_7-C_{10} alkoxyphenyl; and

R^{14} is H or C_1-C_9 alkyl or C_1-C_9 alkyl independently substituted with OH, halogen, $COOR^{11}$, O or N; C_3-C_6 aryl; C_3-C_6 aryl which is independently substituted with OH, halogen, $COOR^{11}$, O or N; or C_3-C_6 arylalkyl which is independently substituted with OH, halogen, $COOR^{11}$, O or N.

Preferably, R^{11} is C_1-C_6 alkyl, most preferably isopropyl, R^{13} is the side chain of a naturally occurring amino acid, n = 1, R^{12} is H and R^{14} is H. In the compound of structure (2), the invention includes metabolites in which the phenoxy and isopropyl esters have been hydrolyzed to -OH. Similarly, the de-esterified enriched phosphonoamidate metabolites of compounds (5a), 5(b) and (6) are included within the scope of this invention.

Aryl and "O" or "N" substitution are defined in column 16, lines 42-58, of

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United States Patent No. 5,798,340.

Typically, the amino acids are in the natural or *l* amino acids. Suitable specific examples are set forth in U. S. Patent No. 5,798,340, for instance Table 4 and col. 8-10 therein.

Alkyl as used herein, unless stated to the contrary, is a normal, secondary, tertiary or cyclic hydrocarbon. Unless stated to the contrary alkyl is C_1-C_{12}. Examples are -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$), -$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_2CH_3$, -$CH(CH_2CH_3)_2$, -$C(CH_3)_2CH_2CH_3$), -$CH(CH_3)CH(CH_3)_2$, -$CH_2CH_2CH(CH_3)_2$), -$CH_2CH(CH_3)CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_2CH_2CH_3$, -$CH(CH_2CH_3)(CH_2CH_2CH_3)$, -$C(CH_3)_2CH_2CH_2CH_3$, -$CH(CH_3)CH(CH_3)CH_2CH_3$, -$CH(CH_3)CH_2CH(CH_3)_2$, -$C(CH_3)(CH_2CH_3)_2$, -$CH(CH_2CH_3)CH(CH_3)_2$, -$C(CH_3)_2CH(CH_3)_2$, and -$CH(CH_3)C(CH_3)_3$. Alkenyl and alkynyl are defined in the same fashion, but contain at least one double or triple bond, respectively.

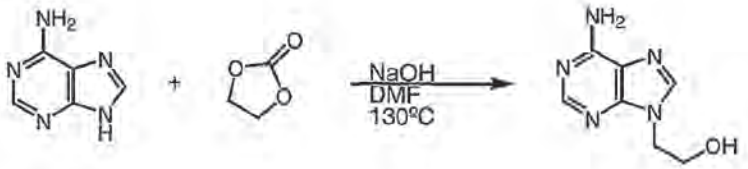
Where enol or keto groups are disclosed, the corresponding tautomers are to be construed as taught as well.

The prodrug compounds of this invention are provided in the form of free base or the various salts enumerated in U. S. Patent No. 5,798,340, and are formulated with pharmaceutically acceptable excipients or solvating diluents for use as pharmaceutical products also as set forth in U. S. Patent No. 5,798,340. These prodrugs have the antiviral and utilities already established for the parent drugs (see U. S. Patent 5,798,340 and other citations relating to the methoxyphosphonate nucleotide analogues). It will be understood that the diastereomer of structure (4) at least is useful as an intermediate in the chemical production of the parent drug by hydrolysis *in vitro*, regardless of its relatively unselective character as revealed in the studies herein.

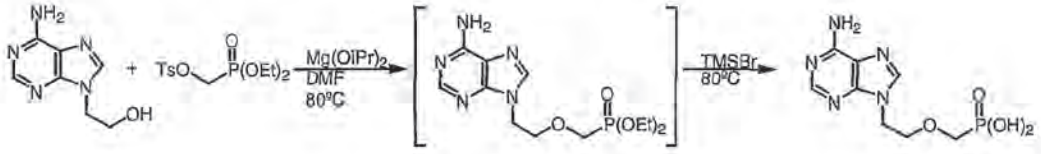
The invention will be more fully understood by reference to the following examples:

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Example 1a



Adenine to PMEA using Magnesium Isopropoxide. To a suspension of adenine (16.8g, 0.124 mol) in DMF (41.9 ml) was added ethylene carbonate (12.1g, 0.137 mol) and sodium hydroxide (.100g, 0.0025 mol). The mixture was heated at 130°C overnight. The reaction was cooled to below 50°C and toluene (62.1 ml) was added. The slurry was further cooled to 5°C for 2 hours, filtered, and rinsed with toluene (2x). The wet solid was dried *in vacuo* at 65°C to yield 20.0g (90%) of 9-(2-hydroxyethyl)adenine as an off-white solid. Mp: 238-240°C.

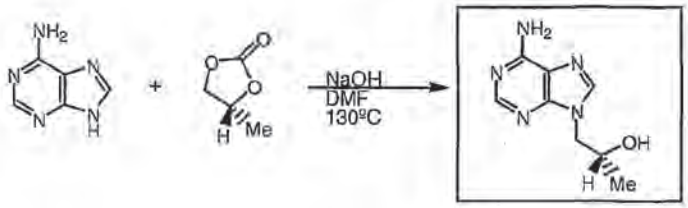


9-(2-Hydroxyethyl)adenine (HEA) (20.0g, 0.112 mol) was suspended in DMF (125 ml) and heated to 80°C. Magnesium isopropoxide (11.2g, 0.0784 mol) , or alternatively magnesium t-butoxide, was added to the mixture followed by diethyl *p*-toluenesulfonyloxymethylphosphonate (66.0g, 0.162 mol) over one hour. The mixture was stirred at 80°C for 7 hours. 30 ml of volatiles were removed via vacuum distillation and the reaction was recharged with 30 ml of fresh DMF. After cooling to room temperature, bromotrimethylsilane (69.6g, 0.450 mol) was added and the mixture heated to 80°C for 6 hours. The reaction was concentrated to yield a thick gum. The gum was dissolved into 360 ml water, extracted with 120 ml dichloromethane, adjusted to pH 3.2 with sodium hydroxide, and the resulting slurry stirred at room temperature overnight. The slurry was cooled to 4°C for one hour. The solids were isolated by filtration, washed with water (2x), and dried *in*

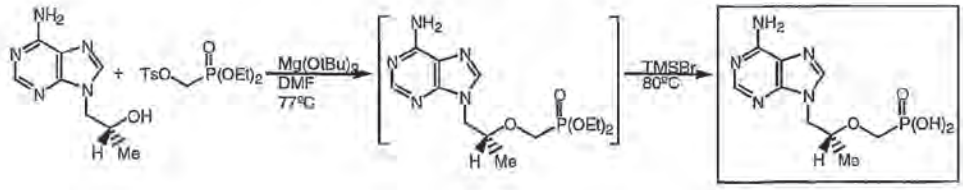
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vacuo at 56°C to yield 20g (65.4%) of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as a white solid. Mp: > 200°C dec. ^{1}H NMR (D_2O) • 3.49 (t, 2H); 3.94 (t, 2H); 4.39 (t, 2H); 8.13 (s, 1H); 8.22 (s, 1H).

Example 1b



Adenine to PMPA using Magnesium t-Butoxide. To a suspension of adenine (40g, 0.296 mol) in DMF (41.9 ml) was added *(R)*-propylene carbonate (34.5g, 0.338 mol) and sodium hydroxide (.480g, 0.012 mol). The mixture was heated at 130°C overnight. The reaction was cooled to 100°C and toluene (138 ml) was added followed by methanesulfonic acid (4.7g, 0.049 mol) while maintaining the reaction temperature between 100-110°C. Additional toluene (114 ml) was added to create a homogeneous solution. The solution was cooled to 3°C over 7 hours and then held at 3°C for one hour. The resulting solid was isolated by filtration and rinsed with acetone (2x). The wet solid was dried *in vacuo* at 80°C to yield 42.6g (75%) of *(R)*-9-[2-(hydroxy)propyl]adenine (HPA) as an off-white solid. Mp: 188-190°C.



(R)-9-[2-(hydroxy)propyl]adenine (HPA) (20.0g, 0.104 mol) was suspended in DMF (44.5 ml) and heated to 65°C. Magnesium t-butoxide (14.2g, 0.083 mol), or alternatively magnesium isopropoxide, was added to the mixture over one hour followed by diethyl *p*-toluenesulfonyloxymethylphosphonate (66.0g, 0.205 mol)

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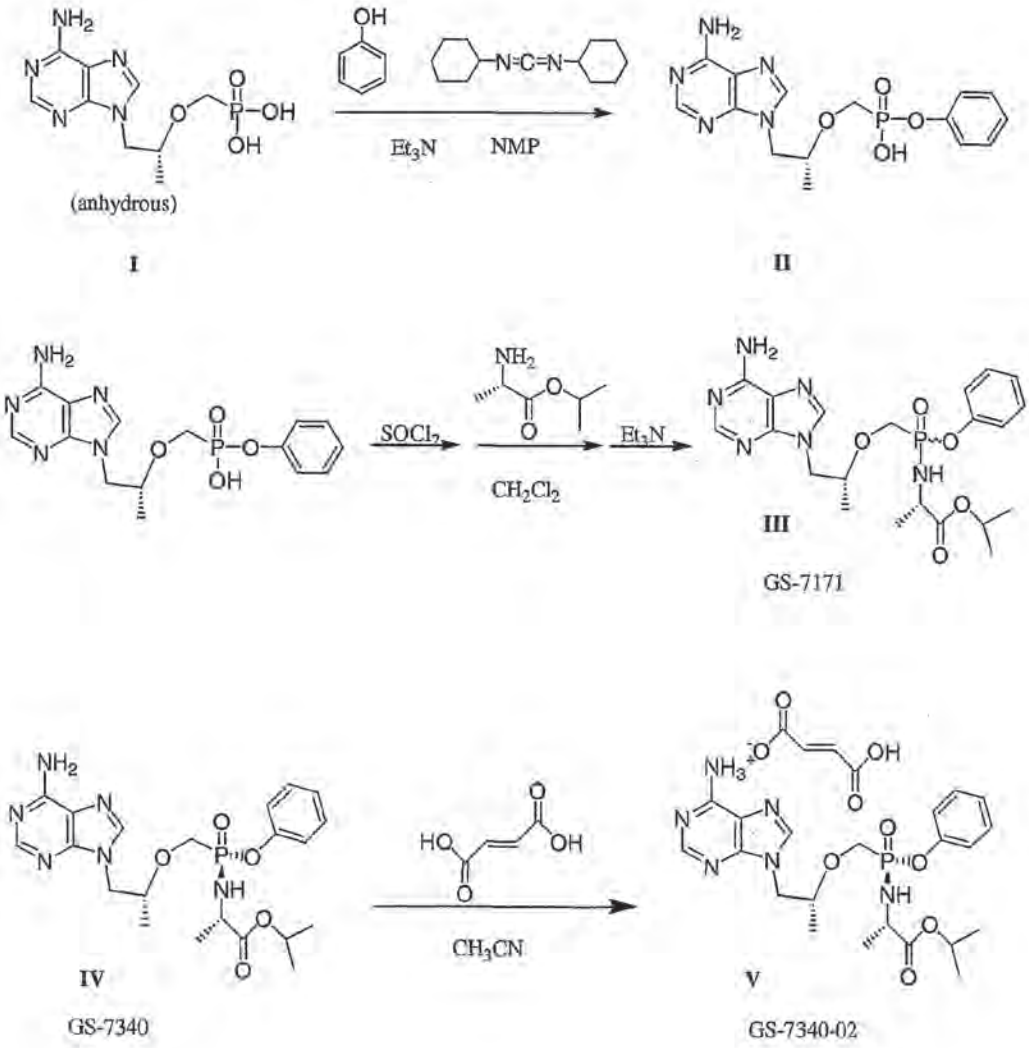
over two hours while the temperature was kept at 78°C. The mixture was stirred at 75°C for 4 hours. After cooling to below 50°C, bromotrimethylsilane (73.9g, 0.478 mol) was added and the mixture heated to 77°C for 3 hours. When complete, the reaction was heated to 80°C and volatiles were removed via atmospheric distillation. The residue was dissolved into water (120 ml) at 50°C and then extracted with ethyl acetate (101 ml). The pH of the aqueous phase was adjusted to pH 1.1 with sodium hydroxide, seeded with authentic *(R)*-PMPA, and the pH of the aqueous layer was readjusted to pH 2.1 with sodium hydroxide. The resulting slurry was stirred at room temperature overnight. The slurry was cooled to 4°C for three hours. The solid was isolated by filtration, washed with water (60 ml), and dried *in vacuo* at 50°C to yield 18.9g (63.5%) of crude*(R)*-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as an off-white solid.

The crude*(R)*-9-[2-(phosphonomethoxy)propyl]adenine was heated at reflux in water (255 ml) until all solids dissolved. The solution was cooled to room temperature over 4 hours. The resulting slurry was cooled at 4°C for three hours. The solid was isolated by filtration, washed with water (56 ml) and acetone (56 ml), and dried *in vacuo* at 50°C to yield 15.0g (50.4%) of *(R)*-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) as a white solid. Mp: 278-280°C.

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Example 2
Preparation of GS-7171 (III)

Scheme 1



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A glass-lined reactor was charged with anhydrous PMPA, (I) (14.6 kg, 50.8 mol), phenol (9.6 kg, 102 mol), and 1-methyl-2-pyrrolidinone (39 kg). The mixture was heated to 85°C and triethylamine (6.3 kg, 62.3 mol) added. A solution of 1,3-dicyclohexylcarbodiimide (17.1 kg, 82.9 mol) in 1-methyl-2-pyrrolidinone (1.6 kg) was then added over 6 hours at 100°C. Heating was continued for 16 hours. The reaction was cooled to 45°C, water (29 kg) added, and cooled to 25°C. Solids were removed from the reaction by filtration and rinsed with water (15.3 kg). The combined filtrate and rinse was concentrated to a tan slurry under reduced pressure, water (24.6 kg) added, and adjusted to pH = 11 with NaOH (25% in water). Fines were removed by filtration through diatomaceous earth (2 kg) followed by a water (4.4 kg) rinse. The combined filtrate and rinse was extracted with ethyl acetate (28 kg). The aqueous solution was adjusted to pH = 3.1 with HCl (37% in water) (4 kg). Crude II was isolated by filtration and washed with methanol (12.7 kg). The crude II wet cake was slurried in methanol (58 kg). Solids were isolated by filtration, washed with methanol (8.5 kg), and dried under reduced pressure to yield 9.33 kg II as a white powder: ^{1}H NMR (D_2O) δ 1.2 (d, 3H), 3.45 (q, 2H), 3.7 (q, 2H), 4 (m, 2H), 4.2 (q, 2H), 4.35 (dd, 2H), 6.6 (d, 2H), 7 (t, 1H), 7.15 (t, 2H), 8.15 (s, 1H), 8.2 (s, 1H); ^{31}P NMR (D_2O) δ 15.0 (decoupled).

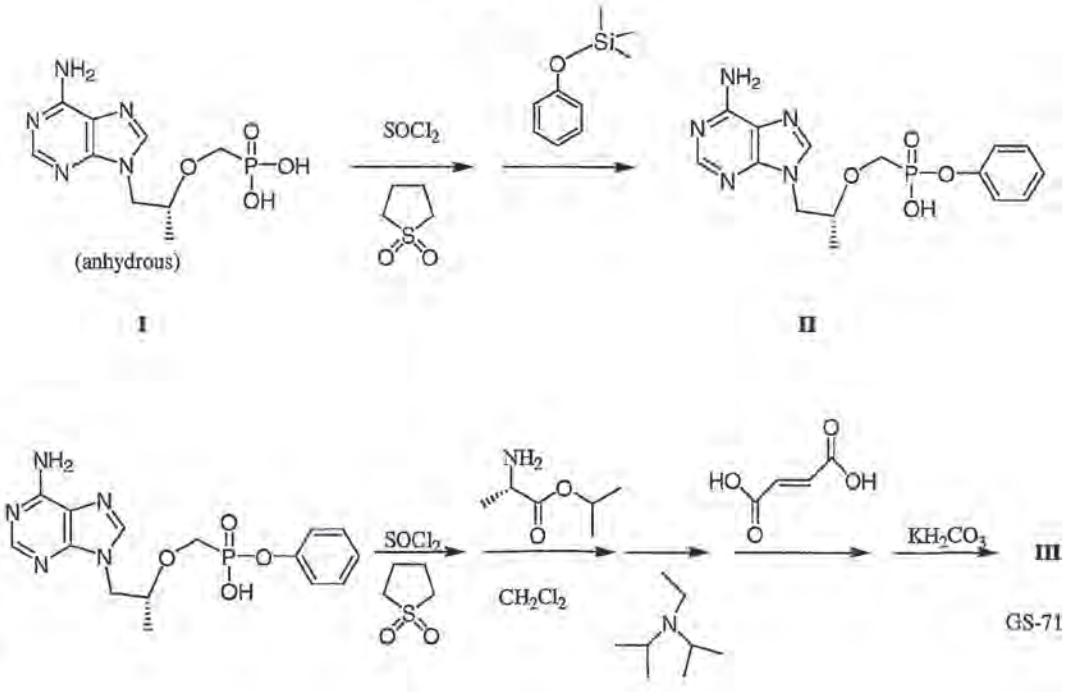
GS-7171 (III). (Scheme 1) A glass-lined reactor was charged with monophenyl PMPA, (II), (9.12 kg, 25.1 mol) and acetonitrile (30.7 kg). Thionyl chloride (6.57 kg, 56.7 mol) was added below 50°C. The mixture was heated at 75°C until solids dissolved. Reaction temperature was increased to 80°C and volatiles (11.4 kg) collected by atmospheric distillation under nitrogen. The pot residue was cooled to 25°C, dichloromethane (41 kg) added, and cooled to –29°C. A solution of (L)-alanine isopropyl ester (7.1 kg, 54.4 mol) in dichloromethane (36 kg) was added over 60 minutes at –18°C followed by triethylamine (7.66 kg, 75.7 mol) over 30 minutes at –18 to –11°C. The reaction mixture was warmed to room temperature and washed five times with sodium dihydrogenphosphate solution (10% in water, 15.7 kg each wash). The organic solution was dried with anhydrous sodium sulfate (18.2 kg), filtered, rinsed with dichloromethane (28 kg), and concentrated to an oil

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under reduced pressure. Acetone (20 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetone (18.8 kg) was charged to the resulting oil. Half the product solution was purified by chromatography over a 38 x 38 cm bed of 22 kg silica gel 60, 230 to 400 mesh. The column was eluted with 480 kg acetone. The purification was repeated on the second half of the oil using fresh silica gel and acetone. Clean product bearing fractions were concentrated under reduced pressure to an oil. Acetonitrile (19.6 kg) was charged to the oil and the mixture concentrated under reduced pressure. Acetonitrile (66.4 kg) was charged and the solution chilled to 0 to –5°C for 16 hours. Solids were removed by filtration and the filtrate concentrated under reduced pressure to 5.6 kg III as a dark oil: ^{1}H NMR ($CDCl_3$) δ 1.1 (m 12H), 3.7 (m, 1H), 4.0 (m, 5H), 4.2 (m, 1H), 5.0 (m, 1H), 6.2 (s, 2H), 7.05 (m, 5H), 8.0 (s, 1H), 8.25 (d, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0, 22.5 (decoupled).

Alternate Method for GS-7171(III)

Scheme 2



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Monophenyl PMPA (II). A round-bottom flask with reflux condenser and nitrogen inlet was placed in a 70°C oil bath. The flask was charged with anhydrous PMPA (I) (19.2 g, 67 mmol), *N,N*-dimethylformamide (0.29 g, 3.3 mmol), and tetramethylene sulfone (40 mL). Thionyl chloride (14.2 g, 119 mmol) was added over 4 hours. Heating was increased to 100°C over the same time. A homogeneous solution resulted. Phenoxytrimethylsilane (11.7 g, 70 mmol) was added to the solution over 5 minutes. Heating in the 100°C oil bath continued for two hours more. The reaction was poured into rapidly stirring acetone (400 mL) with cooling at 0°C. Solids were isolated by filtration, dried under reduced pressure, and dissolved in methanol (75 mL). The solution pH was adjusted to 3.0 with potassium hydroxide solution (45% aq.) with cooling in ice/water. The resulting solids were isolated by filtration, rinsed with methanol, and dried under reduced pressure to 20.4 g II (Scheme 2) as a white powder.

GS-7171 (III). Monophenyl PMPA (II) (3 g, 8.3 mmol), tetramethylene sulfone (5 mL), and *N,N*-dimethylformamide (1 drop) were combined in a round bottom flask in a 40°C oil bath. Thionyl chloride (1.96 g, 16.5 mmol) was added. After 20 minutes the clear solution was removed from heat, diluted with dichloromethane (10 ml), and added to a solution of (L)-alanine isopropyl ester (5g, 33 mmol) and diisopropylethylamine (5.33 g, 41 mmol) in dichloromethane (20 mL) at -10°C. The reaction mixture was warmed to room temperature and washed three times with sodium dihydrogenphosphate solution (10% aq., 10 mL each wash). The organic solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to a oil. The oil was combined with fumaric acid (0.77g, 6.6 mmol) and acetonitrile (40 mL) and heated to reflux to give a homogeneous solution. The solution was cooled in an ice bath and solids isolated by filtration. The solid GS-7171 fumarate salt was dried under reduced pressure to 3.7 g. The salt (3.16 g, 5.3 mmol) was suspended in dichloromethane (30 mL) and stirred with potassium carbonate solution (5 mL, 2.5 M in water) until the solid dissolved. The organic layer was isolated, then washed with water (5 mL), dried over anhydrous

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sodium sulfate, and concentrated under reduced pressure to afford 2.4 g III as a tan foam.

Example 3

A. Diastereomer Separation by Batch Elution Chromatography

The diastereomers of GS-7171 (III) were resolved by batch elution chromatography using a commercially available Chiralpak AS, 20 μm, 21 x 250 mm semi-preparative HPLC column with a Chiralpak AS, 20 μm, 21 x 50 mm guard column. Chiralpak® AS is a proprietary packing material manufactured by Diacel and sold in North America by Chiral Technologies, Inc. (U. S. Patent Nos. 5,202,433, RE 35,919, 5,434,298, 5,434,299 and 5,498,752). Chiralpak AS is a chiral stationary phase (CSP) comprised of amylosetris[(*S*)-α-methylbenzyl carbamate] coated onto a silica gel support.

The GS-7171 diastereomeric mixture was dissolved in mobile phase, and approximately 1 g aliquots of GS-7171 were pumped onto the chromatographic system. The undesired diastereomer, designated GS-7339, was the first major broad (approx. 15 min. duration) peak to elute from the column. When the GS-7339 peak had finished eluting, the mobile phase was immediately switched to 100% methyl alcohol, which caused the desired diastereomer, designated GS-7340 (IV), to elute as a sharp peak from the column with the methyl alcohol solvent front. The methyl alcohol was used to reduce the over-all cycle time. After the first couple of injections, both diastereomers were collected as a single large fractions containing one of the purified diastereomers (>99.0% single diastereomer). The mobile phase solvents were removed *in vacuo* to yield the purified diastereomer as a friable foam.

About 95% of the starting GS-7171 mass was recovered in the two diastereomer fractions. The GS-7340 fraction comprised about 50% of the total recovered mass.

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The chromatographic conditions were as follows:

Mobile Phase(Initial)	: GS-7171 – Acetonitrile : Isopropyl Alcohol (90:10)
(Final)	: 100% Methyl Alcohol
Flow	: 10 mL/minute
Run Time	: About 45 minute
Detection	: UV at 275 nm
Temperature	: Ambient
Elution Profile	: GS-7339 (diastereomer B)
	: GS-7340 (diastereomer A; **(IV)**)

B. Diastereomer Separation of GS-7171 by SMB Chromatography

For a general description of simulated moving bed (SMB) chromatography, see Strube et al., "Organic Process Research and Development" 2:305-319 (1998).

GS-7340 (IV). GS-7171 **(III)**, 2.8 kg, was purified by simulated moving bed chromatography over 10 cm by 5 cm beds of packing (Chiral Technologies Inc., 20 micron Chiralpak AS coated on silica gel) (1.2 kg). The columns were eluted with 30% methanol in acetonitrile. Product bearing fractions were concentrated to a solution of **IV** in acetonitrile (2.48 kg). The solution solidified to a crystalline mass wet with acetonitrile on standing. The crystalline mass was dried under reduced pressure to a tan crystalline powder, 1.301 kg **IV**, 98.7% diastereomeric purity: mp 117 – 120°C; ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 4.0 (m, 5H), 4.2 (dd, 1H), 5.0 (m, 1H), 6.05 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21.0 (decoupled).

C. Diastereomer Separation by C18 RP-HPLC

GS-7171 (III) was chromatographed by reverse phase HPLC to separate the diastereomers using the following summary protocol.

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Chromatographic column: Phenomenex Luna™ C18(2), 5 µm, 100 Å pore size, (Phenomenex, Torrance, CA), or equivalent
Guard column: Pellicular C18 (Alltech, Deerfield, IL), or equivalent
Mobile Phase: A — 0.02% (85%) H_3PO_4 in water : acetonitrile (95:5)
B — 0.02% (85%) H_3PO_4 in water : acetonitrile (50:50)

Mobile Phase Gradient:

Time	% Mobile Phase A	% Mobile Phase B
0	100	0
5	100	0
7	70	30
32	70	30
40	0	100
50	0	100

Run Time: 50 minutes
Equilibration Delay: 10 min at 100% mobile phase A
Flow Rate: 1.2 mL/min
Temperature: Ambient
Detection: UV at 260 nm
Sample Solution: 20 mM sodium phosphate buffer, pH 6
Retention Times: GS-7339, about 25 minutes
GS-7340, about 27 minutes

D. Diastereomer Separation by Crystallization

GS-7340 (IV). A solution of GS-7171 (**III**) in acetonitrile was concentrated to an amber foam (14.9g) under reduced pressure. The foam was dissolved in acetonitrile (20 mL) and seeded with a crystal of **IV**. The mixture was stirred overnight, cooled to 5°C, and solids isolated by filtration. The solids were dried to 2.3 g **IV** as white crystals, 98% diastereomeric purity (^{31}P NMR): ^{1}H NMR ($CDCl_3$) δ 1.15 (m 12H), 3.7 (t, 1H), 3.95 (m, 2H), 4.05 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 6.4 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.2 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 19.5 (decoupled). X-ray crystal analysis of a single crystal selected from this product yielded the following data:

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Crystal Color, Habit	colorless, column
Crystal Diminsions	0.25 X 0.12 X 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 8.352(1) Å
	b = 15.574(2) Å
	c = 18.253(2) Å
	V = 2374.2(5) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.333 g/cm^3
F_{000}	1008.00
μ(MoKα)	1.60 cm^{-1}

Example 4

Preparation of Fumarate Salt of **GS-7340**

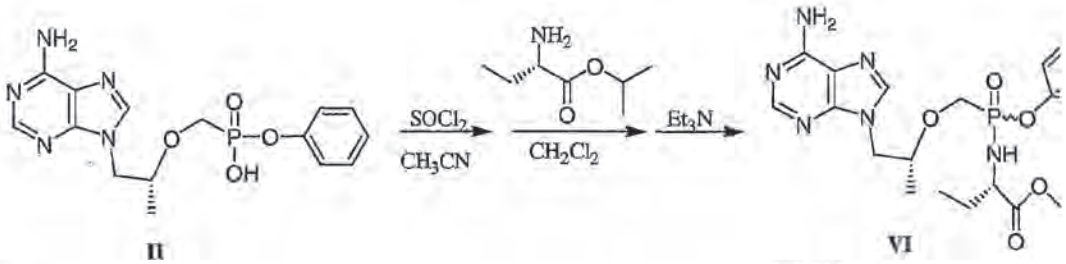
GS-7340-02 (V). (Scheme 1) A glass-lined reactor was charged with GS-7340 (**IV**), (1.294 kg, 2.71 mol), fumaric acid (284 g, 2.44 mol), and acetonitrile (24.6 kg). The mixture was heated to reflux to dissolve the solids, filtered while hot and cooled to 5°C for 16 hours. The product was isolated by filtration, rinsed with acetonitrile (9.2 kg), and dried to 1329 g (**V**) as a white powder: mp 119.7 - 121.1°C; $[\alpha]_D^{20}$ –41.7° (*c* 1.0, acetic acid).

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Example 5

Preparation of **GS-7120 (VI)**

Scheme 3



II VI

GS-7120

A 5 L round bottom flask was charged with monophenyl PMPA, (II), (200 g, 0.55 mol) and acetonitrile (0.629 kg). Thionyl chloride (0.144 kg, 1.21 mol) was added below 27°C. The mixture was heated at 70°C until solids dissolved. Volatiles (0.45 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25°C, dichloromethane (1.6 kg) was added and the mixture was cooled to –20°C. A solution of (L)-α aminobutyric acid ethyl ester (0.144 kg, 1.1 mol) in dichloromethane (1.33 kg) was added over 18 minutes at –20 to -10°C followed by triethylamine (0.17 kg, 1.65 mol) over 15 minutes at –8 to –15°C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.3 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.5 kg) and filtered. The solids were rinsed with dichloromethane (0.6 kg) and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was purified by chromatography over a 15 x 13 cm bed of 1.2 kg silica gel 60, 230 to 400 mesh. The column was eluted with a gradient of dichloromethane and methanol. Product bearing fractions were concentrated under reduced pressure to afford 211 g **VI** (Scheme 3) as a tan foam.

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Example 5a

Diastereomer Separation of **GS-7120** by Batch Elution Chromatography

The diastereomeric mixture was purified using the conditions described for GS-7171 in Example 3A except for the following:

Mobile Phase	(Initial)	: GS-7120 – Acetonitrile : Isopropyl Alcohol (98:2)
	(Final)	: 100% Methyl Alcohol
Elution Profile		: GS-7341 (diastereomer B)
		: GS-7342 (diastereomer A)

Example 6

Diastereomer Separation of **GS-7120** by Crystallization

A 1 L round bottom flask was charged with monophenyl PMPA, (**II**), (50 g, 0.137 mol) and acetonitrile (0.2 L). Thionyl chloride (0.036 kg, 0.303 mol) was added with a 10°C exotherm. The mixture was heated to reflux until solids dissolved. Volatiles (0.1 L) were removed by atmospheric distillation under nitrogen. The pot residue was cooled to 25°C, dichloromethane (0.2 kg) was added, and the mixture was cooled to –20°C. A solution of (L)-α aminobutyric acid ethyl ester (0.036 kg, 0.275 mol) in dichloromethane (0.67 kg) was added over 30 minutes at –20 to -8°C followed by triethylamine (0.042 kg, 0.41 mol) over 10 minutes at up to –6°C. The reaction mixture was warmed to room temperature and washed four times with sodium dihydrogenphosphate solution (10% aq., 0.075 L each wash). The organic solution was dried with anhydrous sodium sulfate (0.1 kg) and filtered. The solids were rinsed with ethyl acetate (0.25 L, and the combined filtrate and rinse was concentrated to an oil under reduced pressure. The oil was diluted with ethyl acetate (0.25 L), seeded, stirred overnight, and chilled to – 15°C. The solids were isolated by filtration and dried under reduced pressure to afford 17.7 g of GS-7342 (Table 5) as a tan powder: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.3 (m, 6H), 1.7, (m, 2H),

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3.7 (m, 2H), 4.1(m, 6H), 4.4 (dd, 1H), 5.8 (s, 2H), 7.1 (m, 5H), 8.0 (s, 1H), 8.4 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 21 (decoupled).

Example 7

Diastereomer Separation of GS-7097

The diastereomeric mixture was purified using the conditions described for GS-7171 (Example 3A) except for the following:

Mobile Phase	(Initial)	: GS-7120 – Acetonitrile : Isopropyl Alcohol (95:5)
	(Final)	: 100% Methyl Alcohol
Elution Profile		: GS-7115 (diastereomer B)
		: GS-7114 (diastereomer A)

Example 8

Alternative Procedure for Preparation of GS-7097

GS-7097: Phenyl PMPA, Ethyl L-Alanyl Amidate. Phenyl PMPA (15.0 g, 41.3 mmol), L-alanine ethyl ester hydrochloride (12.6 g, 83 mmol) and triethylamine (11.5 mL, 83 mmol) were slurried together in 500 mL pyridine under dry N_2. This suspension was combined with a solution of triphenylphosphine (37.9 g, 145 mmol), Aldrithiol 2 (2,2'-dipyridyl disulfide) (31.8 g, 145 mmol), and 120 mL pyridine. The mixture was heated at an internal temperature of 57°C for 15 hours. The complete reaction was concentrated under vacuum to a yellow paste, 100 g. The paste was purified by column chromatography over a 25 x 11 cm bed of 1.1 kg silica gel 60, 230 to 400 mesh. The column was eluted with 8 liters of 2% methanol in dichloromethane followed by a linear gradient over a course of 26 liters eluent up to a final composition of 13% methanol. Clean product bearing fractions were concentrated to yield 12.4 g crude (5), 65% theory. This material was contaminated with about 15% (weight) triethylamine hydrochloride by ^1H NMR. The contamination was removed by dissolving the product in 350 mL ethyl acetate, extracting with 20 mL water, drying the organic solution over anhydrous sodium

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sulfate, and concentrating to yield 11.1 g pure GS-7097 as a white solid, 58% yield. The process also is employed to synthesize the diastereomeric mixture of GS-7003a and GS-7003b (the phenylalanyl amidate) and the mixture GS-7119 and GS-7335 (the glycyl amidate). These diastereomers are separated using a batch elution procedure such as shown in Example 3A, 6 and 7.

Example 9

In Vitro Studies of Prodrug Diastereomers

The *in vitro* anti-HIV-1 activity and cytotoxicity in MT-2 cells and stability in human plasma and MT-2 cell extracts of GS-7340 (freebase) and tenofovir disoproxil fumarate (TDF), are shown in Table 1. GS-7340 shows a 10-fold increase in antiviral activity relative to TDF and a 200-fold increase in plasma stability. This greater plasma stability is expected to result in higher circulating levels of GS-7340 than TDF after oral administration.

Table 1. *In Vitro* Activity and Stability

	HIV-1 Activity	Cytotoxicity	Stability T 1/2 (min)		
	$IC_{50\mu M}$	$CC_{50\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0.005	> 40	90.0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	--	--	--

In order to estimate the relative intracellular PMPA resulting from the intracellular metabolism of TDF as compared to that from GS-7340, both prodrugs and PMPA were radiolabeled and spiked into intact human whole blood at equimolar concentrations. After 1 hour, plasma, red blood cells (RBCs) and peripheral blood mononuclear cells (PBMCs) were isolated and analyzed by HPLC with radiometric detection. The results are shown in Table 2.

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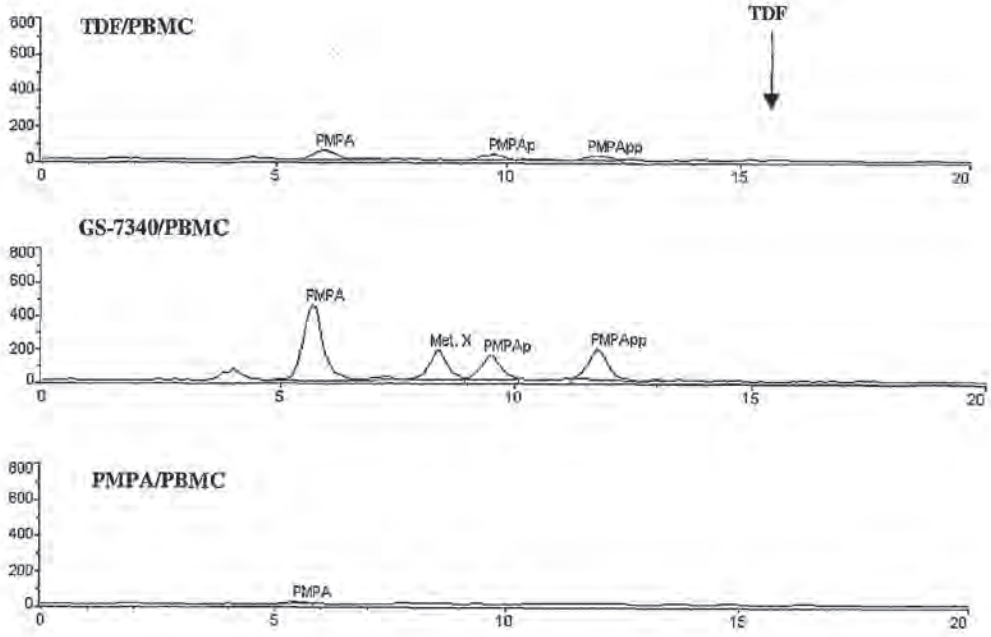
After 1 hour, GS-7340 results in 10x and 30x the total intracellular concentration of PMPA species in PBMCs as compared to TDF and PMPA, respectively. In plasma after 1 hour, 84% of the radioactivity is due to intact GS-7340, whereas no TDF is detected at 1 hour. Since no intact TDF is detected in plasma, the 10x difference at 1 hour between TDF and GS-7340 is the minimum difference expected *in vivo*. The HPLC chromatogram for all three compounds in PBMCs is shown in Figure 1.

Table 2. PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340 (60 µg-eq)	Plasma/FP	43.0	1	-	-	2	13	84
	PBMC	1.25	45	16	21	18	-	-
	RBC/FP	12.6	8	-	-	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331 (TDF) (60 µg-eq)	Plasma/FP	48.1	11	-	-	89	-	
	PBMC	0.133	50	25	18	7	-	
	RBC/FP	10.5	93	7.0	-	-	-	
			PMPA	PMPAp	PMPApp			
PMPA (60 µg-eq)	Plasma/FP	55.7	100	-	-			
	PBMC	0.033	86	14	-			
	RBC/FP	3.72	74	10	16			

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Figure 1. HPLC/C-14 Traces of PBMC Extracts from Human Blood Incubated for 1 h at 37°C with TDF, GS-7340 or PMPA.



Met. X and Met Y (metabolites X and Y) are shown in Table 5. Lower case "p" designates phosphorylation. These results were obtained after 1 hour in human blood. With increasing time, the *in vitro* differences are expected to increase, since 84% of GS-7340 is still intact in plasma after one hour. Because intact GS-7340 is present in plasma after oral administration, the relative clinical efficacy should be related to the IC_{50} values seen *in vitro*.

In Table 3 below, IC_{50} values of tenofovir, TDF, GS-7340, several nucleosides and the protease inhibitor nelfinivir are listed. As shown, nelfinavir and GS-7340 are 2-3 orders of magnitude more potent than all other nucleotides or nucleosides.

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Table 3. *In Vitro* Anti-HIV-1 Activities of Antiretroviral Compounds

Compound	IC_{50} (μM)
Adefovir (PMEA)	13.4 ± 4.2[1]
Tenofovir (PMPA)	6.3 ± 3.3[1]
AZT	0.17 ± 0.08[1]
3TC	1.8 ± 0.25[1]
d4T	8 ± 2.5[1]
Nelfinavir	0.006 ± 0.002[1]
TDF	0.05
GS 7340	0.005

1. A. S. Mulato and J. M. Cherrington, *Antiviral Research* **36**, 91 (1997)

Additional studies of the *in vitro* cell culture anti-HIV-1 activity and CC_{50} of separated diastereomers of this invention were conducted and the results tabulated below.

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Table 4. Effect of Diastereomer

Compound	Diastereomer	IC_{50} (μM)	Fold change	A/B activity	CC_{50} (μM)
PMPA	-	5	1x	-	6000
Ala-methylester	Mixture 1:1	0.025	200x	20x	80
GS-6957a	A	0.0075	670x		
GS-6957b		0.15	33x		
Phe-methylester	Mixture 1:1	0.03	170x	10x	60
GS-7003a	A	0.01	500x		
GS-7003b	B	0.1	50x		
Gly-ethylester	Mixture 1:1	0.5	10x	20x	
GS-7119	A	0.05	100x		>100
GS-7335	B	1.0	5x		
Ala-isopropyl	Mixture 1:1	0.01	500x	12x	
GS-7340	A	0.005	1,000x		40
GS-7339	B	0.06	83x		>100
ABA-ethyl	Mixture 1:1	0.008	625x	7.5x	>100
GS-7342	A	0.004	1,250x		
GS-7341	B	0.03	170x		
Ala-ethyl	Mixture 1:1	0.02	250x	10x	60
GS- 7114	A	0.005	1,000x		
GS- 7115	B	0.05	100x		

Assay reference: Arimilli, MN, et al., (1997) Synthesis, *in vitro* biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Antiviral Chemistry and Chemotherapy 8(6):557-564.

"Phe-methylester" is the methylphenylalaninyl monoamidate, phenyl monoester of tenofovir; "gly-methylester" is the methylglycyl monoamidate, phenyl monoester of tenofovir.

In each instance above, isomer A is believed to have the same absolute stereochemistry as GS-7340 (*S*), and isomer B is believed to have the same absolute stereochemistry that of GS-7339.

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The *in vitro* metabolism and stability of separated diastereomers were determined in PLCE, MT-2 extract and human plasma. A biological sample listed below, 80 µL, was transferred into a screw-capped centrifuge tube and incubated at 37°C for 5 min. A solution containing 0.2 mg/mL of the test compound in a suitable buffer, 20 µL, was added to the biological sample and mixed. The reaction mixture, 20 µL, was immediately sampled and mixed with 60 µL of methanol containing 0.015 mg/mL of 2-hydroxymethylnaphthalene as an internal standard for HPLC analysis. The sample was taken as the time-zero sample. Then, at specific time points, the reaction mixture, 20 µL, was sampled and mixed with 60 µL of methanol containing the internal standard. The mixture thus obtained was centrifuged at 15,000 G for 5 min and the supernatant was analyzed with HPLC under the conditions described below.

The biological samples evaluated are as follows.

(1) PLCE (porcine liver carboxyesterase from Sigma, 160 u/mg protein, 21 mg protein/mL) diluted 20 fold with PBS (phosphated-buffered saline).

(2) MT-2 cell extract was prepared from MT-2 cells according to the published procedure [A. Pompon, I. Lefebvre, J.-L. Imbach, S. Kahn, and D. Farquhar, "Antiviral Chemistry & Chemotherapy", 5:91–98 (1994)] except for using HEPES buffer described below as the medium.

(3) Human plasma (pooled normal human plasma from George King Biomedical Systems, Inc.)

The buffer systems used in the studies are as follows.

In the study for PLCE, the test compound was dissolved in PBS. PBS (phosphate-buffered saline, Sigma) contains 0.01 M phosphate, 0.0027 M potassium chloride, and 0.137 M sodium chloride. pH 7.4 at 37°C.

In the study for MT-2 cell extracts, the test compound was dissolved in HEPES buffer. HEPES buffer contains 0.010 M HEPES, 0.05 M potassium chloride, 0.005 M magnesium chloride, and 0.005 M *dl*-dithiothreitol. pH 7.4 at 37°C.

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In the study for human plasma, the test compound was dissolved in TBS. TBS (tris-buffered saline, Sigma) contains 0.05 M Tris, 0.0027 M potassium chloride, and 0.138 M sodium chloride. pH 7.5 at 37°C.

The HPLC analysis was carried out under the following conditions.

Column:	Zorbax R_X-C8, 4.6 x 250 mm, 5 µ (MAC-MOD Analytical, Inc. Chadds Ford, PA)
Detection:	UV at 260 nm
Flow Rate:	1.0 mL/min
Run Time:	30 min
Injection Volume:	20 µL
Column Temperature:	Ambient temperature

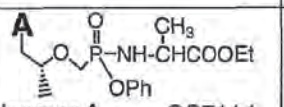
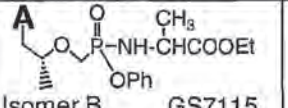
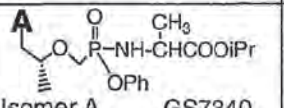
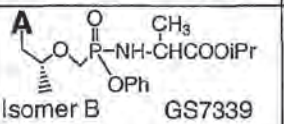
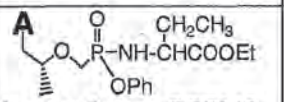
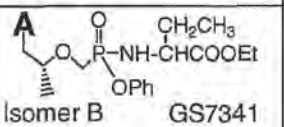
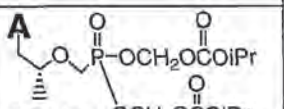
Mobile Phase A:	50 mM potassium phosphate (pH 6.0)/CH_3CN = 95/5 (v/v)
Mobile Phase B:	50 mM Potassium phosphate (pH 6.0)/CH_3CN = 50/50 (v/v)

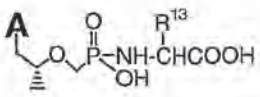
Gradient Run:	0 min	100% Mobile Phase A
	25 min	100% Mobile Phase B
	30 min	100% Mobile Phase B

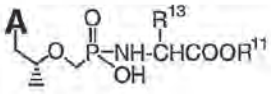
The results are shown below in Table 5 (also including selected IC_{50} data from Table 4).

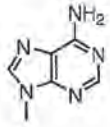
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Table 5. In Vitro Metabolism of Isomers A and B of PMPA monoamidate at 37°C

No	PMPA monoamidate structure	HIV IC_{50} (μM)	PLCE hydrolysis rate and product	MT-2 extract hydrolysis rate and product	Human Plasma Stability (HP)
1	 Isomer A GS7114	0.005	$t_{1/2}$ = 2.9 min Met. X & PMPA	$t_{1/2}$ = 2.9 min Met. X & PMPA	$t_{1/2}$ = 148 min Met. Y
2	 Isomer B GS7115	0.05	$t_{1/2}$ = 8.0 min Met. X & PMPA	$t_{1/2}$ = 150.6 min Met. X & PMPA	$t_{1/2}$ = 495 min Met. Y
3	 Isomer A GS7340	0.005	$t_{1/2}$ = 3.3 min Met. X & PMPA	$t_{1/2}$ = 28.3 min Met. X & PMPA	$t_{1/2}$ = 90.0 min Met. Y
4	 Isomer B GS7339	0.06	$t_{1/2}$ = 10.1 min Met. X & PMPA	$t_{1/2}$ > 1000 min	$t_{1/2}$ = 231 min Met. Y
5	 Isomer A GS7342	0.004	$t_{1/2}$ = 3.9 min Met. X	$t_{1/2}$ = 49.2 min Met. X & PMPA	$t_{1/2}$ = 103 min Met. Y
6	 Isomer B GS7341	0.03	$t_{1/2}$ = 11.3 min Met. X	$t_{1/2}$ > 1000 min	$t_{1/2}$ = 257 min Met. Y
7	 GS4331	0.05	$t_{1/2}$ < 0.14 min MonoPOC PMPA	$t_{1/2}$ = 70.7 min monoPOC PMPA	$t_{1/2}$ = 0.41 min monoPOC PMPA

Met. X: 

Met. Y: 

A = 

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Example 10

Plasma and PBMC Exposures Following Oral Administration Of Prodrug Diastereomers to Beagle Dogs

The pharmacokinetics of GS 7340 were studied in dogs after oral administration of a 10 mg-eq/kg dose.

Formulations. The prodrugs were formulated as solutions in 50 mM citric acid within 0.5 hour prior to dose. All compounds used in the studies were synthesized by Gilead Sciences. The following lots were used:

GSI	Amidate Amino acid	AA Ester	Diastereoisomer	Lot Number
GS-7340-2	Alanine	i-Propyl	Isomer A	1504-187-19
GS-7339	Alanine	i-Propyl	Isomer B	1509-185-31
GS7114	Alanine	Ethyl	Isomer A	1509-181-26
GS7115	Alanine	Ethyl	Isomer B	1509-181-22
GS7119	Glycine	Ethyl	Isomer A	1428-163-28
GS7342	α-Aminobutyric Acid	Ethyl	Isomer A	1509-191-12
GS7341	α-Aminobutyric Acid	Ethyl	Isomer B	1509-191-7

Dose Administration and Sample Collection. The in-life phase of this study was conducted in accordance with the recommendations of the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health publication 86-23) and was approved by an Institutional Animal Care and Use Committee. Fasted male beagle dogs (10 ± 2 kg) were used for the studies. Each drug was administered as a single dose by oral gavage (1.5–2 ml/kg). The dose was 10 mg-equivalent of PMPA/kg. For PBMCs, blood samples were collected at 0 (pre-dose), 2, 8, and 24 h post-dose. For plasma, blood samples were collected at 0 (pre-dose), 5, 15, and 30 min, and 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose. Blood (1.0 ml) was processed immediately for plasma by centrifugation at 2,000 rpm for 10 min. Plasma samples were frozen and maintained at 70°C until analyzed.

Peripheral Blood Mononuclear Cell (PBMC) preparation. Whole blood (8 ml) drawn at specified time points was mixed in equal proportion with phosphate buffered saline (PBS), layered onto 15 ml of Ficoll-Paque solution (Pharmacia Biotech,) and centrifuged at 400 x g for 40 min. PBMC layer was removed and

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washed once with PBS. Formed PMBC pellet was reconstituted in 0.5 ml of PBS, cells were resuspended, counted using hemocytometer and maintained at 70°C until analyzed. The number of cells multiplied by the mean single-cell volume was used in calculation of intracellular concentrations. A reported value of 200 femtoliters/cell was used as the resting PBMC volume (B. L. Robins, R.V. Srinivas, C. Kim, N. Bischofberger, and A. Fridland, Antimicrob. Agents Chemother. 42, 612 (1998).

Determination of PMPA and Prodrugs in plasma and PBMCs. The concentration of PMPA in dog plasma samples was determined by derivatizing PMPA with chloroacetaldehyde to yield a highly fluorescent N^1, N^6-ethenoadenine derivative (L. Naesens, J. Balzarini, and E. De Clercq, Clin. Chem. 38, 480 (1992). Briefly, plasma (100 µl) was mixed with 200 µl acetonitrile to precipitate protein. Samples were then evaporated to dryness under reduced pressure at room temperature. Dried samples were reconstituted in 200 µl derivatization cocktail (0.34% chloroacetaldehyde in 100 mM sodium acetate, pH 4.5), vortexed, and centrifuged. Supernatant was then transferred to a clean screw-cap tube and incubated at 95°C for 40 min. Derivatized samples were then evaporated to dryness and reconstituted in 100 µl of water for HPLC analysis.

Before intracellular PMPA could be determined by HPLC, the large amounts of adenine related ribonucleotides present in the PBMC extracts had to be removed by selective oxidation. We used a modified procedure of Tanaka et al (K. Tanaka, A. Yoshioka, S. Tanaka, and Y. Wataya, Anal. Biochem., 139, 35 (1984). Briefly, PBMC samples were mixed 1:2 with methanol and evaporated to dryness under reduced pressure. The dried samples were derivatized as described in the plasma assay. The derivatized samples were mixed with 20 µL of 1M rhamnose and 30 µL of 0.1M sodium periodate and incubated at 37°C for 5 min. Following incubation, 40 µL of 4M methylamine and 20 µL of 0.5M inosine were added. After incubation at 37°C for 30 min, samples were evaporated to dryness under reduced pressure and reconstituted in water for HPLC analysis.

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No intact prodrug was detected in any PBMC samples. For plasma samples potentially containing intact prodrugs, experiments were performed to verify that no further conversion to PMPA occurred during derivatization. Prodrug standards were added to drug-free plasma and derivatized as described. There were no detectable levels of PMPA present in any of the plasma samples, and the projected % of conversion was less than 1%.

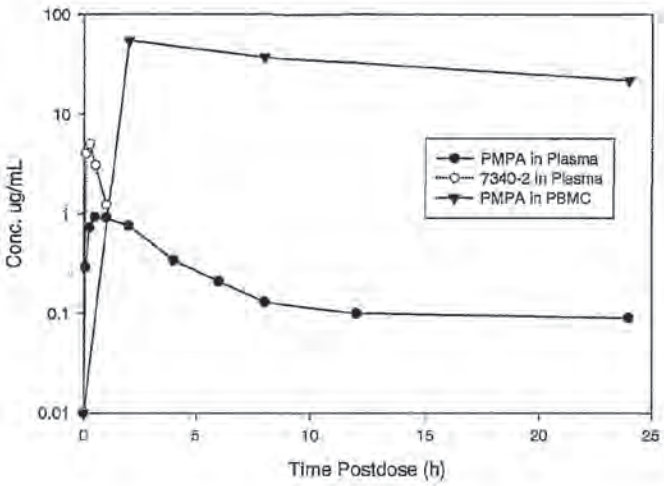
The HPLC system was comprised of a P4000 solvent delivery system with AS3000 autoinjector and F2000 fluorescence detector (Thermo Separation, San Jose, CA). The column was an Inertsil ODS-2 column (4.6 × 150 mm). The mobile phases used were: A, 5% acetonitrile in 25 mM potassium phosphate buffer with 5 mM tetrabutyl ammonium bromide (TBABr), pH 6.0; B, 60% acetonitrile in 25 mM potassium phosphate buffer with 5 mM TBABr, pH 6.0. The flow rate was 2 ml/min and the column temperature was maintained at 35°C by a column oven. The gradient profile was 90% A/10% B for 10 min for PMPA and 65%A/35%B for 10 min for the prodrug. Detection was by fluorescence with excitation at 236 nm and emission at 420 nm, and the injection volume was 10 µl. Data was acquired and stored by a laboratory data acquisition system (PeakPro, Beckman, Allendale, NJ).

Pharmacokinetic Calculations. PMPA and prodrug exposures were expressed as areas under concentration curves in plasma or PBMC from zero to 24 hours (AUC). The AUC values were calculated using the trapezoidal rule.

Plasma and PBMC Concentrations. The results of this study is shown in Figures 2 and 3. Figure 2 shows the time course of GS 7340-2 metabolism summary of plasma and PBMC exposures following oral administration of pure diastereoisomers of the PMPA prodrugs.

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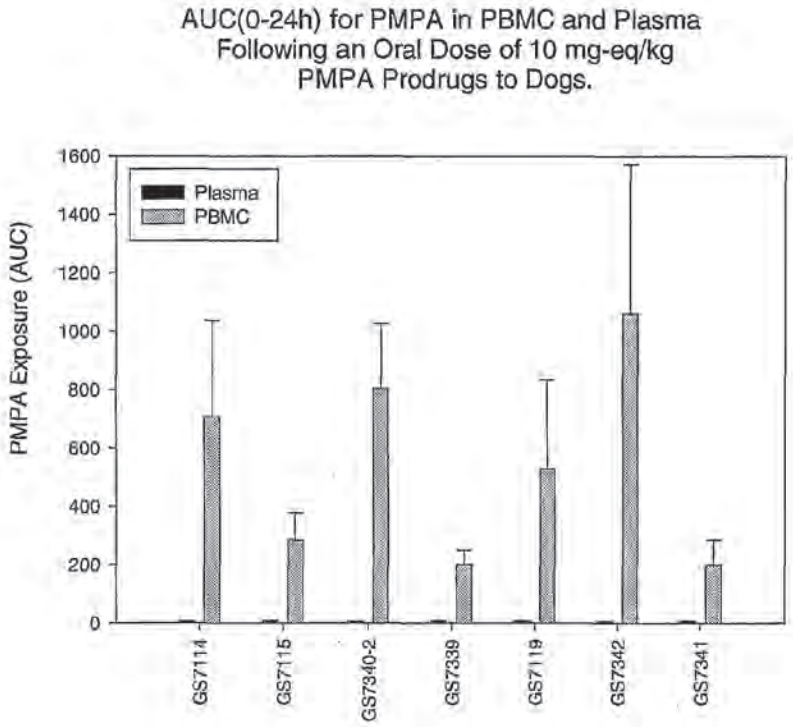
Figure 2. PMPA and Prodrug Concentration in Plasma and PBMCs Following Oral Administration of GS 7340-2 to Dogs at 10 mg-eq/kg.



The bar graph in Figure 2 shows the AUC (0-24h) for tenofovir in dog PBMCs and plasma after administration of PMPA s.c., TDF and amidate ester prodrugs. All of the amidate prodrugs exhibited increases in PBMC exposure. For example, GS 7340 results in a ~21-fold increase in PBMC exposure as compared to PMPA s.c. and TDF; and a 6.25-fold and 1.29-fold decrease in plasma exposure, respectively.

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Figure 3. Depicts Tenofovir Exposure in PBMCs and Plasma Upon Administration of 10 mg-eq/kg in dogs



These data establish *in vivo* that GS 7340 can be delivered orally, minimizes systemic exposure to PMPA and greatly enhances the intracellular concentration of PMPA in the cells primarily responsible for HIV replication.

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Table 6

PMPA Exposure in PBMC and Plasma from Oral Prodrugs of PMPA in Dogs

GS#	Moiety	PMPA AUC in Plasma			PMPA AUC in PBMC			Prodrug in Plasma	PBMC/Plasma Exposure Ratio
		Mean	StDev	N	Mean	StDev	N		
GS-7114	Mono-Ala-Et-A	5.8	0.9	2	706	331	5	YES	122
GS-7115	Mono-Ala-Et-B	6.6	1.5	2	284	94	5	YES	43
GS-7340-2	Mono-Ala-iPr-A	5.0	1.1	5	805	222	5	YES	161
GS-7339	Mono-Ala-iPr-A	6.4	1.3	2	200	57	5	YES	31
GS-7119	Mono-Gly-Et-A	6.11	1.86	2	530	304	5	YES	87
GS-7342	Mono-ABA-Et-A	4.6	1.2	2	1060	511	5	YES	230
GS7341	Mono-ABA-Et-B	5.8	1.4	2	199	86	5	YES	34

Example 11

Biodistribution of GS-7340

As part of the preclinical characterization of GS-7340, its biodistribution in dogs was determined. The tissue distribution of GS-7340 (isopropyl alaninyl monoamidate, phenyl monoester of tenofovir) was examined following oral administration to beagle dogs. Two male animals were dosed orally with ^{14}C=GS-7340 (8.85 mg-equiv. of PMPA/kg, 33.2 μCi/kg; the 8-carbon of adenine is labeled) in an aqueous solution (50 mM citric acid, pH 2.2). Plasma and peripheral blood mononuclear cells (PBMCs) were obtained over the 24-hr period. Urine and feces were cage collected over 24 hr. At 24 h after the dose, the animals were sacrificed and tissues removed for analysis. Total radioactivity in tissues was determined by oxidation and liquid scintillation counting.

The biodistribution of PMPA after 24 hours after a single oral dose of radiolabelled GS 7340 is shown in Table 4 along with the data from a previous study with TDF (GS-4331). In the case of TDF, the prodrug concentration in the plasma is below the level of assay detection, and the main species observed in plasma is the parent drug. Levels of PMPA in the lymphatic tissues, bone marrow, and skeletal muscle are increased 10-fold after administration of GS-7340.

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Accumulation in lymphatic tissues is consistent with the data observed from the PBMC analyses, since these tissues are composed primarily of lymphocytes. Likewise, accumulation in bone marrow is probably due to the high percentage of lymphocytes (70%) in this tissue.

Table 7. Excretion and Tissue Distribution of Radiolabelled GS-7340 in Dogs (Mean, N=2) Following an Oral Dose at 10 mg-eq. PMPA/kg.

Tissue/Fluid	GS-4331		GS-7340		Tissue Conc. Ratio of GS 7340 to GS-4331
	% Dose	Conc. (ug-eq/g)	% Dose	Conc. (ug-eq/g)	
Liver	12.40	38.30	16.45	52.94	1.4
Kidney	4.58	87.90	3.78	80.21	0.9
Lungs	0.03	0.53	0.34	4.33	8.2
Iliac Lymph Nodes	0.00	0.51	0.01	5.42	10.6
Axillary Lymph Nodes	0.00	0.37	0.01	5.54	14.8
Inguinal Lymph Nodes	0.00	0.28	0.00	4.12	15.0
Mesenteric Lymph Nodes	0.00	1.20	0.04	6.88	5.7
Thyroid Gland	0.00	0.30	0.00	4.78	15.8
Pituitary Gland	0.00	0.23	0.00	1.80	7.8
Salivary Gland (L+R)	0.00	0.45	0.03	5.54	12.3
Adrenal Gland	0.00	1.90	0.00	3.47	1.8
Spleen	0.00	0.63	0.17	8.13	12.8
Pancreas	0.00	0.57	0.01	3.51	6.2
Prostate	0.00	0.23	0.00	2.14	9.1
Testes (L+R)	0.02	1.95	0.02	2.01	1.0
Skeletal Muscle	0.00	0.11	0.01	1.12	10.1
Heart	0.03	0.46	0.15	1.97	4.3
Femoral Bone	0.00	0.08	0.00	0.28	3.5
Bone Marrow	0.00	0.20	0.00	2.05	10.2
Skin	0.00	0.13	0.00	0.95	7.2
Abdominal fat	0.00	0.16	0.00	0.90	5.8
Eye (L+R)	0.00	0.06	0.00	0.23	3.7
Brain	0.00	<LOD	0.00	<LOD	n.d.
Cerebrospinal Fluid	0.00	<LOD	0.00	0.00	n.d.
Spinal Cord	0.00	<LOD	0.00	0.04	n.d.
Stomach	0.11	1.92	0.26	2.68	1.4
Jejunum	1.34	3.01	0.79	4.16	1.4
Duodenum	0.49	4.96	0.44	8.77	1.8
Ileum	0.01	0.50	0.16	4.61	9.2
Large Intestine	1.63	5.97	2.65	47.20	7.9
Gall bladder	0.00	3.58	0.04	25.02	7.0
Bile	0.00	9.63	0.22	40.48	4.2
Feces	40.96	n.d.	0.19	n.d.	n.a.
Total GI Tract Contents	5.61	n.d.	21.64	n.d.	n.a.
Urine	23.72	n.d.	14.73	n.d.	n.a.
Plasma at 24 h	0.00	0.20	0.00	0.20	1.0
Plasma at 0.25 h	n.a.	3.68	n.a.	3.48	0.9
PBMC*	0.00	n.d.	0.00	63.20	n.d.
Whole Blood	0.00	0.85	0.16	0.20	0.2
Total Recovery	81.10		68.96		

* Calculated using typical recovery of 15 x 10^6 cells total, and mean PBMC volume of 0.2 picoliters/cell

n.s. = no sample, n.a. = not applicable, n.d. = not determined.

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CLAIMS:

1. A screening method for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue;

(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and

(d) determining the relative activity conferred by the prodrug in the tissues in step (c).

2. The method of claim 1 wherein the activity is antiviral activity or antitumor activity.

3. The method of claim 2 wherein the activity is antiviral activity.

4. The method of claim 3 wherein the activity is anti-HIV or anti-HBV activity.

5. The method of claim 1 wherein the prodrug is a prodrug of PMPA or PMEA.

6. The method of claim 5 wherein the prodrug is a phosphonoamidate, phosphonoester or mixed phosphonoamidate/phosphonoester.

7. The method of claim 6 wherein the amidate is an amino acid amidate.

8. The method of claim 6 wherein the ester is an aryl ester.

9. The method of claim 1 further comprising selecting a prodrug having a relative activity in the target tissue that is greater than 10 times that of the non-target tissue.

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10. The method of claim 1 wherein the target and non-target tissue are in an animal, the prodrug is administered to the animal and the relative activity is determined by analysis of the animal tissues after administration of the prodrug.

11. The method of claim 1 wherein activity in the target and non-target tissues is determined by assaying the amount of at least one metabolite of the prodrug in the tissues.

12. The method of claim 12 wherein the metabolite is the parental drug.

13. The method of claim 12 wherein the metabolite is the diphosphate of the parental drug.

14. The method of claim 1 wherein the target tissue is virally infected tissue and the non-target tissue is the same tissue which is not virally infected.

15. The method of claim 1 wherein the target tissue is lymphoid tissue and the activity is anti-HIV activity.

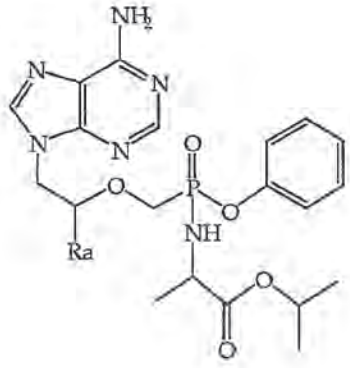
16. The method of claim 1 wherein the target tissue is liver and the activity is anti-HBV activity.

17. The method of claim 1 wherein the target tissue is hematological and the activity is antitumor activity.

18. The method of claim 1 wherein the target tissue is malignant and the non-target tissue is the same tissue but non-malignant.

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19. A compound having the structure (1)

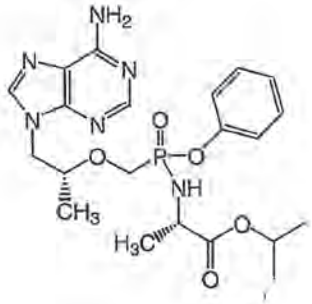


(1)

where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

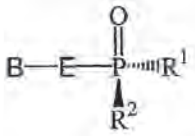
20. A compound having the structure (2)



(2)

and its enriched diasteromers, salts, free base and solvates.

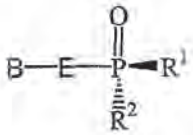
21. A diastereomerically enriched compound having the structure (3)



(3)

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which is substantially free of the diastereomer (4)



(4)

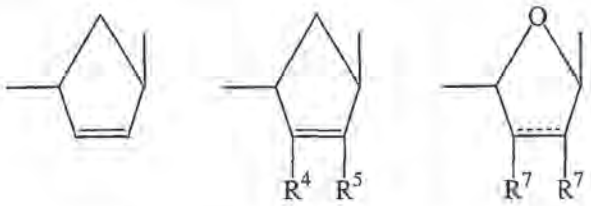
wherein

R^1 is an oxyester which is hydrolyzable *in vivo*, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $-(CH_2)_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2F)CH_2-$, $-CH(CH_2OH)CH_2-$, $-CH(CH=CH_2)CH_2-$, $-CH(C\equiv CH)CH_2-$, $-CH(CH_2N_3)CH_2-$,



$-CH(R^6)OCH(R^{6'})-$, $-CH(R^9)CH_2O-$ or $-CH(R^8)O-$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

R^7 is independently H, C_1-C_6 alkyl, or are taken together to form -O- or $-CH_2-$;

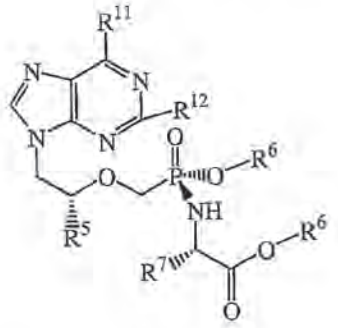
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PGR2023-00046 - Page 00995

R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

R^9 is H, hydroxymethyl or acyloxymethyl;

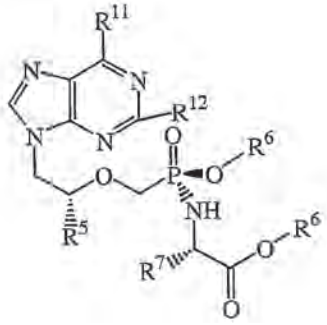
and their salts, free base, and solvates.

22. A diastereomerically enriched compound having the structure (5a)



(5a)

which is substantially free of diastereomer (5b)



(5b)

wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy,

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PGR2023-00046 - Page 00996

alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

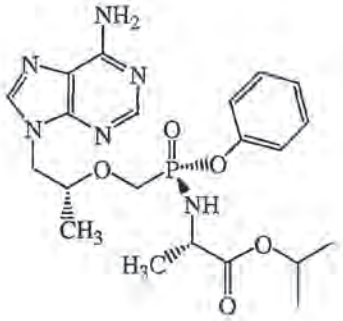
R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

and it salts, tautomers, free base and solvates.

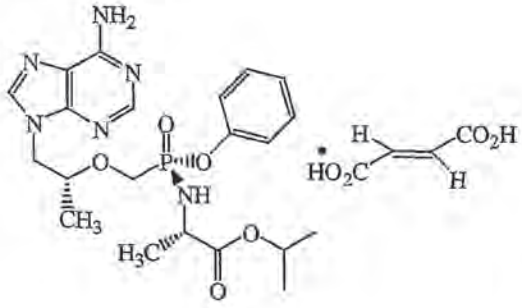
23. A compound of structure (6)



(6)

and its salts and solvates.

24. A compound of structure (7)



(7)

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PGR2023-00046 - Page 00997

25. A composition comprising a compound of any of claims 19-24 and a pharmaceutically effective excipient.

26. The composition of claim 25 wherein the excipient is a gel.

27. The composition of claim 25 which is suitable for topical administration.

28. A method for antiviral therapy or prophylaxis comprising administering a compound of any of claims 19-24 in a therapeutically or prophylactically effective amount to a subject in need of such therapy or prophylaxis.

29. A method for use of magnesium alkoxide comprising reacting 9-(2-hydroxypropyl)adenine (HPA) or 9-(2-hydroxyethyl)adenine (HEA), magnesium alkoxide, and protected *p*-toluenesulfonyloxymethylphosphonate.

30. The method of claim 29 further comprising recovering PMPA or PMEA, respectively.

31. The method of claim 29 wherein the phosphonate of the *p*-toluenesulfonyloxymethylphosphonate is protected by ethyl ester.

32. The method of claim 29 wherein the alkoxide is a C_1-C_6 alkoxide.

33. The method of claim 32 wherein the alkoxide is t-butyl or isopropyl oxide.

Gilead Exhibit 2018
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Electronic Acknowledgement Receipt

EFS ID:	17636357
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.3
Receipt Date:	12-DEC-2013
Filing Date:	29-AUG-2013
Time Stamp:	09:45:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	039560538003_IDSTransmittal_2013-12-12.pdf	54634 [illegible]	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	03956053800-3-IDS-SB08.PDF	612795 de20a922089310d0326a67fb4c8aca1eff7eb8203	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Foreign Reference	FOR1_WO2006067606.pdf	4412294 c6350c370280a837af8e697bd0d1d54a06741803	no	46
Warnings:					
Information:					
4	Foreign Reference	FOR2_WO2002008241.pdf	4724247 cf4e0cb57eb0419e757e6d8ae48e8e84156c39	no	59
Warnings:					
Information:					
5	Non Patent Literature	NPL1_McGuigan_FEBS_1994.pdf	608235 319e1117eb6ab80ca51066e6e0953ab08fdd6604	no	4
Warnings:					
Information:					
6	Non Patent Literature	NPL2_Cahard_MiniRev_2004.pdf	552500 5a8e30f96d92e408039405b5bdab0223383e6c	no	12
Warnings:					
Information:					
		Total Files Size (in bytes):	10964705		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/013,237	)	
	:	Examiner: Not yet assigned
First Named Inventor:	)	
	:	Group Art Unit: 1623
JINFA DU	)	
	:	Confirmation No.: 7005
Filed: August 29, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	December 12, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the documents listed on the attached PTO/SB/08a form. It is respectfully requested that this information be considered by the Examiner and that a copy of the attached PTO/SB/08a form be returned indicating that such information has been considered.

In accordance with 37 C.F.R. §1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether these references are, or are considered to be, material to patentability.

Pursuant to 37 C.F.R. § 1.97(b), it is believed that no fees are due in connection with this submission. However, should the U.S. Patent and Trademark Office determine that fees are due, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-3939.

Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

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PGR2023-00046 - Page 001003

03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/013,237	)	
	:	Examiner: Not yet assigned
First Named Inventor:	)	
	:	Group Art Unit: 1623
JINFA DU	)	
	:	Confirmation No.: 7005
Filed: August 29, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	
	:	
	)	December 13, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the following U.S. Application, which is electronically viewable:

Appln. No.	Filing Date	Group Art Unit	Examiner's Initials
13/956,195	July 31, 2013	1629	

It is respectfully requested that the above information be considered by the Examiner and that a copy of this document be returned indicating that such information has been considered.

In accordance with 37 C.F.R. §1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether this references is, or is considered to be, material to patentability.

It is believed that no fees are due in connection with this submission. However, should the U.S. Patent and Trademark Office determine that fees are due, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-3939.

Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

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1290 Avenue of the Americas
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Facsimile: (212) 218-2200

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PGR2023-00046 - Page 001005

Electronic Acknowledgement Receipt

EFS ID:	17650468
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.3
Receipt Date:	13-DEC-2013
Filing Date:	29-AUG-2013
Time Stamp:	10:28:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	03956053800-3IDSTransmittal.pdf	54998 6d6f031632186702de28364a1c7d1db50e7d9	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	54998

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	JINFA DU
Art Unit	1623
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2007-505742	JP	A	2007-03-15	E.I. DU PONT DE NEMOURS AND COMPANY		☐
	2	2005/030891	WO	A1	2005-04-07	E.I. DU PONT DE NEMOURS AND COMPANY		☐

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PGR2023-00046 - Page 001008

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	JINFA DU
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1		☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04 [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	JINFA DU
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2014-01-02
Name/Print	Alicia A. Russo	Registration Number	46,192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Gilead Exhibit 2018
PGR2023-00046 - Page 001011

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030891 A1

(51) International Patent Classification[7]: C09D 175/04, 133/06

(21) International Application Number:
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22 September 2004 (22.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/668,992 22 September 2003 (22.09.2003) US

(71) Applicant *(for all designated States except US)*: **E.I. DUPONT DE NEMOURS AND COMPANY** [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GRAHAM, William, Frank** [US/US]; 29 Newport Drive, Wayne, PA 19087 (US). **ANTON, Douglas, Robert** [US/US]; 6 Perth Drive, Wilmington, DE 19803 (US). **JOHNSON, Jeffery, W.** [US/US]; 1253 Harvard Drive, Rochester Hills, MI 48307 (US). **MICHALCZK, Michael, Joseph** [US/US]; 16 Servan Court, Wilmington, DE 19805 (US). **QUASHIE, Sape, Kewsi** [US/US]; 30060 Northgate Drive, Southfield, MI 48076 (US).

(74) Agent: **BENJAMIN, Steven, C.**; E.I. Du Pont de Nemours and Company, Legal Patent Records Center, 4417 Lancaster Pike, Wilmington, DE 19805 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

Published:
— *with international search report*

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

WO 2005/030891 A1

(54) Title: METHOD FOR ACHIEVING RECOAT ADHESION OVER A FLUORINATED TOPCOAT

(57) Abstract: A method for repairing a basecoat/clearcoat finish or coating comprised of a fluorinated organosilane topcoat. A fluorinated urethane additive is added to the fluorinated organosilane topcoat composition to improve recoat adhesion with the repair basecoat.

METHOD FOR ACHIEVING RECOAT ADHESION OVER A FLUORINATED TOPCOAT

BACKGROUND OF THE INVENTION

This invention is directed to a method for recoating a substrate previously coated with a basecoat/topcoat system in which the topcoat composition comprises a fluorinated organosilane polymer. In particular, this invention is directed to a method for obtaining recoat adhesion, especially during in-line and end-of-line repair of the finish of an automobile or truck during their original manufacture.

In order to protect and preserve the aesthetic qualities of the finish on an automobile or other vehicle, it is generally known to provide a clear (unpigmented or slightly pigmented) topcoat over a colored (pigmented) basecoat, so that the basecoat remains unaffected even on prolonged exposure to the environment or weathering. This is referred to as a basecoat/topcoat or basecoat/clearcoat finish. It is also generally known that fluorocarbons provide top coatings that remain relatively dirt free under exterior use conditions and are easily cleaned when soiled, for example by washing with water. Exemplary of prior art patents disclosing top coatings containing fluorocarbon constituents are U.S. Pat. No. 4,812,337; U.S. Pat. No. 5,597,874; U.S. Pat. No. 5,605,956; U.S. Pat. No. 5,627,238; U.S. Pat. No. 5,629,372; and U.S. Pat. No. 5,705,276. Given that it is well known that consumers prefer automobiles and trucks with an exterior finish having an attractive aesthetic appearance, rapid soiling of the finish is ever more undesirable.

Commercialization of fluorinated topcoat finishes, however, has been hindered by several significant or even critical technical hurdles. For example, a commercially practical finish, among other requirements, must have adequate adhesion to repair coatings, or what is known in the art as recoat adhesion, since defects in the finish may occasionally occur during the original manufacturing process, necessitating on-site repair. Additionally, a commercially practical finish must not be problematic or difficult to apply.

SUMMARY OF THE INVENTION

In conventional in-line or end-of-line repair of an automobile finish, a repair basecoat/clearcoat system is applied over a previously cured, but defective original basecoat/clearcoat. The total finish is then subjected to another cure cycle. Sanding or removal of the defective finish is normally omitted. The repair (second) basecoat is expected to adhere to the original (first) clearcoat at normal cure conditions.

During the development of fluorinated topcoat compositions, particularly topcoats containing fluorinated silane polymers which due to strong silane bonding when cured provide finishes with excellent scratch resistance and resistance to etching from acid rain and other environmental pollutants, applicants found that conventional repair basecoats showed poor or inadequate adhesion to the cured topcoat. This poor adhesion is believed due to the phenomenon of fluorine stratification at the outside surface (the side in contact with air) of the clearcoat. While such stratification is generally desirable, since it contributes to very low surface energy, high water and oil repellency, and hence outstanding stain resistance and cleanability, nevertheless such stratification appears to also have an adverse effect on what is known in the art as recoat adhesion. Applicants were able to solve this problem of recoat adhesion by including in the original topcoat composition an adhesion improving additive comprising a fluorinated urethane compound, which is reactive with an alkylated melamine formaldehyde or other aminoplast resin crosslinking agent normally present in the repair basecoat.

The claimed invention is therefore directed to a method for repairing an original basecoat/topcoat finish in which the original topcoat comprises a cured fluorinated silane polymer. The repair method comprises:

(a) applying a basecoat composition, comprising an aminoplast resin crosslinking agent, to a substrate having a top coating comprising a fluorinated silane polymer and an adhesion improving additive comprising a fluorinated urethane compound substantially cured thereon;

(b) applying a topcoat composition over said basecoat; and

(c) curing the new basecoat/topcoat finish.

By the term "substantially cured" or "partially cured" is meant that, although at least some curing has occurred, further curing may occur over time. In a preferred embodiment, the repair and original basecoat compositions are the same and the original and repair topcoat or clearcoat compositions are the same.

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The topcoat composition suitably comprises from about 45 to 90% by weight of binder, and the binder comprises 10 to 90% by weight, preferably 40 to 80%, of a fluorinated silane polymer. Preferably, the fluorinated silane polymer is the polymerization product of a monomer mixture of which about 1.5 to 70% by weight, preferably 5 to 50%, are ethylenically unsaturated monomers which contain a silane functionality and of which about 0.5 to 25% by weight, preferably 1 to 10%, are ethylenically unsaturated monomers which contain a fluorine functionality.

The claimed invention further includes a repairable topcoat composition usable in the present method and a coated substrate prepared according to the present method.

The method of the present invention is especially useful for forming a clear fluorinated topcoat over a pigmented basecoat. Such a topcoat can be applied over a variety of basecoats, including basecoats containing water or organic solvent and powder basecoats.

DETAILED DESCRIPTION OF THE INVENTION

As indicated above, this invention relates to the application of coatings involving fluorine chemistry and more particularly coatings involving fluorinated organosilane polymers, since silane polymers are generally known to provide coatings with improved scratch and mar resistance and resistance to etching from acid rain and other environmental pollutants, as shown, for example, in U.S. Pat No. 4,043,953; U.S. Pat. No. 4,518,726; and U.S. Pat. No. 4,368,397. More particularly, this invention provides a method for obtaining recoat adhesion when repairing a finish having a topcoat comprising a cured or at least partially cured fluorinated silane polymer. The method is especially useful for in-line and end-of-line repair of an original finish on the exterior of automobile and truck bodies or parts thereof. This method involves incorporating in the original topcoat an adhesion improving additive comprising a fluorinated urethane compound and applying thereover a repair basecoat which employs an aminoplast resin crosslinking agent.

Typically, an automobile steel panel or substrate is first coated with an inorganic rust-proofing zinc or iron phosphate layer over which is provided a primer which can be an electrocoated primer or a repair primer. A typical electrocoated primer comprises a cathodically deposited epoxy modified resin. A typical repair primer comprises an alkyd resin. Optionally, a primer surfacer can

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be applied over the primer coating to provide for better appearance and/or improved adhesion of the basecoat to the primer coat. A pigmented basecoat or colorcoat is next applied. A typical basecoat comprises a pigment, which may include metallic flakes in the case of a metallic finish, and a polyester or acrylourethane film-forming binder and an aminoplast resin crosslinking agent.

A clear topcoat (clearcoat) may then be applied to the pigmented basecoat (colorcoat). The colorcoat and clearcoat are preferably deposited to have thicknesses of about 0.1-2.5 mils and 1.0-3.0 mils, respectively. In the present invention, the topcoat comprises a fluorinated organosilane polymer.

As indicated above, according to the present invention, for the purpose of repairing an original basecoat/clearcoat finish, the original clearcoat is formulated to contain an adhesion improving additive comprising one or more fluorinated urethane compounds and the repair basecoat contains at least one aminoplast resin crosslinking agent such as those normally used to cure a repair basecoat.

The original topcoat is neither adversely affected nor effectively cured by the inclusion therein of a fluorinated urethane compound of the kind used herein, even though the topcoat sometimes also contains an aminoplast resin crosslinking agent which is reactive with the fluorinated urethane compound. During a normal cure cycle, no substantial reaction occurs, allowing the additive to remain available at the surface to react with the aminoplast crosslinking agent in the repair basecoat.

In commercial application of the present invention, it is most convenient to use the same coating compositions for both the original finishes and the repair finishes, so that only one topcoat and basecoat composition are necessary. Another advantage is that, for in-line repair, the same delivery lines and production cycle can be used for the original compositions and the repair compositions. Hence, the topcoat composition used in the repair finish will contain the fluorinated urethane adhesion improving additive even though it has may have no effect on the recoat adhesion.

The topcoat composition employed in the present invention is a clear coating composition, i.e., containing no pigments or a small amount of transparent pigment. The composition also has a relatively high solids content of about 45-90% by weight of film-forming binder and about 10-55% by weight of an organic carrier which can be a solvent for the binder or a mixture of solvents and non solvent which would form a non aqueous dispersion. Typically, the coating composition contains about 50-80% by weight of the film-forming binder and about 20-50% by weight of the organic solvent carrier. The coating of the present

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invention is also preferably a low VOC (volatile organic content) coating composition, which means a coating that includes less than 0.6 kilograms of organic solvent per liter (5 pounds per gallon) of the composition as determined under the procedure provided in ASTM D3960.

As indicated above, the film-forming portion of the present topcoat composition, comprising polymeric components, is referred to as the "binder" or "binder solids" and is dissolved, emulsified or otherwise dispersed in an organic solvent or liquid carrier. The binder solids generally include all the normally solid polymeric non-liquid components of the composition. Generally, catalysts, pigments or chemical additives such as stabilizers and adhesion improving additives as used herein are not considered part of the binder solids. Non-binder solids other than pigments usually do not amount to more than about 10% by weight of the composition. In this disclosure, with respect to the present top coat composition, the term binder includes the fluorinated silane polymer, the dispersed polymer, and all other optional film-forming polymers, as described herein below.

The binder employed in the present invention contains about 10-90% by weight, preferably 40-80%, of a film-forming fluorinated organosilane polymer, herein also referred to as a fluorinated silane polymer.

The fluorinated silane polymer portion of the binder typically has a weight average molecular weight of about 500-30,000, preferably about 3,000-10,000. All molecular weights disclosed herein are determined by gel permeation chromatography using a polystyrene standard, unless otherwise noted.

Preferably, the fluorinated silane polymer is the polymerization product of a mixture of monomers of which about 1.5-70%, preferably 5-50%, by weight are ethylenically unsaturated monomers which contain a hydrolysable silane functionality, about 5-98%, preferably about 40-95%, by weight are ethylenically unsaturated non-silane and non-fluorine containing monomers, and about 0.5-25%, preferably about 1-10%, by weight are ethylenically unsaturated monomers which contain a fluorine functionality. An acrylosilane resin having 8% by weight polymerized silane monomer and 1.5% fluoroalkyl monomer has been found to have good acid etch resistance, mar resistance, and cleanability.

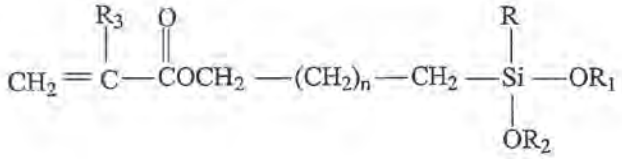
Suitable ethylenically unsaturated non-silane and non-fluorine containing monomers used to form the fluorinated silane polymer are alkyl acrylates, alkyl methacrylates and any mixtures thereof, where the alkyl groups have 1-12 carbon atoms, preferably 2-8 carbon atoms. Suitable alkyl methacrylate monomers used to form the fluorinated silane polymer are methyl methacrylate, ethyl

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methacrylate, propyl methacrylate, butyl methacrylate, isobutyl methacrylate, pentyl methacrylate, hexyl methacrylate, octyl methacrylate, nonyl methacrylate, lauryl methacrylate and the like. Similarly, suitable alkyl acrylate monomers include methyl acrylate, ethyl acrylate, propyl acrylate, butyl acrylate, isobutyl acrylate, pentyl acrylate, hexyl acrylate, octyl acrylate, nonyl acrylate, lauryl acrylate and the like. Cycloaliphatic methacrylates and acrylates also can be used, for example, such as trimethylcyclohexyl methacrylate, trimethylcyclohexyl acrylate, isobornyl methacrylate, isobornyl acrylate, t-butyl cyclohexyl acrylate, or t-butyl cyclohexyl methacrylate. Aryl acrylate and aryl methacrylates also can be used, for example, such as benzyl acrylate and benzyl methacrylate. Of course, mixtures of two or more of the above mentioned monomers are also suitable.

In addition to alkyl acrylates or methacrylates, other non-silane and non-fluorine containing polymerizable monomers, up to about 50% by weight of the polymer, can be used in an acrylosilane polymer for the purpose of achieving the desired physical properties such as hardness, appearance, mar resistance, and the like. Exemplary of such other monomers are styrene, methyl styrene, acrylamide, acrylonitrile, methacrylonitrile, and the like. Hydroxy functional monomers can also, and preferably are, incorporated into the fluorinated silane polymer to produce a polymer having a hydroxy number of 20 to 160. Suitable hydroxy functional monomers are hydroxy alkyl (meth)acrylates meaning hydroxy alkyl acrylates and hydroxy alkyl methacrylates having 1-4 carbon atoms in the alkyl groups such as hydroxy methyl acrylate, hydroxy methyl methacrylate, hydroxy ethyl acrylate, hydroxy ethyl methacrylate, hydroxy propyl methacrylate, hydroxy propyl acrylate, hydroxy butyl acrylate, hydroxy butyl methacrylate and the like. The presence of hydroxy functional monomers enables additional crosslinking to occur between the hydroxy groups and silane moieties on the silane polymer and/or between the hydroxy groups with other crosslinking groups on binder components that may be present in the top coat composition.

Suitable silane containing monomers that can be used to form the fluorinated silane polymer are alkoxy silanes having the following structural



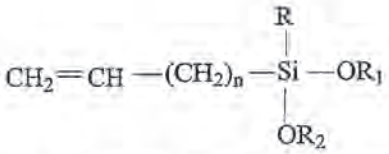
formula:

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wherein R is either CH_3, CH_3CH_2, CH_3O, $CH_3OCH_2CH_2O$, or CH_3CH_2O; R_1 and R_2 are independently CH_3, CH_3CH_2, or $CH_3OCH_2CH_2$; and R_3 is either H, CH_3, CH_3CH_2, or $CH_3OCH_2CH_2$; and n is 0 or a positive integer from 1 to 10. Preferably, R is CH_3O or CH_3CH_2O and n is 1.

Typical examples of such alkoxysilanes are the acrylatoalkoxy silanes, such as gamma-acryloxypropyl trimethoxysilane and the methacrylatoalkoxy silanes, such as gamma-methacryloxypropyl trimethoxysilane, and gamma-methacryloxypropyltris(2-methoxyethoxy) silane.

Other suitable alkoxy silane monomers have the following structural formula:



wherein R, R_1 and R_2 are as described above and n is a positive integer from 1 to 10.

Examples of such alkoxysilanes are the vinylalkoxy silanes, such as vinyltrimethoxy silane, vinyltriethoxy silane and vinyltris(2-methoxyethoxy) silane.

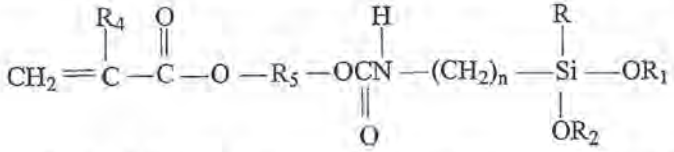
Other suitable silane containing monomers are ethylenically unsaturated acryloxysilanes, including acrylatoxy silane, methacrylatoxy silane and vinylacetoxy silanes, such as vinylmethyldiacetoxy silane, acrylatopropyl triacetoxy silane, and methacrylatopropyltriacetoxy silane. Of course, mixtures of the above-mentioned silane containing monomers are also suitable.

Silane functional macromonomers also can be used in forming the fluorinated silane polymer. For example, one such macromonomer is the reaction product of a silane containing compound, having a reactive group such as epoxide or isocyanate, with an ethylenically unsaturated non-silane containing monomer having a reactive group, typically a hydroxyl or an epoxide group, that is co-reactive with the silane monomer. An example of a useful macromonomer is the reaction product of a hydroxy functional ethylenically unsaturated monomer such as a hydroxyalkyl acrylate or methacrylate having 1-4 carbon atoms in the alkyl group and an isocyanatoalkyl alkoxysilane such as isocyanatopropyl triethoxysilane.

Typical of such above-mentioned silane functional macromonomers are those having the following structural formula:

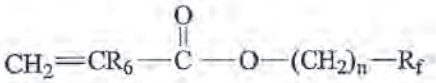
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where R, R_1, and R_2 are as described above; R_4 is H or CH_3, R_5 is an



alkylene group having 1-8 carbon atoms and n is a positive integer from 1-8.

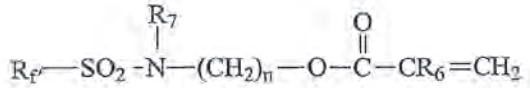
The fluorine containing monomers are preferably used in amounts of about 0.5-10% by weight, based on the total weight of the fluorinated silane polymer. Since fluorocarbon monomers are expensive, the present composition preferably has a low content of fluorocarbon constituents. Useful fluorine containing monomers are fluoroalkyl monomers represented by the formula



where R_6 is hydrogen or an alkyl group having 1-2 carbon atoms, n is an integer of 1-18 and R_f is a fluoroalkyl containing group having at least 4 carbon atoms and preferably a straight chain or branched chain fluoroalkyl group having 4-20 carbon atoms which optionally can contain an oxygen atom.

Typical useful fluoroalkyl containing monomers are perfluoro methyl ethyl methacrylate, perfluoro ethyl ethyl methacrylate, perfluoro butyl ethyl methacrylate, perfluoro pentyl ethyl methacrylate, perfluoro hexyl ethyl methacrylate, perfluoro octyl ethyl methacrylate, perfluoro decyl ethyl methacrylate, perfluoro lauryl ethyl methacrylate, perfluoro stearyl ethyl methacrylate, perfluoro methyl ethyl acrylate, perfluoro ethyl ethyl acrylate, perfluoro butyl ethyl acrylate, perfluoro pentyl ethyl acrylate, perfluoro hexyl ethyl acrylate, perfluoro octyl ethyl acrylate, perfluoro decyl ethyl acrylate, perfluoro lauryl ethyl acrylate, perfluoro stearyl ethyl acrylate, and the like. Preferred are perfluoro alkyl ethyl methacrylates wherein the fluoroalkyl group contains 4-20 carbon atoms.

Other useful fluoroalkyl containing monomers are represented by the formula



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where

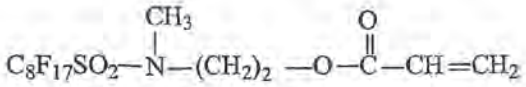
R_6 is as defined above,

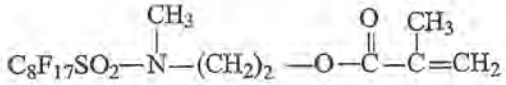
R_f is a fluoroalkyl group having 4-12 carbon atoms,

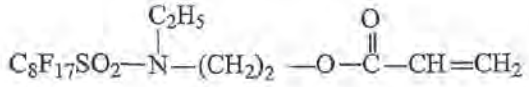
R_7 is an alkyl group having 1-4 carbon atoms and

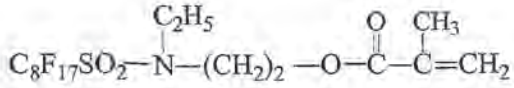
n is an integer of 1-4.

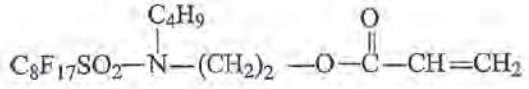
Typical of these monomers are the following:











Consistent with the above mentioned components, an example of a fluorinated acrylosilane polymer useful in the top coat composition of this invention may contain the following constituents: about 10-30% by weight

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styrene, about 2-20% by weight gamma-methacryloxypropyl trimethoxysilane, and about 10-30% by weight isobutyl methacrylate, 5-30% by weight 2-ethyl hexyl acrylate, 15-45% by weight hydroxy ethyl methacrylate and about 0.5-5% by weight fluoroalkyl ethyl methacrylate having 4-20 atoms in the alkyl group.

One particularly preferred fluorinated acrylosilane polymer contains about 20% by weight styrene, about 8% by weight gamma-methacryloxypropyl trimethoxysilane, about 70.5% by weight of nonfunctional acrylates or methacrylates such as trimethylcyclohexyl methacrylate, butyl acrylate, and iso-butyl methacrylate and any mixtures thereof, and about 1.5% by weight of the above fluoroalkyl ethyl methacrylate monomer.

The fluorinated silane polymer used in the coating composition is preferably prepared by conventional polymerization techniques in which the monomers, solvent, and polymerization initiator are charged over a 1-24 hour period of time, preferably in a 2-8 hour time period, into a conventional polymerization reactor in which the constituents are heated to about 60-175°C, preferably about 110-170°C.

In a preferred process for forming the fluorinated silane polymer, the fluoroalkyl containing monomers are not added over an extended period of time with the other monomers but at any time during the polymerization process such as the beginning, end or middle. The polymerizable fluoroalkyl containing monomers usually are blended with solvent and then added to the reactor. The fluoroalkyl containing monomers are added in about 0.01-10% of the total time of polymerization of the polymer. Preferably, the fluoroalkyl containing monomers are added after at least some of the other monomers have been added and polymerized to some extent. The addition of the fluoroalkyl containing monomers in the above manner, typically as a shot towards the end of the polymerization reaction, is a way of making a certain percentage of the polymer chains high in fluorine content without using large amounts of expensive fluorine monomers. This allows one to achieve high cleanability while offering substantial cost savings. It is also beneficial to add a portion of the other functional monomers, for instance, the silane containing- and hydroxyl containing- monomers, typically as a shot towards the end of the polymerization reaction, to provide chains not only rich in fluorine content, but also rich in other functional groups, such as the crosslinkable groups, to achieve other desired film properties, such as high scratch and mar resistance and excellent adhesion to windshield sealants. This technique is also a way of increasing the lifetime of the fluorine surface, since it allows at least a portion of the fluorine groups to become crosslinked through the other

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functional groups into the final film network, which prevents the fluorine groups from slowly washing away and ultimately disappearing from the surface of the coating film.

Typical polymerization initiators that are used in the process are azo type initiators such as azo-bis-isobutyronitrile, 1,1'-azo-bis(cyanocyclohexane), peroxy acetates such as t-butyl peracetate, peroxides such as di-t-butyl peroxide, benzoates such as t-butyl perbenzoate, octoates such as t-butyl peroctoate and the like.

Typical solvents that can be used in the process are alcohols such as methanol, ethanol, n-butanol, n-propanol, and isopropanol, ketones such as methyl amyl ketone, methyl isobutyl ketone, methyl ethyl ketone, aromatic hydrocarbons such as toluene, xylene, Solvesso® 100, alkylene carbonates such as propylene carbonate, n-methyl pyrrolidone, ethers, esters, acetates and mixture of any of the above.

Additional to the fluorinated silane polymer, other film-forming and/or crosslinking solution polymers may be included in the present application. Examples include conventionally known acrylosilanes, acrylics, cellulosics, aminoplasts, isocyanates, urethanes, polyesters, epoxies or mixtures thereof. One preferred optional film-forming polymer is a polyol, for example an acrylic polyol solution polymer of polymerized monomers. Such monomers may include any of the aforementioned alkyl acrylates and/or methacrylates and in addition, hydroxy alkyl acrylates and/or methacrylates. Suitable alkyl acrylates and methacrylates have 1-12 carbon atoms in the alkyl groups. The polyol polymer preferably has a hydroxyl number of about 50-200 and a weight average molecular weight of about 1,000-200,000 and preferably about 1,000-20,000.

To provide the hydroxy functionality in the polyol, up to about 90% preferably 20 to 50%, by weight of the polyol comprises hydroxy functional polymerized monomers. Suitable monomers include hydroxy alkyl acrylates and methacrylates, for example, such as the hydroxy alkyl acrylates and methacrylates listed hereinabove and mixtures thereof. Other polymerizable non-hydroxy-containing monomers may be included in the polyol polymer component, in an amount up to about 90% by weight, preferably 50 to 80%. Such polymerizable monomers include, for example, styrene, methylstyrene, acrylamide, acrylonitrile, methacrylonitrile, methacrylamide, methylol methacrylamide, methylol acrylamide, and the like, and mixtures thereof.

One example of an acrylic polyol polymer comprises about 10-20% by weight of styrene, 40-60% by weight of alkyl methacrylate or acrylate having 1-6

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carbon atoms in the alkyl group, and 10-50% by weight of hydroxy alkyl acrylate or methacrylate having 1-4 carbon atoms in the alkyl group. One such polymer contains about 15% by weight styrene, about 29% by weight iso-butyl methacrylate, about 20% by weight 2- ethylhexyl acrylate, and about 36% by weight hydroxy propylacrylate.

In addition to the above components, a dispersed polymer may optionally be included in the coating composition. Polymers dispersed in an organic (substantially non-aqueous) medium have been variously referred to, in the art, as a non-aqueous dispersion (NAD) polymer, a non-aqueous microparticle dispersion, a non-aqueous latex, or a polymer colloid. See generally, Barrett, DISPERSION POLYMERIZATION IN ORGANIC MEDIA (John Wiley 1975). See also U.S. Pat. Nos. 4,147,688; 4,180,489; 4,075,141; 4,415, 681; and 4,591,533, hereby incorporated by reference. In general, a dispersed polymer is characterized as a polymer particle dispersed in an organic media, which particle is stabilized by steric stabilization accomplished by the attachment of a solvated polymeric or oligomeric layer at the particle-medium interface. The dispersed polymers are used in the present invention to solve the problem of cracking heretofore associated with silane coatings. Suitable dispersed polymers for use in conjunction with silane polymers are disclosed in U.S. Pat. Nos. 5,162,426, hereby incorporated by reference in its entirety. Preferably, about 20% by weight of such a dispersed polymer is included to prevent cracking.

For a two-component or two-package system, which is generally preferred, a polyfunctional organic isocyanate can be used as the crosslinking agent without particular limitation so long as the isocyanate compound has at least two isocyanate groups in the one molecule. The preferable polyisocyanate compounds are isocyanate compounds having 2 to 3 isocyanate groups per molecule. Typical examples of polyfunctional organic isocyanate compounds are, for instance, 1,6-hexamethylene diisocyanate, isophorone diisocyanate, 2,4-toluene diisocyanate, diphenylmethane-4,4'-diisocyanate, dicyclohexylmethane-4,4'-diisocyanate, tetramethylxylidene diisocyanate, and the like. Trimers of diisocyanates also can be used such as the trimer of hexamethylene diisocyanate (isocyanurate) which is sold under the tradename Desmodur® N-3390, the trimer of isophorone diisocyanate (isocyanurate) which is sold under the tradename Desmodur® Z-4470 and the like. Polyisocyanate functional adducts can also be used that are formed from any of the forgoing organic polyisocyanate and a polyol. Polyols such as trimethylol alkanes like trimethylol propane or ethane can be used. One useful adduct is the reaction product of tetramethylxylidene diisocyanate and trimtheylol propane and is sold under the tradename of Cythane® 3160. When the

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crosslinkable resin of the present invention is used in exterior coatings, the use of an aliphatic or cycloaliphatic isocyanate is preferable to the use of an aromatic isocyanate, from the viewpoint of weatherability and yellowing resistance.

Optionally, the present coating composition may further include, particularly in conjunction with an optional polyol polymer, an additional crosslinking agent, for example, an aminoplast crosslinking agent. Particularly preferred aminoplast resins are any of the conventionally used alkylated melamine formaldehyde crosslinking agents. Typically useful alkylated melamine formaldehyde crosslinking agents are, for example, conventional monomeric or polymeric alkylated melamine formaldehyde resin that are partially or fully alkylated. One useful crosslinking agent is a methylated and butylated or isobutylated melamine formaldehyde resin that has a degree of polymerization of about 1-3. Generally, this melamine formaldehyde resin contains about 50% butylated groups or isobutylated groups and 50% methylated groups. Such crosslinking agents typically have a number average molecular weight of about 300-600 and a weight average molecular weight of about 500-1500. Examples of commercially available resins are Cymel® 1168, Cymel®1161, Cymel® 1158, Resimine® 4514 and Resimine® 354. Preferably, the crosslinking agent is used in the amount of about 5-50% by weight, based on the weight of the binder. Other contemplated crosslinking agents are urea formaldehyde, benzoquanamine formaldehyde and blocked polyisocyanates or compatible mixtures of any of the forgoing crosslinkers. Preferably about 10-60% by weight of such crosslinking agent in included in the binder of the coating.

The clear coat composition described above can also be formulated (minus the unblocked organic polyisocyanate) as a one-package system that has extended shelf life.

A catalyst is typically added to catalyze the crosslinking of the silane moieties of the silane polymer with itself and/or with other components of the composition. A wide variety of catalysts can be used, such as dibutyl tin dilaurate, dibutyl tin dilaurate, dibutyl tin diacetate, dibutyl tin dioxide, dibutyl tin dioctoate, tin octoate, aluminum titanate, aluminum chelates, zirconium chelate and the like. Sulfonic acids, such as dodecylbenzene sulfonic acid, either blocked or unblocked, are effective catalysts. Alkyl acid phosphates, such as phenyl acid phosphate, either blocked or unblocked, may also be employed. Any mixture of the aforementioned catalysts may be useful, as well. Other useful catalysts will readily occur to one skilled in the art. Preferably, the catalysts are used in the

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amount of about 0.1 to 5.0%, based on the total weight of the binder used in the composition.

A key component of the coating composition of the present invention is, in addition to the above components, an adhesion improving additive, also referred to herein as an adhesion promoter or a recoat adhesion improving additive. An effective adhesion enhancing amount of adhesion improving additive is added to the top coat composition to solve the recoat adhesion problem mentioned above. The adhesion improving additive of this invention also provides the top coat composition with excellent primerless adhesion to commercially available moisture-cure windshield bonding adhesives, which are needed to properly affix a windshield to the body of a vehicle. The adhesion improving additive is typically added to the topcoat composition in an adhesion enhancing amount ranging from about 0.1 to 15% by weight, preferably from about 5-10% by weight, based on the total weight of the binder used in the composition.

More particularly, the adhesion improving additive used herein is a fluorinated urethane compound which is an polyisocyanate-derived adduct of a conventional organic polyisocyanate, a fluorinated monofunctional alcohol, and an oligomeric or polymeric ethoxylated/propoxylated glycol, and contains no residual or free –NCO groups. The fluorinated urethane additive also is preferably substantially free of residual hydroxyl groups capable of reacting with the film-forming binder components in the topcoat composition, to prevent the additive from becoming a permanent part of the paint film. The additive thereby can remain an unreacted mobile component in the paint film which is preferred.

While not wishing to be bound by any particular theory, it is surmised that the fluorinated urethane additive migrates to the surface of the film during curing and since urethane groups (i.e., carbamate groups) are capable of reacting with melamine groups, there is enough intermixing at the interface so that repair basecoat containing melamine will react with the urethane groups in the original topcoat and result in improved recoat adhesion.

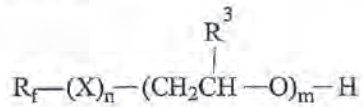
Preferably, the fluorinated urethane adduct of the present invention is formed from a conventional organic polyisocyanate resin which is reacted with a fluorinated monoalcohol and further reacted with a polyether polyol to provide an adduct with reactive carbamate groups that can subsequently react with an aminoplast resin present in a repair basecoat.

The organic polyisocyanates that may be used to form the adduct can be any conventional aromatic, aliphatic, cycloaliphatic di and trifunctional polyisocyanates can be used, such as any of the organic polysiocyanates listed

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above. Typical diisocyanates that can be used include any of those listed hereinabove including 1,6-hexamethylene diisocyanate, isophorone diisocyanate, 4,4'-biphenylene diisocyanate, toluene diisocyanate, bis cyclohexyl diisocyanate, tetramethylene xylene diisocyanate, ethyl ethylene diisocyanate, 2,3-dimethyl ethylene diisocyanate, 1-methyltrimethylene diisocyanate, 1,3-cyclopentylene diisocyanate, 1,4-cyclohexylene diisocyanate, 1,3-phenylene diisocyanate, 1,5-naphthalene diisocyanate, bis-(4-isocyanatocyclohexyl)-methane, 4,4'-diisocyanatodiphenyl ether and the like. Typical trifunctional isocyanates that can be used are any of those listed hereinabove including triphenylmethane triisocyanate, 1,3,5-benzene triisocyanate, 2,4,5-toluene triisocyanate and the like. Oligomers of diisocyanates also can be used such as the trimer of hexamethylene diisocyanate (isocyanurate) which is sold under the tradename Desmodur® N. One particularly preferred oligomer is Desmodur® N-3390. Also suitable are any other polyisocyanates which contain carbodiimide groups, urethane groups, allophanate groups, isocyanurate groups, biuret groups, and urea groups.

The organic polyisocyanate can be reacted with, for example, any fluorinated monofunctional alcohol. Suitable fluorinated monofunctional alcohols are represented by the formula



where R_f is as defined above, a fluoroalkyl containing group having at least 4 carbon atoms and preferably a straight chain or branched chain fluoroalkyl group having 4-20 carbon atoms which optionally can contain oxygen atoms as ether groups or can contain 1-5 chlorine atoms or 1-5 hydrogen atoms. Preferably, R_f is a perfluoroalkyl group having 4-20 carbon atoms and most preferably, R_f is a perfluoroalkyl group containing 6-12 carbon atoms. X is a divalent radical, preferably $-CH_2CH_2O-$, $-SO_2N(R^4)CH_2CH_2O-$, $-CH_2-$, -O-, $-CH_2O-$ where R^4 is an alkyl group preferably having 1-4 carbon atoms. R^3 is H or an alkyl group having 1-4 carbon atoms, H and methyl being preferred, n is 0-1 and m is 0-30, provided that if n is 0, then m must be greater than or equal to 1, if m is 0, then n is 1; if X is -O-, m must be greater than or equal to 1; and m preferably 1-20.

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The following are preferred fluorinated monofunctional alcohols:

$$F(CF_2CF_2)_a(CH_2CH_2O)_bH$$

where a is 1 to about 8, or a mixture thereof, and preferably is from about 3 to about 6, and b is 5-15;

$$H-(CF_2CF_2)_n-CH_2OH$$

where n is 1-6;

$$C_cF_d-SO_2-N(R^5)-(CH_2-CH_2-O)_n-H$$

where c is 4-8 and d is 2c + 1; R^5 is an alkyl group having 1-4 carbon atoms and n is 1-30;

$$CF_3-(O-C(CF_3)F-CF_2)_n-O-(CH_2-CH_2-O)_m-H$$

where n is 0-10 and m is 1-20; and

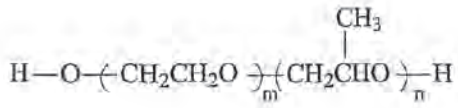
$$F(CF_2CF_2)_a(CH_2)_cOH$$

where a is described above and c is from about 2 to about 10, and preferably is 2.

Specific examples of such fluorinated monoalcohols are sold under the tradename ZONYL® BA, BA-L, BA-N or BA-LD Fluoroalcohols. Zonyl® Fluoroalcohols are mixtures of alcohols of formula $F(CF_2CF_2)_{2-8}CH_2CH_2OH$ available from E. I. du Pont de Nemours and Company, Wilmington, DE.

Polyether polyols are used to cap, i.e., react with the residual isocyanate end groups, to form the fluorinated urethane additive. Preferred polyols are oligomeric or polymeric ethoxylated/propoxylated glycol or a combinations of these glycols. Suitable ethoxylated/propoxylated glycols include polyoxyethylene glycol and polyoxyethylene-polyoxypropylene glycol of the general formula

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where m and n are the average number of repeating oxyethylene (EO) and oxypropylene (PO) groups, respectively; provided that m is always a positive integer, while n is a positive integer or zero (designating an EO homopolymer in the latter case).

The EO/PO glycols used herein preferably are oligomeric materials that have a weight average molecular weight of from about 500 to about 5,000, preferably about 980 to about 2,500. Typical examples of such polyoxyethylene-polyoxypropylene glycols are available under the tradename "Ucon 75-H", from Union Carbide. "Ucon 75-H Series" EO/PO glycols are linear copolymers having 75% by weight oxyethylene (EO) groups and 25% by weight oxypropylene (PO) groups and have molecular weights within the range mentioned above. The only side chains on the essentially linear copolymer are due to the methyl groups of the oxyproylene residue. One particularly preferred EO/PO glycol is "Ucon-75-H-450" which has a weight molecular weight of about 980 and a viscosity at 37.8°C of 450 sus.

In the present invention, it is believed that the fluorochemical portion of the additive provides additional water and oil repellency and soil resistance to the topcoat, while the EO/PO glycol portion imparts water solubility to the additive and therefore solubility in a typical basecoat composition. By suitable choice of the EO/PO groups, the diffusion rate of the fluorinated additive into the basecoat can be predictably controlled.

The fluorinated urethane additive can be, and preferably is, prepared by conventional polymerization techniques using a simultaneous or stepwise procedure. In a preferred embodiment, a stepwise procedure is employed. In this embodiment, the polyisocyanate is reacted first with the fluorinated monofunctional alcohol to make sure that fluorine functionality is included in the adduct. The fluorinated isocyanate intermediate is then capped with the polyether glycol to provide the fluorinated urethane adduct having no residual isocyanate groups.

Step one thus entails reacting the organic polyisocyanate with the fluorinated mono-alcohol. Typically, the constituents are reacted with a catalyst such as dibutyl tin dilaurate for about 0.1-4 hours at temperatures of about 45-

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120°C in an inert solvent to form the intermediate. The amount of monoalcohol reacted with the polyisocyanate in step one should be one stoichiometric equivalent or less per equivalent of isocyanate. Preferably, the amount of monoalcohol employed is not less than about 0.45 of an equivalent per equivalent of isocyanate, more preferable form about 0.50 to 1.0 of monoalcohol to isocyanate equivalent.

In step two, the EO/PO glycol is reacted with the fluorinated polyisocyanate intermediate made in the first step. The amount of EO/PO glycol employed is typically 5-15% in excess of one stoichiometric equivalent sufficient to consume about 99%, preferably 100% of the isocyanate functionality without leaving any of the remaining isocyanate reactive functionality in the resulting polyisocyanate derived adduct.

Reaction of the glycol with the fluorinated isocyanate intermediate can be monitored by isocyanate absorbance band by using a Fourier transform infrared spectrometer and isocyanate titration. The reaction end point is achieved when no isocyanate functionality remains in the resulting polyisocyanate derived adduct.

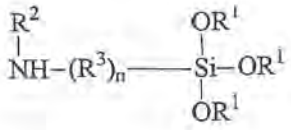
Although in principle, it is intended that all of the isocyanate functionality of the polyisocyanate be reacted it should be understood that 100 percent complete reaction cannot always be attained, and therefore, trace amounts of unreacted isocyanate and/or unreacted hydroxyls can be expected. Alternatively, reacting "all" of the isocyanate for the purposes of the present invention may be defined as at least 99 percent complete reaction, preferably 100 percent.

One particularly preferred fluorinated urethane adduct is the reaction product of isophorone diisocyanate reacted with one equivalent of Zonyl® BA fluoroalcohol and then capped with one equivalent of Ucon® 75-H-450.

In another embodiment, the adhesion improving additive may contain additional hydrolyzable silane functionality, in order to improve the adhesion of the cured or at least partially cured topcoat composition to commercially available moisture-cure urethane windshield sealants used to affix a windshield to a vehicle. To provide hydrolyzable silane functionality in the additive, the polyether polyols, which are used to cap the isocyanate groups, may be replaced with an amino-functional silane. The additive may be prepared in the same manner as described above, except for the change in the cap.

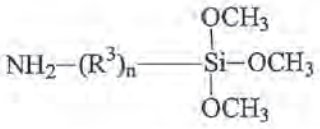
Amino-functional silanes that can be used to form this fluorourethane silane additive are represented by the formula

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where R^1 is independently C_1-C_{16} alkyl, R^2 is independently H or C_1-C_{12} alkyl, and R^3 is a moiety independently selected from the group consisting of alkylene, cycloalkylene, heterocyclic, arylene, alkoxylene, aralkylene, alkenylene and low molecular weight polymer moiety, and n is an integer from 1 to 16. Preferred for R^1 are alkyls of C_1 to C_4, most preferably C_1 to C_2. Alkyl substituents can be linear or cyclic and the amine function can be primary or secondary. Representative low molecular weight polymer values for R^3 are polyester, polyurethane, polyether, polyamine and the like. By "low molecular weight" it is meant no more than about 3000 (number average). When R^3 are low molecular weight polymers, n is 1. Preferably, however, for R^3 are alkylene groups containing 2 to 20 carbon atoms and n is 1 to 3.

The following are preferred amino-functional silanes:



where R^3 is an alkylene group containing 1 to 20 carbon atoms, more preferably 1 to 2 carbon atoms, and n is 1 to 3.

Specific examples of such amino functional silanes that are commercially available are 3-aminopropyl trimethoxy silane and analogs thereof, such as where the trimethoxysilane group is replaced by various combinations of methyldialkoxysilane groups.

It is believed that fluorochemical portion of this additive provides additional water and oil repellency and soil resistance to the topcoat, while the aminosilane portion imparts water solubility to the additive and therefore solubility in a typical basecoat composition as well as improved adhesion without a primer to windshield sealants. By suitable choice of amino groups, the diffusion rate of the fluorinated additive into the basecoat can also be predictably controlled.

In addition to the above components, to improve the weatherability of the clear finish made with the topcoat composition, an ultraviolet light stabilizer or a combination of ultraviolet light stabilizers can be added to the topcoat composition in the amount of about 0.1-10% by weight, based on the weight of

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the binder. Such stabilizers include ultraviolet light absorbers, screeners, quenchers, and specific hindered amine light stabilizers. Also, an antioxidant can be added, in the amount of about 0.1-5% by weight, based on the weight of the binder. Typical ultraviolet light stabilizers that are useful include benzophenones, triazoles, triazines, benzoates, hindered amines and mixtures thereof.

A suitable amount of water scavenger such as trimethyl orthoacetate, triethyl orthoformate, tetrasilicate and the like (preferably 2 to 6% by weight of binder) is typically added to the topcoat composition for extending its pot life. About 3% microgel (preferably acrylic) and 1% hydrophobic silica may be employed for rheology control. The composition may also include other conventional formulation additives such as flow control agents, for example, such as Resiflow® S (polybutylacrylate), BYK® 320 and 325 (high molecular weight polyacrylates).

Small amounts of pigment can also be added to the topcoat composition to eliminate undesirable color in the finish such as yellowing.

According to the present method, when the repair basecoat is applied over the original topcoat described above, recoat adhesion can now be attained. In general, the composition of the basecoat is not limited by the present invention except to the extent that it must contain an aminoplast resin crosslinking agent. Preferred basecoats comprise a polyester or polyester urethane in combination with a melamine crosslinking agent and a polyol. Suitable polyols include acrylic, polyester, polyester urethane, or an acrylic urethane polyol having a hydroxy number of 60-160. Such polyols may contribute to recoat adhesion over a silane clearcoat by hydroxy groups on the polyol reacting with some of the unreacted or residual silane groups in the clearcoat even though the topcoat has substantially or partially cured. An example of a suitable basecoat, in addition to pigments, aluminum flakes, and UV absorber, comprises by weight of composition, about 25% microgel for rheology control, 21% melamine formaldeyde resin, 17% branched polyester resin, 3% acrylourethane having a hydroxy number of 120, 2% blocked dibutyl dodecyl benzyl sulfonic acid catalyst, and 2% dibutyl diacetate.

Additional film-forming and/or crosslinking polymers may be included in the basecoat employed in the present invention. Examples include conventionally known acrylics, cellulosics, aminoplasts, urethanes, polyesters, epoxides or mixtures thereof. One example of an additional optional acrylic polymer is an acrylic polyol solution polymer. Such polyols preferably have a hydroxyl number of about 50-200 and a weight average molecular weight of about 1,000-200,000 and preferably about 1,000-20,000. A preferred polyol is comprised by weight of

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25% styrene, 31% butyl methacrylate, 17% butyl acrylate and 38% hydroxy propyl acrylate and has a Tg of 18.5°C.

Although not wishing to be bound by theory, it is surmised that the presence of the fluorinated urethane additive in the original topcoat may cause the reaction of the aminoplast resin in the repair basecoat with the urethane groups in the clearcoat to form carbamate bonds which promote adhesion between the original clearcoat and repair basecoat interface.

A variety of pigments and metallic flakes may be employed in the basecoat, as would be apparent to those skilled in the art. Typical pigments in the basecoat composition include the following: metallic oxides such as titanium dioxide, zinc oxide, iron oxides of various colors, carbon black, filler pigments such as talc, china clay, barytes, carbonates, silicates and a wide variety of organic colored pigments such as quinacridones, copper phthalocyanines, perylenes, azo pigments, indanthrone blues, carbazoles such as carbozole violet, isoindolinones, isoindolones, thioindigo reds, benzimidazolinones, metallic flake pigments such as aluminum flake, pearlescent flakes, and the like.

The pigments can be introduced into the basecoat by first forming a mill base or pigment dispersion with any of the aforementioned polymers used in the coating composition or with another compatible polymer or dispersant by conventional techniques, such as high speed mixing, sand grinding, ball milling, attritor grinding or two roll milling. The mill base is then blended with the other constituents used in the coating composition.

The basecoat compositions employed in the present invention may also include other conventional formulation additives such as flow control agents, for example, such as Resiflow®S (polybutylacrylate), BYK®320 and 325 (high molecular weight polyacrylates); and rheology control agents, such as fumed silica.

In both the basecoat and topcoat employed in this invention, conventional solvents and diluents are also generally used to disperse and/or dilute the above mentioned polymers. Typical solvents and diluents include toluene, xylene, butyl acetate, acetone, methyl isobutyl ketone, methyl ethyl ketone, methanol, isopropanol, butanol, hexane, acetone, ethylene glycol, monoethyl ether, VM and P naptha, mineral spirits, heptane and other aliphatic, cycloaliphatic, aromatic hydrocarbons, esters, ethers and ketones and the like. In a typical basecoat, water is typically used as a cosolvent, since most basecoats used nowadays are waterborne systems.

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According to the present invention, any of the coating compositions can be applied by conventional techniques such as spraying, electrostatic spraying, dipping, brushing, flowcoating and the like. The preferred techniques are spraying and electrostatic spraying. After application, a coating composition is typically baked at 100-150°C. for about 15-30 minutes to form a coating about 0.1-3.0 mils thick. When a composition is used as a clearcoat, it is applied over the colorcoat which may be dried to a tack-free state and cured or preferably flash dried for a short period before the clearcoat is applied. The colorcoat/clearcoat finish may then be baked as mentioned above to provide a dried and cured finish.

It has become customary, particularly in the auto industry, to apply a clear topcoat over a basecoat by means of a "wet-on-wet" application, i.e., the topcoat is applied to the basecoat without curing or completely drying the basecoat. The coated substrate is then heated for a predetermined time period to allow simultaneous curing of the base and clear coats.

Upon curing of clear topcoat compositions of the present invention, a portion of the fluorinated silane-containing polymer may also preferentially migrate to, and stratify within, the top portion of the clearcoat, particularly when the fluorinated organosilane polymer is used in combination with a polyol, so as to produce a durable, weather-resistant clearcoat. Such stratification is also generally desirable, since it contributes to very low surface energy, high water and oil repellency, and hence outstanding stain resistance and cleanability, by virtue of the presence of the fluorocarbon constituents. Such stratification has been shown by electron scanning chemical analysis (ESCA) of a cross section of the cured layer of topcoat.

The coating compositions of this invention when applied to a substrate and fully cured most desirably have a water advancing contact angle at least 100°, preferably 100°-120° and a hexadecane advancing angle of at least 40°, preferably 45-85° and more preferably 60°-85°, which provides for a finish, as discussed above, that remains relatively dirt free and easily washed or wiped clean. The relationship between water and organic liquid contact angles and cleanability and dirt retention is more fully described below in the Examples.

In another embodiment, the composition of this invention can be pigmented and used as the colorcoat, or as a monocoat or even as a primer or primer surfacer. When used as a monocoat, these compositions are especially useful for aviation, farm and construction equipment, and architectural coatings where improved cleanability is also desired. When the present coating composition is used as a basecoat, monocoat, primer or primer surfacer, the

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pigments can be introduced into the coating composition by first forming a mill base or pigment dispersion with any of the aforementioned polymers used in the coating composition or with another compatible polymer or dispersant by conventional techniques, such as high speed mixing, sand grinding, ball milling, attritor grinding or two roll milling. The mill base is then blended with the other constituents used in the coating composition. Conventional solvents and diluents are used to disperse and/or dilute the above mentioned polymers to obtain the pigmented coating composition.

In still another embodiment of the present invention, the fluorinated urethane additive described above may be effective as a "mix-in" polymer or additive (typically in the amount from about 0.1-15% by weight, based on the weight of the binder) to any commercially available coating system. For example, the fluorourethane can be used as an additive in polishes, waxes, paints, varnishes and architectural coatings for improved cleanability and stain-resistance. The fluorourethane can be used as an additive for hard flooring to provide enhanced cleanability. The fluorourethane can also be used to improve cleanability and stain-resistance to coatings for appliances, range hoods, auto wheels, etc.

EXAMPLES

The following Examples illustrate the invention. All parts and percentages are on a weight basis unless otherwise indicated. All molecular weights disclosed herein are determined by GPC using a polystyrene standard.

The following oligomers and polymers were prepared and used as indicated in Example 1 and Comparative Examples 2 and 3.

Preparation of Fluorinated Acrylosilane Polymer

A fluorinated acrylosilane polymer was prepared by charging the following constituents into a nitrogen blanketed 12-liter reaction flask equipped with an agitator, thermocouple, a reflux condenser, and heating mantle:

Ingredients	Parts by Weight
Portion I	
Aromatic solvent (Solvesso®100 from Exxon)	1049.8
n-Butanol	524.9
Portion II	
Styrene	923.8

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2-Ethylhexyl acrylate	706.7
Hydroxyethyl methacrylate	1340
Isobutyl methacrylate (iBMA)	1071.6
Gamma-methacryloxypropyl trimethoxysilane (Silquest® A-174 from Crompton)	231
2,2'-azobis(2-methylbutyronitrile) (Vazo® 67 from DuPont)	332.6
Aromatic solvent (Solvesso®100 from Exxon)	1417.2
n-Butanol	182.7
Portion III	
1,1,2,2 Perfluoroalkyl ethyl methacrylate (Zonyl TM® from DuPont; mixed perfluoroalkylethylmethacrylates of formula $F(CF_2CF_2)_{3-8}CH_2CH_2OC(O)C(CH_3)=CH_2$)	69.3
2,2'-azobis(2-methylbutyronitrile) (Vazo® 67 from DuPont)	32.3
Gamma-methacryloxypropyl trimethoxysilane (Silquest® A-174 from Crompton)	138.6
Hydroxyethyl methacrylate	138.6
Aromatic solvent (Solvesso®100 from Exxon)	69.3
Portion IV	
2,2'-azobis(2-methylbutyronitrile) (Vazo® 67 from DuPont)	36.9
Aromatic solvent (Solvesso®100 from Exxon)	105.0
n-Butanol	52.4
Total	8422.8

Portion I was charged into the reaction flask and heated to its reflux temperature under agitation. Portion II was premixed and then added thereto over a 240 minute period while maintaining the reaction mixture at the reflux temperature. Portion III was premixed and then added at one time to the reaction mixture 230 minutes after the start of the addition of Portion II. After completion of the 240 minute feed, Portion IV that had been premixed was added over a 30 minute period and then the reaction mixture was held at its reflux for an additional 60 minutes. The resulting polymer solution was then cooled to room temperature.

The resulting polymer solution had a weight solids of 56.7%, Gardner-Holdt viscosity measured at 25°C of J, a number average molecular weight of

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about 2,175 and a polydispersity of 1.9, and contains the following constituents Sty / 2-EHA / iBMA / A-174 / HEMA // Zonyl TM® (shot) / A174(shot) / HEMA(shot) in a weight ratio of 20 / 15 / 23.5 / 5 / 29 // 1.5 / 3 / 3.

Preparation of Fluorinated Urethane Additive

A fluoro-urethane additive was prepared by charging the following constituents into a nitrogen blanketed 500-mililiter reaction flask equipped as above:

Portion I	Parts by Weight
Isophorone Diisocyanate (Desmodur® I from Bayer)	44.44
Methyl isobutyl ketone	60.32
1,1,2,2,-Tetrahydroperfluoro alcohol {or Perfluoroalkylethyl alcohol} (Zonyl BA® from DuPont; mixed fluoroalcohols of formula $F(CF_2CF_2)_{2\text{-}8}CH_2CH_2OH$)	95.91
Portion II	
Dibutyltin dilaurate	0.04
Portion III	
Polyalkylene Glycol (Ucon® 75-H-450 from Dow Chemical; Polyalkylene group contains 75 weight % oxyethylene and 25 weight % oxypropylene groups; number average molecular weight 980)	205.8
Total	406.51

The ingredients of Portion I were charged into the reaction flask in the order given and heated to 46 °C under agitation and a nitrogen blanket. Portions II was then added to Portion I, a slight exotherm was observed, and the solution was held at 46°C with stirring for 2 hours. Then, Portion III was added over a 30 minute period and the solution was held at 75°C for 2 hours and then cooled to room temperature giving a 96 % yield of fluorinated urethane additive solution.

The resulting fluorinated urethane additive solution has a 82.6 % solids content.

Preparation of Fluorinated Urethane Additive with Silane Functionality

A fluoro-urethane additive with silane functionality was prepared by charging the following constituents into a nitrogen blanketed 2-liter reaction flask equipped as above:

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Portion I	Parts by Weight
Isophorone Diisocyanate (Desmodur® I from Bayer)	44.4 g
Methyl isobutyl ketone	60 g
1,1,2,2,-Tetrahydroperfluoro alcohol {or Perfluoroalkylethyl alcohol}(Zonyl BA® from DuPont; mixed fluoroalcohols of formula $F(CF_2CF_2)_{2-8}CH_2CH_2OH$)	95.8 g
Portion II	
Dibutyltin dilaurate	0.11 g
Portion III	
3-Aminopropyl trimethoxysilane	37.6 g
Total	237.91

The ingredients of Portion I were charged into the reaction flask in the order given and heated to reflux temperature under agitation and a nitrogen blanket. Portion II was then added to Portion I, and the solution was held at 45-50 °C with stirring for 3 hours. Then, Portion III was added over a 120 minute period, at a solution temperature of 75°C. The solution was held until the NCO peak as monitored by Infra Red Spectroscopy disappeared.

Preparation of Non-Fluorinated Acrylosilane Resin

For comparative purposes, a non-fluorinated hydroxy functional acrylosilane resin was prepared by charging the following to a nitrogen blanketed flask equipped as above:

Portion I	Parts by Weight
Aromatic solvent (Solvesso® 100 from Exxon)	96.8
n-Butanol	44.9
Portion II	
Styrene	98.9
Hydroxyethyl methacrylate	155.8
Isobutyl methacrylate	128.1
2-Ethyl hexyl acrylate	62.3
gamma-Methacryloxypropyl trimethoxysilane (Silquest® A-174 from Crompton Corp.)	49.5
Aromatic solvent (Solvesso® 100 from Exxon)	18.3

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Portion III	
Aromatic solvent (Solvesso® 100 from Exxon)	64.3
n-Butanol	68.8
2,2'-azobis(2-methylbutyronitrile) (Vazo® 67 from DuPont)	42.0
Total	829.7

Portion I was charged into the reaction flask and heated to reflux temperature under agitation and a nitrogen blanket. Portions II and III were separately premixed and added to Portion I over a 270 minute period, while the solution was maintained at reflux temperature. The resulting polymer solution was then held at reflux temperature for 30 minutes.

The resulting polymer solution has a 64% solids content, a T viscosity as measured on a Gardner-Holtz scale, and a weight average molecular weight of about 5,000.

Preparation of Acrylic Polyol Resin

An acrylic polyol resin, which may optionally be included in the composition of the present invention, was prepared by charging the following to a nitrogen blanketed flask equipped as above:

Portion I	Parts by Weight
Aromatic solvent (Solvesso® 100 from Exxon)	164.5
n-Butyl Acetate	18.8
Portion II	
Hydroxy ethyl acrylate	174.0
Butyl methacrylate	233.8
Styrene	136.0
Aromatic solvent (Solvesso® 100 from Exxon)	27.4
n-Butyl Acetate	3.0
Portion III	
2,2'-azobis(2-methylbutyronitrile) (Vazo® 67 from DuPont)	21.7
Aromatic solvent (Solvesso® 100 from Exxon)	63.6
n-Butyl Acetate	12.1
Total	854.9

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Portion I was charged into the reactor and heated to reflux temperature. Portions II and III were premixed separately and then added simultaneously to the reactor while the reaction mixture was held at reflux temperature, over a 260 minute period. The solution was then held at reflux temperature for 30 minutes.

The resulting acrylic polyol resin is 66% by weight solids, and has a weight average molecular weight of about 6,000.

Preparation of Acrylic NAD Resin

A hydroxy functional acrylic NAD resin, which may optionally be included in the composition of the present invention, was prepared by charging the following to a nitrogen blanketed flask equipped as above:

Portion I	Parts by Weight
Isopropanol	29.9
Mineral spirits (Exxsol® D40 from Exxon)	35.9
Heptane	245.6
Acrylic polymer solution (60% solids of an acrylic polymer of 15% styrene, 20% butyl methacrylate, 38.5% ethyl hexyl methacrylate, 22.5% hydroxy ethyl acrylate, 4% acrylic acid, and 1.4% glycidyl methacrylate having a weight average molecular weight of 10,000 in a solvent blend of 77.5% Solvesso® 150 and 22.5% butanol)	179.7
Portion II	
t-Butyl peroxy-2-ethyl hexanoate	0.45
Portion III	
Styrene	35.9
Methyl methacrylate	194.7
Acrylonitrile	6.0
Acrylic polymer solution (from above)	89.9
Hydroxy ethyl acrylate	29.9
Methyl acrylate	15.0
Glycidyl methacrylate	6.0
Acrylic acid	12.0
Isobutyl alcohol	26.9

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Portion IV	
Mineral spirits (Exxsol® D40 from Exxon)	21.0
Heptane	27.0
t-Butyl peroxy-2-ethyl hexanoate	3.0
Portion V	
Isobutyl alcohol	42.0
t-Butyl peroxy-2-ethyl hexanoate	1.5
Total	1002.35

Portion I was charged into the reaction vessel and heated to reflux temperature. Portion II was then added to the reaction vessel within 5 minutes before Portions III and IV begin feeding into the reaction vessel. Portions III and IV were separately premixed, and simultaneously fed into the reaction vessel, at reflux temperature, over a 210 minute period. Portion V was premixed and added over a 60 minute period while maintaining reflux temperature. The reaction solution was then held at reflux temperature for 60 minutes. Vacuum was then applied to the reaction vessel, and 236.84 parts by weight solvent are stripped off.

The resulting NAD resin has a weight solids of 60%, a core having a weight average molecular weight of about 100,000-200,000 and arms attached to the core having a weight average molecular weight of about 10,000-15,000.

Preparation of an Acrylic Microgel Resin

A methyl methacrylate / glycidyl methacrylate copolymer was prepared as an intermediate stabilizing polymer used in the synthesis of the below acrylic microgel resin, also optionally included in the composition of the present invention. This stabilizing polymer was prepared by charging the following to a nitrogen blanketed flask equipped as above:

Portion I	Parts by Weight
n-Butyl acetate	195.8
Portion II	
Methyl methacrylate	139.0
n-Butyl acetate	14.4
Glycidyl methacrylate	13.1
Glycidyl methacrylate / 12-Hydroxystearic acid copolymer (60% by weight solids solution of 89.2% 12-HAS /	181.7

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10.8% GMA in a 80 / 20 blend of toluene and petroleum naphtha)	
Petroleum Naphtha (Exxsol® D-3135 from Exxon)	40.6
n-Butyl acetate	13.1
Portion III	
2,2'-azobis(2-methylbutyronitrile)	8.0
n-Butyl acetate	71.6
Petroleum Naphtha (Exxsol® D-3135 from Exxon)	74.3
Portion IV	
4-tert-Butyl catechol	0.04
n-Butyl acetate	2.7
Portion V	
Methacrylic acid	2.7
n-Butyl acetate	6.0
Portion VI	
N,N'-dimethyl dodecyl amine	0.4
n-Butyl acetate	2.7
Total	766.14

Portion I was charged to the reactor and brought to a temperature of 96 to 100°C. Portions II and III were separately premixed and then added concurrently over a 180 minute period, while maintaining a reaction temperature of 96 to 100°C. The solution was then held for 90 minutes. In sequence, Portions IV, V, and VI were separately premixed and added to the reactor. The reaction solution was then heated to reflux and held until the acid number is 0.5 or less. The resulting polymer solution has a 40% solids content.

The acrylic microgel resin was then prepared by charging the following to a nitrogen blanketed flask equipped as above:

Portion I	Parts by Weight
Methyl methacrylate	11.3
Mineral spirits (Exxsol® D40 from Exxon)	73.7
Methyl methacrylate / Glycidyl methacrylate stabilizer copolymer (prepared above)	5.4
Heptane	60.7

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2,2'-azobis(2-methylbutyronitrile) (Vazo® 67 from DuPont)	0.35
Portion II	
N,N-dimethylethanolamine	0.5
Methyl methacrylate	216.2
Methyl methacrylate / Glycidyl methacrylate stabilizer copolymer (prepared above)	41.2
Glycidyl methacrylate	2.1
Methacrylic acid	2.1
Heptane	35.8
Mineral Spirits (Exxsol® D40 from Exxon)	73.7
Portion III	
2,2'-azobis(2-methylbutyronitrile) (Vazo® 67 from DuPont)	0.8
Toluene	9.7
Heptane	23.4
Portion IV	
n-Butanol	7.8
Portion V	
Hydroxy propyl acrylate	49.1
Methyl methacrylate / Glycidyl methacrylate stabilizer copolymer (prepared above)	10.3
Butyl methacrylate	73.7
Heptane	11.5
Portion VI	
t-Butylperoxy 2-Ethylhexanoate	9.0
n-Butanol	43.0
Heptane	3.9
Total	765.25

Portion I was charged into the reaction vessel, heated to its reflux temperature, and held for 45 minutes. Portions II and III were premixed separately and then added simultaneously over a 120 minute period to the reaction vessel mixed while maintaining the reaction mixture at its reflux temperature. Portion IV was then added. Portions V and VI were premixed separately and then added concurrently to the batch over a 120 minute period while the mixture was

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maintained at reflux temperature. The mixture was then held at reflux temperature for 30 minutes.

The resulting polymer solution has a weight solids of 50%, and a viscosity of 60 centipoise.

Preparation of Clearcoat Example 1 and Comparative Examples 2 and 3

Clearcoat compositions useful in practicing the present process were prepared by blending together the following ingredients in the order given:

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CLEARCOAT EXAMPLES

INGREDIENTS (all amounts parts by weight)	Ex. 1	C.Ex. 2	C.Ex. 3
Fluorinated Acrylosilane Resin (from above)	614.853	614.853	
Fluoro-Urethane Additive (from above)	8.131		
Non-fluorinated Acrylosilane Resin (from above)			372.575
Acrylic Microgel (from above)	33.304	33.304	16.979
Acrylic Polyol Resin (from above)			187.030
Acrylic NAD Resin (from above)			28.338
Solvesso® 100	114.973	114.973	194.133
Tinuvin® 1130[1] (Benzotriazole UV Light Absorber)	14.286	14.286	7.028
Tinuvin® 123[1] (Hindered Amine UV Light Absorber)	2.968	2.968	1.460
Tinuvin® 384[1] (UV Light Absorber)	12.689	12.689	6.242
Tinuvin® 079L[1] (Hindered Amine UV Light Absorber)	26.531	26.531	13.052
Disparlon® LC-955 Surfactant[2]	6.298	6.298	5.563
Disparlon® L-1984 Surfactant[2]	2.563	2.563	
Blocked Acid Catalyst Solution (48.0% DDBSA / 10.8% 2-amino methyl propanol / 41.2% Methanol)	21.772	21.772	17.803
Ethyl 3-ethoxy Propionate	25.576	25.576	
n-Butanol	2.890	2.890	2.890
Ethylene Glycol Monobutyl Ether	38.617	38.617	38.617
Desmodur® N-3300 [3] Polyisocyanate	175.845	175.845	175.845
Phenyl Acid Phosphate	2.442	2.442	2.442

Sources of above constituents are:

[1]Product of Ciba Specialty Chemical Company
[2]Product of King Industries
[3]Product of Bayer Corporation

Phosphated steel panels that had been electrocoated with an electrocoating primer were sprayed and coated respectively with conventional solid black, silver metallic, and blue metallic solvent-borne base coating composition to form a

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basecoat about 0.5 to 1.0 mils thick. The basecoats were each given a flash of 5 minutes. Then the clearcoat paints formulated above were applied "wet-on-wet" over each of the basecoats to form a clearcoat layer about 1.8-2.2 mil thick. The panels were then fully cured by baking for 30 minutes at about 250°F, which is a typical OEM bake. The resulting coated panels were measured for the below properties, and results are tabulated in Table 2. A second set of panels were coated as specified above. Additionally, after cooling, a second basecoat / clearcoat repair coat layer was applied by the same procedure as the initial coat. No sanding or surface preparation was prepared prior to application of the repair basecoat. The resulting coated panels were also subjected to the tests specified below to evaluate adhesion and the amount of pickoff off the repair topcoating from the original topcoating was recorded. Results are reported in Tables 1 and 3 below.

The following properties of the OEM and Repair coat panel were measured: 20° Gloss, Distinctness of Image (DOI), Hardness, advancing and receding water contact angles and advancing and receding hexadecane solvent contact angles as determined by video contact angle system, initial cross hatch adhesion, cross hatch adhesion after 96 or 240 hours of exposure to 100% relative humidty at 40° Celsius, and primerless windshield bonding adhesion.

The contact angle measurements described above, in particular, were used to assess the cleanability and dirt retention of the clearcoated surfaces. Contact angles are measured by the Sessile Drop Method which is fully described in A. W. Adamson, The Physical Chemistry of Surfaces, 5th Ed., Wiley & Sons, New York, 1990, Chapter II which is hereby incorporated herein by reference.

Briefly, in the Sessile Drop Method, a drop of liquid, either water or solvent, is placed on a surface and the tangent is precisely determined at the point of contact between the drop and the surface. An advancing angle is determined by increasing the size of the drop of liquid and a receding angle is determined by decreasing the size of the drop of liquid. Additional information on the equipment and procedure needed to measure these contact angles are more fully described in R. H. Dettre, R. E. Johnson Jr., Wettability, Ed. by J. C. Berg, Marcel Dekker, New York, 1993, Chapter 1 which is incorporated herein by reference.

The relationship between water and organic liquid contact angles and cleanability and dirt retention is described in chapters XII and XIII of A. W. Adamson, above. In general, the higher the contact angle the more dirt or soil resistant the surface is and the easier the surface is to clean.

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The cross-hatch adhesion measurements described above, in particular, were used to assess the adhesion of the original clearcoat to the original basecoat and the recoat adhesion of the repair basecoat to the original clearcoat. As indicated above, for recoat adhesion, the applied basecoats and clearcoats were baked for 30 minutes at 250°C. Within 24 hrs of the bake, the same basecoats and clearcoats were applied by the same procedure described above over the top of the baked OEM basecoat and clearcoat. The newly applied topcoats were baked again at 250°C for 30 minutes. These recoated panels were then aged for a minimum of 24 hrs and tested for recoat adhesion according to the cross-hatch adhesion method described below.

Briefly, cross hatch adhesion was tested according to General Motors Test Procedure GM9071P published by General Motors Corporation and ASTM D-3359-93. The test is performed on panels aged at room temperature for 72 hours after baking. Panels are scribed in a grid pattern and adhesive tape is applied over scribe marks, then tape is pulled rapidly from the film. The magnitude of observed removal of coating from the substrate indicates adhesion quality. Rate the percentage of grid or cross hatch area from which coating was removed. A rating of 5% or more paint film removed is considered a failure.

In order to test for primerless windshield bonding adhesion, a bead of windshield adhesive was applied to the clearcoat surface after baking. The windshield adhesive used is commercially available from Dow Essex Specialty Products Company. Approximately a 5 mm×5 mm×250 mm adhesive bead was placed on the cured clearcoat surface. The adhesive plus clear composite was cured for 72 hours at about 75°F (24°C.) and 20-50% relative humidity. The cured adhesive bead was cut with a razor blade. A cut was made through the adhesive bead at a 60° angle at 12mm intervals while pulling back the edge of the adhesive at a 180° angle. A minimum of 10 cuts was done for each system. The desired result is described as 100% cohesive failure (CF). Cohesive failure (CF) occurs when the integrity of the adhesive bead is lost as a result of cutting and pulling rather than the bond between the adhesive bead and the clearcoat surface. The results over a few colored basecoats, for both OEM initial coat and Repair coat films are summarized in the tables, below.

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Table 1

Repair Coat Test Results

					Contact Angles using Video Contact Angle System								Humidity Adhesion	
					Deionized Water				Hexadecane				Initial	96 hr hum
					Advancing		Receding		Advancing		Receding		Cross Hatch	
Clearcoat	Basecoat	DOI	20° Gloss	Tukon	Avg.	S.D.	Avg.	S.D.	Avg.	S.D.	Avg.	S.D.	% Film Loss	
Ex 1	Blue Met												0	0
C.Ex. 2	Blue Met												>65	>65

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The above results show that the clear coating compositions made using the fluorinated urethane additive of this invention (Ex. 1) exhibit recoat adhesion, while comparative systems that do not contain the additive (C.Ex. 2) do not possess the required recoat adhesion properties.

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Table 2
OEM Initial Coat Test Results

				Contact Angles using Video Contact Angle System								Humidity Adhesion		Windshield
				Deionized Water				Hexadecane				Initial	240 hr hum	Bonding
				Advancing		Receding		Advancing		Receding		Cross Hatch		Humidity
Clearcoat	Basecoat	DOI	20° Gloss	Tukon	Avg.	S.D.	Avg.	S.D.	Avg.	S.D.	Avg.	S.D.	% Film Loss		Result
Ex 1	SilverMet	84	90	15.1	98.5	1.0	75.3	1.5	44.3	1.5	36.3	0.5	0	0	Pass 100 CF
C.Ex 3	SilverMet	91	91	12.6	90.0	0.0	72.0	1.5	10.7	1.4	6.3	0.5	0	0	Pass 100 CF
Ex. 1	Black	88	88	12.6	99.5	1.0	77.3	0.5	49.7	0.5	38.7	1.4	0	0	Pass 100 CF
C.Ex. 3	Black	93	87	12.1	89.8	0.8	74.0	0.9	13.7	1.0	7.0	0.0	0	0	Pass 100 CF

Table 3
Repair Coat Test Results

							Contact Angles using Video Contact Angle System						Humidity Adhesion	
							Deionized Water				Hexadecane		Initial	240 hr hum.
					Advancing		Receding		Advancing		Receding		Cross Hatch	
Clearcoat	Basecoat	DOI	20° Gloss	Tukon	Avg.	S.D.	Avg.	S.D.	Avg.	S.D.	Avg.	S.D.	% Film Loss	
Ex.1	SilverMet	77	89	15.5	102.0	1.5	75.0	1.5	1.5	46.7	0.5	0.0	0	0
CEx 1	SilverMet	77	89	11.4	91.7	1.4	75.5	0.5	11.7	11.7	0.5	0.9	0	0
Ex.1	Black	85	88	12.2	101.7	0.5	77.0	0.9	48.5	2.7	37.3	0.5	0	0
C.Ex.3	Black	97	87	9.7	90.0	0.0	74.7	1.4	13.0	0.9	5.3	0.5	0	0

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The above results show that the clear coating compositions made using the fluorinated urethane additive of this invention (Ex. 1) not only have a high contact angle for water and for solvents which provides for a finish which is resistant to soiling and is easily washed or wiped clean, but also have the required recoat adhesion properties which enable the operation of the process of the present invention. The non-fluorinated acrylosilane polymer-containing clearcoat composition (C.Ex. 3), which corresponds to a commercial clearcoat composition, does not exhibit as good as cleanability for nearly all colors.

Various modifications, alterations, additions or substitutions of the process and compositions of this invention will be apparent to those skilled in the art without departing form the scope and spirit of this invention, and it should be understood that this invention is not limited to the illustrated embodiments set forth herein, but rather as recited in the following claims.

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CLAIMS

What is claimed is:

1. A method for in-line or end-of line repair of an original basecoat/topcoat finish on an automobile or truck during their original manufacture, in which the original topcoat comprises a substantially cured fluorinated silane polymer, wherein the improvement comprises:

(a) incorporating in the original topcoat, an adhesion improving additive comprising a fluorinated urethane compound;

(b) applying over said original topcoat, a repair basecoat composition comprising an aminoplast resin crosslinking agent;

(c) applying over said repair basecoat, a repair topcoat composition; and

(d) curing the new basecoat/topcoat finish.

2. The method of claim 1, wherein the repair topcoat is applied over said repair basecoat wet-on-wet and the new top coat and basecoat are cured together.

3. The method of claim 1, wherein the coating compositions for both the original basecoat/topcoat and repair basecoat/topcoat are the same, so that only one topcoat and one basecoat composition are used.

4. The method of claim 1, wherein the fluorinated urethane compound consists essentially of an adduct of an organic polyisocyanate, a polyoxyethylene/polyoxypropylene glycol, and a fluorinated monofunctional alcohol, and contains substantially no residual isocyanate groups.

5. The method of claim 1, wherein the fluorinated urethane compound consists essentially of an adduct of an organic polyisocyanate, an amino-functional silane, and a fluorinated monofunctional alcohol, and contains substantially no residual isocyanate groups.

6. The method of claim 1, wherein the fluorinated urethane compound is employed in the original topcoat composition in an amount of about 0.1-10% by weight, based on the weight of the binder of the original topcoat.

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7. A method for improving the adhesion of a repair coating to a coated substrate, which comprises:

(a) applying to a substrate at least one coating composition comprising a film-forming binder comprising a fluorinated silane polymer and an adhesion improving additive comprising a fluorinated urethane compound;

(b) curing the at least one coating composition to provide a coated substrate;

(c) applying to the coated substrate one or more repair coatings wherein the first repair coating applied to the substrate comprise an aminoplast resin crosslinking agent;

(d) curing the one or more repair coatings to form a new finish over said substrate.

8. A substrate coated according to the method of claim 1.

9. A coating composition containing about 45-90% by weight of film forming binder and 10-55% by weight of an organic liquid carrier; wherein the binder comprises:

(A) about 10 to 90% by weight, based on the weight of the binder, of a film-forming fluorinated organosilane polymer consisting essentially of about 5 to 98% by weight, based on the weight of the polymer, of polymerized ethylenically unsaturated monomers which do not contain a silane or a fluorine functionality, about 1.5 to 70% by weight, based on the weight of the polymer, of ethylenically unsaturated monomers which contain a silane functionality, and about 0.5-25% by weight, based on the weight of the polymer, of polymerized ethylenically unsaturated monomers which contain a fluorine functionality,

(B) about 0 to 60%, based on the weight of the binder, of a non-aqueous dispersed polymer, and

(C) about 10 to 90% by weight, based on the weight of the binder, of an crosslinking agent selected from one or both of an organic polyisocyanate and melamine crosslinking agent; and wherein the composition further comprises:

(D) about 0.1 to 15% by weight, based on the total weight of binder solids in the composition, of a fluorinated urethane compound.

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10. The composition of claim 9 wherein the fluorinated urethane compound consists essentially of an adduct of an organic polyisocyanate, a polyoxyethylene/polyoxypropylene glycol, and a fluorinated monofunctional alcohol, and contains substantially no residual isocyanate groups.

11. The method of claim 9, wherein the fluorinated urethane compound consists essentially of an adduct of an organic polyisocyanate, an amino-functional silane, and a fluorinated monofunctional alcohol, and contains substantially no residual isocyanate groups.

12. An automobile or truck top coated with the composition of claim 9.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/031243

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C09D175/04 C09D133/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C09D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 796 904 A (NIPPON PAINT CO LTD) 24 September 1997 (1997-09-24) page 2, lines 5-15 page 2, line 38 - page 3, line 32 page 4, lines 29-52 page 5, line 46 - page 6, line 30 page 10, lines 5-46; claims	1-3,6-9, 12
X	US 2003/017349 A1 (SCHNEIDER RICHARD A ET AL) 23 January 2003 (2003-01-23) paragraphs '0002!, '0027!, '0028!, '0036!, '0073! - '0077!, '0087! - '0089!, '0094! - '0100!, '0108!; claims	1-3,6-9, 12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2004	14/12/2004

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

Form PCT/ISA/210 (second sheet) (January 2004)

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/027198 A (BASF CORP ; RIHAN ALI (US); COLYER EMERSON KEITH (US)) 3 April 2003 (2003-04-03) paragraphs '0001!, '0007! - '0034!; claims	1-3,6,8
A	WO 97/22646 A (PPG INDUSTRIES INC) 26 June 1997 (1997-06-26) page 1, lines 6-9 page 4, line 11 - page 8, line 16; claims; examples	1-12
A	US 4 812 337 A (NUMA NOBUSHIGE ET AL) 14 March 1989 (1989-03-14) cited in the application column 1, lines 4-10 column 2, line 60 - column 4, line 27 claims; examples	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/031243

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(54)【発明の名称】フッ素化トップコート上への再コーティング接着を達成する方法

(57)【要約】
フッ素化有機シラン・トップコートよりなるベースコート／クリアコート仕上げまたはコーティングの修理方法。フッ素化ウレタン添加物が修理ベースコートとの再コーティング接着性を改良するためにフッ素化有機シラン・トップコート組成物に添加される。

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【特許請求の範囲】
【請求項1】
自動車またはトラックの最初の製造中における自動車またはトラックの元のベースコート／トップコート仕上げのインラインまたはエンドオブライン修理方法であって、元のトップコートが実質的に硬化したフッ素化シランポリマーを含み、
（ａ）フッ素化ウレタン化合物を含む接着性改良添加物を前記元のトップコートに組み込む工程と、
（ｂ）アミノプラスト樹脂架橋剤を含む修理ベースコート組成物を前記元のトップコート上に塗布する工程と、
（ｃ）修理トップコート組成物を前記修理ベースコート上に塗布する工程と、
（ｄ）新たなベースコート／トップコート仕上げを硬化させる工程と
を改良点として含むことを特徴とする方法。
【請求項2】
修理トップコートが前記修理ベースコート上にウェット・オン・ウェット（ｗｅｔ－ｏｎ－ｗｅｔ）で塗布され、そして新たなトップコートおよびベースコートが一緒に硬化させられることを特徴とする請求項１に記載の方法。
【請求項3】
元のベースコート／トップコートおよび修理ベースコート／トップコートの両方のコーティング組成物が同じものであり、その結果、１種類だけのトップコート組成物および１種類だけのベースコート組成物が使用されることを特徴とする請求項１に記載の方法。
【請求項4】
フッ素化ウレタン化合物が有機ポリイソシアネート、ポリオキシエチレン／ポリオキシプロピレングリコール、およびフッ素化一官能性アルコールの付加体から本質的になり、かつ、残留イソシアネート基を実質的に含有しないことを特徴とする請求項１に記載の方法。
【請求項5】
フッ素化ウレタン化合物が有機ポリイソシアネート、アミノ官能性シラン、およびフッ素化一官能性アルコールの付加体から本質的になり、かつ、残留イソシアネート基を実質的に含有しないことを特徴とする請求項１に記載の方法。
【請求項6】
フッ素化ウレタン化合物が、元のトップコートのバインダーの重量を基準にして約０．１～１０重量％の量で元のトップコート組成物に用いられることを特徴とする請求項１に記載の方法。
【請求項7】
修理コーティングの被覆基材への接着性の改良方法であって、
（ａ）フッ素化シランポリマーと、フッ素化ウレタン化合物を含む接着性改良添加物とを含むフィルム形成性バインダーを含む少なくとも１つのコーティング組成物を基材に塗布する工程と、
（ｂ）少なくとも１つのコーティング組成物を硬化させて被覆基材を提供する工程と、
（ｃ）基材に塗布された第１修理コーティングがアミノプラスト樹脂架橋剤を含む、１つまたは複数の修理コーティングを被覆基材に塗布する工程と、
（ｄ）１つまたは複数の修理コーティングを硬化させて新たな仕上げを前記基材上に形成する工程と
を含むことを特徴とする方法。
【請求項8】
請求項１に記載の方法に従ってコーティングされることを特徴とする基材。
【請求項9】
約４５～９０重量％のフィルム形成性バインダーおよび１０～５５重量％の有機液体キャリアを含有するコーティング組成物であって、バインダーが

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（Ａ）ポリマーの重量を基準にして約５～９８重量％の、シランまたはフッ素官能基を含有しない重合したエチレン性不飽和モノマー、ポリマーの重量を基準にして約１．５～７０重量％の、シラン官能基を含有するエチレン性不飽和モノマー、およびポリマーの重量を基準にして約０．５～２５重量％の、フッ素官能基を含有する重合したエチレン性不飽和モノマーから本質的になる、バインダーの重量を基準にして約１０～９０重量％のフィルム形成性フッ素化有機シランポリマーと、

（Ｂ）バインダーの重量を基準にして約０～６０％の非水性分散ポリマーと、

（Ｃ）有機ポリイソシアネートおよびメラミン架橋剤の１つまたは両方から選択された、バインダーの重量を基準にして約１０～９０重量％の架橋剤とを含み、そしてさらに組成物が、

（Ｄ）組成物中のバインダー固形分の総重量を基準にして約０．１～１５重量％のフッ素化ウレタン化合物

を含むことを特徴とする組成物。

【請求項10】

フッ素化ウレタン化合物が有機ポリイソシアネート、ポリオキシエチレン／ポリオキシプロピレングリコール、およびフッ素化一官能性アルコールの付加体から本質的になり、かつ、残留イソシアネート基を実質的に含有しないことを特徴とする請求項９に記載の組成物。

【請求項11】

フッ素化ウレタン化合物が有機ポリイソシアネート、アミノ官能性シラン、およびフッ素化一官能性アルコールの付加体から本質的になり、かつ、残留イソシアネート基を実質的に含有しないことを特徴とする請求項９に記載の方法。

【請求項12】

請求項９に記載の組成物でトップコーティングされていることを特徴とする自動車またはトラック。

【発明の詳細な説明】

【技術分野】

【0001】

本発明は、トップコート組成物がフッ素化有機シランポリマーを含むベースコート／トップコート・システムで以前にコーティングされた基材を再コーティングする方法に関する。具体的には、本発明は、特に自動車またはトラックの最初の製造中の自動車またはトラックの仕上げのインラインおよびエンドオブライン修理中に再コーティング接着を得るための方法に関する。

【背景技術】

【0002】

自動車または他の車両上の仕上げの美的品質を保護するおよび保持するために、ベースコートが環境または風化への長期にわたる曝露時にさえも影響を受けないままであるように、着色した（顔料入り）ベースコート上にクリア（顔料なしまたは僅かに顔料入り）トップコートを提供することは一般に公知である。これは、ベースコート／トップコートまたはベースコート／クリアコート仕上げと言われる。フルオロカーボンが、屋外使用条件下で比較的汚れのないままであり、かつ、汚れた時に例えば水で洗浄することによって容易にきれいにされるトップコーティングを提供することもまた一般に公知である。フルオロカーボン成分を含有するトップコーティングを開示する先行技術特許の模範的なものは、米国特許公報（特許文献１）、米国特許公報（特許文献２）、米国特許公報（特許文献３）、米国特許公報（特許文献４）、米国特許公報（特許文献５）、および米国特許公報（特許文献６）である。消費者が魅力的な美的外観を有する外装仕上げの自動車およびトラックを好むことが周知であることを考えれば、仕上げの急速な汚れはなおさらに望ましくないことである。

【0003】

しかしながら、フッ素化トップコート仕上げ剤の商業化は、幾つかの重大なまたは決定的に重要でさえある技術的ハードルによって妨げられてきた。仕上げ中の欠陥は正規製造

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工程中に時々起こり、オンサイト修理を必要とするかもしれないので、例えば、商業上実用的な仕上げは、他の要件の中でも特に、修理コーティングへの十分な接着性、または当該技術で再コーティング接着性として知られているものを持たなければならない。さらに、商業上実用的な仕上げは、塗布するのに問題があってはまたは困難であってはならない。

【0004】

【特許文献1】米国特許第４，８１２，３３７号明細書
【特許文献2】米国特許第５，５９７，８７４号明細書
【特許文献3】米国特許第５，６０５，９５６号明細書
【特許文献4】米国特許第５，６２７，２３８号明細書
【特許文献5】米国特許第５，６２９，３７２号明細書
【特許文献6】米国特許第５，７０５，２７６号明細書
【特許文献7】米国特許第４，０４３，９５３号明細書
【特許文献8】米国特許第４，５１８，７２６号明細書
【特許文献9】米国特許第４，３６８，３９７号明細書
【特許文献10】米国特許第４，１４７，６８８号明細書
【特許文献11】米国特許第４，１８０，４８９号明細書
【特許文献12】米国特許第４，０７５，１４１号明細書
【特許文献13】米国特許第４，４１５、６８１号明細書
【特許文献14】米国特許第４，５９１，５３３号明細書
【特許文献15】米国特許第５，１６２，４２６号明細書
【非特許文献1】バレット（Ｂａｒｒｅｔｔ）著、「有機媒体中での分散重合（ＤＩＳＰＥＲＳＩＯＮ　ＰＯＬＹＭＥＲＩＺＡＴＩＯＮ　ＩＮ　ＯＲＧＡＮＩＣ　ＭＥＤＩＡ）」、ジョンワイリー社、１９７５年
【非特許文献2】エー．ダブリュ．アダムソン（Ａ．Ｗ．Ａｄａｍｓｏｎ）著、「表面の物理化学（Ｔｈｅ　Ｐｈｙｓｉｃａｌ　Ｃｈｅｍｉｓｔｒｙ　ｏｆ　Ｓｕｒｆａｃｅｓ）」、第５版、ニューヨーク、ワイリー・アンド・ソンズ（Ｗｉｌｅｙ　＆　Ｓｏｎｓ）社、１９９０年、第ＩＩ章
【非特許文献3】アール．エッチ．デットレ（Ｒ．Ｈ．Ｄｅｔｔｒｅ）、アール．イー．ジョンソン・ジュニア（Ｒ．Ｅ．Ｊｏｈｎｓｏｎ　Ｊｒ．）著、「湿潤性（Ｗｅｔｔａｂｉｌｉｔｙ）」、ジェー．シー．バーグ（Ｊ．Ｃ．Ｂｅｒｇ）、マーセル　デッカー（Ｍａｒｃｅｌ　Ｄｅｋｋｅｒ）編、ニューヨーク、１９９３年、第１章
【非特許文献4】エー．ダブリュ．アダムソン著、「表面の物理化学」、第５版、ニューヨーク、ワイリー・アンド・ソンズ社、１９９０年、第ＸＩＩ章および第ＸＩＩＩ章

【発明の開示】

【課題を解決するための手段】

【0005】

自動車仕上げの通常のインラインまたはエンドオブライン修理では、修理ベースコート／クリアコート・システムが、以前に硬化したが欠陥のある元のベースコート／クリアコート上に塗布される。全仕上げは次に別の硬化サイクルにかけられる。欠陥のある仕上げの研磨または除去は通常省略される。修理（第２）ベースコートは、通常の硬化条件で元の（第１）クリアコートに接着することが期待される。

【0006】

フッ素化トップコート組成物、特に硬化した時に強いシラン結合のために優れた引っ掻き抵抗性と酸性雨および他の環境汚染物質によるエッチングに対する耐性とを仕上げに提供する、フッ素化シランポリマーを含有するトップコートの開発中に、出願者らは、従来の修理ベースコートは硬化したトップコートへの不満足なまたは不十分な接着性を示すことを見いだした。この不満足な接着性は、クリアコートの外面（空気に接触する面）でのフッ素層化の現象のためと考えられる。かかる層化は、それが非常に低い表面エネルギー、高い撥水性および撥油性、ならびに従って顕著な耐汚染性およびクリーナビリティに寄

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与するので一般には望ましいが、それにもかかわらずかかる層化はまた当該技術で再コーティング接着性として知られるものへの悪影響を有すると思われる。出願者らは、アルキル化メラミン・ホルムアルデヒドまたは修理ベースコート中に通常存在する他のアミノプラスト樹脂架橋剤とよく反応するフッ素化ウレタン化合物を含む接着性改良添加物を元のトップコート組成物に含めることによって再コーティング接着性のこの問題を解決することができた。

【0007】

特許請求される本発明は、それ故、元のトップコートが硬化したフッ素化シランポリマーを含む元のベースコート／トップコート仕上げの修理方法に関する。本修理方法は、

（ａ）アミノプラスト樹脂架橋剤を含むベースコート組成物を、フッ素化シランポリマーとその上に実質的に硬化したフッ素化ウレタン化合物を含む接着性改良添加物とを含むトップコーティングを有する基材に塗布する工程と、

（ｂ）トップコート組成物を前記ベースコート上に塗布する工程と、

（ｃ）新たなベースコート／トップコート仕上げを硬化させる工程と

を含む。

【0008】

用語「実質的に硬化した」または「部分的に硬化した」とは、少なくとも幾らかの硬化は起こったが、さらなる硬化が時間と共に起こってもよいことを意味する。好ましい実施形態では、修理および元のベースコート組成物は同じものであり、かつ、元のおよび修理トップコートまたはクリアコート組成物は同じものである。トップコート組成物は好適には約４５～９０重量％のバインダーを含み、バインダーは１０～９０重量％、好ましくは４０～８０％のフッ素化シランポリマーを含む。好ましくは、フッ素化シランポリマーは、そのうち約１．５～７０重量％、好ましくは５～５０％がシラン官能基を含有するエチレン性不飽和モノマーであり、そのうち約０．５～２５重量％、好ましくは１～１０％がフッ素官能基を含有するエチレン性不飽和モノマーであるモノマー混合物の重合生成物である。

【0009】

特許請求される本発明はさらに、本方法で使用できる修理可能なトップコート組成物と本方法に従って製造された被覆基材とを含む。

【0010】

本発明の方法は、クリア・フッ素化トップコートを顔料入りベースコート上に形成するために特に有用である。かかるトップコートは、水または有機溶剤を含有するベースコートおよび粉体ベースコートをはじめとする、様々なベースコート上に塗布することができる。

【発明を実施するための最良の形態】

【0011】

上に示されたように、本発明は、例えば、米国特許公報（特許文献７）、米国特許公報（特許文献８）および米国特許公報（特許文献９）に示されるように、シランポリマーが改良された引っ掻きおよび表面損傷抵抗性と酸性雨および他の環境汚染物質によるエッチングに対する耐性とをコーティングに提供することが一般に知られているので、フッ素化学を含むコーティング、より具体的にはフッ素化有機シランポリマーを含むコーティングの塗布に関する。より具体的には、本発明は、硬化したまたは少なくとも部分的に硬化したフッ素化シランポリマーを含むトップコートを有する仕上げを修理する時に再コーティング接着性を得るための方法を提供する。本方法は、自動車およびトラック本体またはそれらの部品の外装上の元の仕上げのインラインおよびエンドオブライン修理に特に有用である。本方法は、フッ素化ウレタン化合物を含む接着性改良添加物を元のトップコートに組み込む工程と、アミノプラスト樹脂架橋剤を用いる修理ベースコートをその上に塗布する工程とを含む。

【0012】

典型的には、自動車スチールパネルまたは基材は先ず、無機錆止めリン酸亜鉛または鉄

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層でコーティングされ、その上に電着プライマーまたは修理プライマーであり得るプライマーが提供される。典型的な電着プライマーは陰極電着エポキシ変性樹脂を含む。典型的な修理プライマーはアルキド樹脂を含む。場合により、プライマーサーフェーサーを、より良好な外観および／またはプライマーコートへのベースコートの改良された接着性を提供するためにプライマーコーティング上に塗布することができる。顔料入りベースコートまたはカラーコートが次に塗布される。典型的なベースコートは、メタリック仕上げのケースでは金属粉を含んでもよい顔料、ならびにポリエステルまたはアクリロウレタン・フィルム形成性バインダーおよびアミノプラスト樹脂架橋剤を含む。

【0013】

クリア・トップコート（クリアコート）が次に顔料入りベースコート（カラーコート）に塗布されてもよい。カラーコートおよびクリアコートは好ましくは、それぞれ、約０．１～２．５ミルおよび１．０～３．０ミルの厚さを有するように溶着される。本発明では、トップコートはフッ素化有機シランポリマーを含む。

【0014】

上に示されたように、本発明によれば、元のベースコート／クリアコート仕上げの修理目的のために、元のクリアコートは、１つまたは複数のフッ素化ウレタン化合物を含む接着性改良添加物を含有するように調合され、修理ベースコートは、修理ベースコートを硬化させるために通常使用されるもののような少なくとも１つのアミノプラスト樹脂架橋剤を含有する。

【0015】

トップコートは時々またフッ素化ウレタン化合物とよく反応するアミノプラスト樹脂架橋剤を含有するけれども、元のトップコートは、本明細書で使用される種類のフッ素化ウレタン化合物をその中に含むことによって悪影響も受けず、また効果的に硬化もしない。通常の硬化サイクル中に、何の実質的な反応も起こらず、修理ベースコート中のアミノプラスト架橋剤と反応させるために添加物を表面で利用可能であるままにする。

【0016】

本発明の商業的な応用では、１種類だけのトップコートおよびベースコート組成物が必要であるように、元の仕上げ剤および修理仕上げ剤の両方に同じコーティング組成物を使用することが最も便利である。別の利点は、インライン修理のために、同じ配送ラインおよび製造サイクルを元の組成物および修理組成物に利用できることである。従って、修理仕上げに使用されるトップコート組成物は、それが再コーティング接着性に何の効果も持たないかもしれないが、フッ素化ウレタン接着性改良添加物を含有するであろう。

【0017】

本発明で用いられるトップコート組成物は、クリアコーティング組成物、すなわち、何の顔料も含有しないかまたは少量の透明な顔料を含有する組成物である。組成物はまた、約４５～９０重量％の比較的高い固形分含有率のフィルム形成性バインダーと、バインダー用の溶剤または溶剤の混合物および非水性分散系を形成するであろう非溶剤であり得る約１０～５５重量％の有機キャリアとを有する。典型的には、コーティング組成物は約５０～８０重量％のフィルム形成性バインダーおよび約２０～５０重量％の有機溶剤キャリアを含有する。本発明のコーティングはまた、好ましくは低いＶＯＣ（揮発性有機含有率）コーティング組成物であり、それは、米国材料試験協会（ＡＳＴＭ）Ｄ３９６０に提供される手順下に測定されるように組成物のリットル当たり０．６キログラム（ガロン当たり５ポンド）未満の有機溶剤を含むコーティングを意味する。

【0018】

上に示されたように、ポリマー成分を含む本発明のトップコート組成物のフィルム形成部分は、「バインダー」または「バインダー固形分」と言われ、有機溶剤または液体キャリア中に溶解、乳化または別のやり方で分散されている。バインダー固形分には一般に、組成物の普通は固体のポリマー非液体成分すべてが含まれる。一般に、触媒、顔料または本明細書で用いられるように安定剤および接着性改良添加物のような化学添加剤は、バインダー固形分の一部とは考えられない。顔料以外の非バインダー固形分は通常、合計して

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組成物の約１０重量％より多くにならない。本開示では、本発明のトップコート組成物に関して、用語バインダーには、本明細書で下に記載されるように、フッ素化シランポリマー、分散ポリマー、およびすべての他の任意のフィルム形成性ポリマーが含まれる。

【0019】

本発明で用いられるバインダーは、本明細書ではフッ素化シランポリマーとも言われる、約１０～９０重量％、好ましくは４０～８０％のフィルム形成性フッ素化有機シランポリマーを含有する。

【0020】

バインダーのフッ素化シランポリマー部分は典型的には、約５００～３０，０００、好ましくは約３，０００～１０，０００の重量平均分子量を有する。本明細書で開示されるすべての分子量は、特に記載のない限り、ポリスチレン標準を用いるゲル浸透クロマトグラフィーによって測定される。

【0021】

好ましくは、フッ素化シランポリマーは、そのうち約１．５～７０重量％、好ましくは５～５０重量％が加水分解性シラン官能基を含有するエチレン性不飽和モノマーであり、約５～９８重量％、好ましくは約４０～９５重量％がエチレン性不飽和非シランおよび非フッ素含有モノマーであり、そして約０．５～２５重量％、好ましくは約１～１０重量％がフッ素官能基を含有するエチレン性不飽和モノマーであるモノマーの混合物の重合生成物である。８重量％の重合したシランモノマーおよび１．５％フロオロアルキルモノマーを有するアクリロシラン樹脂は、良好な耐酸エッチング性、表面損傷抵抗性、およびクリーナビリティを有することが分かった。

【0022】

使用されてフッ素化シランポリマーを形成する好適なエチレン性不飽和非シランおよび非フッ素含有モノマーは、アルキル基が１～１２個の炭素原子、好ましくは２～８個の炭素原子を有する、アクリル酸アルキル、メタクリル酸アルキルおよびそれらの任意の混合物である。使用されてフッ素化シランポリマーを形成する好適なメタクリル酸アルキルモノマーは、メタクリル酸メチル、メタクリル酸エチル、メタクリル酸プロピル、メタクリル酸ブチル、メタクリル酸イソブチル、メタクリル酸ペンチル、メタクリル酸ヘキシル、メタクリル酸オクチル、メタクリル酸ノニル、メタクリル酸ラウリルなどである。同様に、好適なアクリル酸アルキルモノマーには、アクリル酸メチル、アクリル酸エチル、アクリル酸プロピル、アクリル酸ブチル、アクリル酸イソブチル、アクリル酸ペンチル、アクリル酸ヘキシル、アクリル酸オクチル、アクリル酸ノニル、アクリル酸ラウリルなどが含まれる。例えば、メタクリル酸トリメチルシクロヘキシル、アクリル酸トリメチルシクロヘキシル、メタクリル酸イソボルニル、アクリル酸イソボルニル、アクリル酸ｔ－ブチルシクロヘキシル、またはメタクリル酸ｔ－ブチルシクロヘキシルのような脂環式メタクリレートおよびアクリレートもまた使用することができる。例えば、アクリル酸ベンジルおよびメタクリル酸ベンジルのようなアクリル酸アリールおよびメタクリル酸アリールもまた使用することができる。勿論、上述モノマーの２つ以上の混合物もまた好適である。

【0023】

アルキルアクリレートまたはメタクリレートに加えて、ポリマーの約５０重量％までの他の非シランおよび非フッ素含有重合性モノマーを、硬度、外観、表面損傷抵抗性などのような所望の物理的性質を達成するという目的のためにアクリロシランポリマーに使用することができる。かかる他のモノマーの模範的なものはスチレン、メチルスチレン、アクリルアミド、アクリロニトリル、メタクリロニトリルなどである。ヒドロキシ官能性モノマーもまた、２０～１６０のヒドロキシ価を有するポリマーを生み出すためにフッ素化シランポリマー中へ組み込むことができるし、好ましくは組み込まれる。好適なヒドロキシ官能性モノマーは、ヒドロキシメチルアクリレート、ヒドロキシメチルメタクリレート、ヒドロキシエチルアクリレート、ヒドロキシエチルメタクリレート、ヒドロキシプロピルメタクリレート、ヒドロキシプロピルアクリレート、ヒドロキシブチルアクリレート、ヒドロキシブチルメタクリレートなどのような、アルキル基中に１～４個の炭素原子を有す

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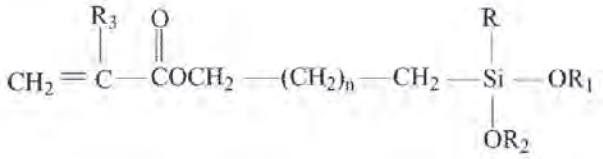
るヒドロキシアルキルアクリレートおよびヒドロキシアルキルメタクリレートを意味するヒドロキシアルキル（メタ）アクリレートである。ヒドロキシ官能性モノマーの存在は、ヒドロキシ基とシランポリマー上のシラン部分との間および／またはヒドロキシ基とトップコート組成物中に存在するかもしれないバインダー成分上の他の架橋基との間で追加の架橋が起こるのを可能にする。

【0024】

フッ素化シランポリマーを形成するために使用することができる好適なシラン含有モノマーは、次の構造式

【0025】

【化1】



【0026】

（式中、RはCH$_3$、CH$_3$CH$_2$、CH$_3$O、CH$_3$OCH$_2$CH$_2$O、またはCH$_3$CH$_2$Oのいずれかであり、R$_1$およびR$_2$は独立してCH$_3$、CH$_3$CH$_2$、またはCH$_3$OCH$_2$CH$_2$であり、R$_3$はH、CH$_3$、CH$_3$CH$_2$、またはCH$_3$OCH$_2$CH$_2$のいずれかであり、nは0または1～10の正の整数である。好ましくは、RはCH$_3$OまたはCH$_3$CH$_2$Oであり、かつ、nは1である）

を有するアルコキシシランである。

【0027】

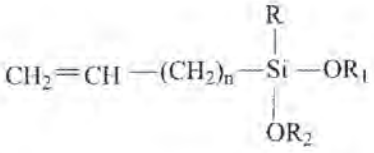
かかるアルコキシシランの典型的な例は、ガンマ－アクリルオキシプロピルトリメトキシシランのようなアクリラトアルコキシシラン、ならびにガンマ－メタクリルオキシプロピルトリメトキシシランおよびガンマ－メタクリルオキシプロピルトリス（２－メトキシエトキシ）シランのようなメタクリラトアルコキシシランである。

【0028】

他の好適なアルコキシシランモノマーは次の構造式

【0029】

【化2】



【0030】

（式中、R、R$_1$およびR$_2$は上記の通りであり、nは1～10の正の整数である）

を有する。

【0031】

かかるアルコキシシランの例は、ビニルトリメトキシシラン、ビニルトリエトキシシランおよびビニルトリス（２－メトキシエトキシ）シランのようなビニルアルコキシシランである。

【0032】

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他の好適なシラン含有モノマーは、アクリラトオキシシラン、メタクリラトオキシシランならびにビニルメチルジアセトキシシランのようなビニルアセトキシシラン、アクリラトプロピルトリアセトキシシラン、およびメタクリラトプロピルトリアセトキシシランをはじめとする、エチレン性不飽和アクリルオキシシランである。勿論、上述のシラン含有モノマーの混合物もまた好適である。

【0033】

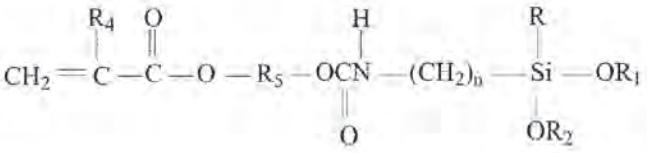
シラン官能性マクロモノマーもまたフッ素化シランポリマーを形成するのに使用することができる。例えば、かかるマクロモノマーは、エポキシドまたはイソシアネートのような反応性基を有するシラン含有化合物と、反応性基、典型的にはシランモノマーと共反応性（ｃｏ－ｒｅａｃｔｉｖｅ）であるヒドロキシルまたはエポキシド基を有するエチレン性不飽和非シラン含有モノマーとの反応生成物である。有用なマクロモノマーの例は、アルキル基中に１～４個の炭素原子を有するヒドロキシルアルキルアクリレートまたはメタクリレートのようなヒドロキシ官能性エチレン性不飽和モノマーと、イソシアナトプロピルトリエトキシシランのようなイソシアナトアルキルアルコキシシランとの反応生成物である。

【0034】

かかる上述のシラン官能性マクロモノマーの典型的なものは、次の構造式

【0035】

【化3】



【0036】

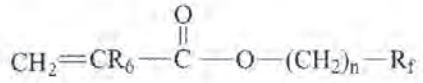
（式中、Ｒ、R_1、およびR_2は上記の通りであり、R_4はＨまたはCH_3であり、R_5は１～８個の炭素原子を有するアルキレン基であり、ｎは１～８の正の整数である）を有するものである。

【0037】

フッ素含有モノマーは好ましくは、フッ素化シランポリマーの総重量を基準にして約０．５～１０重量％の量で使用される。フルオロカーボンモノマーは高価であるので、本発明組成物は好ましくはフルオロカーボン成分の低い含有率を有する。有用なフッ素含有モノマーは式

【0038】

【化4】



【0039】

（式中、R_6は水素または１～２個の炭素原子を有するアルキル基であり、ｎは１～１８の整数であり、R_fは少なくとも４個の炭素原子を有するフルオロアルキル含有基であり、好ましくは、場合により酸素原子を含有することができる４～２０個の炭素原子を有する直鎖または分岐鎖フルオロアルキル基である）

で表されるフルオロアルキルモノマーである。

【0040】

典型的な有用なフルオロアルキル含有モノマーは、パーフルオロメチルエチルメタクリ

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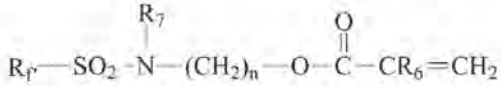
レート、パーフルオロエチルエチルメタクリレート、パーフルオロブチルエチルメタクリレート、パーフルオロペンチルエチルメタクリレート、パーフルオロヘキシルエチルメタクリレート、パーフルオロオクチルエチルメタクリレート、パーフルオロデシルエチルメタクリレート、パーフルオロラウリルエチルメタクリレート、パーフルオロステアリルエチルメタクリレート、パーフルオロメチルエチルアクリレート、パーフルオロエチルエチルアクリレート、パーフルオロブチルエチルアクリレート、パーフルオロペンチルエチルアクリレート、パーフルオロヘキシルエチルアクリレート、パーフルオロオクチルエチルアクリレート、パーフルオロデシルエチルアクリレート、パーフルオロラウリルエチルアクリレート、パーフルオロステアリルエチルアクリレートなどである。フルオロアルキル基が４～２０個の炭素原子を含有するパーフルオロアルキルエチルメタクリレートが好ましい。

【0041】

他の有用なフルオロアルキル含有モノマーは式

【0042】

【化5】



【0043】

（式中、

R_6 は上に定義された通りであり、

R_f ・ は4～１２個の炭素原子を有するフルオロアルキル基であり、

R_7 は１～４個の炭素原子を有するアルキル基であり、そして

ｎは１～４の整数である）

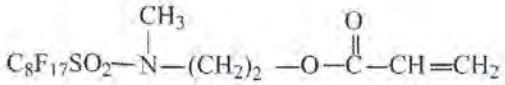
で表される。

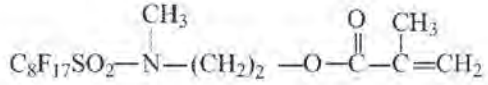
【0044】

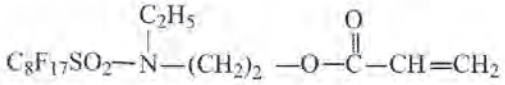
これらのモノマーの典型的なものは下記である。

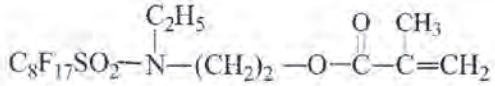
【0045】

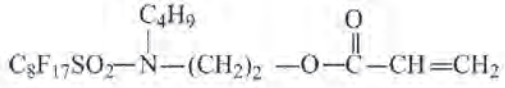
【化6】











【0046】
上述の成分と一致して、本発明のトップコート組成物で有用なフッ素化アクリロシランポリマーの例は次の成分を含有してもよい：約１０～３０重量％のスチレン、約２～２０重量％のガンマーメタクリルオキシプロピルトリメトキシシラン、約１０～３０重量％のメタクリル酸イソブチル、５～３０重量％のアクリル酸２－エチルヘキシル、１５～４５重量％のヒドロキシエチルメタクリレートおよびアルキル基中に４～２０個の炭素原子を有する約０．５～５重量％のフルオロアルキルエチルメタクリレート。

【0047】
特に好ましいーフッ素化アクリロシランポリマーは、約２０重量％スチレン、約８重量％ガンマーメタクリルオキシプロピルトリメトキシシラン、約７０．５重量％の、メタクリル酸トリメチルシクロヘキシル、アクリル酸ブチルおよびメタクリル酸イソブチルならびにそれらの任意の混合物のような非官能性アクリレートまたはメタクリレート、ならびに約１．５重量％の上記フルオロアルキルエチルメタクリレートモノマーを含有する。

【0048】
コーティング組成物に使用されるフッ素化シランポリマーは、モノマー、溶媒、および重合開始剤が１～２４時間、好ましくは２～８時間にわたって通常の重合反応器中へ装入され、その反応器中で成分が約６０～１７５℃、好ましくは約１１０～１７０℃に加熱される通常の重合技術によって好ましくは製造される。

【0049】
フッ素化シランポリマーの好ましい形成方法では、フルオロアルキル含有モノマーは長時間にわたって他のモノマーと一緒に加えられないが、開始、終了または中間のような重合プロセス中の任意の時間に加えられる。重合性のフルオロアルキル含有モノマーは通常溶媒とブレンドされ、次に反応器に加えられる。フルオロアルキル含有モノマーは、ポリ

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マーの総重合時間の約０．０１～１０％で加えられる。好ましくは、フルオロアルキル含有モノマーは、他のモノマーの少なくとも幾らかが加えられ、ある程度重合した後で加えられる。上記やり方での、典型的には重合反応の終わりごろにショットでのフルオロアルキル含有モノマーの添加は、大量の高価なフッ素モノマーを使用することなく、ある一定百分率のポリマー鎖をフッ素含有率の点で高くする方法である。これは、実質的なコスト削減を提供しながら高いクリーナビリティを達成させる。フッ素含有率の点で富むだけでなく、架橋性基のような他の官能性基の点でも富む鎖を提供して、高い引っ掻きおよび表面損傷抵抗性ならびに風防シーラントへの優れた接着性のような他の所望のフィルム特性を達成するために、他の官能性モノマー、例えば、シラン含有－およびヒドロキシル含有－モノマーの一部を典型的には重合反応の終わりごろにショットで加えることもまた有益である。この技法はまた、フッ素基の少なくとも一部分が他の官能基によって最終フィルムネットワーク中へ架橋されるのを可能にし、それはフッ素基がだんだん洗い落とされ、究極的にコーティングフィルムの表面から消失するのを防ぐので、フッ素表面の寿命を延ばす方法でもある。

【0050】

本方法で使用される典型的な重合開始剤は、アゾ－ビス－イソブチロニトリル、１，１’－アゾービス（シアノシクロヘキサン）のようなアゾタイプ開始剤、過酢酸ｔ－ブチルのような過酢酸エステル、ジ－ｔ－ブチルペルオキシドのようなペルオキシド、過安息香酸ｔ－ブチルのような安息香酸エステル、過オクタン酸ｔ－ブチルのようなオクタン酸エステルなどである。

【0051】

本方法で使用することができる典型的な溶媒は、メタノール、エタノール、ｎ－ブタノール、ｎ－プロパノール、およびイソプロパノールのようなアルコール、メチルアミルケトン、メチルイソブチルケトン、メチルエチルケトンのようなケトン、トルエン、キシレン、ソルベッソ（Ｓｏｌｖｅｓｓｏ）（登録商標）１００のような芳香族炭化水素、プロピレンカーボネートのようなアルキレンカーボネート、Ｎ－メチルピロリドン、エーテル、エステル、アセテートならびに上記の任意の混合物である。

【0052】

フッ素化シランポリマーに加えて、他のフィルム形成性および／または架橋溶液ポリマーが本出願に含まれてもよい。例には、通常公知のアクリロシラン、ポリアクリレート、セルロース誘導体、アミノプラスト、イソシアネート、ウレタン、ポリエステル、エポキシドまたはそれらの混合物が挙げられる。好ましい任意のフィルム形成性ポリマーは、ポリオール、例えば、重合したモノマーのアクリルポリオール溶液ポリマーである。かかるモノマーには、前述のアルキルアクリレートおよび／またはメタクリレートならびにさらに、ヒドロキシアルキルアクリレートおよび／またはメタクリレートが含まれてもよい。好適なアルキルアクリレートおよび／またはメタクリレートは、アルキル基中に１～１２個の炭素原子を有する。ポリオールポリマーは好ましくは、約５０～２００のヒドロキシル価および約１，０００～２００，０００、好ましくは約１，０００～２０，０００の重量平均分子量を有する。

【0053】

ポリオール中にポリオールの約９０重量％まで、好ましくは２０～５０重量％のヒドロキシ官能基を提供することは、ヒドロキシ官能基の重合したモノマーを含む。好適なモノマーには、例えば、本明細書で上にリストされたヒドロキシアルキルアクリレートおよびメタクリレートならびにそれらの混合物のような、ヒドロキシアルキルアクリレートおよびメタクリレートが含まれる。他の重合性の非ヒドロキシ含有モノマーが約９０重量％まで、好ましくは５０～８０％の量で、ポリオールポリマー成分に含まれてもよい。かかる重合性モノマーには、例えば、スチレン、メチルスチレン、アクリルアミド、アクリロニトリル、メタクリロニトリル、メタクリルアミド、メチロールメタクリルアミド、メチロールアクリルアミドなど、およびそれらの混合物が含まれる。

【0054】

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アクリルポリオールポリマーの一例は、約１０～２０重量％のスチレン、アルキル基中に１～６個の炭素原子を有する４０～６０重量％のアルキルメタクリレートまたはアクリレート、およびアルキル基中に１～４個の炭素原子を有する１０～５０重量％のヒドロキシアルキルアクリレートまたはメタクリレートを含む。かかるポリマーは、約１５重量％スチレン、約２９重量％メタクリル酸イソブチル、約２０重量％アクリル酸２－エチルヘキシル、および約３６重量％ヒドロキシプロピルアクリレートを含有する。

【0055】

上記の成分に加えて、分散ポリマーが場合によりコーティング組成物中に含まれてもよい。有機（実質的に非水性）媒体中に分散されたポリマーは、当該技術では、非水性分散系（ＮＡＤ）ポリマー、非水性微小粒子分散系、非水性ラテックス、またはポリマーコロイドと様々に言われてきた。一般的には、（非特許文献１）を参照されたい。また、参照により本明細書によって援用される、米国特許公報（特許文献１０）、米国特許公報（特許文献１１）、米国特許公報（特許文献１２）、米国特許公報（特許文献１３）および米国特許公報（特許文献１４）も参照されたい。一般に、分散ポリマーは、その粒子が粒子－媒体界面での溶媒和ポリマーまたはオリゴマー層の付着により成し遂げられる立体安定化によって安定化されている、有機媒体中に分散されたポリマー粒子として特徴づけられる。分散ポリマーは、シランコーティングに関連した従来の亀裂の問題を解決するために本発明で使用される。シランポリマーと併せた使用に好適な分散ポリマーは、そっくりそのまま参照により本明細書によって援用される米国特許公報（特許文献１５）に開示されている。好ましくは、約２０重量％のかかる分散ポリマーが亀裂を防ぐために含まれる。

【0056】

一般に好ましい２構成要素または２パッケージ・システム用に、多官能性有機イソシアネートを、イソシアネート化合物が１分子中に少なくとも２個のイソシアネート基を有する限り特定の制限なしに架橋剤として使用することができる。好ましいポリイソシアネート化合物は、分子当たり２～３個のイソシアネート基を有するイソシアネート化合物である。多官能性有機イソシアネート化合物の典型的な例は、例えば、１，６－ヘキサメチレンジイソシアネート、イソホロンジイソシアネート、２，４－トルエンジイソシアネート、ジフェニルメタン－４，４’－ジイソシアネート、ジシクロヘキシルメタン－４，４’－ジイソシアネート、テトラメチルキシリデンジイソシアネートなどである。商品名デスモデュール（Ｄｅｓｍｏｄｕｒ）（登録商標）Ｎ－３３９０で販売されているヘサメチレンジイソシアネートの三量体（イソシアヌレート）、商品名デスモデュール（登録商標）Ｚ－４４７０で販売されているイソホロンジイソシアネートの三量体（イソシアヌレート）などのようなジイソシアネートの三量体もまた使用することができる。前述の有機ポリイソシアネートの任意のものとポリオールとから形成されるポリイソシアネート官能性付加体もまた使用することができる。トリメチロールプロパンまたはエタンのようなトリメチロールアルカンなどのポリオールを使用することができる。有用な一付加体はテトラメチルキシリデンジイソシアネートとトリメチロールプロパンとの反応生成物であり、サイセーン（Ｃｙｔｈａｎｅ）（登録商標）３１６０の商品名で販売されている。本発明の架橋性樹脂が外装コーティングに使用される場合、耐候性および耐黄変性の観点から、脂肪族または脂環式イソシアネートの使用が芳香族イソシアネートの使用よりも好ましい。

【0057】

場合により、本発明コーティング組成物は、特に任意のポリオールポリマーと併せて、追加の架橋剤、例えば、アミノプラスト架橋剤をさらに含んでもよい。特に好ましいアミノプラスト樹脂は、通常使用されるアルキル化メラミン・ホルムアルデヒド架橋剤の任意のものである。典型的に有用なアルキル化メラミン・ホルムアルデヒド架橋剤は、例えば、部分または完全アルキル化されている通常のモノマーまたはポリマーのアルキル化メラミン・ホルムアルデヒド樹脂である。有用な一架橋剤は、約１～３の重合度を有するメチル化およびブチル化またはイソブチル化メラミン・ホルムアルデヒド樹脂である。一般に、このメラミン・ホルムアルデヒド樹脂は、約５０％ブチル化基またはイソブチル化基と５０％メチル化基とを含有する。かかる架橋剤は典型的には約３００～６００の数平均分

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子量および約５００～１５００の重量平均分子量を有する。商業的に入手可能な樹脂の例は、サイメル（Ｃｙｍｅｌ）（登録商標）１１６８、サイメル（登録商標）１１６１、サイメル（登録商標）１１５８、レジミン（Ｒｅｓｉｍｉｎｅ）（登録商標）４５１４およびレジミン（登録商標）３５４である。好ましくは、架橋剤は、バインダーの重量を基準にして約５～５０重量％の量で使用される。他の熟慮される架橋剤は、尿素ホルムアルデヒド、ベンゾクォーナミン（ｂｅｎｚｏｑｕａｎａｍｉｎｅ）ホルムアルデヒドおよびブロックされたポリイソシアネートまたは前述の架橋剤の任意の相溶性混合物である。好ましくは約１０～６０重量％のかかる架橋剤がコーティングのバインダーに含まれる。

【0058】

上記のクリアコート組成物はまた、延びた貯蔵寿命を有するワン－パッケージ・システムとして（ブロックされていない有機ポリイソシアネートなしで）調合することができる。

【0059】

触媒は、シランポリマーのシラン部分のそれ自体とのおよび／または組成物の他の成分との架橋を触媒するために典型的には添加される。ジブチル錫ジラウレート、ジブチル錫ジアセテート、ジブチル錫ジオキシド、ジブチル錫ジオクトエート、オクタン酸錫、チタン酸アルミニウム、アルミニウムキレート、ジルコニウムキレートなどのような、多種多様な触媒を使用することができる。ブロックされているかブロックされていないかのどちらかの、ドデシルベンゼンスルホン酸のようなスルホン酸は有効な触媒である。ブロックされているかブロックされていないかのどちらかの、フェニル酸性リン酸エステルのようなアルキル酸性リン酸エステルもまた用いられてもよい。前述の触媒の任意の混合物も同様に有用であるかもしれない。他の有用な触媒は当業者には容易に思い浮かぶであろう。好ましくは、触媒は、組成物に使用されるバインダーの総重量を基準にして約０．１～５．０％の量で使用される。

【0060】

本発明のコーティング組成物の鍵となる成分は、上記の成分に加えて、本明細書では接着促進剤または再コーティング接着性改良添加物とも言われる、接着性改良添加物である。有効な接着性増強量の接着性改良添加物が上述の再コーティング接着性問題を解決するためにトップコート組成物に添加される。本発明の接着性改良添加物はまた、車両の本体に風防を適切に貼り付けるために必要とされる、商業的に入手可能な湿気硬化風防接合接着剤への優れたプライマーなし接着をトップコート組成物に提供する。接着性改良添加物は、組成物に使用されるバインダーの総重量を基準にして約０．１～１５重量％、好ましくは約５～１０重量％の範囲の接着性増強量でトップコート組成物に典型的には添加される。

【0061】

より具体的には、本明細書で使用される接着性改良添加物は、通常の有機ポリイソシアネート、フッ素化一官能性アルコール、およびオリゴマーまたはポリマーのエトキシル化／プロポキシル化グリコールのポリイソシアネート由来付加体であるフッ素化ウレタン化合物であり、何の残留または遊離－ＮＣＯ基も含有しない。フッ素化ウレタン添加物はまた好ましくは、添加物が塗膜の永久的な部分になるのを防ぐために、トップコート組成物中のフィルム形成性バインダー成分と反応することができる残留ヒドロキシル基なしである。添加物はそれによって塗膜中で未反応の可動性成分のままであることができ、それは好ましい。

【0062】

いかなる特定の理論で縛られることを欲しないが、フッ素化ウレタン添加物は硬化中にフィルムの表面に移行し、そしてウレタン基（すなわち、カルバメート基）はメラミン基と反応することができるので、界面で十分な混り合いがあり、その結果メラミンを含有する修理ベースコートが元のトップコート中のウレタン基と反応し、改良された再コーティング接着性をもたらすであろうと推測される。

【0063】

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好ましくは、本発明のフッ素化ウレタン付加体は、フッ素化モノアルコールと反応し、さらにポリエーテルポリオールと反応して、後で修理ベースコート中に存在するアミノプラスト樹脂と反応することができる反応性カルバメート基を持った付加体を提供する通常の有機ポリイソシアネート樹脂から形成される。

【0064】

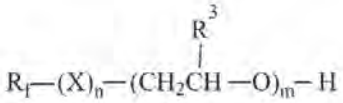
付加体を形成するために使用されてもよい有機ポリイソシアネートは、使用可能な任意の通常の芳香族、脂肪族、脂環式の二官能性および三官能性ポリイソシアネートであることができ、上にリストされた有機ポリイソシアネートの任意のものなどである。使用することができる典型的なジイソシアネートには、１，６－ヘキサメチレンジイソシアネート、イソホロンジイソシアネート、４，４’－ビフェニレンジイソシアネート、トルエンジイソシアネート、ビスシクロヘキシルジイソシアネート、テトラメチレンキシレンジイソシアネート、エチルエチレンジイソシアネート、２，３－ジメチルエチレンジイソシアネート、１－メチルトリメチレンジイソシアネート、１，３－シクロペンチレンジイソシアネート、１，４－シクロヘキシレンジイソシアネート、１，３－フェニレンジイソシアネート、１，５－ナフタレンジイソシアネート、ビス－（４－イソシアナトシクロヘキシル）－メタン、４，４’－ジイソシアナトジフェニルエーテルなどをはじめとする、本明細書で上にリストされたものの任意のものが含まれる。使用することができる典型的な三官能性イソシアネートは、トリフェニルメタントリイソシアネート、１，３，５－ベンゼントリイソシアネート、２，４，５－トルエントリイソシアネートなどをはじめとする、本明細書で上にリストされたものの任意のものである。商品名デスモデュール（登録商標）Ｎで販売されているヘサメチレンジイソシアネートの三量体（イソシアヌレート）のような、ジイソシアネートのオリゴマーもまた使用することができる。特に好ましいオリゴマーはデスモデュール（登録商標）Ｎ－３３９０である。カルボジイミド基、ウレタン基、アロファネート基、イソシアヌレート基、ビウレット基、およびウレア基を含有する任意の他のポリイソシアネートもまた好適である。

【0065】

有機ポリイソシアネートは、例えば、任意のフッ素化一官能性アルコールと反応させることができる。好適なフッ素化一官能性アルコールは式

【0066】

【化7】



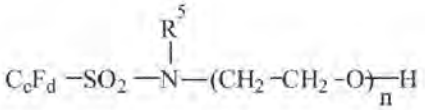
【0067】

（式中、R_fは上に定義されたように、場合によりエーテル基のような酸素原子を含有することができる、または１～５個の塩素原子または１～５個の水素原子を含有することができる少なくとも４個の炭素原子を有するフルオロアルキル含有基．好ましくは４～２０個の炭素原子を有する直鎖または分岐鎖フルオロアルキル基である。好ましくは、R_fは４～２０個の炭素原子を有するパーフルオロアルキル基であり、最も好ましくは、R_fは６～１２個の炭素原子を含有するパーフルオロアルキル基である。Ｘは二価基、好ましくは$-CH_2CH_2O-$、$-SO_2N(R^4)CH_2CH_2O-$、$-CH_2-$、$-O-$、$-CH_2O-$（ここで、R^4は好ましくは１～４個の炭素原子を有するアルキル基である）である。R^3はＨまたは１～４個の炭素原子を有するアルキル基であり、Ｈおよびメチルが好ましく、ｎは０～１であり、ｍは０～３０である、ただし、ｎが０である場合、ｍは１より大きいかまたはそれに等しくなければならず、ｍが０である場合、ｎは１であり、Ｘが－Ｏ－である場合、ｍは１より大きいかまたはそれに等しくなければならず、ｍは好ましくは１～２０である）

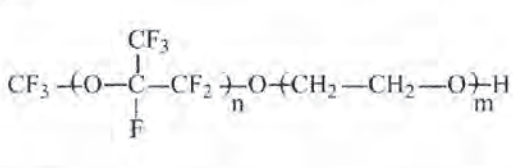
で表される。

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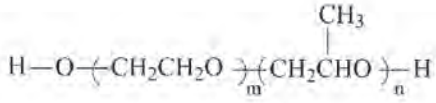
【0068】
下記が好ましいフッ素化一官能性アルコールである。
Ｆ（ＣＦ$_2$ＣＦ$_2$）$_a$（ＣＨ$_2$ＣＨ$_2$Ｏ）$_b$Ｈ
（式中、ａは１～約８、またはその混合物であり、好ましくは約３～約６であり、ｂは３～１５である）
Ｈ－（ＣＦ$_2$ＣＦ$_2$）$_n$－ＣＨ$_2$ＯＨ
（式中、ｎは１～６である）
【0069】
【化8】



【0070】
（式中、ｃは４～８であり、ｄは２ｃ＋１であり、Ｒ^{5}は１～４個の炭素原子を有するアルキル基であり、ｎは１～３０である）
【0071】
【化9】



【0072】
（式中、ｎは０～１０であり、ｍは１～２０である）、および
Ｆ（ＣＦ$_2$ＣＦ$_2$）$_a$（ＣＨ$_2$）$_e$ＯＨ
（式中、ａは上に記載されており、ｅは約２～約１０、好ましくは２である）
【0073】
かかるフッ素化モノアルコールの具体的な例は、商品名ゾニール（ＺＯＮＹＬ）（登録商標）ＢＡ、ＢＡ－Ｌ、ＢＡ－NまたはＢＡ－ＬＤフルオロアルコール（Ｆｌｕｏｒｏａｌｃｏｈｏｌ）で販売されている。ゾニール（登録商標）フルオロアルコールは、本願特許出願人、（デラウェア州ウィルミントン（Ｗｉｌｍｉｎｇｔｏｎ、ＤＥ））から入手可能な式Ｆ（ＣＦ$_2$ＣＦ$_2$）$_{2-8}$ＣＨ$_2$ＣＨ$_2$ＯＨのアルコールの混合物である。
【0074】
ポリエーテルポリオールが、キャップして、すなわち、残留イソシアネート末端基と反応してフッ素化ウレタン付加体を形成するために使用される。好ましいポリオールはオリゴマーもしくはポリマーのエトキシル化／プロポキシル化グリコールまたはこれらのグリコールの組み合わせである。好適なエトキシル化／プロポキシル化グリコールには、一般式
【0075】
【化10】



【0076】

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（式中、mおよびnは、それぞれ、繰り返しオキシエチレン（ＥＯ）およびオキシプロピレン（ＰＯ）基の平均数である、ただし、mは常に正の整数であるが、nは正の整数またはゼロである（後者のケースではＥＯホモポリマーを意味する））のポリオキシエチレングリコールおよびポリオキシエチレン－ポリオキシプロピレングリコールが含まれる。

【0077】

本明細書で使用されるＥＯ／ＰＯグリコールは好ましくは、約５００～約５，０００、好ましくは約９８０～約２，５００の重量平均分子量を有するオリゴマー材料である。かかるポリオキシエチレン／ポリオキシプロピレングリコールの典型的な例は、ユニオン・カーバイド（Ｕｎｉｏｎ　Ｃａｒｂｉｄｅ）から商品名「ユーコン（Ｕｃｏｎ）７５－Ｈ」で入手可能である。「ユーコン７５－Ｈシリーズ（Ｓｅｒｉｅｓ）」ＥＯ／ＰＯグリコールは、７５重量％オキエチレン（ＥＯ）基および２５重量％オキシプロピレン（ＰＯ）基を有する線状共重合体であり、上述の範囲内の分子量を有する。本質的に線状の共重合体上の唯一の側鎖は、オキシプロピレン残基のメチル基による。特に好ましいＥＯ／ＰＯグリコールは、約９８０の重量分子量および３７．８℃で４５０ｓｕｓの粘度を有する「ユーコン－７５－Ｈ－４５０」である。

【0078】

本発明では、添加物のフルオロケミカル部分は追加の撥水性および撥油性ならびに耐汚染性をトップコートに提供するが、ＥＯ／ＰＯグリコール部分は添加物に水溶性、それ故典型的なベースコート組成物への溶解性を与えると考えられる。ＥＯ／ＰＯ基の好適な選択によって、ベースコート中へのフッ素化添加物の拡散速度を予測通りに制御することができる。

【0079】

フッ素化ウレタン添加物は、同時法またはステップワイズ法を用いる通常の重合技術によって製造することができ、好ましくは製造される。好ましい実施形態では、ステップワイズ法が用いられる。この実施形態では、ポリイソシアネートは先ずフッ素化一官能性アルコールと反応されられてフッ素官能基が付加体に含まれることを確実にする。フッ素化イソシアネート中間体は次にポリエーテルグリコールでキャップされて何の残留イソシアネート基も持たないフッ素化ウレタン付加体を提供する。

【0080】

工程１はこのように有機ポリイソシアネートをフッ素化モノアルコールと反応させることを伴う。典型的には、成分は、ジブチル錫ジラウレートのような触媒で不活性溶媒中約４５～１２０℃の温度で約０．１～４時間反応して中間体を形成する。工程１でポリイソシアネートと反応するモノアルコールの量は、当量のイソシアネート当たり化学量論的１当量またはそれ未満であるべきである。好ましくは、用いられるモノアルコールの量は、イソシアネートの当量当たり約０．４５当量以上、より好ましくはイソシアネート当量に対して約０．５０～１．０のモノアルコールを形成する。

【0081】

工程２で、ＥＯ／ＰＯグリコールが第１工程で製造されたフッ素化ポリイソシアネート中間体と反応させられる。用いられるＥＯ／ＰＯグリコールの量は典型的には、生じたポリイソシアネート由来付加体中に残留イソシアネート反応性官能基のいかなるものも残すことなくイソシアネート官能基の約９９％、好ましくは１００％を消費するのに十分な化学量論的１当量の５～１５％過剰である。

【0082】

グリコールとフッ素化イソシアネート中間体との反応は、フーリエ（Ｆｏｕｒｉｅｒ）変換赤外分光光度計を用いることによるイソシアネート吸光度バンドおよびイソシアネート滴定によって監視することができる。反応終点は、何のイソシアネート官能基も生じたポリイソシアネート由来付加体中に残っていない時に達成される。

【0083】

原則として、ポリイソシアネートのイソシアネート官能基のすべてを反応させることが意図されるが、１００パーセント完全な反応が達成できるとは限らず、それ故、微量の未

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反応イソシアネートおよび／または未反応ヒドロキシルが予期され得ることは理解されるべきである。あるいはまた、本発明の目的のためにはイソシアネートの「すべて」を反応させることは、少なくとも９９パーセント完全な反応、好ましくは１００パーセントと定義されるかもしれない。

【0084】

特に好ましいフッ素化ウレタン付加体は、１当量のゾニール（登録商標）ＢＡフルオロアルコールと反応させられ、次に１当量のユーコン（登録商標）７５－Ｈ－４５０でキャップされたイソホロンジイソシアネートの反応生成物である。

【0085】

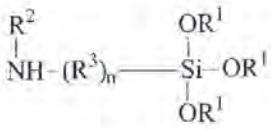
別の実施形態では、接着性改良添加物は、風防を車両に付けるために使用される商業的に入手可能な湿気硬化ウレタン風防シーラントへの硬化したまたは少なくとも部分的に硬化したトップコート組成物の接着を改良するために、追加の加水分解性シラン官能基を含有してもよい。添加物中に加水分解性シラン官能基を提供するために、イソシアネート基をキャップするために使用されるポリエーテルポリオールは、アミノ官能性シランで置き換えられてもよい。添加物は、キャップの変更を除いて上記と同じ方法で製造されてもよい。

【0086】

このフルオロウレタンシラン添加物を形成するために使用することができるアミノ官能性シランは式

【0087】

【化11】



【0088】

（式中、R^1は独立してC_1～C_{16}アルキルであり、R^2は独立してＨまたはC_1～C_{12}アルキルであり、R^3は独立してアルキレン、シクロアルキレン、複素環、アリーレン、アルコキシレン、アラルキレン、アルケニレンおよび低分子量ポリマー部分よりなる群から選択された部分であり、ｎは１～１６の整数である。R^1にとってはC_1～C_4のアルキルが好ましく、C_1～C_2が最も好ましい。アルキル置換基は線状または環式であることができ、アミン機能は第一級または第二級であることができる。R^3に代表的な低分子量ポリマー価値（ｖａｌｕｅｓ）はポリエステル、ポリウレタン、ポリエーテル、ポリアミンなどである。「低分子量」とは、約３０００（数平均）以下を意味する。R^3が低分子量ポリマーである時、ｎは１である。しかしながら、好ましくは、R^3については２～２０個の炭素原子を含有するアルキレン基であり、ｎは１～３である）

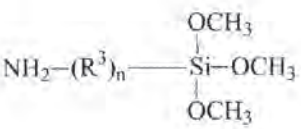
で表される。

【0089】

下記は好ましいアミノ官能性シランである。

【0090】

【化12】



【0091】

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式中、R^{3}は１～２０個、より好ましくは１～２個の炭素原子を含有するアルキレン基であり、ｎは１～３である。

【0092】

商業的に入手可能であるかかるアミノ官能性シランの具体的な例は、３－アミノプロピルトリメトキシシラン、およびトリメトキシシラン基がメチルジアルコキシシラン基の様々な組み合わせによって置換されている場合のようなその類似物である。

【0093】

この添加物のフルオロケミカル部分は追加の撥水性および撥油性ならびに耐汚染性をトップコートに提供するが、アミノプラスト部分はプライマーなしで風防シーラントに改良された接着性だけでなく添加物に水溶性、それ故典型的なベースコート組成物での溶解性を与えると考えられる。アミノ基の好適な選択によって、ベースコート中へのフッ素化添加物の拡散速度もまた予測通りに制御することができる。

【0094】

上記の成分に加えて、トップコート組成物で製造されたクリア仕上げの耐候性を改良するために、紫外線安定剤または紫外線安定剤の組み合わせを、バインダーの重量を基準にして約０．１～１０重量％の量でトップコート組成物に添加することができる。かかる安定剤には、紫外線吸収剤、スクリーナー、失活剤、および特有のヒンダードアミン光安定剤が含まれる。また、酸化防止剤も、バインダーの重量を基準にして約０．１～５重量％の量で添加することができる。有用である典型的な紫外線安定剤には、ベンゾフェノン、トリアゾール、トリアジン、ベンゾエート、ヒンダードアミンおよびそれらの混合物が含まれる。

【0095】

オルト酢酸トリメチル、オルトギ酸トリエチル、テトラシリケートなどのような好適な量（好ましくはバインダーの２～６重量％）の水捕捉剤が、典型的にはそのポットライフを延ばすためにトップコート組成物に添加される。約３％ミクロゲル（好ましくはアクリル）および１％疎水性シリカがレオロジー調整のために用いられてもよい。組成物はまた、例えば、レジフロー（Ｒｅｓｉｆｌｏｗ）（登録商標）Ｓ（ポリアクリル酸ブチル）、ＢＹＫ（登録商標）３２０および３２５（高分子量ポリアクリレート）などの流動調整剤のような他の通常の調合添加剤を含んでもよい。

【0096】

少量の顔料もまた、黄変のような仕上げでの望ましくない色を排除するためにトップコート組成物に添加することができる。

【0097】

本方法によれば、修理ベースコートが上記の元のトップコート上に塗布される時に、再コーティング接着性を達成することができる。一般に、ベースコートの組成物は、それがアミノプラスト樹脂架橋剤を含有しなければならない程度を除いて、本発明によって限定されない。好ましいベースコートは、メラミン架橋剤およびポリオールと組み合わせてポリエステルまたはポリエステルウレタンを含む。好適なポリオールには、アクリル、ポリエステル、ポリエステルウレタン、または６０～１６０のヒドロキシ価を有するアクリルウレタンポリオールが含まれる。かかるポリオールは、トップコートが実質的にまたは部分的に硬化してしまったけれどもクリアコート中の未反応または残留シラン基の幾らかと反応するポリオール上のヒドロキシ基によってシラン・クリアコート上の再コーティング接着性に寄与するかもしれない。好適なベースコートの例は、顔料、アルミニウムフレーク、およびＵＶ吸収剤に加えて、組成物の重量で、約２５％のレオロジー調整のためのミクロゲル、２１％のメラミン・ホルムアルデヒド樹脂、１７％の分岐ポリエステル樹脂、３％の１２０のヒドロキシ価を有するアクリロウレタン、２％のブロックト・ジブチルドデシルベンジルスルホン酸触媒、および２％のジブチルジアセテートを含む。

【0098】

追加のフィルム形成性および／または架橋ポリマーが本発明で用いられるベースコートに含まれてもよい。例には、通常知られているポリアクリレート、セルロース誘導体、ア

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ミノプラスト、ウレタン、ポリエステル、エポキシドまたはそれらの混合物が挙げられる。追加の任意のアクリルポリマーの一例はアクリルポリオール溶液ポリマーである。かかるポリオールは好ましくは、約５０～２００のヒドロキシル価および約１，０００～２００，０００、好ましくは約１，０００～２０，０００の重量平均分子量を有する。好ましいポリオールは、２５重量％スチレン、３１重量％メタクリル酸ブチル、１７％アクリル酸ブチルおよび３８％ヒドロキシプロピルアクリレートからなり、１８．５℃のＴｇを有する。

【0099】

理論で縛られることを欲しないが、元のトップコート中のフッ素化ウレタン添加物の存在は、修理ベースコート中のアミノプラスト樹脂とクリアコート中のウレタン基との反応を引き起こして元のクリアコート界面と修理ベースコート界面との間の接着を促進するカーバメート結合を形成するかもしれないと推測される。

【0100】

様々な顔料および金属粉が、当業者に明らかであるように、ベースコートに用いられてもよい。ベースコート組成物中の典型的な顔料には次のものが含まれる：二酸化チタン、酸化亜鉛、様々な色の酸化鉄のような金属酸化物、カーボンブラック；タルク、陶土、バライト、炭酸塩、ケイ酸塩のようなフィラー顔料；およびキナクリドン、銅フタロシアニン、ペリレン、アゾ顔料、インダンスロンブルー、例えばカルバゾールバイオレットなどのカルバゾール、イソインドリノン、イソインドロン、チオインジゴレッド、ベンゾイミダゾリノンのような多種多様な有機着色顔料；アルミニウムフレークのような金属粉顔料、真珠光沢フレークなど。

【0101】

顔料は、高速混合、サンド研削、ボールミリング、磨砕機研削または２ロールミリングのような通常の技法によりコーティング組成物に使用される前述ポリマーの任意のものでまたは別の相溶性ポリマーもしくは分散剤で練り顔料または顔料分散系を先ず形成することによってベースコート中へ導入することができる。練り顔料は次にコーティング組成物に使用される他の成分とブレンドされる。

【0102】

本発明で用いられるベースコート組成物はまた、例えば、レジフロー（登録商標）Ｓ（ポリアクリル酸ブチル）、ＢＹＫ（登録商標）３２０および３２５（高分子量ポリアクリレート）などの流動調整剤；例えば溶融シリカなどのレオロジー調整剤のような他の通常の調合添加剤を含んでもよい。

【0103】

本発明で用いられるベースコートおよびトップコートの両方で、通常の溶剤および希釈剤がまた一般に、上述のポリマーを分散させるおよび／または希釈させるために使用される。典型的な溶剤および希釈剤には、トルエン、キシレン、酢酸ブチル、アセトン、メチルイソブチルケトン、メチルエチルケトン、メタノール、イソプロパノール、ブタノール、ヘキサン、アセトン、エチレングリコール、モノエチルエーテル、ＶＭおよびＰナフサ、ミネラルスピリット、ヘプタンおよび他の脂肪族、脂環式、芳香族炭化水素、エステル、エーテルならびにケトンなどが含まれる。典型的なベースコートでは、現在使用されるほとんどのベースコートは水性システムであるので、水が典型的には共溶剤として使用される。

【0104】

本発明によれば、コーティング組成物の任意のものを、吹き付け塗り、静電塗装、浸し塗り、刷毛塗り、流し塗りなどのような通常の技法によって塗布することができる。好ましい技法は吹き付け塗りおよび静電塗装である。塗布後に、コーティング組成物は典型的には１００～１５０℃で約１５～３０分間ベークされて約０．１～３．０ミル厚さのコーティングを形成する。組成物がクリアコートとして使用される場合、それは、クリアコートが塗布される前に粘着性なしの状態まで乾燥され、硬化させられてもまたは好ましくは短時間フラッシュ乾燥されてもよいカラーコート上に塗布される。カラーコート／クリア

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コート仕上げは次に、上述のようにベークされて乾燥し、硬化した仕上げを提供する。

【0105】

「ウェット・オン・ウェット」塗布を用いてベースコート上にクリア・トップコートを塗布することは、特に自動車産業で慣例になった、すなわち、トップコートは、ベースコートを硬化させるまたは完全に乾燥させることなくベースコートに塗布される。被覆基材は次に、予め定められた時間加熱されてベースコートおよびクリアコートを同時硬化させる。

【0106】

本発明のクリア・トップコート組成物の硬化時に、フッ素化シラン含有ポリマーの一部はまた、耐久性の耐候性クリアコートを生み出すために、特にフッ素化有機シランポリマーがポリオールと組み合わせて使用される場合に、クリアコートのトップ部分に優先的に移行し、その中で層状になるかもしれない。かかる層化はまた、フルオロカーボン成分の存在のおかげで、それが非常に低い表面エネルギー、高い撥水性および撥油性、ならびに従って顕著な耐汚染性およびクリーナビリティに寄与するので一般には望ましい。かかる層化は、トップコートの硬化した層の断面の電子走査化学分析（ＥＳＣＡ）によって示されてきた。

【0107】

本発明のコーティング組成物は、基材に塗布され十分に硬化させられた時に、最も望ましくは少なくとも１００°、好ましくは１００°～１２０°の水前進接触角および少なくとも４０°、好ましくは４５～８５°、より好ましくは６０°～８５°のヘキサデカン前進接触角を有し、それは、上に議論されたように、比較的汚れのないままであり、かつ、容易に洗浄されるまたはきれいに拭かれる仕上げを提供する。水および有機液体接触角とクリーナビリティおよび汚れ固着との関係は、実施例で下により十分に記載される。

【0108】

別の実施形態では、本発明の組成物は顔料入りであり、カラーコートとして、またはモノコートとしてもしくはさらにプライマーもしくはプライマーサーフェーサーとして使用することができる。モノコートとして使用される場合、これらの組成物は、航空、農場および建設機械、ならびに改良されたクリーナビリティが同様に望まれる建築コーティング向けに特に有用である。本発明のコーティング組成物がベースコート、モノコート、プライマーまたはプライマーサーフェーサーとして使用される場合、顔料は、高速混合、サンド研削、ボールミリング、磨砕機研削または２ロールミリングのような通常の技法によりコーティング組成物に使用される前述ポリマーの任意のものでまたは別の相溶性ポリマーもしくは分散剤で練り顔料または顔料分散系を先ず形成することによってコーティング組成物中へ導入することができる。練り顔料は次に、コーティング組成物に使用される他の成分とブレンドされる。通常の溶剤および希釈剤が、上述のポリマーを分散させておよび／または希釈させて顔料入りコーティング組成物を得るために使用される。

【0109】

本発明のさらに別の実施形態では、上記のフッ素化ウレタン添加物は、「ミックス－イン」ポリマーまたは添加物（典型的にはバインダーの重量を基準にして約０．１～１５重量％の量で）として任意の商業的に入手可能なコーティング・システムに有効であるかもしれない。例えば、フルオロウレタンは、改良されたクリーナビリティおよび耐汚染性のために艶出剤、ワックス、ペイント、ワニスおよび建設用塗料で添加物として使用することができる。フルオロウレタンは、高められたクリーナビリティを提供するために硬質フローリング用の添加物として使用することができる。フルオロウレタンはまた、器具、レンジフード、自動車車輪など用のコーティングへのクリーナビリティおよび耐汚染性を改良するために使用することができる。

【実施例】

【0110】

次の実施例は本発明を例示する。すべての部および百分率は特に明記しない限り重量基準である。本明細書で開示されるすべての分子量はポリスチレン標準を用いるＧＰＣによ

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って測定する。

【0111】

次のオリゴマーおよびポリマーを製造し、実施例１ならびに比較例２および３に示すように使用した。

【0112】

（フッ素化アクリロシランポリマーの製造）

フッ素化アクリロシランポリマーを、かき混ぜ機、熱電対、還流冷却器、および加熱マントルを備えた、窒素で覆われた１２リットル反応フラスコ中へ次の成分を装入することによって製造した。

【0113】

【表1】

成分	重量部
部分 I	
芳香族溶媒（エクソン製ソルベッソ® 100）	1049.8
n-ブタノール	524.9
部分 II	
スチレン	923.8
アクリル酸2-エチルヘキシル	706.7
ヒドロキシエチルメタクリレート	1340
メタクリル酸イソブチル（iBMA）	1071.6
ガンマ-メタクリルオキシプロピルトリメトキシシラン（クロンプトン(Crompton)製シルクェスト(Silquest)® A-174）	231
2,2'-アゾビス（2-メチルブチロニトリル）（本願特許出願人製ヴァゾ(Vazo)® 67）	332.6
芳香族溶媒（エクソン製ソルベッソ® 100）	1417.2
n-ブタノール	182.7
部分 III	
1,1,2,2-パーフルオロアルキルエチルメタクリレート（本願特許出願人製ゾニールTM®；式$F(CF_2CF_2)_{3,8}CH_2CH_2OC(O)C(CH_3)=CH_2$の混合パーフルオロアルキルエチルメタクリレート）	69.3
2,2'-アゾビス(2-メチルブチロニトリル)（本願特許出願人製ヴァゾ® 67）	32.3
ガンマ-メタクリルオキシプロピルトリメトキシシラン（クロンプトン製シルクェスト® A-174）	138.6
ヒドロキシエチルメタクリレート	138.6
芳香族溶媒（エクソン製ソルベッソ® 100）	69.3
部分 IV	
2,2'-アゾビス(2-メチルブチロニトリル)（本願特許出願人製ヴァゾ® 67）	36.9
芳香族溶媒（エクソン製ソルベッソ® 100）	105.0
n-ブタノール	52.4
合計	8422.8

【0114】
部分Ｉを反応フラスコ中へ装入し、かき混ぜ下にその還流温度まで加熱した。部分ＩＩを予め混合し、次に、反応混合物を還流温度に維持しながら、それに２４０分間にわたって加えた。部分ＩＩＩを予め混合し、次に、部分ＩＩの添加の開始２３０分後に反応混合物に一度に加えた。２４０分フィードの完了後に、予め混合した部分ＩＶを３０分間にわたって加え、次に反応混合物をその還流に追加の６０分間保持した。生じたポリマー溶液を次に室温まで冷却した。

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【0115】
生じたポリマー溶液は５６．７％の重量固形分、２５℃で測定されたＪのガードナーホルツ（Ｇａｒｄｎｅｒ－Ｈｏｌｄｔ）粘度、約２，１７５の数平均分子量および１．９の多分散性を有し、そして２０／１５／２３．５／５／２９／／１．５／３／３の重量比で次の成分Ｓｔｙ／２－ＥＨＡ／ｉＢＭＡ／Ａ－１７４／ＨＥＭＡ／／ゾニールＴＭ（登録商標）（ショット）／Ａ１７４（ショット）／ＨＥＭＡ（ショット）を含有する。
【0116】
（フッ素化ウレタン添加物の製造）
フルオロウレタン添加物を、上記のように装備された窒素で覆われた５００ミリリットル反応フラスコ中へ次の成分を装入することによって製造した。
【0117】
【表2】

部分 I	重量部
イソホロンジイソシアネート(バイエル(Bayer)製デスモデュール® I)	44.44
メチルイソブチルケトン	60.32
1,1,2,2-テトラヒドロパーフルオロアルコール (またはパーフルオロアルキルエチルアルコール) (本願特許出願人製ゾニールBA®; 式F(CF_2CF_2)$_{2-8}$$CH_2CH_2OH$の混合フルオロアルコール)	95.91
部分 II	
ジブチル錫ジラウレート	0.04
部分 III	
ポリアルキレングリコール(ダウ・ケミカル(Dow Chemical)製 ユーコン® 75-H-450;ポリアルキレン基は75重量%オキシエチレンと 25重量%オキシプロピレン基とを含有する;数平均分子量980)	205.8
合計	406.51

【0118】
部分Ｉの成分を与えられた順に反応フラスコ中へ装入し、かき混ぜおよび窒素雰囲気下に４６℃に加熱した。部分ＩＩを次に部分Ｉに加え、僅かな発熱を観察し、溶液を撹拌しながら４６℃に２時間保持した。次に、部分ＩＩＩを３０分間にわたって加え、溶液を７５℃に２時間保持し、次に室温まで冷却して９６％収率のフッ素化ウレタン添加物溶液を与えた。
【0119】
生じたフッ素化ウレタン添加物溶液は８２．６％固形分含有率を有する。
【0120】
（シラン官能基を持ったフッ素化ウレタン添加物の製造）
シラン官能基を持ったフルオロウレタン添加物を、上記のように装備された窒素で覆われた２リットル反応フラスコ中へ次の成分を装入することによって製造した。
【0121】

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【表3】

部分 I	重量部
イソホロンジイソシアネート(バイエル製デスモデュール※ i)	44.4g
メチルイソブチルケトン	60g
1,1,2,2-テトラヒドロパーフルオロアルコール (またはパーフルオロアルキルエチルアルコール) (本願特許出願人製ゾニールBA®; 式F(CF_2CF_2)$_{2-8}$$CH_2CH_2OH$の混合フルオロアルコール)	95.8g
部分 II	
ジブチル錫ジラウレート	0
部分 III	
3-アミノプロピルトリメトキシシラン	37.6g
合計	237.91

【0122】
部分Ｉの成分を与えられた順に反応フラスコ中へ装入し、かき混ぜおよび窒素雰囲気下に還流温度まで加熱した。部分ＩＩを次に部分Ｉに加え、溶液を撹拌しながら４５～５０℃に３時間保持した。次に、部分ＩＩＩを７５℃の溶液温度で１２０分間にわたって加えた。溶液を、赤外分光分析法によって監視されるようにＮＣＯピークが消失するまで保持した。

【0123】
（非フッ素化アクリロシラン樹脂の製造）
比較目的のために、非フッ素化ヒドロキシ官能性アクリロシラン樹脂を、上記のように装備された窒素で覆われたフラスコ中へ次の成分を装入することによって製造した。

【0124】

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【表4】

部分 I	重量部
芳香族溶媒（エクソン製ソルベッソ® 100）	96.8
n-ブタノール	44.9
部分 II	
スチレン	98.9
ヒドロキシエチルメタクリレート	155.8
メタクリル酸イソブチル	128.1
アクリル酸2-エチルヘキシル	62.3
ガンマ-メタクリルオキシプロピルトリメトキシシラン（クロンプトン社製シルクェスト® A-174）	49.5
芳香族溶媒（エクソン製ソルベッソ® 100）	18.3
部分 III	
芳香族溶媒（エクソン製ソルベッソ® 100）	64.3
n-ブタノール	68.8
2,2`-アゾビス（2-メチルプチロニトリル）（本願特許出願人製ヴァゾ® 67）	42.0
合計	829.7

【0125】
部分Ｉを反応フラスコ中へ装入し、かき混ぜおよび窒素雰囲気下に還流温度まで加熱した。部分ＩＩおよびＩＩＩを別々に予め混合し、溶液を還流温度に維持しながら、２７０分間にわたって部分Ｉに加えた。生じたポリマー溶液を次に還流温度に３０分間保持した。

【0126】
生じたポリマー溶液は６４％固形分含有率、ガードナーホルツ尺度で測定されるようにT粘度、および約５，０００の重量平均分子量を有する。

【0127】
（アクリルポリオール樹脂の製造）
場合により本発明の組成物に含まれてもよいアクリルポリオール樹脂を、上記のように装備された窒素で覆われたフラスコ中へ下記を装入することによって製造した。

【0128】

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【表5】

部分 I	重量部
芳香族溶媒（エクソン製ソルベッソ® 100）	164.5
酢酸n-ブチル	18.8
部分 II	
ヒドロキシエチルアクリレート	174.0
メタクリル酸ブチル	233.8
スチレン	136.0
芳香族溶媒（エクソン製ソルベッソ® 100）	27.4
酢酸n-ブチル	3.0
部分 III	
2,2'-アゾビス（2-メチルブチロニトリル）（本願特許出願人製ヴァゾ® 67）	21.7
芳香族溶媒（エクソン製ソルベッソ® 100）	63.6
酢酸n-ブチル	12.1
合計	854.9

【0129】
部分Ｉを反応器中へ装入し、還流温度まで加熱した。部分ＩＩおよびＩＩＩを別々に予め混合し、次に、反応混合物を還流温度に保持しながら、２６０分間にわたって反応器に同時に加えた。溶液を次に還流温度に３０分間保持した。

【0130】
生じたアクリルポリオール樹脂は６６重量％固形分であり、約６，０００の重量平均分子量を有する。

【0131】
（アクリルＮＡＤ樹脂の製造）
場合により本発明の組成物に含まれてもよいヒドロキシ官能性アクリルＮＡＤ樹脂を、上記のように装備された窒素で覆われたフラスコ中へ下記を装入することによって製造した。

【0132】

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【表6】

部分 I	重量部
イソプロパノール	29.9
ミネラルスピリット(エクソン製エクソール(Exxsol)® D40)	35.9
ヘプタン	245.6
アクリルポリマー溶液(77.5%ソルベッソ® 150と22.5%ブタノールとの溶媒ブレンド中の10,000の重量平均分子量を有する15%スチレン、20%メタクリル酸ブチル、38.5%メタクリル酸エチルヘキシル、22.5%ヒドロキシエチルアクリレート、4%アクリル酸、および1.4%メタクリル酸グリシジルのアクリルポリマーの60%固形分)	179.7
部分 II	
ペルオキシ-2-エチルヘキサン酸 t-ブチル	0.45
部分 III	
スチレン	35.9
メタクリル酸メチル	194.7
アクリロニトリル	6.0
アクリルポリマー溶液(上からの)	89.9
ヒドロキシエチルアクリレート	29.9
アクリル酸メチル	15.0
メタクリル酸グリシジル	6.0
アクリル酸	12.0
イソブチルアルコール	26.9
部分 IV	
ミネラルスピリット(エクソン製エクソール® D40)	21.0
ヘプタン	27.0
ペルオキシ-2-エチルヘキサン酸 t-ブチル	3.0
部分 V	
イソブチルアルコール	42.0
ペルオキシ-2-エチルヘキサン酸 t-ブチル	1.5
合計	1002.35

【0133】
部分Ｉを反応容器中へ装入し、還流温度まで加熱した。部分ＩＩを次に、部分ＩＩＩおよびＩＶが反応容器中へのフィードを始める前の５分以内に反応容器に加えた。部分ＩＩＩおよびＩＶを別々に予め混合し、２１０分間にわたって還流温度で反応容器中へ同時にフィードした。部分Ｖを予め混合し、還流温度を維持しながら６０分間にわたって加えた。反応溶液を次に還流温度に６０分間保持した。真空を次に反応容器にかけ、２３６．８４重量部溶媒を取り除いた。

【0134】
生じたＮＡＤ樹脂は６０％の重量固形分、約１００，０００～２００，０００の重量平均分子量を有するコア、およびコアに結合した約１０，０００～１５，０００の重量平均

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分子量を有するアームを有する。

【0135】

（アクリルミクロゲル樹脂の製造）

メタクリル酸メチル／メタクリル酸グリシジル共重合体を、下記のアクリルミクロゲル樹脂の合成で使用される、また、場合により本発明の組成物中に含まれる中間体安定化ポリマーとして製造した。この安定化ポリマーを、上記のように装備された窒素で覆われたフラスコ中へ下記を装入することによって製造した。

【0136】

【表7】

部分 I	重量部
酢酸n-ブチル	195.8
部分 II	
メタクリル酸メチル	139.0
酢酸n-ブチル	14.4
メタクリル酸グリシジル	13.1
メタクリル酸グリシジル/12-ヒドロキシステアリン酸共重合体 (トルエンと石油ナフサとの80/20ブレンド中の 89.2%12-HAS/10.8%GMAの 60重量%固形分溶液)	181.7
石油ナフサ(エクソン製エクソール® D-3135)	40.6
酢酸n-ブチル	13.1
部分 III	
2,2'-アゾビス(2-メチルブチロニトリル)	8.0
酢酸n-ブチル	71.6
石油ナフサ(エクソン製エクソール® D-3135)	74.3
部分 IV	
4-第三ブチルカテコール	0.04
酢酸n-ブチル	2.7
部分 V	
メタクリル酸	2.7
酢酸n-ブチル	6.0
部分 VI	
N,N'-ジメチルドデシルアミン	0.4
酢酸n-ブチル	2.7
合計	766.14

【0137】

部分Ｉを反応器に装入し、９６～１００℃の温度にした。部分ＩＩおよびＩＩＩを別々に予め混合し、次に、９６～１００℃の反応温度を維持しながら、１８０分間にわたって同時に加えた。溶液を次に９０分間保持した。順に、部分ＩＶ、Ｖ、およびＶＩを別々に予め混合し、反応器に加えた。反応溶液を次に還流まで加熱し、酸価が０．５以下である

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まで保持した。生じたポリマー溶液は４０％固形分含有率を有する。
【0138】
アクリルミクロゲル樹脂を次に、上記のように装備された窒素で覆われたフラスコ中へ、下記を装入することによって製造した。
【0139】

【表8】

部分 I	重量部
メタクリル酸メチル	11.3
ミネラルスピリット(エクソン製エクソール® D40)	73.7
メタクリル酸メチル/メタクリル酸グリシジル安定剤共重合体(上で製造された)	5.4
ヘプタン	60.7
2,2'-アゾビス(2-メチルブチロニトリル)(本願特許出願人製ヴァゾ® 67)	0.35
部分 II	
N,N-ジメチルエタノールアミン	0.5
メタクリル酸メチル	216.2
メタクリル酸メチル/メタクリル酸グリシジル安定剤共重合体(上で製造された)	41.2
メタクリル酸グリシジル	2.1
メタクリル酸	2.1
ヘプタン	35.8
ミネラルスピリット(エクソン製エクソール® D40)	73.7
部分 III	
2,2'-アゾビス(2-メチルブチロニトリル)(本願特許出願人製ヴァゾ® 67)	0.8
トルエン	9.7
ヘプタン	23.4
部分 IV	
n-ブタノール	7.8
部分 V	
ヒドロキシプロピルアクリレート	49.1
メタクリル酸メチル/メタクリル酸グリシジル安定剤共重合体(上で製造された)	10.3
メタクリル酸ブチル	73.7
ヘプタン	11.5
部分 V	
ペルオキシ-2-エチルヘキサン酸 t-ブチル	9.0
n-ブタノール	43.0
ヘプタン	3.9
合計	765.25

【0140】
部分Ｉを反応容器中へ装入し、その還流温度まで加熱し、４５分間保持した。部分ＩＩ

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およびＩＩＩを別々に予め混合し、次に、反応混合物をその還流温度に維持しながら、混合される反応容器に１２０分間にわたって同時に加えた。部分ＩＶを次に加えた。部分ＶおよびＶＩを別々に予め混合し、次に、混合物を還流温度に維持しながら１２０分間にわたってバッチに同時に加えた。混合物を次に還流温度に３０分間保持した。

【0141】

生じたポリマー溶液は５０％の重量固形分、および６０センチポイズの粘度を有する。

【0142】

（クリアコート実施例１ならびに比較例２および３の調製）

本方法の実施で有用なクリアコート組成物は、次の成分を与えられた順に一緒にブレンドすることによって調製した。

【0143】

【表9】

	クリアコート例		
成分	実施例1	比較例2	比較例3
（すべての量は重量部）			
フッ素化アクリロシラン樹脂（上から）	614.853	614.853	
フルオロ-ウレタン添加物（上から）	8.131		
非フッ素化アクリロシラン樹脂（上から）			372.575
アクリルミクロゲル（上から）	33.304	33.304	16.979
アクリルポリオール樹脂（上から）			187.030
アクリルNAD樹脂（上から）			28.338
ソルベッソ® 100	114.973	114.973	194.133
チヌビン（Tinuvin）® 1130[1]（ベンゾトリアゾールUV光吸収剤）	14.286	14.286	7.028
チヌビン® 123[1]（ヒンダードアミンUV光吸収剤）	2.968	2.968	1.460
チヌビン® 384[1]（UV光吸収剤）	12.689	12.689	6.242
チヌビン® 079L[1]（ヒンダードアミンUV光吸収剤）	26.531	26.531	13.052
ディスパーロン（Disparlon）® LC-955界面活性剤[2]	6.298	6.298	5.563
ディスパーロン® L-1984界面活性剤[2]	2.563	2.563	
ブロックされた酸触媒溶液（48.0%DDBSA/10.8%2-アミノメチルプロパノール/41.2%メタノール）	21.772	21.772	17.803
3-エトキシプロピオン酸エチル	25.576	25.576	
n-ブタノール	2.890	2.890	2.890
エチレングリコールモノブチルエーテル	38.617	38.617	38.617
デスモデュール® N-3300[3]ポリイソシアネート	175.845	175.845	175.845
フェニル酸性リン酸エステル	2.442	2.442	2.442

上記成分のソース

[1] チバ・スペシャルティ・ケミカル・カンパニー（Ciba Specialty Chemical Company）の製品
[2] キング・インダストリーズの（King Industries）の製品
[3] バイエル・コーポレーション（Bayer Corporation）の製品

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【0144】
電着プライマーで電着したリン酸塩処理スチールパネルを、それぞれ、通常の無地のブラック、シルバーメタリック、およびブルーメタリック溶剤希釈型ベースコーティング組成物で吹き付け塗りし、コートして約０．５～１．０ミル厚さのベースコートを形成した。ベースコートにそれぞれ５分のフラッシュを与えた。次に、上に調合したクリアコート・ペイントをベースコートのそれぞれの上に「ウェット・オン・ウェット」塗布して約１．８～２．２ミル厚さのクリアコート層を形成した。パネルを次に、典型的なＯＥＭベークである、約２５０°Ｆで３０分間ベークすることによって十分に硬化させた。生じた被覆パネルを下記の特性について測定した。結果を表２に一覧にする。第２セットのパネルを上に明記したようにコートした。さらに、冷却後に、第２のベースコート／クリアコート修理コート層を最初のコートと同じ手順によって塗布した。何の研磨も表面処理も、修理ベースコートの塗布前に行わなかった。生じた被覆パネルをまた下に明記される試験にかけて接着性を評価し、元のトップコーティングからの修理トップコーティングのピックオフの量を記録した。結果を下の表１および３に報告する。

【0145】
ＯＥＭおよび修理コートパネルの次の特性を測定した：２０°光沢、画像の明確さ（ＤＯＩ）、硬度、ビデオ接触角システムによって測定されるような前進および後退水接触角ならびに前進および後退ヘキサデカン溶剤接触角、初期クロスハッチ接着性、４０℃で１００％相対湿度への曝露の９６または２４０時間後のクロスハッチ接着性、ならびにプライマーなし風防接合接着性。

【0146】
上記の接触角測定値は、具体的には、クリアコートした表面のクリーナビリティおよび汚れ固着を評価するために用いた。接触角は、参照により本明細書によって本明細書に援用される（非特許文献２）に十分に記載されている液滴法（Ｓｅｓｓｉｌｅ　Ｄｒｏｐ　Ｍｅｔｈｏｄ）によって測定する。

【0147】
手短に言えば、液滴法では、水か溶剤かどちらかの液体の滴を表面上に置き、正接を滴と表面との接触ポイントで正確に測定する。前進角は、液体の滴のサイズを大きくすることによって測定し、後退角は液体の滴のサイズを小さくすることによって測定する。機器およびこれらの接触角を測定するために必要な手順に関する追加情報は、参照により本明細書に援用される（非特許文献３）にさらに十分に記載されている。

【0148】
水および有機液体接触角とクリーナビリティおよび汚れ固着との関係は、（非特許文献４）に記載されている。一般に、接触角が高ければ高いほど、表面はより耐汚れまたは汚染性であり、表面はきれいにするのがより容易である。

【0149】
上記のクロスハッチ接着性測定値は、具体的には、元のベースコートへの元のクリアコートの接着性と元のクリアコートへの修理ベースコートの再コーティング接着性とを評価するために用いた。上に示したように、再コーティング接着性については、塗布されたベースコートおよびクリアコートを２５０℃で３０分間ベークした。ベークの２４時間以内に、同じベースコートおよびクリアコートを、ベークしたＯＥＭベースコートおよびクリアコートのトップ上に上記の同じ手順によって塗布した。新たに塗布したトップコートを再び２５０℃で３０分間ベークした。これらの再コーティングパネルを次に最低２４時間老化させ、下記のクロスハッチ接着性法に従って再コーティング接着性について試験した。

【0150】
手短に言えば、クロスハッチ接着性は、ジェネラル・モーターズ・コーポレーション（Ｇｅｎｅｒａｌ　Ｍｏｔｏｒｓ　Ｃｏｒｐｏｒａｔｉｏｎ）によって公表されたジェネラル・モーターズ試験手順（Ｔｅｓｔ　Ｐｒｏｃｅｄｕｒｅ）ＧＭ９０７１ＰおよびＡＳＴＭ　Ｄ－３３５９－９３に従って試験した。試験は、ベーキング後室温で７２時間老化さ

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せたパネルについて行う。パネルを格子パターンに刻みをつけ、粘着テープを刻みマーク上に貼り付け、次にテープをフィルムから素早く引っ張る。基材からのコーティングの観察される剥離の大きさが接着性を示す。コーティングがそれから剥離した格子またはクロスハッチ面積の百分率を格付けされたい。５％以上の剥離した塗膜の格付けは不合格と見なされる。

【0151】

プライマーなし風防接合接着性について試験するために、風防接着剤のビーズをベーキング後にクリアコート表面に塗布した。使用した風防接着剤は、ダウ・エセックス・スペシャルティ・プロダクツ・カンパニー（Ｄｏｗ　Ｅｓｓｅｘ　Ｓｐｅｃｉａｌｔｙ　Ｐｒｏｄｕｃｔｓ　Ｃｏｍｐａｎｙ）から商業的に入手可能である。おおよそ５ｍｍ×５ｍｍ×２５０ｍｍ接着剤ビーズを硬化したクリアコート表面上に置いた。接着剤プラスクリア複合体を約７５°Ｆ（２４℃）および２０～５０％相対湿度で７２時間硬化させた。硬化した接着剤ビーズをかみそりの刃でカットした。カットは、１８０°角度で接着剤のエッジを引き戻しながら１２ｍｍ間隔で６０°角度で接着剤ビーズを通して行った。最低１０カットを各システムについて行った。所望の結果は、１００％凝集破壊（ＣＦ）として記載する。凝集破壊（ＣＦ）は、接着剤ビーズの完全性がカットすることおよび接着剤ビーズとクリアコート表面との間の接合よりかなり引っ張ることの結果として失われた時に起こる。ＯＥＭ初期コートおよび修理コートフィルムの両方について、２、３の着色ベースコートにわたる結果を下の表にまとめる。

【0152】

【表10】

表1
修理コート試験結果

					ビデオ接触角システムを用いる接触角										湿気接着性	
					脱イオン水				ヘキサデカン						初期	96時間湿気
					前進		後退		前進		後退				クロスハッチ	
クリアコート	ベースコート	DOI	20°光沢	ツーコン	平均値	標準偏差	平均値	標準偏差	平均値	標準偏差	平均値	標準偏差			%フィルム損失	
実施例1	ブルーメタリック														0	0
比較例2	ブルーメタリック														>65	>65

【0153】
上の結果は、本発明のフッ素化ウレタン添加物を使用して製造したクリアコーティング組成物（実施例１）が再コーティング接着性を示すが、該添加物を含有しない比較システム（比較例２）が必要な再コーティング接着性を持たないことを示す。

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【0154】
【表11】

表2
OEM初期コート試験結果

					ビデオ接触角システムを用いる接触角								湿気接着性		耐候
					脱イオン水				ヘキサデカン				初期	240時間湿気	接合
					前進		後退		前進		後退		クロスハッチ		湿気
クリアコート	ベースコート	DOI	20°光沢	ツーコン	平均値	標準偏差	平均値	標準偏差	平均値	標準偏差	平均値	標準偏差	%フィルム損失		結果
実施例1	シルバーメタリック	84	90	15.1	98.5	1.0	75.3	1.5	44.3	1.5	36.3	0.5	0	0	100CF合格
比較例3	シルバーメタリック	91	91	12.6	90.0	0.0	72.0	1.5	10.7	1.4	6.3	0.5	0	0	100CF合格
実施例1	ブラック	88	88	12.6	99.5	1.0	77.3	0.5	49.7	0.5	38.7	1.4	0	0	100CF合格
比較例3	ブラック	93	87	12.1	89.8	0.8	74.0	0.9	13.7	1.0	7.0	0.0	0	0	100CF合格

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【0155】
【表12】

表3
修理コート試験結果

					ピデオ接触角システムを用いる接触角								湿気接着性	
					脱イオン水				ヘキサデカン				初期	240時間湿気
					前進		後退		前進		後退		クロスハッチ	
クリアコート	ベースコート	DOI	20°光沢	ツーコン	平均値	標準偏差	平均値	標準偏差	平均値	標準偏差	平均値	標準偏差	%フィルム損失	
実施例1	シルバーメタリック	77	89	15.5	102.0	1.5	75.0	1.5	1.5	46.7	0.5	0.0	0	0
比較例1	シルバーメタリック	77	89	11.4	91.7	1.4	75.5	0.5	11.7	11.7	0.5	0.9	0	0
実施例1	ブラック	85	88	12.2	101.7	0.5	77.0	0.9	48.5	2.7	37.3	0.5	0	0
比較例3	ブラック	97	87	9.7	90.0	0.0	74.7	1.4	13.0	0.9	5.3	0.5	0	0

【0156】
上の結果は、本発明のフッ素化ウレタン添加物を使用して製造したクリアコーティング組成物（実施例１）が、耐汚染性である、かつ、容易に洗浄されるまたはきれいに拭かれ

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る仕上げを提供する水についておよび溶剤について高い接触角を有するだけでなく、本発明の方法の操作を可能にする必要な再コーティング接着性を有することを示す。市販のクリアコート組成物に相当する非フッ素化アクリロシランポリマー含有クリアコート組成物（比較例３）は、ほとんどすべての色についてそれほど良好なクリーナビリティを示さない。

【0157】

本発明の方法および組成物の様々な修正、変更、追加または置換は、本発明の範囲および精神から逸脱することなしに当業者に明らかであろうし、本発明が本明細書に述べられた例示された実施形態に限定されないが、むしろ次の特許請求の範囲に列挙されるようであることが理解されるべきである。

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INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 796 904 A (NIPPON PAINT CO LTD) 24 September 1997 (1997-09-24) page 2, lines 5-15 page 2, line 38 - page 3, line 32 page 4, lines 29-52 page 5, line 46 - page 6, line 30 page 10, lines 5-46; claims	1-3,6-9, 12
X	US 2003/017349 A1 (SCHNEIDER RICHARD A ET AL) 23 January 2003 (2003-01-23) paragraphs '0002!, '0027!, '0028!, '0036!, '0073! - '0077!, '0087! - '0089!, '0094! - '0100!, '0108!; claims	1-3,6-9, 12

-/—

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

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2004	14/12/2004

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

Form PCT/ISA/210 (second sheet) (January 2004)

Gilead Exhibit 2018
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/031243

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/027198 A (BASF CORP ; RIHAN ALI (US); COLYER EMERSON KEITH (US)) 3 April 2003 (2003-04-03) paragraphs '0001!, '0007! - '0034!; claims	1-3,6,8
A	WO 97/22646 A (PPG INDUSTRIES INC) 26 June 1997 (1997-06-26) page 1, lines 6-9 page 4, line 11 - page 8, line 16; claims; examples	1-12
A	US 4 812 337 A (NUMA NOBUSHIGE ET AL) 14 March 1989 (1989-03-14) cited in the application column 1, lines 4-10 column 2, line 60 - column 4, line 27 claims; examples	1-12

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

Gilead Exhibit 2018
PGR2023-00046 - Page 001097

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/031243

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0796904	A	24-09-1997	JP	9249732 A	22-09-1997
			JP	10067844 A	10-03-1998
			JP	10067945 A	10-03-1998
			EP	0796904 A2	24-09-1997
			US	5780530 A	14-07-1998
US 2003017349	A1	23-01-2003	US	6447919 B1	10-09-2002
			US	6156389 A	05-12-2000
			US	5853894 A	29-12-1998
			US	2004131789 A1	08-07-2004
			US	2004082699 A1	29-04-2004
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			BR	0212851 A	13-10-2004
			CA	2445943 A1	03-04-2003
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WO 9722646	A	26-06-1997	WO	9722646 A1	26-06-1997
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			JP	7038969 B	01-05-1995
			JP	63134084 A	06-06-1988
			JP	2022842 C	26-02-1996
			JP	7041203 B	10-05-1995
			JP	63171676 A	15-07-1988
			DE	3739791 A1	26-05-1988

Form PCT/ISA/210 (patent family annex) (January 2004)

(51)Int.Cl.		F I		テーマコード（参考）
Ｃ０９Ｄ 161/28	(2006.01)	Ｂ０５Ｄ 1/36	Ｂ	
		Ｃ０９Ｄ 161/28		

(81)指定国　AP(BW,GH,GM,KE,LS,MW,MZ,NA,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PL,PT,RO,SE,SI,SK,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BW,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,EG,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NA,NI,NO,NZ,OM,PG,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,SL,SY,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,YU,ZA,ZM,ZW

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Ｆターム(参考)　4D075 AE06 BB26Z CA13 DA27 DB39 DC12 EB16 EB20 EB32 EB37 EB38 EB42 EB45 EB56 EC30 EC54
4J038 DG061 DG062 DG092 FA051 FA052 FA071 FA072 FA231 FA232 GA12 GA15 JB34 KA03 KA06 NA12 PB07 PB12

Gilead Exhibit 2018
PGR2023-00046 - Page 001099

Electronic Acknowledgement Receipt

EFS ID:	17794844
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.3
Receipt Date:	02-JAN-2014
Filing Date:	29-AUG-2013
Time Stamp:	10:19:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	039560538003_IDSTransmittal_2014-01-02.pdf	55051 f65e5e5c6cb03fe49fb669944940ed8f070534	no	2
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	039560538003_SB08a_2014-01-02.pdf	612441 c0a278f6f4e8e3e082b3dd02be21c04955869948c	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Foreign Reference	F1_WO2005030891A1.pdf	3981013 f76efd830cc30ee22f57840e501752c7ef1b28c	no	46
Warnings:					
Information:					
4	Foreign Reference	F2_JP2007505742A_JPT2006528162.pdf	1817389 cc4155dc0bcc1d917c8dba4167dd693bbfaee9	no	42
Warnings:					
Information:					
		Total Files Size (in bytes):	6465894		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/013,237	)	
	:	Examiner: Not yet assigned
First Named Inventor:	)	
	:	Group Art Unit: 1623
JINFA DU	)	
	:	Confirmation No.: 7005
Filed: August 29, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	January 2, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the documents listed on the attached Form PTO/SB/08a. A copy of each document that is not a U.S. patent document is submitted herewith.

An explanation of relevance of the non-English document Japanese Patent Application No. 2007-505742 (JP-T 2006-528162), listed on the attached Form PTO/SB/08a, may be found in corresponding WO 2005/030891 A1 submitted herewith. Japanese Patent Application No. 2007-505742 (JP-T 2006-528162) was brought to the Applicant's attention in an

Office Action issued on December 3, 2013 for corresponding Japanese Patent Application No. 2012-032352.

It is respectfully requested that the above information be considered by the Examiner and that a copy of the attached Form PTO/SB/08a be returned indicating that such information has been considered.

In accordance with 37 C.F.R. §1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether the disclosed references are, or are considered to be, material to patentability.

It is believed that no fees are due in connection with this submission. However, should the U.S. Patent and Trademark Office determine that fees are due, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-3939.

Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Alicia A. Russo/
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Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

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PGR2023-00046 - Page 001103

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/013,237

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	28 minus 20 =	* 8			OR	x 80 =	640
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						4000
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	6240

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/013,237	08/29/2013	1623	6380	03956.053800.3	28	2

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

FILING RECEIPT



Date Mailed: 01/13/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jinfa Du, Redwood City, CA;
Dhanapalan Nagarathnam, Bethany, CT;
Michael Joseph Sofia, Doylestown, PA;
Peiyuan Wang, Totowa, NJ;

Applicant(s)

Gilead Pharmasset LLC, Foster City, CA

Assignment For Published Patent Application

GILEAD PHARMASSET LLC, Foster City, CA

Power of Attorney: The patent practitioners associated with Customer Number 104538

Domestic Priority data as claimed by applicant

This application is a CON of 13/609,614 09/11/2012 PAT 8580765
which is a CON of 13/099,671 05/03/2011 PAT 8334270
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/19/2013

Gilead Exhibit 2018
PGR2023-00046 - Page 001105

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/013,237**

Projected Publication Date: To Be Determined - pending completion of Sequence Disclosures

Non-Publication Request: No

Early Publication Request: No

Title

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

Gilead Exhibit 2018
PGR2023-00046 - Page 001106

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

FORMALITIES LETTER

OC000000065991794

Date Mailed: 01/13/2014

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Filing Date Granted

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to comply with the sequence rules, 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136.

Applicant filed a request or letter regarding the use of the computer readable form (CRF) of a sequence listing from another application as the CRF of the sequence listing in this application in lieu of filing a CRF in this application. The request or letter, however, does not comply with the requirements of 37 CFR 1.821(e) for the reason(s) listed below. Applicant must make the appropriate correction(s), or file a CRF in this application in compliance with 37 CFR 1.821(e), within the time period for reply set forth in the notice to avoid the abandonment of the instant application. Applicant is encouraged to use form PTO/SB/93 for requesting a transfer of a computer readable form under 37 CFR 1.821(e).

- Applicant did not submit a statement that the sequence information in the paper or compact disc copy of the sequence listing (required by 37 CFR 1.821(c)) of this application is identical to the sequence information in the CRF of the other application. Note that a sequence listing filed electronically via EFS-Web in a PDF file is considered to be a paper copy under 37 CFR 1.821(c).
- No paper or compact disc copy of the sequence listing has been filed in this application, or the paper or compact disc copy filed is not identical to that of the requested computer readable form. Note that a sequence listing filed electronically via EFS-Web in a PDF file is considered to be a paper copy under 37 CFR 1.821(c).

For more information and a sample letter for requesting the use of a CFR from another application, *see* MPEP 2422.05. For more information regarding electronic filing of sequence listings, see the EFS-Web Legal Framework at http://www.uspto.gov/ebc/portal/efs/legal.htm.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to these requirements, please contact:

- **For Rules interpretation, call (571) 270-5300**
- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**

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PGR2023-00046 - Page 001108

- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Jinfa Du
  Dhanapalan Nagarathnam
  Michael Joseph Sofia
  Peiyuan Wang

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

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/ygizaw/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Gilead Exhibit 2018
PGR2023-00046 - Page 001109

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: Not Yet Assigned
JINFA DU ET AL.	)	
	:	Group Art Unit: 1623
Application No.: 14/013,237	)	
	:	Confirmation No.: 7005
Filed: August 29, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	
	:	
	)	January 21, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF DECLARATION

Commissioner:

This paper is in response to the Notices to Comply with Requirements dated September 26, 2013 and January 13, 2014.

Submitted herewith in the above-identified application are the executed Inventors' Declarations. The Applicant believes the fee required for this submission was paid on November 22, 2013. However, please charge any additional fee required for this submission to Deposit Account 50-3939.

The Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

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PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 14/013,237 filed on August 29, 2013.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Peiyuan Wang Date (Optional): 1/16/2014

Signature: Peiyuan Wang

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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LEGAL NAME OF INVENTOR

Inventor: Jinfa Du Date (Optional):

Signature: 1/06/2014

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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LEGAL NAME OF INVENTOR

Inventor: Michael Joseph Sofia Date (Optional): 12/16/13

Signature: Michael Joseph Sofia

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (08-12)
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LEGAL NAME OF INVENTOR

Inventor: Dhanapalan Nagarathnam Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt

EFS ID:	17964208
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Alicia Russo/DAVID NGUY
Filer Authorized By:	Alicia Russo
Attorney Docket Number:	03956.053800.3
Receipt Date:	21-JAN-2014
Filing Date:	29-AUG-2013
Time Stamp:	12:37:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	03956053800-3SubmissionofDeclarations.pdf	53202 7350831d0019884d3ef1f6929b4d299d14a09a44c	no	2
Warnings:					
Information:					

2	Oath or Declaration filed	03956053800-3-ExecutedDeclarations.pdf	387708 34ea33cd2fe999ea5499f2f88db7e57f904aa80	no	4
Warnings:					
Information:					
			Total Files Size (in bytes):	440910	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	JINFA DU
Art Unit	1623
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

Gilead Exhibit 2018
PGR2023-00046 - Page 001118

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	JINFA DU
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	1	U.S. Patent Application No. 14/152,243, as filed January 10, 2014	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	JINFA DU
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2014-01-24
Name/Print	Alicia A. Russo	Registration Number	46,192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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PGR2023-00046 - Page 001121

Electronic Acknowledgement Receipt

EFS ID:	18018000
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Alicia Russo/DAVID NGUY
Filer Authorized By:	Alicia Russo
Attorney Docket Number:	03956.053800.3
Receipt Date:	24-JAN-2014
Filing Date:	29-AUG-2013
Time Stamp:	15:05:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	039560538003_IDSTransmittal.pdf	86692 e4b0014e9dcb5af5888edd8816c0bac4d9844e8	no	2
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	039560538003_SB08a_2014-01-02.pdf	612280 c91dcc1afc5350daab9c6f8e81c3ce724e...77b	no	4

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Information:

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Total Files Size (in bytes):	698972

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New Applications Under 35 U.S.C. 111
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Attorney Docket No. 03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No.: 14/013,237	)	
	:	Examiner: Not yet assigned
First Named Inventor:	)	
	:	Group Art Unit: 1623
JINFA DU	)	
	:	Confirmation No.: 7005
Filed: August 29, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	
	:	
	)	January 24, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the document listed on the attached Form PTO/SB/08a.

Pursuant to MPEP § 609.04(a)(II)(C) and the *Waiver of the Copy Requirement in 37 CFR 1.98 for Cited Pending U.S. Patent Applications*, 1287 O.G. 163 (Oct. 19, 2004), no copy of unpublished U.S. Patent Application No. 14/152,243, filed January 10, 2014, is submitted herewith because it is stored in the Image File Wrapper (IFW) system.

It is respectfully requested that the above information be considered by the Examiner and that a copy of the attached Form PTO/SB/08a be returned indicating that such information has been considered.

In accordance with 37 C.F.R. §1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether the disclosed reference is, or is considered to be, material to patentability.

It is believed that no fees are due in connection with this submission. However, should the U.S. Patent and Trademark Office determine that fees are due, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-3939.

Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

Gilead Exhibit 2018
PGR2023-00046 - Page 001125

03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No. 14/013,237	)	Examiner: Not Yet Assigned
First Named Inventor: Jinfa DU	)	Group Art Unit: 1623
Filed: August 29, 2013	)	Confirmation No. 7005
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	January 29, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

THIRD PRELIMINARY AMENDMENT AND
RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR
PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE
AND/OR AMINO ACID SEQUENCE DISCLOSURES

Sir:

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated January 13, 2014, submitted herewith are both PDF and computer readable copies of the Sequence Listing for the present application.

Prior to examination on the merits, please also amend the above-identified application as follows:

Amendments to the Specification begin on page **2**; and

Remarks begin on page **3**.

Amendments to the Specification:

Please amend the sentence following the subheading "INCORPORATION OF SEQUENCE LISTING" added by the Preliminary Amendment filed November 22, 2013 as follows:

-- The Sequence Listing filed on ~~October 10, 2012 (in U.S. Patent Application No. 13/609,614, filed September 11, 2012)~~January 29, 2014, created on ~~September 30, 2012~~January 28, 2014, named 03956053800[[2]]3_ST25.txt, having a size in bytes of 1,[[091]]166 B, is hereby incorporated by reference herein in its entirety. --

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PGR2023-00046 - Page 001127

REMARKS

This Application has been reviewed in light of the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated January 13, 2014.

The Applicant submits herewith both PDF and computer readable copies of a Sequence Listing for the sequences disclosed on page 675 of the original specification submitted on August 29, 2013. The Applicant also requests entry of the foregoing amendments to page 1 of the specification, incorporating and referencing the Sequence Listing submitted herewith.

The Applicant respectfully submits that the Notice to Comply dated January 13, 2014 has been responded to in full, and an early and favorable action on the merits is respectfully requested.

It is believed that no fee is due in connection with this paper. However, the Commissioner is authorized to charge any fee required in connection with the present submission to Deposit Account No. 50-3939.

Gilead Exhibit 2018
PGR2023-00046 - Page 001128

The Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No. 46,192

Erin J.D. Austin
Registration No. 66,532

Attorneys for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, NY 10104-3800
Facsimile: (212) 218-2200

Gilead Exhibit 2018
PGR2023-00046 - Page 001129

SEQUENCE LISTING

<110> GILEAD PHARMASSET LLC
Du, Jinfa
Nagarathnam, Dhanapalan
Sofia, Michael J
Wang, Peiyuan

<120> NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

<130> 03956.053800.3

<140> US 14/013,237
<141> 2013-08-29

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<151> 2012-09-11

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Electronic Acknowledgement Receipt	
EFS ID:	18058521
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.3
Receipt Date:	29-JAN-2014
Filing Date:	29-AUG-2013
Time Stamp:	15:14:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		03956053800-3ResponsetoNoticetoComply.pdf	111769 [redacted]	yes	4

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Response to Pre-Exam Sequence Notice		1	1	
	Specification		2	2	
	Applicant Arguments/Remarks Made in an Amendment		3	4	
Warnings:					
Information:					
2	Sequence Listing	039560538003_ST25.pdf	19007	no	2
Warnings:					
Information:					
3	Sequence Listing (Text File)	039560538003_ST25.txt	1166	no	0
Warnings:					
Information:					
		Total Files Size (in bytes):	131942		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 14013237 Document Date: 01/29/2014

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

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============================================================
Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Anjum, Durreshwar (CGI Federal)
Timestamp: [year=2014; month=1; day=31; hr=14; min=15; sec=51; ms=823; ]
============================================================
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Validated By CRFValidator v 1.0.4

Application No: 14013237 Version No: 1.0

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Output Set:

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Finished: 2014-01-29 15:14:37.664
Elapsed: 0 hr(s) 0 min(s) 0 sec(s) 187 ms
Total Warnings: 3
Total Errors: 0
No. of SeqIDs Defined: 3
Actual SeqID Count: 3

Error code	Error Description
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SEQUENCE LISTING

<110> GILEAD PHARMASSET LLC
Du, Jinfa
Nagarathnam, Dhanapalan
Sofia, Michael J
Wang, Peiyuan

<120> NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

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<210> 1
<211> 23
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<213> Artificial Sequence

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<223> HCV DNA Sense Primer

<400> 1
agccatggcg ttagtatgag tgt 23

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/013,237

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	28 minus 20 =	* 8			OR	x 80 =	640
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						4000
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL			TOTAL	6240

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/013,237	08/29/2013	1623	6380	03956.053800.3	28	2

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

FILING RECEIPT



Date Mailed: 02/03/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jinfa Du, Redwood City, CA;
Dhanapalan Nagarathnam, Bethany, CT;
Michael Joseph Sofia, Doylestown, PA;
Peiyuan Wang, Totowa, NJ;

Applicant(s)

Gilead Pharmasset LLC, Foster City, CA

Assignment For Published Patent Application

GILEAD PHARMASSET LLC, Foster City, CA

Power of Attorney: The patent practitioners associated with Customer Number 104538

Domestic Priority data as claimed by applicant

This application is a CON of 13/609,614 09/11/2012 PAT 8580765
which is a CON of 13/099,671 05/03/2011 PAT 8334270
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/19/2013

Gilead Exhibit 2018
PGR2023-00046 - Page 001140

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/013,237**

Projected Publication Date: To Be Determined - pending completion of Sequence Disclosures

Non-Publication Request: No

Early Publication Request: No

Title

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

Gilead Exhibit 2018
PGR2023-00046 - Page 001141

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

FORMALITIES LETTER

OC000000066295588

Date Mailed: 02/03/2014

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Filing Date Granted

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to comply with the sequence rules, 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136.

Applicant filed a request or letter regarding the use of the computer readable form (CRF) of a sequence listing from another application as the CRF of the sequence listing in this application in lieu of filing a CRF in this application. The request or letter, however, does not comply with the requirements of 37 CFR 1.821(e) for the reason(s) listed below. Applicant must make the appropriate correction(s), or file a CRF in this application in compliance with 37 CFR 1.821(e), within the time period for reply set forth in the notice to avoid the abandonment of the instant application. Applicant is encouraged to use form PTO/SB/93 for requesting a transfer of a computer readable form under 37 CFR 1.821(e).

- Applicant did not submit a statement that the sequence information in the paper or compact disc copy of the sequence listing (required by 37 CFR 1.821(c)) of this application is identical to the sequence information in the CRF of the other application. Note that a sequence listing filed electronically via EFS-Web in a PDF file is considered to be a paper copy under 37 CFR 1.821(c).
- No paper or compact disc copy of the sequence listing has been filed in this application, or the paper or compact disc copy filed is not identical to that of the requested computer readable form. Note that a sequence listing filed electronically via EFS-Web in a PDF file is considered to be a paper copy under 37 CFR 1.821(c).

For more information and a sample letter for requesting the use of a CFR from another application, *see* MPEP 2422.05. For more information regarding electronic filing of sequence listings, see the EFS-Web Legal Framework at http://www.uspto.gov/ebc/portal/efs/legal.htm.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to these requirements, please contact:

- **For Rules interpretation, call (571) 270-5300**
- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**

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- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/nfissha/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Gilead Exhibit 2018
PGR2023-00046 - Page 001144

03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application No. 14/013,237	)	Examiner: Not Yet Assigned
First Named Inventor: Jinfa DU	)	Group Art Unit: 1623
Filed: August 29, 2013	)	Confirmation No. 7005
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	March 17, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Sir:

Applicant responds to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated February 3, 2014. Consideration of the following remarks is respectfully requested.

REMARKS

This Application has been reviewed in light of the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated February 3, 2014. Applicant also thanks Ms. Kathleen Kalafus from the USPTO for her helpful voicemail left for Applicant's representative, Erin Austin, on February 25, 2014.

On January 29, 2014, Applicant submitted both paper (PDF) and computer-readable copies of a Sequence Listing for the sequence disclosed on page 675 of the original specification submitted on August 29, 2013. Applicant also requested entry of amendments to the specification, incorporating and referencing the submitted Sequence Listing. The Sequence Listing was deemed to comply with the sequence rules and accepted on January 31, 2014. Ms. Kalafus' voicemail also indicated that the incorporation by reference in the specification was proper.

Ms. Kalafus' voicemail stated that while the February 3, 2014 Notice refers to a request to transfer a computer-readable format, the USPTO recognizes that Applicant's January 29, 2014 response was not a request to transfer a computer-readable format but rather a submission of both paper (PDF) and computer-readable copies of the Sequence Listing.

Per Ms. Kalafus' advice, Applicant states the following:

1. Applicant does not seek to transfer a computer-readable format of the Sequence Listing from the parent application, having submitted on January 29, 2014 the required paper (PDF) and computer-readable copies of the Sequence Listing for this application;

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2. The content of the paper (PDF) and computer-readable copies of the Sequence Listing submitted on January 29, 2014 are identical; and

3. Applicant's submission on January 29, 2014 included no new matter.

Applicant respectfully submits that the Notice to Comply has been responded to in full. A favorable action on the merits is respectfully requested.

It is believed that no fee is due in connection with this paper. However, the Commissioner is authorized to charge any fee required in connection with the present submission to Deposit Account No. 50-3939.

The Applicant's undersigned attorneys may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

/Alicia A. Russo/
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Erin J.D. Austin
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Attorneys for Applicant

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UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

FORMALITIES LETTER

OC000000066295588

Date Mailed: 02/03/2014

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Filing Date Granted

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to comply with the sequence rules, 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136.

Applicant filed a request or letter regarding the use of the computer readable form (CRF) of a sequence listing from another application as the CRF of the sequence listing in this application in lieu of filing a CRF in this application. The request or letter, however, does not comply with the requirements of 37 CFR 1.821(e) for the reason(s) listed below. Applicant must make the appropriate correction(s), or file a CRF in this application in compliance with 37 CFR 1.821(e), within the time period for reply set forth in the notice to avoid the abandonment of the instant application. Applicant is encouraged to use form PTO/SB/93 for requesting a transfer of a computer readable form under 37 CFR 1.821(e).

- Applicant did not submit a statement that the sequence information in the paper or compact disc copy of the sequence listing (required by 37 CFR 1.821(c)) of this application is identical to the sequence information in the CRF of the other application. Note that a sequence listing filed electronically via EFS-Web in a PDF file is considered to be a paper copy under 37 CFR 1.821(c).
- No paper or compact disc copy of the sequence listing has been filed in this application, or the paper or compact disc copy filed is not identical to that of the requested computer readable form. Note that a sequence listing filed electronically via EFS-Web in a PDF file is considered to be a paper copy under 37 CFR 1.821(c).

For more information and a sample letter for requesting the use of a CFR from another application, *see* MPEP 2422.05. For more information regarding electronic filing of sequence listings, see the EFS-Web Legal Framework at http://www.uspto.gov/ebc/portal/efs/legal.htm.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to these requirements, please contact:

- **For Rules interpretation, call (571) 270-5300**
- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**

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- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/nfissha/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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Electronic Acknowledgement Receipt

EFS ID:	18495534
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.3
Receipt Date:	17-MAR-2014
Filing Date:	29-AUG-2013
Time Stamp:	16:05:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	RESP-NOTICE-RE-SEQ-LISTNG-03956-0538003.pdf	103626 9c3c12dae5ca0bfc0067291803d0076b0f0162b9	no	3

Warnings:	
Information:	

2	Applicant Response to Pre-Exam Formalities Notice	CPY-OF-NOT-03956-0538003.pdf	136139 83b011d17f8902a7a8cc3b1714e6a6259ec91e9b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	239765	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/013,237

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	28 minus 20 =	* 8			OR	x 80 =	640
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						4000
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	6240

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

WITHDRAWAL NOTICE

OC000000067277924

Date Mailed: 03/25/2014

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 02/03/2014. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web. https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If the reply is not filed electronically via EFS-Web, the reply must be accompanied by a copy of the new notice.

If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

/sareebuddin/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/013,237	08/29/2013	1623	6380	03956.053800.3	28	2

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

UPDATED FILING RECEIPT



Date Mailed: 03/25/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jinfa Du, Redwood City, CA;
Dhanapalan Nagarathnam, Bethany, CT;
Michael Joseph Sofia, Doylestown, PA;
Peiyuan Wang, Totowa, NJ;

Applicant(s)

Gilead Pharmasset LLC, Foster City, CA

Assignment For Published Patent Application

GILEAD PHARMASSET LLC, Foster City, CA

Power of Attorney: The patent practitioners associated with Customer Number 104538

Domestic Priority data as claimed by applicant

This application is a CON of 13/609,614 09/11/2012 PAT 8580765
which is a CON of 13/099,671 05/03/2011 PAT 8334270
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/19/2013

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/013,237**

Projected Publication Date: 07/03/2014

Non-Publication Request: No

Early Publication Request: No

Title

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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PGR2023-00046 - Page 001155

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

PUBLICATION NOTICE

OC000000069402429

Title:NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Publication No.US-2014-0187511-A1
Publication Date:07/03/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office: U.S DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 117796

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

■ The address associated with Customer Number: 117796

OR

☐	Firm or Individual Name			
	Address			
	City		State	Zip
	Country			
	Telephone		Email	

Assignee Name and Address: Gilead Pharmasset LLC
c/o Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	March 4, 2014
Name	J. Elin Hartrum	Telephone	650-522-1871
Title	Associate General Counsel, Intellectual Property		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Gilead Pharmasset LLC

Application No./Patent No.: 14/013,237 Filed/Issue Date: 08/29/2013

Titled: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Gilead Pharmasset LLC, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Michael Joseph, SOFIA, et al. To: Pharmasset, Inc.

   The document was recorded in the United States Patent and Trademark Office at
   Reel 031139, Frame 0548, or for which a copy thereof is attached.

2. From: Pharmasset, Inc. To: Gilead Pharmasset LLC

   The document was recorded in the United States Patent and Trademark Office at
   Reel 031157, Frame 0296, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

NThakur
Signature

6/20/2014
Date

Neeta C. Thakur (Agent for Applicant)
Printed or Typed Name

59,123
Title or Registration Number

Electronic Acknowledgement Receipt	
EFS ID:	19544406
Application Number:	14013237
International Application Number:	
Confirmation Number:	7005
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	104538
Filer:	Lorna Lea Tanner/Elizabeth Gutierrez
Filer Authorized By:	Lorna Lea Tanner
Attorney Docket Number:	03956.053800.3
Receipt Date:	10-JUL-2014
Filing Date:	29-AUG-2013
Time Stamp:	14:58:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		POA-199059-US4.PDF	386508 193d5b01f9312e3e517ec5c74b0675b1552	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	1
	Assignee showing of ownership per 37 CFR 3.73.	2	3
Warnings:			
Information:			
	Total Files Size (in bytes):	386508	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

117796
Gilead Sciences, Inc.
c/o Sheppard Mullin Richter & Hampton LLP
379 Lytton Avenue
Palo Alto, CA 94301

POA ACCEPTANCE LETTER

OC000000069554621

Date Mailed: 07/17/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/10/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/mabebe/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/013,237	08/29/2013	Jinfa Du	03956.053800.3

CONFIRMATION NO. 7005

104538
Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104

POWER OF ATTORNEY NOTICE

OC000000069554598

Date Mailed: 07/17/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/10/2014.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/mabebe/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Gilead Exhibit 2018
PGR2023-00046 - Page 001164

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/013,237	08/29/2013	Jinfa Du	37JD-199059-US4	7005

117796 7590 09/25/2014

Gilead Sciences, Inc.
c/o Sheppard Mullin Richter & Hampton LLP
379 Lytton Avenue
Palo Alto, CA 94301

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1672	

NOTIFICATION DATE	DELIVERY MODE
09/25/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

svipdocketing@sheppardmullin.com
ltanner@sheppardmullin.com
CCarter@sheppardmullin.com

Office Action Summary	Application No. 14/013,237	Applicant(s) DU ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1672	AIA (First Inventor to File) Status No

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *13-40* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *13-40* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *01242014; 01022014; 12122013; 12092013; 09252013; 08292013 (7).*

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____

4) ☐ Other: _____

Gilead Exhibit 2018
PGR2023-00046 - Page 001166

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of

activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

3. Claims 13-40 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,580,765.

The examined claims are either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to all that is recited in claims 1-14 of US 8,580,765.

4. Claims 13-40 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,334,270.

The examined claims are either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to all that is recited in claims 1-25 of U.S. Patent No. 8,334,270.

5. Claims 13-20 and 27-34 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 7,964,580.

The examined claims are either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to all that is recited in claims 1-14 of U.S. Patent No. 7,964,580.

6. Claims 1-40 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3-7 and 9-23 of copending Application No. 14/195,751. Although the claims at issue are not identical, they are not patentably distinct from each other because the examined claims are either anticipated by, or would have been obvious over, the reference claim(s). .

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

7. Claims 13-40 are pending. Claims 13-40 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached on Monday - Thursday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PATRICK LEWIS/
Primary Examiner, Art Unit 1672

/PL/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	DU, Jinfa
Art Unit	1623
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8580765	B2	2013-11-12	SOFIA,Michael Joseph	
	2	8415322	B2	2013-04-29	CLARK, Jeremy	
	3	8551973	B2	2013-10-08	BAO, Donghui	
	4	7754699	B2	2010-07-13	CHUN, Byoung-Kwon	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20120245335	A1	2012-09-27	CLARK, Jeremy	
	2	20130109647	A1	2013-05-02	BERREY, Miriam Michelle	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (09/19/2014)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	3	20130136776	A1	2013-05-30	CLEARY, Darryl G.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Yuodka et al., Bioorganicheskaya Khimiya, 2(11), 1513-1519 (1976) (translated from Russian).	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (09/19/2014)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (09/19/2014)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-12-09
Name/Print	Alicia A. Russo	Registration Number	46,192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Gilead Exhibit 2018
PGR2023-00046 - Page 001173

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14013237	DU ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1672

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE									
Final	Original	09/19/2014									
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	35	✓									
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CLAIM		DATE								
Final	Original	09/19/2014								
	37	✓								
	38	✓								
	39	✓								
	40	✓								

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14013237	DU ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1672

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	9/19/2014	/PL/

INTERFERENCE SEARCH			
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2013-08-29
First Named Inventor	Jinfa Du
Art Unit	NYA
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	17	5405598	A	1995-04-11	Schinazi et al.	
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	2	199 14 474	DE	A1	1999-10-07	Hoffmann La-Roche AG		☐
	3	0 180 276	EP	A1	1986-05-07	OCE ANDENO BV		☐
	4	0 350 287	EP	A2	1990-01-10	VICAL, INC.		☐
	5	1 828 217	EP	A2	2007-09-05	FEBIT BIOTECH GMBH		☐
	6	1 881 001	EP	A1	2008-01-23	TIBOTEC PHARM, LTD.		☐
	7	2 097 430	EP	A1	2009-09-09	CT BADAN MOLEKULAR I MAKRO		☐
	8	2 124 555	EP	A2	2009-12-02	MERCK & CO, INC.		☐

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	9	2 207 786	EP	B1	2012-03-07	EISAI, INC.		☐
	10	5-238939	JP	A	1993-09-17	NODA SANGYO KAGAKU KENKYUSHO KIKKOMAN CORP		☐
	11	89/02733	WO	A1	1989-04-06	UNIV CALIFORNIA		☐
	12	90/00555	WO	A1	1990-01-25	VICAL, INC.		☐
	13	91/16920	WO	A1	1991-11-14	VICAL, INC.		☐
	14	91/19721	WO	A1	1991-12-26	GLAZIER ARNOLD		☐
	15	91/18914	WO	A1	1991-12-12	VICAL, INC.		☐
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	17	94/26273	WO	A1	1994-11-24	HOSTETLER KARL Y		☐
	18	95/13090	WO	A1	1995-05-18	ENZON, INC.		☐
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	20	96/15132	WO	A1	1996-05-23	UNIV CALIFORNIA		☐
	21	96/32403	WO	A2	1996-10-17	SCHERING AG		☐
	22	97/12033	WO	A1	1997-04-03	UNIV EMORY		☐
	23	97/36554	WO	A1	1997-10-09	VIROPHARMA, INC.		☐
	24	98/16184	WO	A2	1998-04-23	ICN PHARMACEUTICALS		☐
	25	98/17679	WO	A1	1998-04-30	VERTEX PHARMA		☐
	26	98/22496	WO	A2	1998-05-28	HOFFMANN LA-ROCHE AG		☐
	27	99/07734	WO	A2	1999-02-18	BOEHRINGER INGELHEIM, LTD.		☐
	28	99/15194	WO	A1	1999-04-01	SCHERING CORP		☐
	29	99/32139	WO	A1	1999-07-01	ENZON, INC.		☐
	30	99/32140	WO	A1	1999-07-01	ENZON, INC.		☐

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	31	99/43691	WO	A1	1999-09-02	UNIV EMORY UNIV GEORGIA RES FOUND		☐
	32	99/59621	WO	A1	1999-11-25	SCHERING CORP.		☐
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	34	00/09531	WO	A2	2000-02-24	NOVIRIO PHARMACEUTICALS, LTD.		☐
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	38	01/32153	WO	A2	2001-05-10	BIOCHEM PHARMA, INC.		☐
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	42	01/81359	WO	A1	2001-11-01	SCHERING CORP.		☐
	43	01/91737	WO	A2	2001-12-06	NOVIRIO PHARMACEUTICALS, LTD.		☐
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	46	02/08187	WO	A1	2002-01-31	SCHERING CORP. CORVAS INT. INC.		☐
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	8	Abraham et al., "Synthesis, Biological Activity and Decomposition Studies of Amino Acid Phosphomonoester Amidates of Acyclovir," Nucleosides, Nucleotides and Nucleic Acids, Vol. 16, No. 10, pages 2079 - 2092 (1997)	☐
	9	Balzarini et al., "Mechanism of anti-HIV action of masked alaninyl d4t-MP derivatives," Proc. Natl. Acad. Sci., Vol. 93, pages 7295 - 7299 (1996)	☐
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	12	Chen et al., "Metabolism of Stavudine-5'-[P-Bromophenyl Methoxyalaninyl Phosphate], Stampidine, in Mice, Dogs, and Cats," Drug Metabolism and Disposition, Vol. 30, No. 12, pages 1523 - 1531 (2002)	☐
	13	Chou et al., "Evidence that Human Histidine Triad Nucleotide Binding Protein 3 (Hint3) is a Distinct Branch of the Histidine Triad (HIT) Superfamily," J. Mol. Biol., Vol. 373, pages 978 - 989 (2007)	☐
	14	Chou et al., "Phosphoramidate Pronucleotides: A Comparison of the Phosphoramidase Substrate Specificity of Human and Escherichia coli Histidine Triad Nucleotide Binding Proteins," Molecular Pharmaceutics, Vol. 4, No. 2, pages 208 - 217 (2006)	☐
	15	Cihlar et al. "Design and Profiling of GS-9148, a Novel Nucleotide Analog Active against Nucleoside-Resistant Variants of Human Immunodeficiency Virus Type 1, and Its Orally Bioavailable Phosphonoamidate Prodrug, GS-9131," Antimicrobial Agents and Chemotherapy, Vol. 52, No. 2, pages 655 - 665 (2008)	☐
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	18	Curley et al., "Synthesis and anti-HIV evaluation of some phosphoramidate derivatives of AZT: studies on the effect of chain elongation on biological activity," Antiviral Research, Vol. 14, pages 345 - 356 (1990)	☐
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	21	Egron et al., "S-Acyl-2-thioethyl Phosphoramidate Diester Derivatives as Mononucleotide Prodrugs" J. Med. Chem., Vol. 46, No. 21, pages 4564 - 4571 (2003)	☐
	22	Howes et al., "The Regiospecific One-Pot Phosphorylation of Either the 5'- or 2'-Hydroxyl in 3'-Deoxycytidines Without Protection: Critical Role of the Base," Nucleosides, Nucleotides, and Nucleic Acids, Vol. 22, No. 5 - 8, pages 687 - 689 (2003)	☐

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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Name/Print	Alicia A. Russo	Registration Number	46192

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2013-08-29
	First Named Inventor	Jinfa Du
	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	50	20030050229	A1	2003-03-13	Sommadossi et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2007/088148	WO	A1	2007-08-09	SMITHKLINE BEECHAM CORP.		☐
	2	2007/092000	WO	A1	2007-08-16	SQUIBB BRISTOL MYERS CO.		☐
	3	2007/093901	WO	A1	2007-08-23	PFIZER LTD.		☐
	4	2007/095269	WO	A2	2007-08-23	MERCK & CO., INC.		☐
	5	2008/010921	WO	A2	2008-01-24	GILEAD SCIENCES INC.		☐
	6	2008/045419	WO	A1	2008-04-17	PHARMASSET INC.		☐
	7	2008/048128	WO	A1	2008-04-24	CT BADAN MOLEKULAR I MAKRO		☐
	8	2008/062206	WO	A2	2008-05-29	UNIV. COLLEGE CARDIFF CONSULTANT LTD.		☐

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	Attorney Docket Number	03956.053800.3

	9	2008/082601	WO	A2	2008-07-10	IDENIX PHARMACEUTICALS INC.		☐
	10	2008/079206	WO	A1	2008-07-03	MERCK & CO., INC.		☐
	11	2008/085508	WO	A2	2008-07-17	MERCK & CO., INC.		☐
	12	2008/142055	WO	A2	2008-11-27	ANGELETTI P IST RICHERCHE BIO		☐
	13	2009/052287	WO	A1	2009-04-23	EISAL CORP OF NORTH AMERICA		☐
	14	2009/115893	WO	A2	2009-09-24	HETERO RESEARCH FOUNDATION		☐
	15	2009/120878	WO	A2	2009-10-01	ALNYLAM PHARMACEUTICALS INC.		☐
	16	2009/129120	WO	A2	2009-10-22	RFS PHARMA LLC		☐
	17	2009/152095	WO	A2	2009-12-17	PHARMASSET INC.		☐
	18	2010/042834	WO	A1	2010-04-15	ANADYS PHARMACEUTICALS INC.		☐
	19	2010/075554	WO	A1	2010-07-01	PHARMASSET INC.		☐

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	Attorney Docket Number	03956.053800.3

	20	2010/080878	WO	A1	2010-07-15	SCYNEXIS INC.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	Halstead, S. B., "Pathogenesis of Dengue: Challenges to Molecular Biology," Science, Vol. 239, pages 476 - 481 (1988)	☐
	2	Hijikata et al., "Two Distinct Proteinase Activities required for the Processing of a Putative Nonstructural Precursor Protein of Hepatitis C Virus," J. Virol., Vol. 67, No. 8, pages 4665 - 4675 (1993)	☐
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	5	Koonin et al., "Evolution and Taxonomy of Positive-Strand RNA Viruses: Implications of Comparatives Analysis of Amino Acid Sequences," Critical Reviews in Biochemistry and Molecular Biology, Vol. 28, No. 5, pages 375 - 430 (1993)	☐
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	7	Meyers et al., "Molecular Characterization of Pestiviruses," Advance in Virus Research, Vol. 47, pages 53 - 119 (1996)	☐
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	9	Monath, T. P., M.D., "Japanese Encephalitis - A Plague of the Orient," N. Engl. J. Med., Vol. 319, No. 10, pages 641 - 643 (September 8, 1988)	☐
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	29	Stuyver et al., "Inhibition of the Subgenomic Hepatitis C Virus Replicon in Huh-7 Cells by 2'-Deoxy-2'-Fluorocytidine," Antimicrobial Agents and Chemotherapy, Vol. 48, No. 2, pages 651 - 654 (2004)	☐
	30	U.S. Application No. 10/828,753, Non-Final Office Action Rejection, mailed 03/30/2007	☐

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	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	31	U.S Application No. 10/828,753, Final Office Action Rejection, mailed 02/26/2008	☐
	32	U.S. Application No. 11/225,425, Non-Final Office Action Rejection, mailed 11/13/2008	☐
	33	U.S. Application No. 11/225,425, Non-Final Office Action Rejection, mailed 07/07/2009	☐
	34	Response to non-final Office Action dated October 1, 2009 for U.S. Application No. 12/142,554	☐
	35	U.S. Application No. 11/225,425, Final Office Action Rejection, mailed 02/18/2010	☐
	36	U.S Application No. 11/353,597, Non-Final Office Action Rejection, mailed 10/02/2007	☐
	37	U.S Application No. 11/353,597, Non-Final Office Action Rejection, mailed 07/17/2008	☐
	38	U.S. Application No. 11/353,597, Final Office Action Rejection, mailed 12/02/2008	☐
	39	U.S. Application No. 11/635,898, Non-Final Office Action Rejection, mailed 07/28/2009	☐
	40	U.S Application No. 11/635,898, Pending claims filed on 12/24/2009	☐
	41	U.S. Application No. 11/854,218, Pending claims filed 09/12/2007	☐

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	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	42	U.S. Application No. 11/854,218, Non-Final Office Action Rejection, mailed 10/01/2009	☐
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	45	U.S Application No. 12/142,554, Non-Final Office Action Rejection, mailed 10/01/2009	☐
	46	U.S. Application No. 12/142,554, Pending claims filed on 12/17/2009	☐
	47	U.S. Application No. 12/240,342, Pending claims filed on 09/29/2008	☐
	48	U.S. Application No. 12/240,342, Non-Final Office Action Rejection, mailed 10/01/2009	☐
	49	U.S. Application No. 12/479,075, filed on 06/05/2009, Group Art Unit 1614	☐
	50	U.S. Application No. 12/553,483, Non-Final Office Action Rejection, mailed 12/17/2009	☐

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	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-08-29
Name/Print	Alicia A. Russo	Registration Number	46192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Attorney Docket Number 03956.053800.3 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: Unassigned
GILEAD PHARMASSET LLC	)	
	:	Group Art Unit: 1623
Application No.: 14/013,237	)	
	:	Confirmation No.: 7005
Filed: August 29, 2013	)	
	:	
For: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS	)	
	:	
	)	September 25, 2013

Commissioner for Patents
P.O. Box 1450
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INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the documents listed on the concurrently submitted Form PTO/SB/08a.

The Examiner's attention is also directed to the following U.S. Applications, which are electronically viewable:

Appln. No.	Filing Date	Group Art Unit	Examiner's Initials
13/925,078	2013-06-24	1623	
13/936,448	2013-07-08	1621	

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In accordance with 37 C.F.R. § 1.97(h) and MPEP § 2129, the Applicant makes no admission regarding whether these references are, or are considered to be, material to patentability.

Pursuant to 37 C.F.R. § 1.97(b), no fee is believed due in connection with this paper. Should the Office determine that any fee is due, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 50-3939.

The Applicant's undersigned attorneys may be reached in their New York office by telephone at (212) 218-2100. All correspondence should be directed to the address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No.: 46,192

Erin J.D. Austin
Registration No.: 66,532

Attorneys for Applicants

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New York, New York 10104
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Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	DU, Jinfa
Art Unit	1623
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Attorney Docket Number	03956.053800.3

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	1	2006/067606	WO	A1	2006-06-29	INSERM, CNRS		☐
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	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	MCGUIGAN, CHRISTOPHER, et al., Certain Phosphoramidate Derivatives of Dideoxy Uridine (ddU) Are Active Against HIV and Successfully By-pass Thymidine Kinase, FEBS Letters (1994), 351, 11-14.	☐
	2	CAHARD, DOMINIQUE, et al., Aryloxy Phosphoramidate Triesters as Pro-Tides, Mini-Reviews in Medicinal Chemistry (2004), 4, 371-381.	☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (09/19/2014)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	DU, Jinfa
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

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☐ See attached certification statement.

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Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-12-12
Name/Print	Alicia A. Russo	Registration Number	46,192

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2013-08-29
First Named Inventor	Jinfa Du
Art Unit	NYA
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7202224	B2	2007-04-10	Merck & Co., Inc. ISIS Pharmaceuticals, Inc.	
	2	7390791	B2	2008-06-24	Gilead Sciences, Inc.	
	3	7879815	B2	2011-02-01	Merck Sharp & Dohme Corp.; Istituto di Ricerche di	
	4	7964580	B2	2011-06-21	Pharmasset, Inc.	
	5	8148349	B2	2012-04-03	Istituto di Ricerche di Biologia Molecolare P. Ang	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020198173	A1	2002-12-26	Schinazi et al.	

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	First Named Inventor	Jinfa Du
	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	2	20020058635	A1	2002-05-16	Averett	
	3	20010034440	A1	2001-10-25	Shepard et al.	
	4	20100137576	A1	2010-06-03	Stec et al.	
	5	20100152128	A1	2010-06-17	Attenni et al.	
	6	20100173863	A1	2010-07-08	Schinazi et al.	
	7	20100227801	A1	2010-09-09	Hopkins et al.	
	8	20100316594	A1	2010-12-16	Sommadossi et al.	
	9	20110124592	A1	2011-05-26	McGuigan et al.	

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	1	02/32414	WO	A2	2002-04-25	SCHERRING CORPORATION		☐

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	Examiner Name	NYA
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	1	U.S. Application No. 12/553,483, Pending claims filed on 02/22/2010	☐
	2	U.S. Application No. 12/645,710, filed on 12/23/2009, Group Art Unit 1614	☐
	3	U.S. Application No. 12/645,765, filed on 12/23/2009, Group Art Unit 1614	☐
	4	U.S. Application No. 12/645,821, filed on 12/23/2009, Group Art Unit 1636	☐
	5	U.S. Application No. 13/099,671, claims filed September 4, 2012	☐

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Examiner Signature	/Patrick Lewis/ (09/19/2014)	Date Considered	

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Name/Print	Alicia A. Russo	Registration Number	46192

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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First Named Inventor	Jinfa Du
Art Unit	NYA
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1	20130029929	A1	2013-01-31	GILEAD PHARMASSET LLC	
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	1	2006/116557	WO	A1	2006-11-02	GENELABS TECHNOLOGIES, INC.		☐
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	1	Written Opinion of the International Searching Authority issued in International Application No. PCT/US2004/012472 (7 pages) (Nov. 30, 2005)	☐
	2	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2004/012472 (8 pages) (Dec. 1, 2005)	☐
	3	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2005/025916 (5 pages) (Jan. 23, 2007)	☐
	4	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2005/032406 (4 pages) (Mar. 10, 2009)	☐
	5	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/EP2006/069060 (7 pages) (Nov. 5, 2008)	☐
	6	Written Opinion of the International Searching Authority issued in the International Application No. PCT/US/2008/058183 (16 pages) (Apr. 1, 2010)	☐
	7	International Search Report issued in International Application No. PCT/US2009/046619 (4 pages) (Sept. 23, 2010)	☐
	8	Partial International Search Report issued in International Application No. PCT/US2009/069475 (7 pages) (Mar. 5, 2010)	☐
	9	International Search Report and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2009/069475 (21 pages) (May 10, 2010)	☐
	10	Invitation to Pay Additional Fees & Partial International Search Report issued in International Application No. PCT/US2010/035641 (10 pages) (July 23, 2010)	☐
	11	International Search Report and Written Opinion of the International Searching Authority issued in PCT/US2010/035641 (23 pages) (Nov. 20, 2011)	☐

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	First Named Inventor	Jinfa Du
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	Attorney Docket Number	03956.053800.3

	12	MURAKAMI, E., et al., "The Mechanism of Action of beta-D-2'-Deoxy-2'-fluoro-2'-C-methylcytidine Involves a Second Metabolic Pathway Leading to beta-D-2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-Triphosphate, a Potent Inhibitor of the HCV RNA-Dependent RNA Polymerase," 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland (September 2007)	☐
	13	STEPHEN G. GILLESPIE, et al., "Stereoselective Inhibition of Cholesterol Esterase by Enantiomeric Phosphonates," Phosphorous, Sulfur and Silicon, 1997, 122: 205-208	☐

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EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (09/19/2014)	Date Considered	

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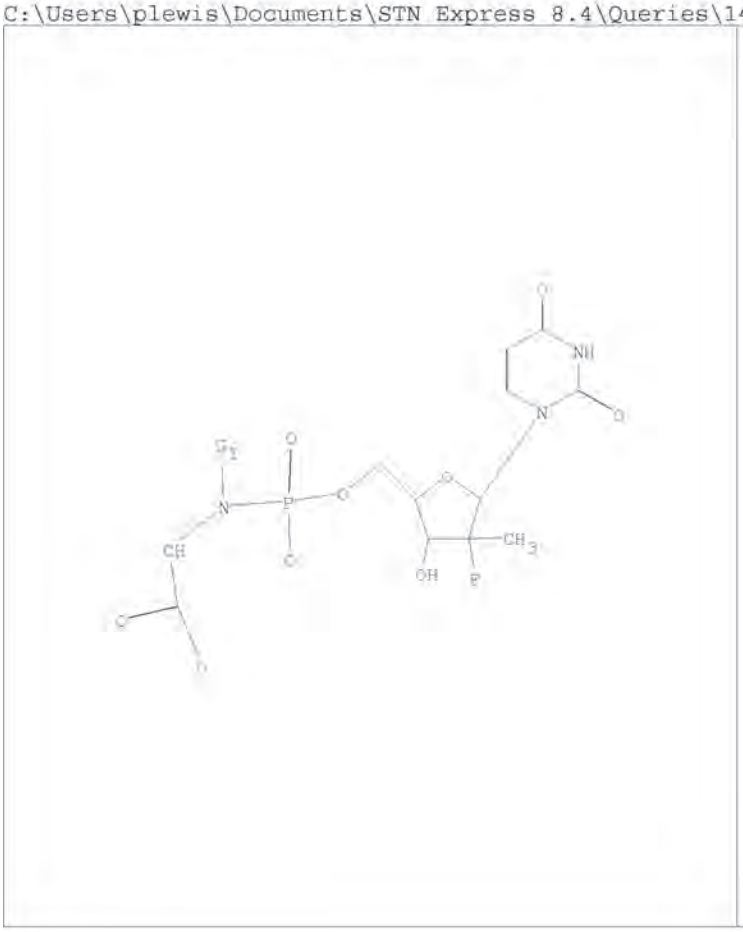
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

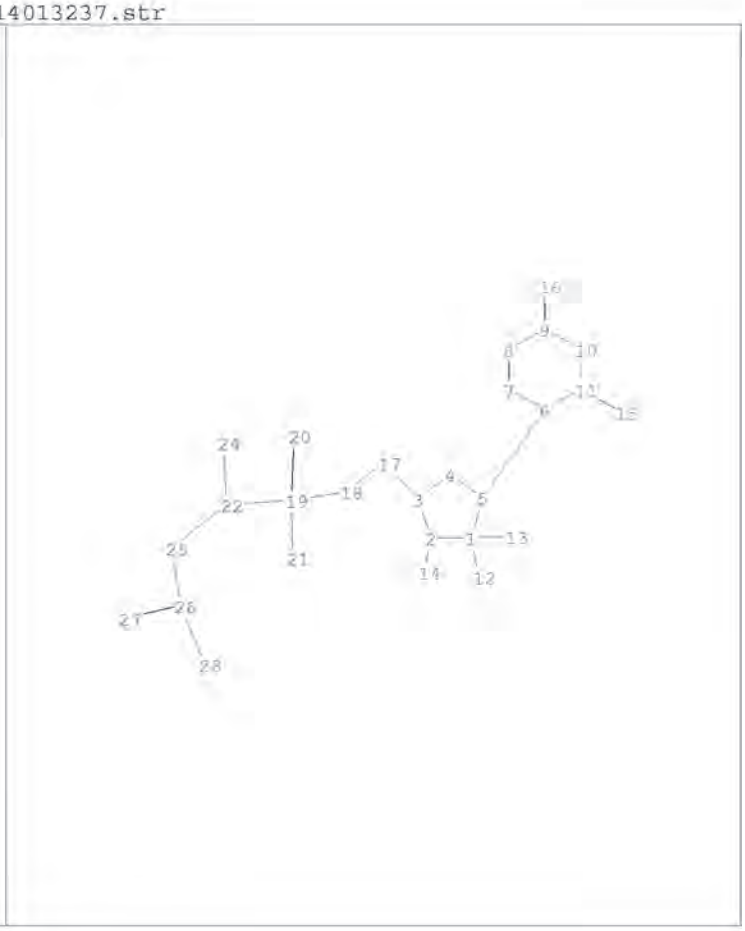
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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PGR2023-00046 - Page 001242

C:\Users\plewis\Documents\STN Express 8.4\Queries\14013237.str





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chain nodes :
    12  13  14  15  16  17  18  19  20  21  22  24  25  26  27  28
ring nodes :
    1  2  3  4  5  6  7  8  9  10  11
chain bonds :
    1-12  1-13  2-14  3-17  5-6  9-16  11-15  17-18  18-19  19-20  19-21  19-22  22-24  22-25
    25-26  26-27  26-28
ring bonds :
    1-2  1-5  2-3  3-4  4-5  6-7  6-11  7-8  8-9  9-10  10-11
exact/norm bonds :
    1-2  1-5  2-3  2-14  3-4  4-5  5-6  6-7  6-11  7-8  8-9  9-10  9-16  10-11  11-15  17-18  18-19
    19-20  19-21  19-22  22-24  22-25  26-27  26-28
exact bonds :
    1-12  1-13  3-17  25-26


G1:H,CH3,Et

Match level :
    1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom  11:Atom
    12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS  19:CLASS  20:CLASS
    21:CLASS  22:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS  28:CLASS
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	JINFA DU
Art Unit	1623
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2007-505742	JP	A	2007-03-15	E.I. DU PONT DE NEMOURS AND COMPANY		☐
	2	2005/030891	WO	A1	2005-04-07	E.I. DU PONT DE NEMOURS AND COMPANY		☐

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PGR2023-00046 - Page 001244

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	JINFA DU
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (09/19/2014)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	JINFA DU
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2014-01-02
Name/Print	Alicia A. Russo	Registration Number	46,192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2013-08-29
First Named Inventor	Jinfa Du
Art Unit	NYA
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7601820	B2	2009-10-13	Wang et al.	
	2	7429572	B2	2008-09-30	Clark	
	3	7365057	B2	2008-04-29	LaColla et al.	
	4	7307065	B2	2007-12-11	Schinazi et al.	
	5	7268119	B2	2007-09-11	Cook et al.	
	6	7217523	B2	2007-05-15	Wagner	
	7	7163929	B2	2007-01-16	Sommadossi et al.	
	8	7148206	B2	2006-12-12	Sommadossi et al.	

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	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	9	7105499	B2	2006-09-12	Carroll et al.	
	10	7081449	B2	2006-07-25	Pietrzkowski et al.	
	11	7018989	B2	2006-03-28	McGuigan et al.	
	12	7018985	B1	2006-03-28	Boyer et al.	
	13	6962991	B2	2005-11-08	Dempcy et al.	
	14	6914054	B2	2005-07-05	Sommadossi et al.	
	15	6911424	B2	2005-06-28	Schinazi et al.	
	16	6908924	B2	2005-06-21	Watanabe et al.	
	17	6897201	B2	2005-05-24	Boyer et al.	
	18	6846810	B2	2005-01-25	Martin et al.	
	19	6815542	B2	2004-11-09	Hong et al.	

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	20	6787526	B1	2004-09-07	Bryant et al.	
	21	6787305	B1	2004-09-07	Li et al.	
	22	6784166	B2	2004-08-31	Devos et al.	
	23	6777395	B2	2004-08-17	Bhat et al.	
	24	6753309	B2	2004-06-22	Klecker et al.	
	25	6703374	B1	2004-03-09	Klecker et al.	
	26	6683045	B2	2004-01-27	Klecker et al.	
	27	6682715	B2	2004-01-27	Klecker et al.	
	28	6680303	B2	2004-01-20	Schinazi et al.	
	29	6677315	B2	2004-01-13	Klecker et al.	
	30	6677314	B2	2004-01-13	Klecker et al.	

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	31	6660721	B2	2003-12-09	Devos et al.	
	32	6642206	B2	2003-11-04	Ramasamy et al.	
	33	6573248	B2	2003-06-03	Ramasamy et al.	
	34	6555677	B2	2003-04-29	Petrillo et al.	
	35	6552183	B1	2003-04-22	Ramasamy et al.	
	36	6534523	B1	2003-03-18	Llinas-Brunet et al.	
	37	6509320	B1	2003-01-21	Wang et al.	
	38	6495677	B1	2002-12-17	Ramasamy et al.	
	39	6479463	B1	2002-11-12	Wang et al.	
	40	6475985	B1	2002-11-05	Wagner et al.	
	41	6455690	B1	2002-09-24	Tam et al.	

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	Attorney Docket Number	03956.053800.3

	42	6455513	B1	2002-09-24	McGuigan et al.	
	43	6420380	B2	2002-07-16	Llinas-Brunet et al.	
	44	6410531	B1	2002-06-25	Llinas-Brunet et al.	
	45	6391859	B1	2002-05-21	Schinazi et al.	
	46	6372883	B1	2002-04-16	Attwood et al.	
	47	6348587	B1	2002-02-19	Schinazi et al.	
	48	6239159	B1	2001-05-29	Brown et al.	
	49	6232300	B1	2001-05-15	Schinazi et al.	
	50	6180134	B1	2001-01-30	Zalipsky et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

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	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	02/32920	WO	A2	2002-04-25	PHARMASSET LTD.		☐
	2	02/32414	WO	A2	2002-04-25	SCHERING CORP.		☐
	3	02/48165	WO	A2	2002-06-20	PHARMASSET LTD.		☐
	4	02/48116	WO	A2	2002-06-20	BRISTOL-MYERS SQUIBB PHARMA CO		☐
	5	02/48157	WO	A2	2002-06-20	BRISTOL-MYERS SQUIBB PHARMA CO		☐
	6	02/48172	WO	A2	2002-06-20	SCHERING CORP.		☐
	7	02/057287	WO	A2	2002-07-25	MERCK & CO., INC.		☐
	8	02/057425	WO	A2	2002-07-25	MERCK & CO., INC.		☐

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	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	9	02/060926	WO	A2	2002-08-08	SQUIBB BRISTOL MYERS CO.		☐
	10	02/100415	WO	A2	2002-12-19	F. HOFFMANN-LA ROCHE AG		☐
	11	03/000713	WO	A1	2003-01-03	GLAXO GROUP LTD.		☐
	12	03/006490	WO	A1	2003-01-23	VERTEX PHARMA., INC.		☐
	13	03/010141	WO	A2	2003-02-06	BOEHRINGER INGELHEIM CA LTD		☐
	14	03/024461	WO	A1	2003-03-27	SCHERING CORP.		☐
	15	03/026589	WO	A2	2003-04-03	IDENIX CAYMAN LTD CENTRE NAT DE LA RECH SCIENT		☐
	16	03/037895	WO	A1	2003-05-08	GLAXO GROUP LTD.		☐
	17	03/051899	WO	A1	2003-06-26	RIBAPHARM INC.		☐
	18	03/053989	WO	A1	2003-07-03	MRC TECHNOLOGY LTD.		☐
	19	03/061576	WO	A2	2003-07-31	RIBAPHARM INC.		☐

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	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	20	03/062256	WO	A1	2003-07-31	RIBAPHARM INC.		☐
	21	03/068244	WO	A1	2003-08-21	MERCK & CO., INC.		☐
	22	03/064456	WO	A1	2003-08-07	BOEHRINGER INGELHEIM INT		☐
	23	03/105770	WO	A2	2003-12-24	MERCK & CO., INC.		☐
	24	03/106477	WO	A1	2003-12-24	ISIS PHARMACEUTICALS INC.		☐
	25	04/000858	WO	A2	2003-12-31	MERCK & CO,. INC.		☐
	26	03/101993	WO	A1	2003-12-11	NEOGENESIS PHARMACEUTICALS INC.		☐
	27	03/104250	WO	A1	2003-12-18	KYLIX B V		☐
	28	2004/003000	WO	A2	2004-01-08	IDENIX CAYMAN LTD CENTRE NAT RECH SCIENT		☐
	29	2004/003138	WO	A2	2004-01-08	MERCK & CO., INC.		☐
	30	2004/007512	WO	A2	2004-01-22	MERCK & CO., INC.		☐

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	Attorney Docket Number	03956.053800.3

	31	2004/009020	WO	A2	2004-01-29	MERCK & CO., INC.		☐
	32	2004/002422	WO	A2	2004-01-08	IDENIX CAYMAN LTD UNIV DEGLI STUDI DI CAGLIARI		☐
	33	2004/002940	WO	A1	2004-01-08	PHARMACIA & UPJOHN CO.		☐
	34	2004/002944	WO	A1	2004-01-08	PHARMACIA & UPJOHN CO.		☐
	35	2004/002977	WO	A1	2004-01-08	PHARMACIA & UPJOHN CO.		☐
	36	2004/002999	WO	A2	2004-01-08	IDENIX CAYMAN LTD.		☐
	37	2004/009610	WO	A2	2004-01-29	PTC THERAPEUTICS INC.		☐
	38	2004/011478	WO	A2	2004-02-05	MICROLOGIX BIOTECH INC.		☐
	39	2004/014313	WO	A2	2004-02-19	SQUIBB BRISTOL MYERS CO.		☐
	40	2004/014852	WO	A2	2004-02-19	SQUIBB BRISTOL MYERS CO.		☐
	41	2004/035571	WO	A1	2004-04-29	RIGEL PHARMACEUTICALS INC.		☐

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	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	42	2004/041201	WO	A2	2004-05-21	VIROPHARMA INC [US] WYETH CORP		☐
	43	2004/046331	WO	A2	2004-06-03	IDENIX CAYMAN LTD.		☐
	44	2004/065367	WO	A1	2004-08-05	BOEHRINGER INGELHEIM INT		☐
	45	2004/080466	WO	A1	2004-09-23	RIBAPHARM INC.		☐
	46	2004/096286	WO	A2	2004-11-11	GILEAD SCIENCES INC.		☐
	47	2004/094452	WO	A2	2004-11-04	SQUIBB BRISTOL MYERS CO.		☐
	48	2004/096210	WO	A1	2004-11-11	GLAXO GROUP LTD.		☐
	49	2004/096234	WO	A2	2004-11-11	GILEAD SCIENCES INC.		☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2013-08-29
	First Named Inventor	Jinfa Du
	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

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	8	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2005/025916 (4 pages)	☐
	9	The Extended search report includes the supplementary European search report issued in European Application No. 05775359.2 dated September 15, 2010 (9 pages)	☐
	10	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2005/032406 (4 pages)	☐
	11	International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/EP2006/069060 (13 pages)	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2013-08-29
	First Named Inventor	Jinfa Du
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	Attorney Docket Number	03956.053800.3

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	14	Partial International Search Report issued in International Application No. PCT/US2009/069475 (7 pages)	☐
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	Filing Date	2013-08-29
	First Named Inventor	Jinfa Du
	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

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☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-08-29
Name/Print	Alicia A. Russo	Registration Number	46192

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
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Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	Jinfa Du
Art Unit	1623
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	1	20130029929	A1	2013-01-31	Sofia et al.	
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Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-09-25
Name/Print	Alicia A. Russo	Registration Number	46,192

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PGR2023-00046 - Page 001268

PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2013-08-29
First Named Inventor	Jinfa Du
Art Unit	NYA
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8334270	B2	2012-12-18	GILEAD PHARMASSET LLC	
	2	8173621	B2	2012-05-08	GILEAD PHARMASSET LLC	

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U.S.PATENT APPLICATION PUBLICATIONS						Remove
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100081628	A1	2010-04-01	PHARMASSET, INC.	
	2	20100279973	A1	2010-11-04	PHARMASSET, INC.	
	3	20110015146	A1	2011-01-20	PHARMASSET, INC.	
	4	20100298257	A1	2010-11-25	PHARMASSET, INC.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (09/19/2014)

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	Filing Date	2013-08-29
	First Named Inventor	Jinfa Du
	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	5	20110251152	A1	2011-10-13	PHARMASSET, INC.	
	6	20100286083	A1	2010-11-11	PHARMASSET, INC.	
	7	20120107278	A1	2012-05-03	PHARMASSET, INC.	
	8	20110245484	A1	2011-10-10	PHARMASSET, INC.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2006/050161	WO	A2	2006-05-11	BIOCRYST PHARMACEUTICALS, INC.		☐
	2	2007/095269	WO	A2	2007-08-23	MERCK & CO., INC.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	GUDMUNDSSON, Kristjan S., et al., "Phosphoramidate Protides of Carbocyclic 2',3'-Dideoxy-2',3'-Didehydro-7-Deazaadenosine with Potent Activity Against HIV and HBV," Nucleosides, Nucleotides & Nucleic Acids (2004) 23(12): 1929-1937.	☐

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	Filing Date	2013-08-29
	First Named Inventor	Jinfa Du
	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	2	SIDDIQUI, Adam Q., et al., "The Presence of Substituents on the Aryl Moiety of the Aryl Phosphoramidate Derivatives of d4T Enhances Anti-HIV Efficacy in Cell Culture: A Structure-Activity Relationship," J. Med. Chem. (1999) 42:393-399.	☐
	3	DUMEZ, Darin, et al., "Large-Scale Synthesis and Formulation of GMP-Grade Stampidine, a New Anti-HIV Agent," Arzneim.-Forsch./Drug Res. (2006) 56(2a):136-151.	☐
	4	GUDMUNDSSON, Kristjan S., et al., "Phosphoramidate Protides of 2',3'-Dideoxy-3'-fluoroadenosine and Related Nucleosides with Potent Activity Against HIV and HBV," Nucleosides, Nucleotides & Nucleic Acids (2003) 22 (10):1953-1961.	☐
	5	NAKAYAMA, Kensaku, et al., "A Highly Enantioselective Synthesis of Phosphate Triesters," J. Am. Chem. Soc. (1990) 112:6936-6942.	☐
	6	WOZNIAK, Lucyna A., et al., "The stereospecific synthesis of P-chiral biophosphates and their analogues by the Stec reaction," Chem. Soc. Rev. (2003) 32:158-169.	☐
	7	UCHIYAMA, Mamoru, et al., "O-Selective Phosphorylation of Nucleosides without N-Protection," J. Org. Chem. (1993) 58:373-379.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (09/19/2014)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (09/19/2014)

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	First Named Inventor	Jinfa Du
	Art Unit	NYA
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2013-08-29
Name/Print	Alicia A. Russo	Registration Number	46192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

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Gilead Exhibit 2018
PGR2023-00046 - Page 001273

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     (FILE 'HOME' ENTERED AT 14:27:22 ON 19 SEP 2014)

     FILE 'REGISTRY' ENTERED AT 14:27:30 ON 19 SEP 2014
L1             STRUCTURE UPLOADED
L2              14 S L1 SSS SAM
L3             325 S L1 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 14:28:05 ON 19 SEP 2014
L4             194 S L3
L5             173 S L4 AND VIRUS

     FILE 'STNGUIDE' ENTERED AT 14:33:48 ON 19 SEP 2014
```

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BIB DATA SHEET

CONFIRMATION NO. 7005

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/013,237	08/29/2013 RULE	514	1672	37JD-199059-US4

APPLICANTS

Gilead Pharmasset LLC, Foster City, CA, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

Jinfa Du, Redwood City, CA;
Dhanapalan Nagarathnam, Bethany, CT;
Michael Joseph Sofia, Doylestown, PA;
Peiyuan Wang, Totowa, NJ;

**** CONTINUING DATA ***************************

This application is a CON of 13/609,614 09/11/2012 PAT 8580765
which is a CON of 13/099,671 05/03/2011 PAT 8334270
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

09/19/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /PATRICK T LEWIS/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	0	28	2

ADDRESS

Gilead Sciences, Inc.
c/o Sheppard Mullin Richter & Hampton LLP
379 Lytton Avenue
Palo Alto, CA 94301
UNITED STATES

TITLE

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
6380	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
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Application Number	14013237
Filing Date	2013-08-29
First Named Inventor	JINFA DU
Art Unit	1623
Examiner Name	NYA
Attorney Docket Number	03956.053800.3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (09/19/2014)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14013237
	Filing Date	2013-08-29
	First Named Inventor	JINFA DU
	Art Unit	1623
	Examiner Name	NYA
	Attorney Docket Number	03956.053800.3

	1	U.S. Patent Application No. 14/152,243, as filed January 10, 2014	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Patrick Lewis/ (09/19/2014)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

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Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2014-01-24
Name/Print	Alicia A. Russo	Registration Number	46,192

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Gilead Exhibit 2018
PGR2023-00046 - Page 001279

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Jinfa Du et al.
Appl. No.:	14/013,237
Title:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
Filing Date:	08/29/2013
Examiner:	Lewis, Patrick T.
Art Unit:	1672
Confirmation Number	7005

AMENDMENT AND REPLY UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amendment and Reply is responsive to the Non-Final Office Action dated September 25, 2014, concerning the above-referenced patent application. The Office set a three-month period to reply. With the accompanying payment of fees for a two-month extension, this Amendment and Reply is timely filed on February 25, 2014.

Amendments to the Specification begin on page 2 of this document.

Amendments to the Claims begins on page 3 of this document.

Remarks/Arguments begin on page 12 of this document.

Gilead Exhibit 2018
PGR2023-00046 - Page 001280

Amendments to the Specification:

Please amend the specification as follows:

Please add the sub-heading "Cross Reference to Related Applications" before the first paragraph on page 1 and replace the first paragraph on page 1 with the following re-written paragraph:

--This application is a continuation of U.S. Patent Application No. 13/609,614, filed September 11, 2012, now U.S. Patent 8,580,765, which is a continuation of U.S. Patent Application No. 13/099,671, filed May 3, 2011, now U.S. Patent [[No.]] 8,334,270, which is a continuation of U.S. Patent Application No. 12/053,015, filed March 21, 2008, now U.S. Patent [[No.]] 7,964,580, which claims priority under 35 U.S.C. 119(e) to U.S. Provisional Application nos. 60/909,315, filed March 30, 2007, and 60/982,309, filed October 24, 2007, all of which are incorporated by reference in their entireties.--

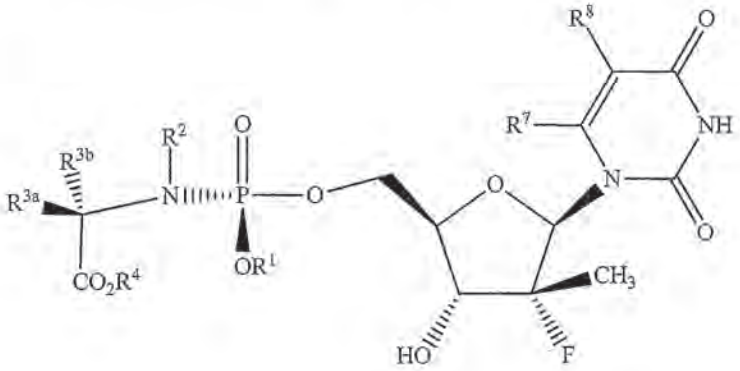
Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. - 12. (Canceled).

13. (Currently amended): A compound represented by ~~the following~~ formula:



wherein

R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, or a substituted or unsubstituted phenyl, where the substitutent of the substituted phenyl is ~~at least one of a~~ CH_3, OCH_3, F, Cl, Br, I, nitro, cyano, [[and]] or a $CH_{3-q}X_q$, where X is F, Cl, Br, or I, and q is 1-3;

R^2 is hydrogen or CH_3;

R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, CH_2-indol-3-yl, [[-]]$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, [[-]]$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-[[Ph]]phenyl), CH_2SH, or lower cycloalkyl, or

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R^{3a} is CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, CH_2-indol-3-yl, [[-]]$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, [[-]]$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-[[Ph]]phenyl), CH_2SH, or lower cycloalkyl and R^{3b} is H;

R^4 is hydrogen, CH_3, [[Et]] ethyl, [[^{i}Pr]] *i*-propyl, [[^{n}Pr]] *n*-propyl, [[^{n}Bu]], *n*-butyl, 2-butyl, [[^{t}Bu]] tert-butyl, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl; and

R^7 and R^8 are independently H, F, Cl, Br, I, OH, OCH_3, SH, SCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2H, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$~~, wherein R' is a C_{1-20} alkyl; a C_{1-20} cycloalkyl; a C_2-C_6 alkenyl, a C_2-C_6 alkynyl~~.

14. (Currently amended): The compound according to claim 13, wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

R^{3a} is H; and

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, CH_2-indol-3-yl, [[-]]$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, [[-]]$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-[[Ph]]phenyl), CH_2SH, or lower cycloalkyl.

15. (Currently amended): The compound according to claim 13, wherein:

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R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

R^{3a} is H;

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, or lower cycloalkyl; and

R^7 and R^8 are independently H, F, Br, SCH_3, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$.

16. (Currently amended): The compound according to claim 13, wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

R^2 is hydrogen;

R^{3a} is H;

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, or lower cycloalkyl; and

R^7 and R^8 are independently H, F, Br, SCH_3, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$.

17. (Currently amended): The compound according to claim 13, wherein:

R^1 is hydrogen, methyl, phenyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

R^2 is hydrogen;

R^{3a} is H;

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, or lower cycloalkyl; and

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R^7 and R^8 are independently H, F, Br, SCH_3, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$.

18. (Previously presented): A composition comprising the compound according to claim 13.

19. (Previously presented): A composition comprising the compound according to claim 13 and a pharmaceutically acceptable medium.

20. (Previously presented): A composition comprising an effective amount of the compound according to claim 13 to treat a hepatitis C virus infection and a pharmaceutically acceptable medium.

21. (Previously presented): A method of treating a subject infected by a virus selected from among hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus, which comprises administering to the subject an effective amount of the compound according to claim 13.

22. (Previously presented): The method of claim 21, wherein the virus is hepatitis C virus.

23. (Previously presented): The method of claim 22, which further comprises administering to the subject an effective amount of another antiviral agent.

24. (Previously presented): The method of claim 22, wherein the subject is a human.

25. (Currently amended): The method of claim 23, wherein;

R^1 is phenyl;

R^2 is hydrogen;

R^{3a} is H;

R^{3b} is CH_3;

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R^4 is [[^{i}Pr]] i-propyl; and

R^7 and R^8 are both H.

26. (Currently amended): The method of claim 24, wherein:

R^1 is phenyl;

R^2 is hydrogen;

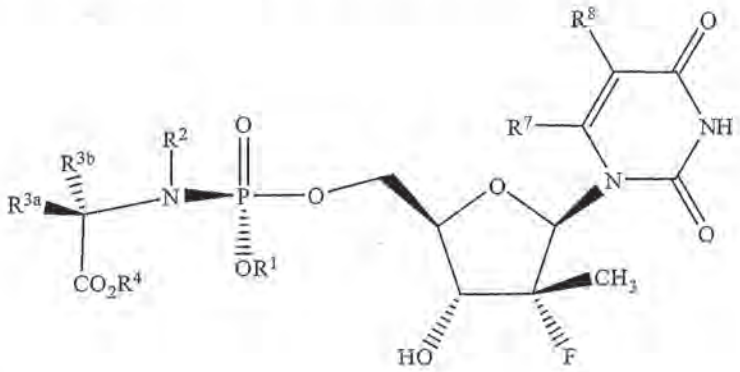
R^{3a} is H;

R^{3b} is CH_3;

R^4 is [[^{i}Pr]] i-propyl; and

R^7 and R^8 are both H.

27. (Currently amended): A compound represented by ~~the following~~ formula:



wherein

R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, or a substituted or unsubstituted phenyl, where the substitutent of the substituted phenyl is ~~at least one of a~~ CH_3, OCH_3, F, Cl, Br, I, nitro, cyano, [[and]] or a $CH_{3-q}X_q$, where X is F, Cl, Br, or I, and q is 1-3;

R^2 is hydrogen or CH_3;

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R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, CH_2-indol-3-yl, [[-]]$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, [[-]]$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl, or

R^{3a} is CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, CH_2-indol-3-yl, [[-]]$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, [[-]]$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-[[Ph]]phenyl), CH_2SH, or lower cycloalkyl and R^{3b} is H;

R^4 is hydrogen, CH_3, [[Et]] ethyl, [[^{i}Pr]] *i*-propyl, [[^{n}Pr]] *n*-propyl, [[^{n}Bu]], *n*-butyl, 2-butyl, [[^{t}Bu]] tert-butyl, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl; and

R^7 and R^8 are independently H, F, Cl, Br, I, OH, OCH_3, SH, SCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2H, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$~~, wherein R' is a C_{1-20} alkyl; a C_{1-20} cycloalkyl; a C_2-C_6 alkenyl, a C_2-C_6 alkynyl~~.

28. (Currently amended): The compound according to claim 27, wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

R^{3a} is H; and

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, CH_2-indol-3-yl, [[-]]$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$,

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CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, [[-]]$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-[[Ph]]phenyl), CH_2SH, or lower cycloalkyl.

29. (Currently amended): The compound according to claim 27, wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

R^{3a} is H;

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, or lower cycloalkyl; and

R^7 and R^8 are independently H, F, Br, SCH_3, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$.

30. (Currently amended): The compound according to claim 27, wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

R^2 is hydrogen;

R^{3a} is H;

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, or lower cycloalkyl; and

R^7 and R^8 are independently H, F, Br, SCH_3, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$.

31. (Currently amended): The compound according to claim 27, wherein:

R^1 is hydrogen, methyl, phenyl, p-bromo[[-]]phenyl, p-chloro[[-]]phenyl, or p-fluorophenyl;

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R^2 is hydrogen;

R^{3a} is H;

R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2[[Ph]]-phenyl, or lower cycloalkyl; and

R^7 and R^8 are independently H, F, Br, SCH_3, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$.

32. (Previously presented): A composition comprising the compound according to claim 27.

33. (Previously presented): A composition comprising the compound according to claim 27 and a pharmaceutically acceptable medium.

34. (Previously presented): A composition comprising an effective amount of the compound according to claim 27 to treat a hepatitis C virus infection and a pharmaceutically acceptable medium.

35. (Previously presented): A method of treating a subject infected by a virus selected from among hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus, which comprises administering to the subject an effective amount of the compound according to claim 27.

36. (Previously presented): The method of claim 35, wherein the virus is hepatitis C virus.

37. (Previously presented): The method of claim 36, which further comprises administering to the subject an effective amount of another antiviral agent.

38. (Previously presented): The method of claim 36, wherein the subject is a human.

39. (Currently amended): The method of claim 37, wherein:

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R^1 is phenyl;

R^2 is hydrogen;

R^{3a} is H;

R^{3b} is CH_3;

R^4 is [[^{i}Pr]] i-propyl; and

R^7 and R^8 are both H.

40. (Currently amended): The method of claim 38, wherein:

R^1 is phenyl;

R^2 is hydrogen;

R^{3a} is H;

R^{3b} is CH_3;

R^4 is [[^{i}Pr]] i-propyl; and

R^7 and R^8 are both H.

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REMARKS

Applicants respectfully request examination of the present application in view of the foregoing amendments and the following remarks.

Specification Amendments

Paragraph 1 on page 1 is amended to update the priority information.

Claim Amendments

Claims 1-12 are canceled without prejudice or disclaimer.

Claims 13-17, 25-31, 39 and 40 are currently being amended.

Claims 13-17 and 27 are amended for the purpose of clarity. Claims 13 and 27 also amended by deleting the definition of variable R' which is absent. Claims 13, 17, 30 and 31 are also amended for the purpose of clarity. Claims 13, 25-28, 39 and 40 are amended by replacing the abbreviations with their full terms for consistency.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

No new matter has been added by this amendment and as such Applicants respectfully request its entry. Applicants reserve the right to pursue canceled subject matter in a continuing application.

After the entry of this amendment, claims 13-40 are now pending in this application.

Non-Statutory Obviousness-Type Double Patenting

1. Claims 13-40 stand rejected as allegedly being unpatentable over claims 1-14 of U.S. Patent 8,580,765. Without acquiescing to the rejection and solely in the interest of advancing prosecution, Applicants attach herewith a terminal disclaimer over U.S. Patent 8,580,765. Accordingly, Applicants request withdrawal of the rejection.

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2. Claims 13-40 stand rejected as allegedly being unpatentable over claims 1-25 of U.S. Patent 8,334,270. Without acquiescing to the rejection and solely in the interest of advancing prosecution, Applicants attach herewith a terminal disclaimer over U.S. Patent 8,334,270. Accordingly, Applicants request withdrawal of the rejection.

3. Claims 13-20 and 27-34 stand rejected as allegedly being unpatentable over claims 1-14 of U.S. Patent 7,964,580. Without acquiescing to the rejection and solely in the interest of advancing prosecution, Applicants attach herewith a terminal disclaimer over U.S. Patent 7,964,580. Accordingly, Applicants request withdrawal of the rejection.

4. Claims 1-40 stand provisionally rejected as allegedly being unpatentable over claims 1, 3-7 and 9-23 of copending U.S. Application No. 14/195,751. Applicants note that this rejection is provisional and wish to hold it in abeyance until allowable subject matter is found in either case.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they request an early indication to this effect.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-6219. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-6219.

Respectfully submitted,

Date February 25, 2015

By /Neeta C. Thakur/

Sheppard, Mullin, Richter & Hampton LLP
379 Lytton Avenue
Palo Alto, CA 94301
Telephone: (650) 815-2600
Customer No.: 117796

Neeta C. Thakur, Ph.D.
Attorney for Applicants
Registration No. 59,123

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Jinfa Du et al.
Appl. No.:	14/013,237
Title:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
Filing Date:	08/29/2013
Examiner:	Lewis, Patrick T.
Art Unit:	1672
Confirmation Number	7005

TERMINAL DISCLAIMER

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Your Petitioner, Gilead Pharmasset LLC, having its principal place of business at 333 Lakeside Drive, c/o Gilead Sciences, Inc., Foster City, CA 94404 represents that it is the owner of the entire right, title, and interest in and to U.S. Patent Application No. 14/013,237, filed August 29, 2013, which is a continuation of U.S. Patent Application No. 13/609,614, filed September 11, 2012, now U.S. Patent No. 8,580,765, issued November 12, 2013, which is a continuation of U.S. Patent Application No. 13/099,671, filed May 3, 2011, now U.S. Patent No. 8,334,270, issued December 18, 2012, which is a continuation of U.S. Patent Application No. 12/053,015, filed March 21, 2008, now U.S. Patent No. 7,964,580, issued June 21, 2011, by virtue of an Assignment filed and recorded on September 5, 2013 on Reel/Frame 031139/0548 and the change of name recorded on September 5, 2013 on Reel/Frame 031157/0296 in the United States Patent and Trademark Office, copies of which are attached hereto as APPENDIX A. Further, your Petitioner represents that it is the owner of U.S. Patent No. 7,964,580, which issued on June 21, 2011 from U.S. Patent Application No. 12/053,015, filed March 21, 2008, by virtue of an Assignment filed and recorded on April 1, 2008 on Reel/Frame 020739/0883 and the

change of name recorded on April 20, 2012 on Reel/Frame 028081/0686 in the United States Patent and Trademark Office, copies of which are attached hereto as APPENDIX A.

Your Petitioner, Gilead Pharmasset LLC, hereby disclaims the terminal part of the term of any patent granted on the above-identified patent application which would extend beyond the full statutory term, as shortened by any terminal disclaimer, of U.S. Patent No. 7,964,580, and hereby agrees that any patent so granted on the above-identified patent application shall be enforceable only for and during such period that the U.S. Patent No. 7,964,580 and any patent granted on the above-identified patent application are commonly owned, this agreement to run with any patent granted on the above-identified patent application and to be binding upon the grantee, its successors or assigns.

In making the above disclaimer, Petitioner does not disclaim any terminal part of any granted patent on the above-identified patent application, prior to the full statutory term of U.S. Patent No. 7,964,580 as defined in 35 U.S.C. §§154 and 156, in the event that U.S. Patent No. 7,964,580 expires for failure to pay a maintenance fee, is held unenforceable or is found invalid in a final judgment by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321(a), has all claims canceled by a reexamination or inter partes review certificate or as a result of an interference proceeding, or is otherwise not deemed to provide the rights conveyed by 35 U.S.C. §154, prior to the full statutory term of U.S. Patent No. 7,964,580 as defined in 35 U.S.C. §§154 and 156, except for the loss of common ownership stated above. Further, Petitioner does not disclaim any terminal part of a patent granted on the above-identified patent application that would extend beyond the present term of U.S. Patent No 7,964,580, in the event that such present term is extended by virtue of compliance with the conditions for term extension of any present or future patent term extension provisions of patent law, including but not limited to 35 U.S.C. §156, and without waiving petitioner's right to extend the term of a patent granted on the above-identified patent application to the extent provided by law. Still further, Petitioner makes this disclaimer without prejudice to its rights to extend the term of any U.S. patent granted on the captioned application beyond the term provided by this Terminal Disclaimer by any patent term adjustment.

The undersigned (whose title is supplied below) certifies that he is empowered to sign this Terminal Disclaimer on behalf of the assignee, that he has reviewed the Assignment attached as APPENDIX A, and to the best of his knowledge and belief, the above-identified patent application and U.S. Patent No. 7,964,580 are commonly owned by Gilead Pharmasset LLC. The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the know ledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the above-identified application or any patent issuing therefrom.

Respectfully submitted,

Date Feb 25, 2015

By Lorna L Tanner

Sheppard, Mullin, Richter & Hampton LLP
379 Lytton Avenue
Palo Alto, CA 94301
Telephone: (650) 815-2600

Customer No.: 117796

Lorna L. Tanner
Attorney for Applicants
Registration No. 50,782

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Jinfa Du et al.
Appl. No.:	14/013,237
Title:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
Filing Date:	08/29/2013
Examiner:	Lewis, Patrick T.
Art Unit:	1672
Confirmation Number	7005

TERMINAL DISCLAIMER

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Your Petitioner, Gilead Pharmasset LLC, having its principal place of business at 333 Lakeside Drive, c/o Gilead Sciences, Inc., Foster City, CA 94404 represents that it is the owner of the entire right, title, and interest in and to U.S. Patent Application No. 14/013,237, filed August 29, 2013, which is a continuation of U.S. Patent Application No. 13/609,614, filed September 11, 2012, now U.S. Patent No. 8,580,765, issued November 12, 2013, which is a continuation of U.S. Patent Application No. 13/099,671, filed May 3, 2011, now U.S. Patent No. 8,334,270, issued December 18, 2012, which is a continuation of U.S. Patent Application No. 12/053,015, filed March 21, 2008, now U.S. Patent No. 7,964,580, issued June 21, 2011, by virtue of an Assignment filed and recorded on September 5, 2013 on Reel/Frame 031139/0548 and the change of name recorded on September 5, 2013 on Reel/Frame 031157/0296 in the United States Patent and Trademark Office, copies of which are attached hereto as APPENDIX A. Further, your Petitioner represents that it is the owner of U.S. Patent No. 8,580,765, which issued on November 12, 2013 from U.S. Patent Application No. 13/609,614, filed September 11, 2012, by virtue of an Assignment filed and recorded on January 7, 2013 on Reel/Frame

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029577/0557, spelling correction of an assignor name recorded on January 9, 2013 on Reel/Frame 029593/0404, and the change of name recorded on January 7, 2013 on Reel/Frame 029577/0277 in the United States Patent and Trademark Office, copies of which are attached hereto as APPENDIX B.

Your Petitioner, Gilead Pharmasset LLC, hereby disclaims the terminal part of the term of any patent granted on the above-identified patent application which would extend beyond the full statutory term, as shortened by any terminal disclaimer, of U.S. Patent No. 8,580,765, and hereby agrees that any patent so granted on the above-identified patent application shall be enforceable only for and during such period that the U.S. Patent No. 8,580,765 and any patent granted on the above-identified patent application are commonly owned, this agreement to run with any patent granted on the above-identified patent application and to be binding upon the grantee, its successors or assigns.

In making the above disclaimer, Petitioner does not disclaim any terminal part of any granted patent on the above-identified patent application, prior to the full statutory term of U.S. Patent No. 8,580,765 as defined in 35 U.S.C. §§ 154 and 156, in the event that U.S. Patent No. 8,580,765 expires for failure to pay a maintenance fee, is held unenforceable or is found invalid in a final judgment by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321(a), has all claims canceled by a reexamination or inter partes review certificate or as a result of an interference proceeding, or is otherwise not deemed to provide the rights conveyed by 35 U.S.C. §154, prior to the full statutory term of U.S. Patent No. 8,580,765 as defined in 35 U.S.C. §§154 and 156, except for the loss of common ownership stated above. Further, Petitioner does not disclaim any terminal part of a patent granted on the above-identified patent application that would extend beyond the present term of U.S. Patent No. 8,580,765, in the event that such present term is extended by virtue of compliance with the conditions for term extension of any present or future patent term extension provisions of patent law, including but not limited to 35 U.S.C. § 156, and without waiving petitioner's right to extend the term of a patent granted on the above-identified patent application to the extent provided by law. Still further, Petitioner makes this disclaimer without prejudice to its rights to extend the term of any U.S. patent granted on the captioned application beyond the term provided by this Terminal Disclaimer by any patent term adjustment.

The undersigned certifies that he is empowered to sign this Terminal Disclaimer on behalf of the assignee, that he has reviewed the Assignments attached as APPENDIX A and APPENDIX B, and to the best of his knowledge and belief, the above-identified patent application and U.S. Patent No. 8,580,765 are commonly owned by Gilead Pharmasset LLC. The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the know ledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the above-identified application or any patent issuing therefrom.

Respectfully submitted,

Date Feb 25, 2015

By Lorna L Tanner

Sheppard, Mullin, Richter & Hampton LLP
379 Lytton Avenue
Palo Alto, CA 94301
Telephone: (650) 815-2600
Customer No.: 117796

Lorna L. Tanner
Attorney for Applicants
Registration No. 50,782

Gilead Exhibit 2018
PGR2023-00046 - Page 001299

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Jinfa Du et al.
Appl. No.:	14/013,237
Title:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
Filing Date:	08/29/2013
Examiner:	Lewis, Patrick T.
Art Unit:	1672
Confirmation Number	7005

TERMINAL DISCLAIMER

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Your Petitioner, Gilead Pharmasset LLC, having its principal place of business at 333 Lakeside Drive, c/o Gilead Sciences, Inc., Foster City, CA 94404 represents that it is the owner of the entire right, title, and interest in and to U.S. Patent Application No. 14/013,237, filed August 29, 2013, which is a continuation of U.S. Patent Application No. 13/609,614, filed September 11, 2012, now U.S. Patent No. 8,580,765, issued November 12, 2013, which is a continuation of U.S. Patent Application No. 13/099,671, filed May 3, 2011, now U.S. Patent No. 8,334,270, issued December 18, 2012, which is a continuation of U.S. Patent Application No. 12/053,015, filed March 21, 2008, now U.S. Patent No. 7,964,580, issued June 21, 2011, by virtue of an Assignment filed and recorded on September 5, 2013 on Reel/Frame 031139/0548 and the change of name recorded on September 5, 2013 on Reel/Frame 031157/0296 in the United States Patent and Trademark Office, copies of which are attached hereto as APPENDIX A. Further, your Petitioner represents that it is the owner of U.S. Patent No. 8,334,270, which issued on December 18, 2012 from U.S. Patent Application No. 13/099,671, filed May 3, 2011, by virtue of an Assignment filed and recorded on January 15, 2013 on Reel/Frame 029631/0199,

Gilead Exhibit 2018
PGR2023-00046 - Page 001300

and the change of name recorded on April 20, 2012 on Reel/Frame 028081/0686 in the United States Patent and Trademark Office, copies of which are attached hereto as APPENDIX A.

Your Petitioner, Gilead Pharmasset LLC, hereby disclaims the terminal part of the term of any patent granted on the above-identified patent application which would extend beyond the full statutory term, as shortened by any terminal disclaimer, of U.S. Patent No. 8,334,270, and hereby agrees that any patent so granted on the above-identified patent application shall be enforceable only for and during such period that the U.S. Patent No. 8,334,270 and any patent granted on the above-identified patent application are commonly owned, this agreement to run with any patent granted on the above-identified patent application and to be binding upon the grantee, its successors or assigns.

In making the above disclaimer, Petitioner does not disclaim any terminal part of any granted patent on the above-identified patent application, prior to the full statutory term of U.S. Patent No. 8,334,270 as defined in 35 U.S.C. §§ 154 and 156, in the event that U.S. Patent No. 8,334,270 expires for failure to pay a maintenance fee, is held unenforceable or is found invalid in a final judgment by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321(a), has all claims canceled by a reexamination or inter partes review certificate or as a result of an interference proceeding, or is otherwise not deemed to provide the rights conveyed by 35 U.S.C. §154, prior to the full statutory term of U.S. Patent No. 8,334,270 as defined in 35 U.S.C. §§154 and 156, except for the loss of common ownership stated above. Further, Petitioner does not disclaim any terminal part of a patent granted on the above-identified patent application that would extend beyond the present term of U.S. Patent No. 8,334,270, in the event that such present term is extended by virtue of compliance with the conditions for term extension of any present or future patent term extension provisions of patent law, including but not limited to 35 U.S.C. §156, and without waiving petitioner's right to extend the term of a patent granted on the above-identified patent application to the extent provided by law. Still further, Petitioner makes this disclaimer without prejudice to its rights to extend the term of any U.S. patent granted on the captioned application beyond the term provided by this Terminal Disclaimer by any patent term adjustment.

The undersigned (whose title is supplied below) certifies that he is empowered to sign this Terminal Disclaimer on behalf of the assignee, that he has reviewed the Assignment attached as APPENDIX A, and to the best of his knowledge and belief, the above-identified patent application and U.S. Patent No. 8,334,270 are commonly owned by Gilead Pharmasset LLC. The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the know ledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the above-identified application or any patent issuing therefrom.

Respectfully submitted,

Date Feb. 25, 2015

By Lorna L. Tanner

Sheppard, Mullin, Richter & Hampton LLP
379 Lytton Avenue
Palo Alto, CA 94301
Telephone: (650) 815-2600
Customer No.: 117796

Lorna L. Tanner
Attorney for Applicants
Registration No. 50,782

Gilead Exhibit 2018
PGR2023-00046 - Page 001302

APPENDIX A

M&G 60137.0034USU1

ASSIGNMENT OF U.S. PATENT APPLICATION

WHEREAS, we, MICHAEL JOSEPH SOFIA, residing at 3066 Antler Drive, Doylestown, PA 18902; JINFA DU, residing at 1206 Reins Circle, New Hope, PA 18938; PEIYUAN WANG, residing at 20 Radburn Road, Glen Rock, NJ 07452, and DHANAPALAN NAGARATHNAM made certain new and useful inventions and improvements for which we filed an application for Letters Patent of the United States on **March 21, 2008**, application no. 12/053,015 which is entitled **NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS.**

AND WHEREAS, **PHARMASSET, INC.**, a corporation organized and existing under and by virtue of the laws of the State of Delaware, and having an office and place of business at 303-A College Road East, Princeton, NJ 08540 (hereinafter "Assignee") is desirous of acquiring the entire right, title and interest in and to said inventions, improvements and application and in and to the Letters Patent to be obtained therefor;

NOW THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, WE, by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

WE hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of OUR entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its successor and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by us had this Assignment and sale not been made.

Further, WE agree that WE will communicate to said ASSIGNEE or its representatives any facts known to us respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letter Patent to be issued to said ASSIGNEE, its successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possession and in any and all foreign countries.

The undersigned hereby grants the law firm of Merchant & Gould, P.C. of 3200 IDS Center, 80 South Eighth Street, Minneapolis, Minnesota 55402-0903 the power to insert on this assignment any further identification, including the application number and filing date, which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

Date: 3/26/08 — (Signature of Inventor) MICHAEL JOSEPH SOFIA

Date: 3/26/08 — (Signature of Inventor) JINFA DU

Date: 3/26/08 — (Signature of Inventor) PEIYUAN WANG

Date: 3/27/08 — (Signature of Inventor) DHANAPALAN NAGARATHNAM

Merchant & Gould, P.C.
ATTORNEYS AT LAW
3200 IDS Center, 80 South Eighth Street
Minneapolis, Minnesota 55402-0903

Delaware

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE DO HEREBY CERTIFY THAT THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF CONVERSION OF A DELAWARE CORPORATION UNDER THE NAME OF "PHARMASSET, INC." TO A DELAWARE LIMITED LIABILITY COMPANY, CHANGING ITS NAME FROM "PHARMASSET, INC." TO "GILEAD PHARMASSET LLC", FILED IN THIS OFFICE ON THE TENTH DAY OF FEBRUARY, A.D. 2012, AT 10:37 O'CLOCK A.M.



Jeffrey W. Bullock, Secretary of State

3796672 8100V

120151180

AUTHENTICATION: 9356784

DATE: 02-10-12

You may verify this certificate online at corp.delaware.gov/authver.shtml

State of Delaware
Secretary of State
Division of Corporations
Delivered 10:37 AM 02/10/2012
FILED 10:37 AM 02/10/2012
SRV 120151180 - 3796672 FILE

CERTIFICATE OF CONVERSION FROM A CORPORATION TO LIMITED LIABILITY COMPANY

Pursuant to Sections 18-204 and 18-214 of the
Delaware Limited Liability Company Act
and Section 266 of the
General Corporation Law of the State of Delaware

1. The name of the corporation immediately prior to the filing of this Certificate of Conversion to Limited Liability Company is Pharmasset, Inc.

2. The corporation was originally incorporated on the 8th day of June, 2004 under the laws of the State of Delaware. The Corporation's jurisdiction of incorporation immediately prior to the filing of this Certificate of Conversion is the State of Delaware.

3. The name of the limited liability company into which the corporation shall be converted, as set forth in its Certificate of Formation, is Gilead Pharmasset LLC.

4. The conversion of the Company to a Delaware limited liability company has been approved accordance with the provisions of Section 266 of the General Corporation Law of the State of Delaware.

[SIGNATURE PAGE FOLLOWS]

IN WITNESS WHEREOF, the undersigned authorized person has caused this Certificate of Conversion to be executed this 10th day of February, 2012.

By: _____
Name: Brett A. Pletcher
Title: Secretary and Authorized Officer

[Signature Page to Certificate of Conversion to LLC for Pharmasset, Inc.]

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APPENDIX B

M&G 60137.0034USU1

ASSIGNMENT OF U.S. PATENT APPLICATION

WHEREAS, we, MICHAEL JOSEPH SOFIA, residing at 3066 Antler Drive, Doylestown, PA 18902; JINFA DU, residing at 1206 Reins Circle, New Hope, PA 18938; PEIYUAN WANG, residing at 20 Radburn Road, Glen Rock, NJ 07452, and DHANAPALAN NAGARATHNAM made certain new and useful inventions and improvements for which we filed an application for Letters Patent of the United States on **March 21, 2008**, application no. 12/053,015 which is entitled **NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS**.

AND WHEREAS, **PHARMASSET, INC.**, a corporation organized and existing under and by virtue of the laws of the State of Delaware, and having an office and place of business at 303-A College Road East, Princeton, NJ 08540 (hereinafter "Assignee") is desirous of acquiring the entire right, title and interest in and to said inventions, improvements and application and in and to the Letters Patent to be obtained therefor;

NOW THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, WE, by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

WE hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of OUR entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its successor and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by us had this Assignment and sale not been made.

Further, WE agree that WE will communicate to said ASSIGNEE or its representatives any facts known to us respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letter Patent to be issued to said ASSIGNEE, its successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possession and in any and all foreign countries.

The undersigned hereby grants the law firm of Merchant & Gould, P.C. of 3200 IDS Center, 80 South Eighth Street, Minneapolis, Minnesota 55402-0903 the power to insert on this assignment any further identification, including the application number and filing date, which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

Date: 3/26/08 (Signature of Inventor) MICHAEL JOSEPH SOFIA

Date: 3/26/08 (Signature of Inventor) JINFA DU

Date: 3/26/08 (Signature of Inventor) PEIYUAN WANG

Date: 3/27/08 (Signature of Inventor) DHANAPALAN NAGARATHNAM

Merchant & Gould, P.C.
ATTORNEYS AT LAW
3200 IDS Center, 80 South Eighth Street
Minneapolis, Minnesota 55402-0903

Delaware

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE DO HEREBY CERTIFY THAT THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF CONVERSION OF A DELAWARE CORPORATION UNDER THE NAME OF "PHARMASSET, INC." TO A DELAWARE LIMITED LIABILITY COMPANY, CHANGING ITS NAME FROM "PHARMASSET, INC." TO "GILEAD PHARMASSET LLC", FILED IN THIS OFFICE ON THE TENTH DAY OF FEBRUARY, A.D. 2012, AT 10:37 O'CLOCK A.M.



Jeffrey W. Bullock, Secretary of State

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AUTHENTICATION: 9680878

DATE: 06-29-12

You may verify this certificate online at corp.delaware.gov/authver.shtml

State of Delaware
Secretary of State
Division of Corporations
Delivered 10:37 AM 02/10/2012
FILED 10:37 AM 02/10/2012
SRV 120151180 - 3796672 FILE

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[SIGNATURE PAGE FOLLOWS]

IN WITNESS WHEREOF, the undersigned authorized person has caused this Certificate of Conversion to be executed this 10th day of February, 2012.

By: _____
Name: Brett A. Pletcher
Title: Secretary and Authorized Officer

[Signature Page to Certificate of Conversion to LLC for Pharmasset, Inc.]