

IP01Rec'd PCT 18 NOV 2011

PTO-1390 (09-11)
Approved for use through 4/30/2013. OMB 0651-0021
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.

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER ChG_00611
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 13/261029
INTERNATIONAL APPLICATION NO. PCT/US2010/001494	INTERNATIONAL FILING DATE 05/19/2010	PRIORITY DATE CLAIMED 05/18/2009
TITLE OF INVENTION Synthesis of labile base protected - modified deoxy & modified ribo nucleosides, corresponding phosphoramidites ...		
APPLICANT(S) FOR DO/EO/US Suresh C. Srivastava and Naveen P. Srivastava		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. ☒ This is a FIRST submission of items concerning a submission under 35 U.S.C. 371. 2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a submission under 35 U.S.C. 371. 3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. ☒ The US has been elected (Article 31). 5. ☐ A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. ☐ is attached hereto (required only if not communicated by the International Bureau). b. ☐ has been communicated by the International Bureau. c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US). 6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. ☐ is attached hereto. b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4). 7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. ☐ are attached hereto (required only if not communicated by the International Bureau). b. ☐ have been communicated by the International Bureau. c. ☐ have not been made; however, the time limit for making such amendments has NOT expired. d. ☐ have not been made and will not be made. 8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). Items 11 to 20 below concern document(s) or information included: 11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. ☐ A preliminary amendment. 14. ☐ An Application Data Sheet under 37 CFR 1.76. 15. ☐ A substitute specification. 16. ☒ A power of attorney and/or change of address letter. 17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.3 and 37 CFR 1.821- 1.825. 18. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4). 19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).		

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. 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 15 minutes to complete, including gathering information, preparing, and submitting the completed 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 FEE S OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. Page 1 of 3

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 13/261029		INTERNATIONAL APPLICATION NO. PCT/US2010/001494		ATTORNEY'S DOCKET NUMBER ChG_00611	
20. Other items or information: Transmittal Cover Letter, 37 CFR 3.73(b) Statement, Original Assignment, Assignment Cover, Payment by credit card PTO-2038, and Return Receipt Postcard					
The following fees have been submitted				CALCULATIONS PTO USE ONLY	
21. ☒ Basic national fee (37 CFR 1.492(a))..... \$380				\$ 380	
22. ☒ Examination fee (37 CFR 1.492(c))				\$ 250	
If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... \$0					
All other situations.....\$250					
23. ☐ Search fee (37 CFR 1.492(b))				\$ 490	
If the written opinion of the ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... \$0					
Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority.....\$120					
International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB..... \$490					
All other situations.....\$620					
TOTAL OF 21, 22 and 23 =				\$ 1,220	
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). The fee is \$310 for each additional 50 sheets of paper or fraction thereof.					
Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE		
- 100 =	/50 =		x \$310	\$	
Surcharge of \$130.00 for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	- 20 =		x \$ 60	\$	
Independent claims	- 3 =		x \$250	\$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$450	\$	
TOTAL OF ABOVE CALCULATIONS =				\$1,220	
☒ Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by 1/2.					
SUBTOTAL =				\$ 610	
Processing fee of \$130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)).				\$	
TOTAL NATIONAL FEE =				\$ 610	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$ 40	
TOTAL FEES ENCLOSED =				\$ 650	
				Amount to be refunded:	\$
				Amount to be charged	\$650

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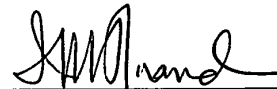
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

- 13/261029
- a. ☐ A check in the amount of \$ _____ to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees.
- c. ☐ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. _____.
- d. ☒ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do NOT attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is not recommended and by doing so your credit card information may be displayed via PAIR. To protect your information, it is recommended paying fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

SEND ALL CORRESPONDENCE TO:



SIGNATURE

Indu M. Anand

NAME

52,557

REGISTRATION NUMBER

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(b)

13/261029

Applicant/Patent Owner: ChemGenes Corporation

Application No./Patent No.: PCT/US 2010/001494 Filed/Issue Date: November 18, 2011

Titled: Synthesis of labile base protected - modified deoxy & modified ribo nucleosides, corresponding phosphoramidites and supports and their use in high purity oligonucleotide synthesis

ChemGenes Corporation, a Massachusetts Corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;
2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or
3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

- 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 therefore is attached.

OR

- B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. 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.

2. 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.

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.

- ☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

- ☒ As required by 37 CFR 3.73(b)(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.


Signature

11/18/2011
Date

Suresh C. Srivastava

President and CEO

Printed or Typed Name

Title

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.

13/281029

1AP01Rec'd PCT 18 NOV 2011

Attorney Docket No.: ChG_00611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Suresh C. Srivastava and Naveen P. Srivastava

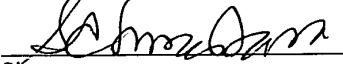
Application: US National Stage Entry for
PCT/US2010/001494

Filed: November 18, 2011

Title: **Synthesis of labile base protected – modified deoxy & modified ribo
nucleosides, corresponding phosphoramidites and supports and their use in
high purity oligonucleotide synthesis**

CERTIFICATE OF EXPRESS MAILING UNDER 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail package Label No. EG 535748897 US on the date signed, addressed to:
Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.


Signature

S.C.Srivastava
(Name)

11/18/2011
Date

TRANSMITTAL COVER LETTER

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

Sir:

Please find enclosed for filing pursuant to 35 USC 371, the US National Stage Patent Application of a prior PCT application with the Title and Inventors named above. The PCT application, no. PCT/US2010/001494 was filed on 5/19/2010 based on US Provisional Patent Application Serial No. 61/216491 filed on 5/18/2009. The Request to Restore the Right Priority to the named Provisional Application was granted by the US/RO.

Please find enclosed in this mailing the following:

- Transmittal Letter, PTO-1390
- Oath/declaration by the joint inventors

13/261029

IAP01Rec'd PGT 18 NOV 2011

Srivastava et al,
Express Mail Label No. EG 535748897 US

Synthesis of labile base protected ...

Attorney Docket No.: ChG_00611

- Power of Attorney executed by the Chief Executive Officer of ChemGenes Corporation, assignee of the invention and applicant for the international application
 - Form PTO/SB/81
 - Statement pursuant to 37 CFR 3.73(b)
 - Original Assignment document – conveyance by inventors
 - Assignment Cover, Form PTO-1595
- Payment by Credit Card, Form PTO-2038
- Return Receipt Postcard

In the event of a deficiency in fees and compliance, you are requested to kindly contact the undersigned representative.

Dated: November 18, 2011

Respectfully submitted,
Suresh C. Srivastava and Naveen P. Srivastava

Applicant Inventors

By 

Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824
(978) 250-9003/ (617) 930-5000

Doc Code: Oath
Document Description: Oath or declaration filed

13/261029
18 NOV 2011
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PTO/SB/01 (04-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)	Attorney Docket Number	ChG_00611
	First Named Inventor	Suresh C. Srivastava
	COMPLETE IF KNOWN	
	Application Number	
	Filing Date	November 18, 2011
	Art Unit	
	Examiner Name	
☒ Declaration Submitted With Initial Filing OR ☐ Declaration Submitted After Initial Filing (surcharge (37 CFR 1.16(f)) required)		

I hereby declare that: (1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and (2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention titled:

Synthesis of labile base protected – modified deoxy & modified ribo nucleosides, corresponding phosphoramidites and supports and their use in high purity oligonucleotide synthesis

(Title of the Invention)

the application of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) _____ as United States Application Number or PCT International Application Number _____ and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Authorization To Permit Access To Application by Participating Offices

☒ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

[Page 1 of 3]

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 21 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.

DECLARATION — Utility or Design Patent Application

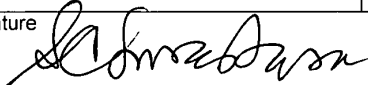
Claim of Foreign Priority Benefits

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
PCT/US2010/001494		05/19/2010	☒	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application number(s) are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

DECLARATION — Utility or Design Patent Application

Direct all correspondence to:	☒	The address associated with Customer Number:	83687	OR	☐	Correspondence address below
Name						
Address						
City		State		Zip		
Country		Telephone		Email		
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. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: <i>Patent Application Files</i>. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: <i>Deposit Accounts and Electronic Funds Transfer Profiles</i>. I hereby declare that all statements made herein of my 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 knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.						
NAME OF SOLE OR FIRST INVENTOR:			☐ A petition has been filed for this unsigned inventor			
Given Name (first and middle (if any))			Family Name or Surname			
Suresh C.			Srivastava			
Inventor's Signature 			Date 11/18/2011			
Residence: City		State		Country		Citizenship
Burlington		Massachusetts		USA		USA
Mailing Address 7 Donald Road						
City		State		Zip		Country
Burlington		MA		01803		USA
☐ Additional inventors or a legal representative are being named on the _____ supplemental sheet(s) PTO/SB/02A or 02LR attached hereto						

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13/261029

PTO/SB/81 (01-09)

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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS	Application Number	
	Filing Date	November 18, 2011
	First Named Inventor	Suresh C. Srivastava
	Title	Synthesis of labile base protected ...
	Art Unit	
	Examiner Name	
	Attorney Docket Number	ChG_00611

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

83687

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☐ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name			
Address			
City	State	Zip	
Country			
Telephone	Email		

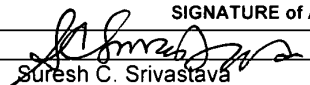
I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature		Date	11/18/2011
Name	Suresh C. Srivastava	Telephone	(978) 694-4500
Title and Company	President and CEO, ChemGenes Corporation		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ *Total of _____ forms are submitted.

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.**

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DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet
Page <u>2</u> of <u>2</u>	

Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any))		Family Name or Surname	
Naveen P.		Srivastava	
Inventor's Signature		Date <u>11-18-2011</u>	
Burlington	<u>8 Baron Park Lane</u>	Massachusetts	<u>01803</u>
Residence: City	<u>Apt # 18</u>	State	USA
Mailing Address		Country	INDIA
<u>8 Baron Park Lane</u>		<u>Apt # 18</u>	
City	<u>Burlington</u>	State	<u>MA</u>
Zip	<u>01803</u>	Country	<u>USA</u>
Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any))		Family Name or Surname	
Inventor's Signature		Date	
Residence: City		State	
		Country	
Mailing Address		Citizenship	
City		State	
		Zip	
		Country	
Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any))		Family Name or Surname	
Inventor's Signature		Date	
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Declarations under Rule 4.17:

[Continued on next page]

(54) Title: SYNTHESIS LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

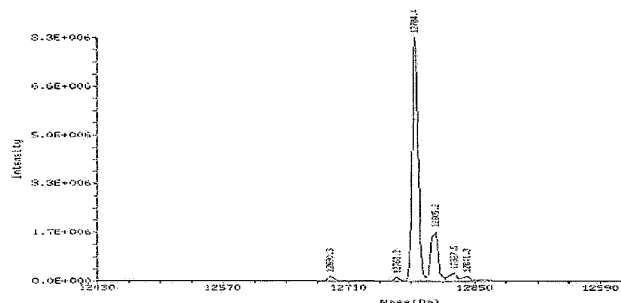


Fig. 5d: ESI-MS Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).

Lot No. CHS-10R-31-01

Targeted mass: 12785.2

Observed Mass: 12784.4

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

(57) **Abstract:** This invention relates to novel method of synthesis of RNA utilizing N-2-acetyl protected guanine as nucleoside base, nucleosides, succinates, phosphoramidites, corresponding solid supports that are suitable for oligo deoxy nucleosides and RNA oligonucleotide synthesis. Our discovery using N-acetyl protected guanine as nucleoside base protecting group, which is significantly faster base labile protecting group, yet significantly more stable than commonly utilized -2- isobutyryl guanosine is a novel approach to obtain highest purity oligonucleotides. This approach is designed to lead to very high purity and very clean oligonucleotide, after efficient removal of the protecting groups, including acetyl group from guanine and to produce high purity therapeutic grade DNA oligonucleotides, RNA oligonucleotides, diagnostic DNA, diagnostic RNA for microarray platform. The deprotection of acetyl protecting groups of the natural deoxy and ribonucleosides occurs under substantially reduced time in contact with mild deprotection conditions such as mild bases, secondary amines for removal of such groups under such conditions would allow synthesis of various DNA and RNA of highest purity for diagnostics and therapeutic application. This approach is designed to lead to high purity large

[Continued on next page]



-
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 - as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

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scale therapeutic grade oligonucleotide chimeras which consist of fluoro sugar modification in conjunction with deoxy nucleosides, ribonucleosides, modified base and modified sugar nucleosides. This approach is further designed to use acetyl guanine protecting group when other bases are sensitive nucleoside, and for use in oligo peptide synthesis and for support bound oligo nucleotides.

Synthesis of labile base protected – modified deoxy & modified ribo nucleosides, corresponding phosphoramidites and supports and their use in high purity oligonucleotide synthesis.

Suresh C. Srivastava and Naveen Srivastava

CROSS REFERENCE TO RELATED APPLICATIONS

This international application for patent claims priority from US Provisional Application Serial No. 61/216491 entitled “Synthesis of N-2-Acetyl guanine –deoxy nucleosides, N-2-Acetyl guanine ribo nucleosides, N-2-Acetyl guanine –modified deoxy & ribo nucleosides, the corresponding phosphoramidites and their use in high purity oligonucleotide synthesis” by the same inventors filed on May 18, 2009. The entire contents of the related provisional application are herein incorporated by reference.

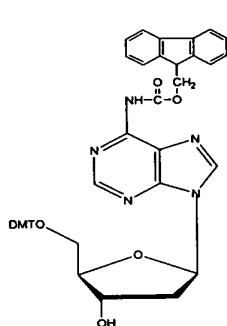
FIELD OF THE INVENTION

This invention relates to synthesis of novel N-2-acetyl protected deoxy and ribo- guanosine, – N-acetyl protected modified guanosine, their succinates, phosphoramidites, corresponding solid supports that are suitable for high purity DNA and RNA synthesis, and it leads to a novel approach to obtain highest purity oligonucleotides. This invention is directed to the synthesis of high purity large scale oligonucleotide synthesis.

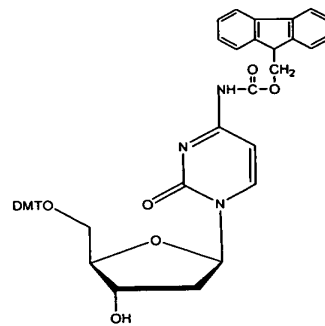
BACKGROUND OF THE INVENTION

The chemical synthesis of oligonucleotides of DNA fragments is performed efficiently by the phosphoramidite chemistry, and the coupling reaction gives excellent yield on various solid supports (Oligodeoxy nucleotide synthesis, Phosphoramidite Approach, Serge L. Beaucage in Protocols For OLigonucleotide s and Analogs, Synthesis and Properties, Editor, Sudhir Agarwal, Humana Press, 1993). Similarly excellent protocols have been developed for the synthesis of RNA, and various biologically active tRNA molecules

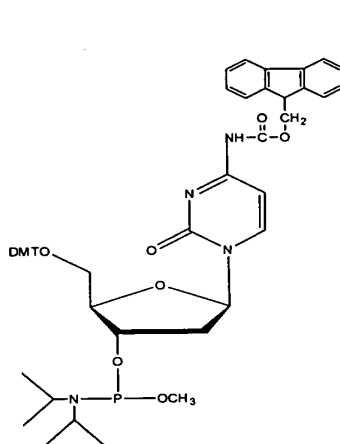
(Oligoribonucleotide synthesis, The Silyl Phosphoramidite Method, Masad J. Damha and Kevin K. Ogilvie in *Protocols For Oligonucleotides and Analogs, Synthesis and Properties*, Editor, Sudhir Agarwal, Humana Press, 1993). A large number of such biologically functional DNA and RNA molecules carry base labile and modified nucleosides which cannot sustain prolonged basic conditions, generally required during deprotection. Thus dihydrouridine present in tRNA requires very mild deprotection conditions, otherwise it is completely decomposed and the quality of synthetic tRNA will be compromised. (C. Chaix, D. Molko and R. Teoule, *Tetrahedron Letters*, 30, 1, 711-74, 1989). In order to develop protecting groups which are milder in nature have been developed in recent past. Thus 2-(acetoxymethyl)benzoyl (AMB) group has been reported which uses potassium carbonate as mild deprotecting group for their removal (W.H.A. Kuijpers, J. Huskens and C.A.A. Van Boeckel, *Tetrahedron Lett.*, 31, 6729-6732, 1990) & W.H.A. Kuijpers, E. Kuyl-Yeheskiely, J.H. Van Boom and C.A.A. Van Boeckel, *Nucl. Acids Res.*, 21, 3493-3500, 1993). The AMB group seems attractive, however there are many practical problems in their use. Fmoc group was reported for the protection of amino function of 2'-deoxycytidine, 2'-deoxy adenosine and 2'-deoxy guanosine and for the corresponding ribonucleosides (H. Heikkilä and J. Chattopadhyaya, *Acta Chem. Scand. B* 37, No.3, 263-265, 1983). Fmoc as N-protecting group as pointed out by these authors for their capability to get cleaved under very mild alkaline deprotection condition, or by bases capable to carry out selective deprotection via B-elimination of Fmoc group (scheme 1). It is therefore not surprising that other attempts to synthesis of N-Fmoc protected nucleoside and phosphoramidites have been carried out. The publication (R.K. Gaur, V. Bobde, M. Atreyi and K.C. Gupta, *Indian Journal of Chemistry*, 29B, 108-112, 1990), reports preparation of 5'-DMT-N-Fmoc-dA (structure 1) and 5'-DMT-N-Fmoc-dC (structure 2). However these authors could not synthesize 5'-DMT-N-Fmoc-dG (structure 5). Further only p-methoxy phosphoramidites of 5'-DMT-N-Fmoc-dC (structure 3) and 5'-DMT-N-Fmoc-dA (structure 4) were synthesized by these authors. The p-methoxy phosphoramidites have only limited application in oligonucleotide synthesis. Further, no N-Fmoc protected solid supports were reported.



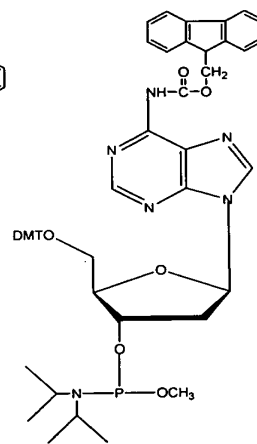
5'-DMT-N6-Fmoc-dA
(Structure 1)



N-2-FMOC-5'-DMT-dC
(Structure 2)

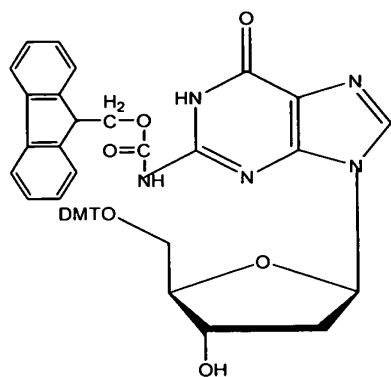


5'-DMT-N4-Fmoc-dC-
p-methoxy-phosphoramidite (Structure 3)



N-6-FMOC-5'-DMT-dA-
p-methoxy - phosphoramidite (Structure 4)

The synthesis of N-FMOC-5'-DMT-dG (structure 5) had eluded so far till our present invention.



5'-DMT-N2-Fmoc-dG

(Structure 5)

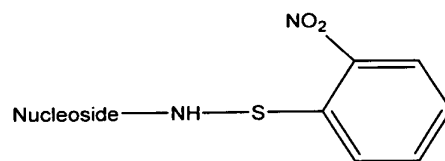
Similarly no solid supports or the succinates of the N-FMOC -5'-DMT-deoxy bases (dA and dC) revealed by these other authors. Hence there is no information as to the applicability of DMT-N-6-FMOC-dA -3'- succinyl-support, which would validate the concept that the solid support containing N-6-Fmoc-dA solid supports are expected to minimize or dramatically reduce formation of N-1, i.e. depurination of 3'- dA base products during oligo synthesis and hence about the quality of the synthesized 2'- deoxy oligonucleotides. The FMOC protected nucleoside products improve the quality of the terminal 3'- dA containing oligonucleotides.

There seem to be no further attempts to make 5'- DMT-N-FMOC dG or the ribonucleoside containing N- Fmoc protected RNA synthesis synthons and the corresponding cyanoethyl phosphoramidites. The cyanoethyl phosphoramidite chemistry in DNA and RNA are currently used in present state of the art in this technology.

It was demonstrated by the authors (J. Heikkila and J. Chattopadhyaya, Acta Chem. Scand. B 37, No.3, 263-265, 1983) that deprotection of FMOC protecting group can be carried out under various very mild basic reaction conditions. It is possible to utilize either aq ammonia condition deprotection, which results in nucleophilic displacement of FMOC protecting group, or by a Non -nucleophilic base such as triethylamine, which causes B-elimination of FMOC - active hydrogen group (scheme 1). These authors however similarly did not pursue the n- FMOC protecting group for further exploration and carried out investigation of other protecting groups such as ortho-nitro phenyl sulfenyl protected

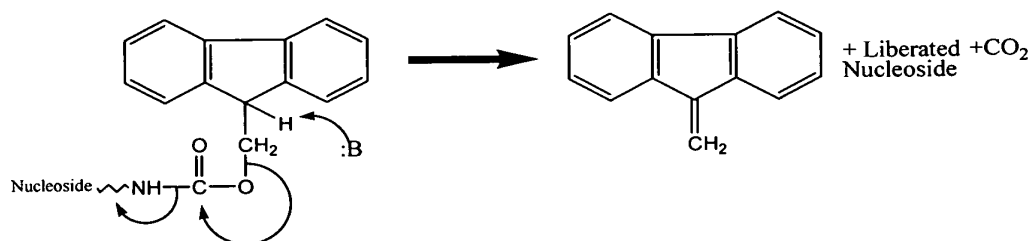
nucleosides(Structure 6).

The Fmoc protecting group is very well established in peptide synthesis and one of the preferred reagents for amino group protection of alpha- amino group of amino acids for step wise peptide synthesis (Carpino, L.A., and Han, G. Y., J.Amer.Chem.Soc., 92, 5748, 1970). But Heikkila and Chattopadyaya (J. Heikkila and J. Chattopadhyaya, Acta Chem. Scand. B 37, No.3, 263-265, 1983), who initially synthesized the Fmoc deoxy and ribo nucleosides switched to (J. Heikkila, N. Balgobin and J. Chattopadhyaya, Acta Chem. Scand B 37, 857-864, 1983) to another N- protecting group, 2- nitrophenyl sulfenyl (Nps) for the protection of amino function of cytidine, adenosine, guanosine and the corresponding 2'- deoxy ribo nucleosides (structure 6).



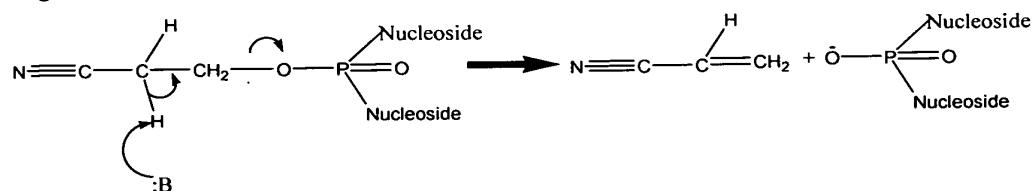
(Structure 6)

(O-nitrophenylsulfenyl protecting group)



Scheme1. Fmoc-B-Elimination scheme

It is well known that cyanoethyl protecting group for internucleotide phosphate is eliminated by B- elimination mechanism leading to acrylonitrile and phosphodiester oligonucleotides.(scheme 2).



Scheme2. Elimination of cyanoethyl phosphate group

It is therefore possible to modulate the Fmoc protecting group removal conditions from oligonucleotides, and the Fmoc as base protecting group can be removed by the process of B-elimination, just like the B- elimination process to remove cyanoethyl group.

This process therefore offers very attractive potential to use ammonia free oligo synthesis. This process, furthermore, has potential to offer deoxyoligonucleotides for complete deprotection of oligos on solid supports. This technology or process has the potential to offer ribonucleotides such as those required for chip based technology as well high purity oligonucleotides for microRNA, Si RNA, RNA chips

This group, in conjunction with cyanoethyl phosphate protecting group, therefore offers opportunity to remove both Fmoc and cyanoethyl groups from the synthesized deoxy and ribo oligonucleotides on the support cleanly, preferably with non aq bases, and on support for many diagnostics application.

Our present invention is revealed by structures such as 7-10 below.

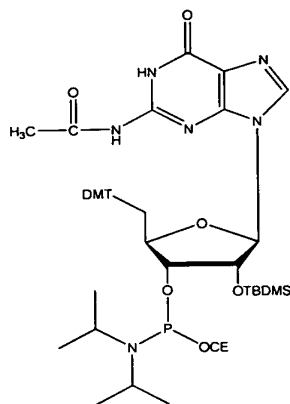
The present inventors recently proposed to utilize N- Fmoc protected purine and pyrimidine bases for the Synthesis of protected Deoxy nucleosides, ribonucleosides, phosphoramidites and their use in the synthesis of oligonucleotides. Although the Fmoc protecting group presents tremendous advantage, practical large scale synthesis is inconvenient and difficult to achieve in order to produce large quantities of therapeutic grade RNA or RNA chimeras having sensitive groups such as 2'- fluoro group. It is also significantly labile so that this group has a tendency to fall off and lead to byproducts or impurities. We therefore turned our attention to N-2- acetyl as guanine base protecting group. This group is significantly more stable than Fmoc protecting group. Yet is quite labile as compared to isobutyryl group at N-2 position.

Our results of RNA synthesis show that quality of RNA's suffer heavily if in the automated RNA synthesis on DNA/RNA synthesizer, DMT-N-2 -isobutyryl guanosine-2'- TBDMS-3'- Cyanoethyl phosphoramidite is utilized. The currently utilized, most popular and industry standard N-2-amino protecting group for guanine bases is isobutyryl. On the other hand, if DMT-N-2 -acetyl guanosine-2'- TBDMS-3'- Cyanoethyl phosphoramidite (structure 6) is used, high quality of RNA's are obtained.

This has been substantiated by oligonucleotide Mass spectral data presented in the present invention.

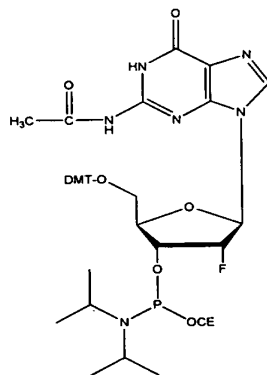
The deprotection kinetics of N-2 acetyl guanine in a nucleoside or oligonucleotide is significantly faster as compared to standard N-2 isobutyryl group on guanine residue, so that the quality of oligonucleotides especially RNA and modified RNA increases dramatically.

Synthons for RNA Synthesis



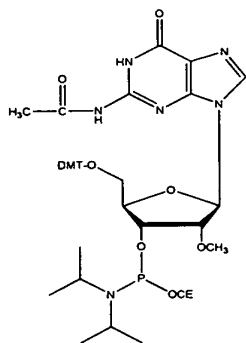
(Structure 6)

N-2-acetyl-guanosine-2'-TBDMS-3'-
CED Phosphoramidite

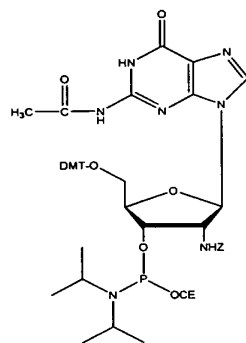


(Structure 7a)

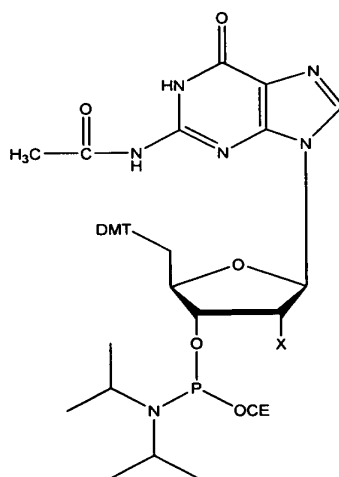
N-2-acetyl-guanosine-2'-fluoro-3'-
CED Phosphoramidite



(Structure 8)
N-2-acetyl-guanosine-2'-O-methyl-3'-
CED Phosphoramidite



(structure 9)
(N-2-acetyl-guanosine-2'-amino-3'-
CED Phosphoramidite); where Z is protecting group

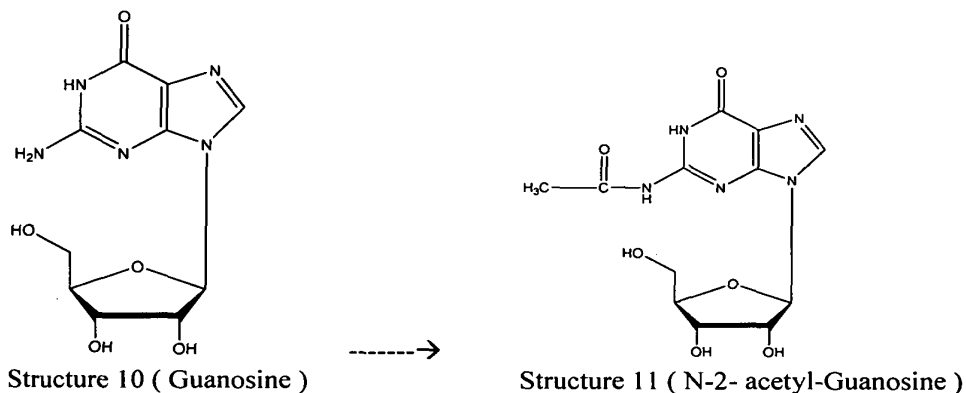


(Structure 7b)
N-2-acetyl-guanine-2'-modified -3'-

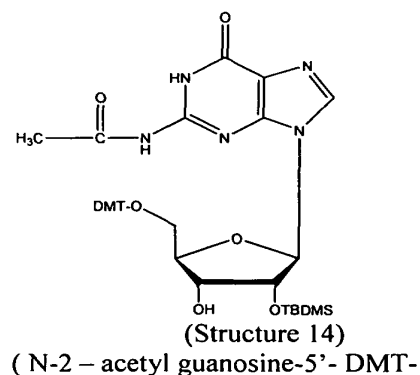
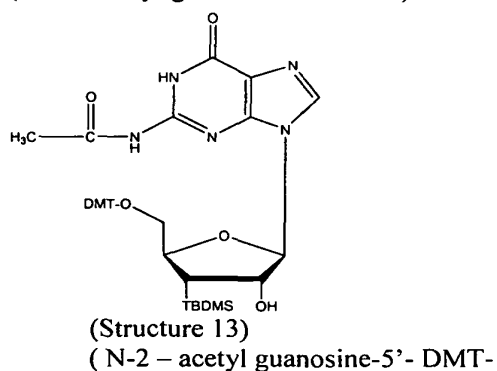
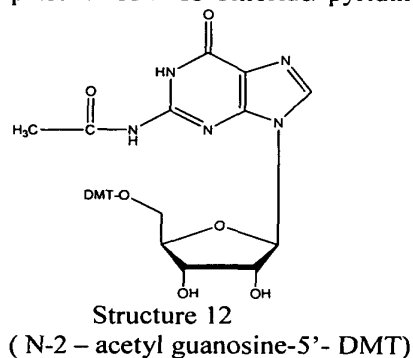
CED Phosphoramidite
(Where X; F, OCH₃, NH₂-Protected)

Scheme 1: Step wise synthesis of Synthons (structures 6) starting from compound 10, followed by 11, followed by compound 12 & 13, for RNA Synthesis:

The synthesis of phosphoramidites, structures 6 was carried out using nucleosides 10, 11, 12 & 14 as depicted by the following structures:

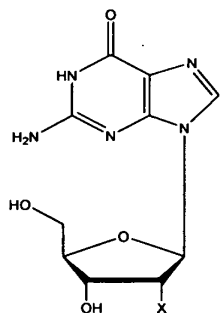


Note: compound (structure 12) is achieved by transient N-2 protected with acetyl chloride in presence of TMS Chloride/ pyridine as standard reaction conditions.

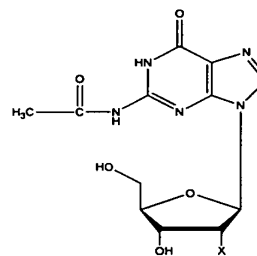


3'- TBDMS)

2'-TBDMS)

Scheme 2: Stepwise synthesis of Synthons (structures 7a, 8 &9) for RNA Synthesis:

(Structure 15)

(modified guanosine-
2'- X; where X;F, OCH₃, NH-protected)

(Structure 16)

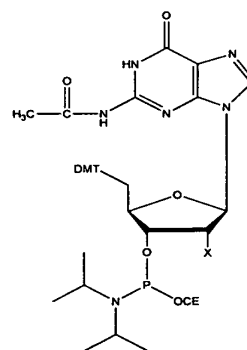
(N-2 – acetyl guanosine-
2'-X; where X; F, OCH₃ and NH-protected)

Note: Compound (structure 16) is produced by transient N-2 protected with acetyl chloride in presence of TMS Chloride/ pyridine as standard reaction conditions.

(N-2 – acetyl guanosine-5'- DMT-

2'- X; where X;F, OCH₃, NH-protected)

----->(structure 16)

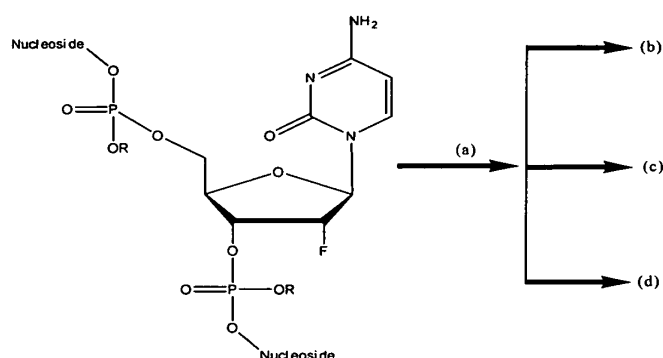


(structure 7b)

(N-2 – acetyl guanosine-5'- DMT-
2'- X; where X;F, OCH₃, NH-protected-
3'-phosphoramidite)

The utility of N-FMOC protected nucleoside was discovered by the present inventors and it was shown to possess additional significance and importance. When oligo ribonucleotide chimeras comprise of mixed bases composed of 2'- fluoro and 2'- ribo bases they present a challenge in obtaining pure chimera oligonucleotides. It has been well documented by several

recent reports that oligonucleotide chimeras having 2'-fluoro-2'-deoxy bases along with natural ribo bases present difficulty in obtaining pure oligos. It has been shown that with strongly basic conditions, there is significant loss of fluorine as loss of Hydrogen Fluoride ("HF") is seen as M-20 peak in Mass spectral analysis. Besides it has also been shown that uracil and cytosine are eliminated to a significant extent, when oligo chimeras containing 2'-fluoro-2'-deoxy uridine and 2'-fluoro-2'-deoxy cytidine are part of chimeras (see scheme 3).



Scheme3. Graphic Representation of effect on quality of oligonucleotides containing 2'-fluoro nucleosides: (a) deprotection using methyl amine, the usual deprotection condition of protecting groups of bases, (b) loss of fluorine leading to loss of HF, generating significant amount of M-20, (c) loss of cytosine and uracil, the pyrimidine bases is observed quite frequently, d) with the loss of pyrimidine, subsequent cleavage of chain occurs.

The studies as shown in scheme 3 were carried out independently by two groups recently. Ken Hill, Agilent Technologies, Boulder, Colorado; Identification of Process Related Impurities – Understanding Oligonucleotide Production, TIDES 2007, Las Vegas, Nevada. The author showed depyrimidation of chimera oligonucleotides carrying 2'-fluoro-2'-deoxy pyrimidine in RNA's; and, Nanda D. Sinha, Avecia Biotechnologies Inc., Massachusetts- Depyrimidation, as well as loss of HF and chain cleavage in chimeras having 2'-fluoro-2'-deoxy pyrimidines in RNA sequences. Eurotides, 2005, Munich, Germany.

Our data shows that by utilizing n- acetyl – guanine protected ribonucleoside phosphoramidites, used in oligo with 2'-fluoro substitution, high quality full length

RNA were obtained.

It is therefore imperative to utilize 2'-fluoro-2'-deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups having N-2 acetyl guanine for mild and shorter base deprotection protocol. Although there is no B-elimination pathway for N-2-acetyl guanosine protecting group, still high purity and integrity oligo chimeras is obtained and RNA high quality for therapeutic and diagnostic applications, such as for applications in SiRNA synthesis.

Besides the 2'-fluoro nucleosides, 2'-O-alkyl nucleoside phosphoramidites are extensively used in the design of biologically active oligonucleotides for therapeutic and diagnostic applications as fully alkylated or as chimeras. Amongst the 2'-O-alkyl nucleosides and phosphoramidites the most common are 2'-O-Methyl oligonucleotides which have shown enormous promise in drug design and specific diagnostics applications. Thus 2'-OMethyl oligoribonucleotides- RNA complexes have higher T_m than corresponding oligo-deoxy ribonucleoside – RNA duplexes, Iribarren, A.M., Sproat, B.S., Neuner, P., Sulston, I., Ryder, U., and Lamond, A.I., Proc. Natl. Acad. Sci. USA 87, 7747-7751, 1990. Various 2'-OMethyl-N-FMOC protected nucleosides and phosphoramidites offer great advantage to produce high quality of DNA- RNA oligonucleotides and chimera for biological applications.

Defined sequence RNA synthesis is now well established and currently in use for synthesis and development of vast variety of therapeutic grade RNA aptamers, tRNA's, Si RNA and biologically active RNA molecules. This approach utilizes a ribonucleoside with suitable N-protecting group, 5'-Protecting group, generally, and most popular being dimethoxytriphenyl, commonly called DMT group, 2'-protecting group, out of which most popular is t-Butyldimethylsilyl ether and a 3'-phosphoramidite, wherein the most popular still is cyanoethyl diisopropyl (component 1). This component is then coupled with a nucleoside with a suitable N-protecting group, 2' or 3' succinate of a ribonucleoside attached to a solid support. The coupling of component 1 and 5'-OH-n-protected –2',3'-protected-nucleoside are also achieved in solution phase in the presence of an activator to lead to dimers and oligoribonucleotides, followed by oxidation (3'→5' direction synthesis), also lead to protected dinucleoside having a 3'-5'-internucleotide linkage, Ogilvie, K.K., Can. J.

Chem., 58, 2686, 1980.

The N- acetyl guanine protecting group offers great potential in RNA synthesis of defined sequence based on our invention as outlined here.

This group can be utilized in conjunction with various 2'- protecting groups required for RNA synthesis. The most widely utilized 2'- protecting, tert- butyl-dimethylsilyl, which has been extensively developed by Ogilvie and coworkers as 2'- hydroxy protecting group for oligo ribonucleotide synthesis (Ogilvie, K.K., Sadana, K.L, Thompson, E.A., Quilliam, M.A., and Westmore, J.B *Tetrahedron Letters*, 15, 2861-2864, 1974; Ogilvie, K.K., Beaucage, S.L, Entwistle, D.W., Thompson, E.A., Quilliam, M.A., and Westmore, J.B. *J. Carbohydrate Nucleosides Nucleotides*, 3, 197-227, 1976 ; Ogilvie, K.K. Proceedings of the 5th International Round Table on Nucleosides, Nucleotides and Their Biological Applications, Rideout, J.L., Henry , D.W., and Beacham L.M., III, eds., Academic, London, pp. 209-256,1983).

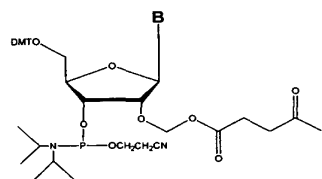
These studies subsequently led to continued developments of methods which were amenable to both solution and solid phase oligonucleotide synthesis, and the first chemical synthesis of RNA molecules of the size and character of tRNA (Usman, N., Ogilvie, K.K., Jiang, M.-Y., and Cedergren, R.J. *J. Am. Chem. Soc.* 109, 7845-7854, 1987; Ogilvie, K.K., Usman, N., Nicoghossian, K, and Cedergren, R.J. *Proc. Natl. Acad. Sci. USA*, 85, 5764-5768, 1988 ; Bratty, J., Wu, T., Nicoghossian, K., Ogilvie, K.K., Perrault, J.-P., Keith, G. and Cedergren, R., *FEBS Lett.* 269, 60-64, 1990). The literature has been amply reviewed in subsequent excellent publication: Gait, M.J., Pritchard, C. and Slim, G., *Oligonucleotides and Their Analogs: A Practical Approach* (Gait, M.J., ed.), Oxford University Press Oxford, England, pp 25-48, 1991. Other protecting groups which have been lately employed for RNA synthesis are; bis (2- acetoxyethyl-oxy) methyl (ACE), Scaringe, S.A., Wincott, F.E., Caruthers, M.H., *J. Am. Chem. Soc.*, 120: 11820-11821, 1998; triisopropylsilyloxy methyl (TOM), Pitsch, S., Weiss, P.A., Jenny, L., Stutz, A., Wu, X., *Helv. Chim. Acta.* 84, 3773-3795, 2001 and t- butyldithiomethyl (DTM) (structure 16), Semenyuk, A., Foldesi, A., Johansson, T., Estmer-Nilsson , C., Blomgren, P., Brannvall, M., Kirsebom, L.A., Kwiatkowski, M., *J. Am. Chem. Soc.*, 128: 12356-12357, 2006 have been introduced.

Recently the scientists at ChemGenes have developed the method of RNA synthesis in reverse direction (5'→3' direction), for efficient incorporation of many ligands and chromophores conveniently and efficiently at the 3'- end of RNA molecules and a recent publication, Srivastava, S.C., Pandey, D.P., Srivastava, N., Bajpai, S.P., *Nucleic Acids Symposium Series No. 52*, 103-104, 2008 (structure 20, 21 & 22). Appropriately N- acetyl protected guanine can nucleosides, deoxy and ribo are envisaged to be synthesized

and DNA and RNA synthesis is proposed to utilize the benefits which reverse DNA and RNA synthesis offer. (US patent application entitled "RNA Synthesis – Phosphoramidites for Synthetic RNA in the Reverse Direction, and Application in Convenient Introduction of Ligands, Chromophores and Modifications of Synthetic RNA at the 3'- End" by

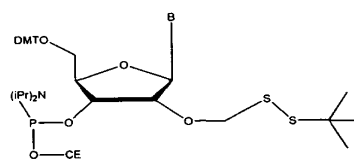
Suresh C. Srivastava et al. filed on September 8, 2009, and US Patent application entitled " "Synthesis of N-Fmoc Protected Deoxy Nucleosides, Ribo Nucleosides ... " by Srivastava et al. filed on November 30, 2009)

A novel 2'- protecting group, acetal levuliny ester (ALE) (structure 15 has been recently proposed (J.G.Lackey and M.J.Damha, Nucleic Acids Symposium Series, No. 52, 35-36, 2008). Similar to this protecting group another 2'- labile protecting group based on similar chemical nature, 2'- O-acetal ester, pivaloyloxy methyl which has been found mild 2'- O protecting group,T. Lavergne, A. Martin, F. Debart, J-J Vasseur, Nucleic Acids Symposium Series No. 52, , 51-52, 2008. The base protecting group used by these authors was n- acetyl and tBPAC. This gives additional credence to our process. And n- acetyl for RNA synthesis with other 2'- protecting groups or 2'- modification would be an ideal group for deprotection under mild basic condition in shorter period of time. '



2'-O-ALE-N-Fmoc amidites

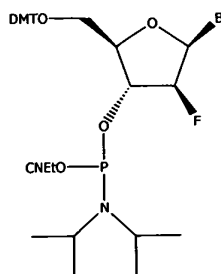
(Structure 17)



2'- DTM-N-Fmoc-amidites

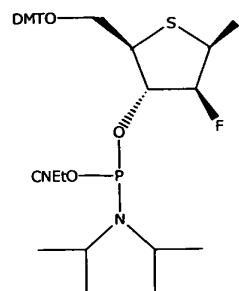
(Structure 18)

Chemically modified RNA have been synthesized having modified arabino sugars, 2'-deoxy-2'- fluoro- beta-D_arabinonucleic acid (FANA; structure 17)) and 2'-deoxy-4'- thio-2'- fluoro- beta-D_arabinonucleic acid (4'-Thio-FANA; structure 18) into sequences for SiRNA activities, Dowler, T., Bergeron, D., Tedeschi, Anna-Lisa, Paquet, L., Ferrari, N., Damha, M.J., Nucl. Acids Res., 34, 1669-1675, 2006. Amongst several new 2' -protecting group chemistry which have been developed , the 2'- protecting 2-cyanoethoxymethyl (CEM) (structure 19) has been shown for producing very long RNA also carries out RNA synthesis in conventional (3'→5'direction). However the quality of these long RNA remain in question.



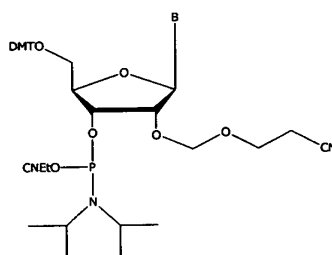
(structure 19)

2'- F-ANA modified phosphoramidites
phosphoramidites



(structure 20)

4'-thio-2'- F-ANA modified

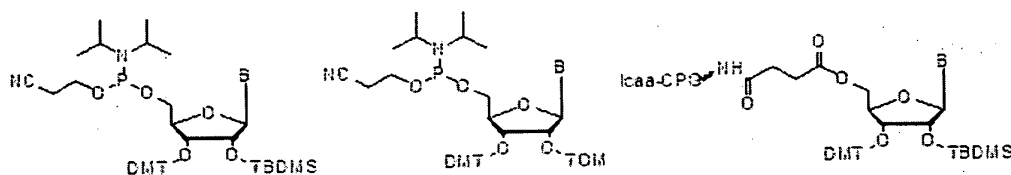


(Structure 21)

2'- CEM Protected RNA Intermediates

The N- acetyl protected guanine as nucleoside base having the 2'- protecting group discussed above can be combined and utilized in high purity RNA synthesis. The N- acetyl guanine protected nucleoside offers great potential in RNA synthesis of defined sequence. This applies to RNA synthesis in the conventional direction (3' → 5' direction as well as using our newly discovered 5' → 3' direction synthons; structures 21, 22 & 23).

Structures of reverse phosphoramidites and solid supports:



Where B = A (N-Bz), C (N-Bz), G (N-Ac), U.

Reverse RNA synthon-2'-
tBDSilyl-3'-DMT-5'- CED amidite
(Structure 22)

Reverse RNA synthon-2'-
TOM-3'-DMT-5'-CED amidite
(Structure 23)

Reverse RNA synthon
2'-tBDMS-3'-DMT-
5'- succinyl Support
(Structure 24)

Chemical synthesis of RNA is desirable because it avoids the inefficiencies and limitation of scale of synthesis such as by in vitro transcription by T7 RNA polymerase, Helm, M., Brule, H., Giege, R., Florence, C., RNA, 5:618-621, 1999. Chemical synthesis of RNA is desirable for studies of RNA structure and function, and many useful modifications can be achieved selectively, such as site specific introduction of functional groups; viz., disulphide cross linking as a probe of RNA tertiary structures, Maglott, E.J., Glick, G.D., Nucl. Acids Res., 26: 1301-1308, 1999. Synthesis of long RNA is very important for biologically active molecules such as tRNA, and such synthesis have been achieved, Persson, T., Kutzke, U., Busch, S., Held, R., Harmann, R.K., Bioorgan. Med. Chem., 9:51-56, 2001; Oglvie, K.K., Usman, N., Nicoghiosian, K., Cedrgren, R.J., Proc. Natl. Acad. Sci., USA, 85:5764-5768, 1988; Bratty, J., Wu, T., Nicoghiosian, K., Ogilvie, K.K., Perreault, J.-P., Keith, G., Cedergren, R.J., F.E.B.S. Lett., 269:60-64, 1990; Gasparutto, D., Livache, T., Bazin, H., Duplaa, A.M., Guy, A., Khorlin, A., Molko, D., Roget, A., Teoule, R., Nucl. Acids. Res., 20:5159-5166, 1992; Goodwin, J.T., Stanick, W.A., Glick, G.D., J.Org. Chem., 59:7941-7943, 1994. The aforementioned techniques cited in this para, employ synthesis of RNA in reverse direction (5'→3'direction), and hence introduction of a number of groups required for selective introduction at 3'- end is practical and convenient. We have observed higher coupling efficiency per step during automated oligo synthesis with our reverse RNA amidites (structures 21, 22, 23), and therefore they have greater ability to get higher purity and produce very long oligos. We also demonstrated that the process of our invention leads oligonucleotide free of M+1 species. Such species lead to closer impurities as shoulder of desired peak during HPLC analysis or purification or Gel purification. Such reverse RNA structures replacing the standard n- protecting group with n- Fmoc protecting group offer additional advantages not previously foreseen.

This invention relates to novel synthesis methodology utilizing N- acetyl guanine protected nucleosides, succinates, phosphoramidites, corresponding solid supports that are suitable for oligo deoxy nucleosides and RNA oligonucleotide synthesis. Our discovery using N- acetyl as nucleoside base protecting group, which is more base labile protecting group as compared to n- isobutyryl group is a novel approach to obtain highest purity oligonucleotides. This approach is designed to lead to very high purity and very clean oligonucleotide, after removal of the protecting groups and efficiently in order to produce

high purity and therapeutic grade DNA oligonucleotides, RNA oligonucleotides, diagnostic DNA, diagnostic RNA for microarray platform. The deprotection of acetyl protecting groups of the natural deoxy and ribonucleosides occurs under the mild deprotection and shorter contact time deprotection conditions and removal of such groups under very mild conditions would allow synthesis of various DNA and RNA of highest purity for diagnostics and therapeutic application. This approach is further designed to use acetyl guanine protecting group on various base sensitive nucleoside, and for use in oligo peptide synthesis.

Defined sequences RNA synthesis is now well established and currently in use for synthesis and development of vast variety of therapeutic grade RNA aptamers, tRNA's, siRNA and biologically active RNA molecules. This approach utilizes a ribonucleoside with suitable N- protecting group, 5'- Protecting group, generally and most popular being dimethoxytriphenyl, commonly called DMT group, 2'- protecting group, out of which most popular being t-Butyldimethylsilyl ether and a 3'- phosphoramidite, the most popular being cyanoethyl diisopropyl (component 1). This component is then coupled with a nucleoside with a suitable N- protecting group, 2' or 3' succinate of a ribonucleoside attached to a solid support (component 2). The coupling of component 1 and 5'- OH-n-protected -2',3'-protected-nucleoside (component 3) are also achieved in solution phase in presence of an activator to lead to dimers and oligoribonucleotides, followed by oxidation (3'→5' direction synthesis), also lead to protected dinucleoside having a 3'-5'- internucleotide linkage, Ogilvie, K.K., Can. J. Chem., 58, 2686, 1980.

For the N- acetyl guanine nucleoside protecting group the widely utilized 2'- protecting group, viz.; TBDMS group, which has been extensively developed by Ogilvie and coworkers as 2'- hydroxy protecting group for oligo ribonucleotide synthesis (Ogilvie, K.K., Sadana, K.L., Thompson, E.A., Quilliam, M.A., and Westmore, J.B. *Tetrahedron Letters*, 15, 2861-2864, 1974; Ogilvie, K.K., Beaucage, S.L, Entwistle, D.W., Thompson, E.A., Quilliam, M.A., and Westmore, J.B. *J. Carbohydrate Nucleosides Nucleotides*, 3, 197-227, 1976 ; Ogilvie, K.K. Proceedings of the 5th International Round Table on Nucleosides, Nucleotides and Their Biological Applications, Rideout, J.L., Henry , D.W., and Beacham L.M., III, eds., Academic, London, pp. 209-256,1983).

These studies subsequently led to continued developments of methods which were

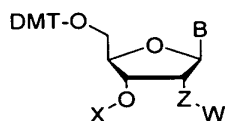
amenable to both solution and solid phase oligonucleotide synthesis, and the first chemical synthesis of RNA molecules of the size and character of tRNA (Usman, N., Ogilvie, K.K., Jiang, M.-Y., and Cedergren, R.J. *J. Am. Chem. Soc.* 109, 7845-7854, 1987; Ogilvie, K.K., Usman, N., Nicoghossian, K., and Cedergren, R.J. *Proc. Natl. Acad. Sci. USA*, 85, 5764-5768, 1988 ; Bratty, J., Wu, T., Nicoghossian, K., Ogilvie, K.K., Perrault, J.-P., Keith, G. and Cedergren, R., *FEBS Lett.* 269, 60-64, 1990). The literature has been amply reviewed in subsequent excellent publication: Gait, M.J., Pritchard, C. and Slim, G., *Oligonucleotides and Their Analogs: A Practical Approach* (Gait, M.J., ed.), Oxford University Press Oxford, England, pp 25-48, 1991. Other protecting groups which have been lately employed for RNA synthesis are ; bis (2- acetoxyethyl-oxy) methyl (ACE), Scaringe, S.A., Wincott, F.E., Caruthers, M.H., *J. Am. Chem. Soc.*, 120: 11820-11821, 1998; triisopropylsilyloxy methyl (TOM), Pitsch, S., Weiss, P.A., Jenny, L., Stutz, A., Wu, X., *Helv. Chim. Acta.* 84, 3773-3795, 2001 and t- butyldithiomethyl (DTM) (structure 1), Semenyuk, A., Foldesi, A., Johansson, T., Estmer-Nilsson, C., Blomgren, P., Brannvall, M., Kirsebom, L.A., Kwiatkowski, M., *J. Am. Chem. Soc.*, 128: 12356-12357, 2006 have been introduced. However none of these are amenable to carry out the synthesis in reverse direction ($5' \rightarrow 3'$ direction), and hence lack the capability of introduction of many ligands and chromophores conveniently and efficiently at the 3'- end of RNA molecules.

Our present invention is directed towards the synthesis of high purity RNA's and specifically to introduce nucleosidic or non – nucleosidic bases, which are labile in nature for synthesis of synthetic RNA's. Such RNA's will have vast application in therapeutics, diagnostics, drug design and selective inhibition of an RNA sequence within cellular environment, on demand blocking a function of different types of RNA present inside cell. Silencing gene expression at mRNA level with nucleic acid based molecules is a fascinating approach. Among these RNA interference (RNAi) has become a proven approach which offers great potential for selective gene inhibition and showing great promise for application in control and management of various biochemical and pharmacological processes. Early studies by Fire et al., Fire, A., Xu, S., Montgomery, M.K., Kostas, S.A., Driver, S.E., and Mello, C.C, *Nature*, 391, 806-811, 1998, showed that RNA interference in *Caenorhabditis elegans* is mediated by 21 and 22 nucleotide RNA sequences. This was further confirmed as general phenomenon of specific inhibition

of gene expression by small double stranded RNA's being mediated by 21 and 22 nucleotide RNA's, *Genes Dev.*, 15, 188-200, 2001. Simultaneous studies by Capie, N.J., Parrish, S., Imani, F., Fire, A., and Morgan, R.A., confirmed such phenomenon of specific gene expression by small double stranded (ds) RNAs in invertebrates and vertebrates alike. Subsequently a vast amount of research led to confirmation of above studies and established RNAi as a powerful tool for selectively and very specific gene inhibition and regulation, Nishikura, K., *Cell*, 107, 415-418, 2001; Nykanen, A., Haley, B., Zamore, P.D., *Cell*, 107, 309-321, 2001; Tuschl, T., *Nat. Biotechnol.*, 20, 446-448, 2002; Mittal, V., *Nature Rev.*, 5, 355-365, 2004; *Proc. Natl. Acad. Sci. USA*, 99, 6047-6052, 2002; Donze, O. & Picard, D., *Nucl. Acids. Res.*, 30, e46, 2002; Sui, G., Soohoo, C., Affar el, B., Gay, F., Shi, Y., Forrester, W.c., and Shi, Y., *Proc. Natl. Acad. Sci. USA*, 99, 5515-5520, 2002; Paddison, P.J., Caudy, A.A., Bernstein, E., Hannon, G.J., and Conklin, D.S., *Genes Dev.*, 16, 948-959, 2002.

SUMMARY OF THE INVENTION

The invention provides a novel method of RNA synthesis utilizing N-2- acetyl guanosine-5'- DMT-2'-TBDMS- protected nucleoside phosphoramidite and other nucleoside phosphoramidites outlined in Formula 1 below. The synthetic route that has been developed allows obtaining desired nucleosides without any contamination with unwanted impurities. The N- 2- acetyl protected guanosine nucleosides and other N-2 acetyl protected nucleosides having various 2'- protecting group discussed or 2'- modification, such as 2'- fluoro or 2'- amino groups can be combined with cyanoethyl phosphate protecting group and utilized in high purity RNA synthesis

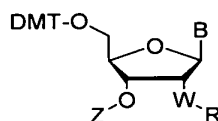


Formula 1

Where B = a) Adenine (*N-bz*), b) Cytosine (*N-acetyl*), c) Guanine (*N-acetyl*), d) 5-methyl cytosine(*N- Fmoc*), e) 5- bromocytidine(*N-Fmoc*), i) 5- iodo cytosine(*N- Fmoc*), j) 5- fluorocytosine(*N-Fmoc*), k) 2,6-diaminopurine(*N-Fmoc*), l) 2- amino purine(*N-Fmoc*), Z= Oxygen & W is H, ; Z=Oxygen and W= tButyldimethyl silyl, TOM (triisopropylloxymethylene), acetal levulinyl ester (ALE), pivaloyloxy;

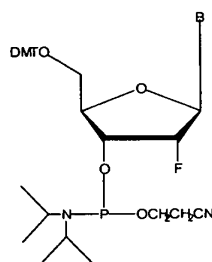
cyanoethylmethylene (CEM); dithiomethylene (DTM); Z= oxygen and W is methyl and other higher alkyls, alkenes and alkynes; Z=W= ribo Fluorine; Z=W=ara fluorine; Z= amino, W= amino protecting group ;X = a) cyanoethyl-dialkyl phosphoramidite.

The nucleic base in our invention protected with N-2 acetyl guanosine (Acetyl; Ac). The solid support having protected nucleosides containing 5'- DMT group and 3' terminus is attached to solid support (Formula 2).



(Formula 2)

Where B = a) Adenine (*N-bz*), b) Cytosine (*N-acetyl*), c) Guanine (*N-acetyl*), d) 5-methyl cytosine(N- Fmoc), e) 5- bromocytidine(N-Fmoc), i) 5- iodo cytosine(N- Fmoc), j) 5- fluorocytosine(N-Fmoc), k) 2,6-diaminopurine(N-Fmoc), l) 2- amino purine(N-Fmoc), Z= Oxygen & W is H, ; Z=Oxygen and W= tButyldimethyl silyl, TOM (triisopropoxyxymethylene), acetal levulinyl ester (ALE), pivaloyloxy; cyanoethylmethylene (CEM); dithiomethylene (DTM); Z= oxygen and W is methyl and other higher alkyls, alkenes and alkynes; Z=W= ribo Fluorine; Z=W=ara fluorine; Z= amino, W= amino protecting group ;Z = a) succinimido long chain attached to a solid support, b) hydroquinone succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support.



(Formula 3)

Where B = a) Adenine (*N-bz*), b) Cytosine (*N-acetyl*), c) Guanine (*N-acetyl*), d) 5-methyl cytosine(N- Fmoc), e) 5- bromocytidine(N-Fmoc), i) 5- iodo cytosine(N- Fmoc), j) 5- fluorocytosine(N-Fmoc), k) 2,6-diaminopurine(N-Fmoc), l) 2- amino purine(N-Fmoc)

Z=W=ara fluorine; Z= amino, W= amino protecting group ;Z = a) succinimido long chain attached to a solid support, b) hydroquinone succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support.

The nucleosides can be used in oligonucleotide synthesis. The base deprotection step can be performed in mild basic conditions or a tertiary amine, secondary amines, such as piperidine capable of removal of Fmoc protecting group via B- elimination in solution phase or on solid support without oligonucleotide detachment.

The invention also envisages kits that contain one or more of the disclosed nucleoside compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawing figures display the experimental results as follows:

Fig.1a: HPLC Chromatogram of 5'-DMT -ribo Guanosine (n-acetyl)

Fig.1b: UV Analysis of 5'-DMT -ribo Guanosine (n-acetyl)

Fig.1c: Table of the UV Analysis of 5'-DMT-ribo Guanosine (n-acetyl)

Fig.2a: HPLC Chromatogram of 5'-DMT-2'-TBDMS-ribo Guanosine (n-acetyl)

Fig.2b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

Fig.2c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

Fig.3a: HPLC Chromatogram of 5'-DMT-2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

Fig.3b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

Fig.3c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

Fig.3d: ³¹P NMR Spectrum of 5'-DMT -2'- TBDMS -ribo Guanosine (n-acetyl)-phosphoramidite

Fig.4a: HPLC Chromatogram of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).

Lot No. CH5-9R-45-01

After purification purity: 91.3%

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.4b: UV Analysis of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.4c: Table of UV Analysis of purified RNA Sequence
(G7799G97GAAAGA79GA9A9AGAGG7).

Lot No. CH5-9R-45-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.4d: ESI-MS Analysis of purified RNA Sequence
(G7799G97GAAAGA79GA9A9AGAGG7).

Lot No. CH5-9R-45-01

Targeted mass: 8757.5

Observed Mass: 8756.3

Note:1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.4e: Synthesis Report of RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).

Lot No. CH5-9R-45-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.5a: HPLC Chromatogram of purified RNA Sequence
(7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).

Lot No. CH5-10R-31-01

After purification purity: 90.53%

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.5b: UV Analysis of purified RNA Sequence
(7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).

Lot No. CH5-10R-31-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.5c: Table of the UV Analysis of purified RNA Sequence

(7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).

Lot No. CH5-10R-31-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.5d: ESI-MS Analysis of purified RNA Sequence

(7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).

Lot No. CH5-10R-31-01

Targeted mass: 12785.2

Observed Mass: 12784.4

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.5e: Synthesis Report of RNA Sequence

(7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).

Lot No. CH5-10R-31-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.6a: ESI-MS Analysis of purified RNA Sequence

(57A7GAGAG9GG97G9777AGGGGAGAA797G9G79779GG5).

Lot No. 092608

Targeted mass: 13831.7

Observed Mass: 13830.2, 13735.8, 13642.9

Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.6b: Synthesis Report of RNA Sequence

(57A7GAGAG9GG97G9777AGGGGAGAA797G9G79779GG5).

Lot No. 092608

Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

Note: 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to synthesis of novel N-2-acetyl protected deoxy and ribo- guanosine, –

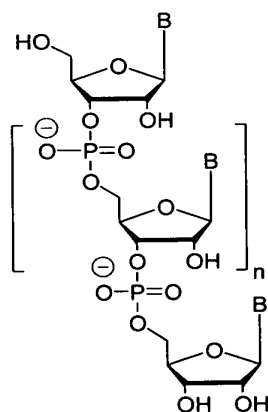
N-acetyl protected modified guanosine, their succinates, phosphoramidites, corresponding solid supports that are suitable for high purity DNA and RNA synthesis. Our discovery using N- acetyl as guanine purine base protecting group, which is more base labile protecting group as compared to traditional N-2-isobutyl guanine, is a novel approach to obtain highest purity oligonucleotides. This approach is designed to lead to high purity and very clean oligonucleotide, after efficient removal of the protecting groups and to produce high purity therapeutic grade DNA oligonucleotides, RNA oligonucleotides, diagnostic DNA, diagnostic RNA for microarray platform and high purity oligonucleotides in general.. The deprotection of N-acetyl protecting groups of the natural deoxy and ribonucleosides and modified deoxy and ribonucleotides occurs during a shorter period of base treatment conditions and removal of acetyl group from guanine moieties under such conditions allows synthesis of various DNA and RNA of highest purity for diagnostics and therapeutic application, RNA synthesis and high quality siRNA in general. This approach is further designed to use N- acetyl guanine protecting group on various base sensitive nucleoside such as sugar fluorinated oligonucleotides synthesis.

The nucleic bases in our invention protected with N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- tert butyl dimethyl silyl and 3'-cyanoethylphosphoramidite (CED) (group 1), N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- fluoro group and 3'-cyanoethylphosphoramidite (CED) (group 2) , N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- Omethyl group and 3'-cyanoethylphosphoramidite (CED) (group 3) , N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- amino (appropriately protected) group and 3'-cyanoethylphosphoramidite (CED) (group 4) , 5'-DMT-3'-succinyl-Icaa CPG-N-acetyl guanine protected nucleosides or 5'-DMT-2'-tBDSilyl (tBDSi) -3'-cyanoethylphosphoramidite (CED) . N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides (group 5), 5'-DMT-3'-succinyl-Icaa CPG-N-acetyl guanine protected nucleosides (group 6) .5'-DMT-2'-TBDMS –N- acetyl protected- guanosine -3'-amidites The invention also contemplates method for preparing the disclosed compositions. The starting base protection with transient protection with TMSChloride/ pyridine at low temperature affording N-acetyl protected nucleoside. The products are invariably crystallized.

Following tritylation reaction (with DMT-Chloride) of the nucleoside with DMT chloride in pyridine gave desired nucleoside in high yields for rG, 2'- fluoro-rG, 2'- Omethyl-guanosine. In the case of 2'- amino, the amino group is protected first with trifluoro methyl group.

Additional Notes for claims, structures

- (i) A method for 3' to 5' direction of oligonucleotide bond formations shown in formula 4 in synthetic RNA oligomers. The RNA could consist of natural of modified nucleo bases as described in claim 1 to synthesize gapmers, phosphodiester, phosphorothiates, phosphoselenate. One of the nucleoside components will have N- acetyl guanosine base. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.



Formula 4.

- (ii) A method for DNA & RNA synthesis using mild amine, secondary or tertiary amine for removal of N-acetyl protecting group of guanosine and cyanoethyl phosphate protecting group for RNA synthesis via 3' to 5' direction of oligonucleotide bond formations shown in formula 4 in synthetic RNA oligomers. The RNA could consist of natural of modified nucleo bases, gapmers, phosphodiester, phosphorothiates, phosphoselenate. The nucleoside components

will have N- Fmoc as protecting group. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.

- (iii) A method for DNA & RNA synthesis using mild basic conditions , such as methyl amine solution, alkylamines , secondary or tertiary amine for removal of N-acetyl guanosine protecting group and cyanoethyl phosphate protecting group for RNA synthesis via 3' to 5' direction of oligonucleotide bond formations shown in formula 4 in synthetic RNA oligomers. This is followed by wash of liberated protecting groups. The RNA could consist of natural or modified nucleobases, gapmers, phosphodiester, phosphorothiates, phosphoselenate. The nucleoside components will have N- Fmoc as protecting group. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.
- (iv) A method for DNA & RNA synthesis using mild basic conditions, such as methyl amine solution, alkylamines, secondary or tertiary amine for removal of N-acetyl guanosine from solid support base as well as nucleosides in the rest of sequence and cyanoethyl phosphate protecting group. DNA and RNA synthesis can be carried out via 3' to 5' direction of oligonucleotide bond formations. This is followed by wash of liberated protecting groups. The support bound DNA and RNA could consist of natural or modified nucleobases, gapmers, phosphodiester, phosphorothiates, phosphoselenate. The nucleoside components during such oligo synthesis will have N-acetyl as protecting group. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.
- (v) The modified nucleosides incorporated by this method could consist of one or more of purine or pyrimidine modifications such as but not limited to , 5- Fluoro-U, 5-Fluoro dU, 5-fluoro-dC, 5-Fluoro-rC, pseudouridine, 5-methyl-dU, 5-methyl-rU, 5-methyl-dC, 5-methyl-rC, 5-bromo-dU, 5-bromo-rU, 5-bromo-dC, 5-bromo-rC, 5-iodo-dU, 5-iodo-rU, 5-vinyl-dU, 5-vinyl-rU, 5-vinyl thymidine, N-3 methyldeoxy uridine, N-3 methyl-ribouridine, N-3 methyl thymidine, 4-thio uridine, 4-thio-2'-deoxyuridine, 2,6-diaminopurine deoxy riboside, N-3 methyl ribothymidine, 2, 6-diaminopurine riboside, 8-bromo 2'- deoxy adenosine, 8-bromo-r

- adenosine, 8-oxo-deoxy adenosine, 8-oxo-riboadenosine, 8-oxo-2'-deoxy- adenosine, 8-oxo-riboadenosine, 8-oxo-deoxy inosine, 8-oxo-ribo inosine, 8-bromo-deoxy inosine, 8-bromo-ribo-inosine, N-1 methyl-riboadenosine, N-1 methyl-2'- deoxy adenosine, N-1 methyl 2'-deoxy inosine, N-1 methyl riboadenosine, N-1 methyldeoxy guanosine, N-1-methyl-riboguanosine, etheno adenosine, etheno 2'- deoxy adenosine, purine 2'- deoxy riboside, purine-ribonucleoside, 2-aminopurine-2'-deoxyriboside, 2-aminopurine-ribonucleoside,
- (vi) Labelling of internal positions of an RNA synthesized by this methods with chromophores such as , but not limited to Fluorescein-C-5 dT, Dabcyl- C-5 thymidine, internal carboxyl group 5-dU-methylacrylate, biotin dT (biotin wattached via spacer to C-5 of dU), amino-dT (terminal amino attached via C-6 spacer to C-5 dU).
 - (vii) The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-fluoro ribo nucleosides (2'-F-ANAs) such as A, C, G, U , Inosine and modified nucleosides containing 2'- Fluoro, in one or more positions of an RNA or DNA sequence synthesized by this method.
 - (viii) The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-methoxy ribo nucleosides (2'-OMe-) such as A, C, G, U , Inosine and modified nucleosides containing 2'- methoxy, in one or more positions of an RNA or DNA sequence synthesized by this method.
 - (ix) The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-amino ribo nucleosides (2'-NH₂) such as A, C, G, U , Inosine and modified nucleosides containing 2'- amino, in one or more positions of an RNA or DNA sequence synthesized by this method.
 - (x) The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-terminal amino ribo nucleosides (2'-terminal NH₂), attached via spacer from 2-10 atoms on nucleosides such as A, C, G, U , Inosine and modified nucleosides containing 2'- terminal amino, in one or more positions of an RNA or DNA sequence synthesized by this method.
 - (xi) The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-methoxy ethoxy ribo nucleosides (2'-MOE), such as A, C, G, U , Inosine and modified nucleosides containing 2'- MOE, in one or more positions of an RNA or DNA sequence synthesized by this method.
 - (xii) The sugar modification of modified nucleosides could consist of other 2'- O-alkyl groups, such as 2'- deoxy-2'-ethoxy, propargyl, butyne ribo nucleosides (2'-OEt, O-Propargyl, 2'-O-Butyne), such as A, C, G, U , Inosine and modified nucleosides containing 2'- 2'-OEt, O-Propargyl, 2'-O-Butyne, in one or more positions of an RNA or DNA sequence synthesized by this method.

- (xiii) The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-fluoro arabino nucleosides (2'-F-ANAs) such as A, C, G, U , Inosine and modified nucleosides containing 2'-F-ANAs), in one or more positions of an RNA or DNA sequence synthesized by this method.
- (xiv) The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-fluoro 4'-thioarabino nucleosides (4'-S-FANAs) such as A, C, G, U, Inosine and modified nucleosides containing 4'-S-FANAs in one or more positions of an RNA or DNA sequence synthesized by this method.
- (xv) The RNA comprising one or more 2'-5'- linkage within the sequence , at the 3'- end of the sequence or at the 5'- end of the sequence.
- (xvi) The RNA having a 3'- end, synthesized by the method of this invention containing reverse attached deoxy nucleosides such as dT, dC, dG , thymidine, attached via their 3'- hydroxyl function.
- (xvii) The RNA having a 3'- end synthesized by the method of this invention containing reverse attached ribonucleosides such as rA, rC, rG, rU, attached via their 2' or 3'- hydroxyl function.
- (xviii) The RNA synthesis comprising 2'- triisopropylsilyloxy methyl (TOM), protecting group.
- (xix) The RNA synthesis comprising 2'- t- butyldithiomethyl (DTM) protecting group.
- (xx) The reverse RNA synthesis comprising the modified base comprising 2'- deoxy-2'- fluoro-beta-D_arabinonucleic acid (FANA).
- (xxi) The RNA synthesis comprising the modified base comprising 4'-thio- 2'- deoxy-2'- fluoro-beta-D_arabinonucleic acid (4'-Thio- FANA).
- (xxii) The RNA synthesis comprising the modified sugar comprising 2'- OMethyl modification.
- (xxiii) The RNA synthesis comprising the modified sugar comprising Bicyclic locked nucleic acids (LNA's).
- (xxiv) The RNA synthesis comprising the modified sugar altritol sugar to lead to modified oligonucleotides (ANA).
- (xxv) The RNA synthesis comprising the step of conjugation of peptides, such as cell penetrating peptides (CPPs) or membrane permeant peptide (MPPs) utilizing either the free amine function of such peptides and a 3'- terminal carboxylic function on the reverse synthesized RNA. The CPPs and MPPs having an appropriate carboxyl function can be coupled to the free terminal amino function of an FMOC protected nucleotide or an oligonucleotide.

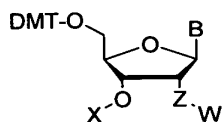
- (xxvi) The DNA and RNA synthesis comprising the 2'-5'- linked DNA units or 2'-5'- RNA units within the sequence , at the 3'- end of the sequence or at the 5'- end of the sequence.

Based on the foregoing disclosure and experimental results obtained which have been reported in the drawing figures herein, and in the earlier patent applications of ChemGenes Corporation,

We claim:

CLAIMS

1. Derivatized nucleoside and phosphoramidites of general formula 1.



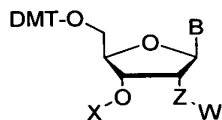
Formula 1

Where B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

Z=W= ribo Fluorine or ara fluorine;

X is cyanoethyl-dialkyl phosphoramidite

2. Derivatized nucleoside and phosphoramidites of general formula 1.



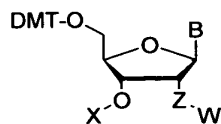
Formula 1

Where B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

Z is Hydrogen or Oxygen; if Z is Hydrogen then W is not used, and if Z is Oxygen then W is a member of the group consisting of (tButyldimethyl silyl, triisopropyloxymethylene (TOM), acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and,

X is cyanoethyl dialkyl phosphoramidite.

3. Derivatized nucleoside and phosphoramidites of general formula 1.



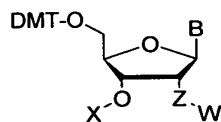
Formula 1

Where B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

Z is Hydrogen or Oxygen; if Z is Hydrogen then W is not used, and if Z is Oxygen then W is a member of the group consisting of (methyl and other higher alkyls, alkenes and alkynes); and

X is cyanoethyl dialkyl phosphoramidite.

4. Derivatized nucleoside and phosphoramidites of general formula 1.



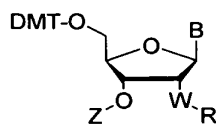
Formula 1

Where B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

Z= amino, W= amino protecting group ;

X is cyanoethyl-dialkyl phosphoramidite.

5. Derivatized nucleosides, succinates and solid supports of general formula 2.



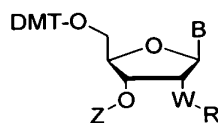
(Formula 2)

Where B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl

cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

W=R= ribo Fluorine or ara fluorine; Z represents a member of the group (succinimido long chain, hydroquinione succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support.

6. Derivatized nucleosides, succinates and solid supports of general formula 2.



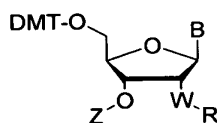
(Formula 2)

wherein, B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

W is Hydrogen or Oxygen; if W is Hydrogen then R is not used, and if W is Oxygen then R is a member of the group consisting of (tButyldimethyl silyl, triisopropyloxymethylene (TOM), acetal levuliny ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and,

Z represents a member of the group (succinimido long chain, hydroquinione succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support.

7. Derivatized nucleosides, succinates and supports of general formula 2,



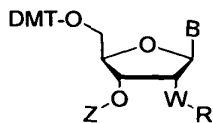
(Formula 2)

Wherein B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

W is Hydrogen or Oxygen; if W is Hydrogen then R is not used, and if W is Oxygen then R is a member of the group consisting of (methyl and other higher alkyls, alkenes and alkynes); and,

Z represents a member of the group (succinimido long chain, hydroquinione succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support.

8. Derivatized nucleosides, succinates and solid supports of general formula 2



(Formula 2)

Where B is a member of the group (Guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

W=amino, R= amino protecting group ; and

Z represents a member of the group (succinimido long chain, hydroquinione succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support.

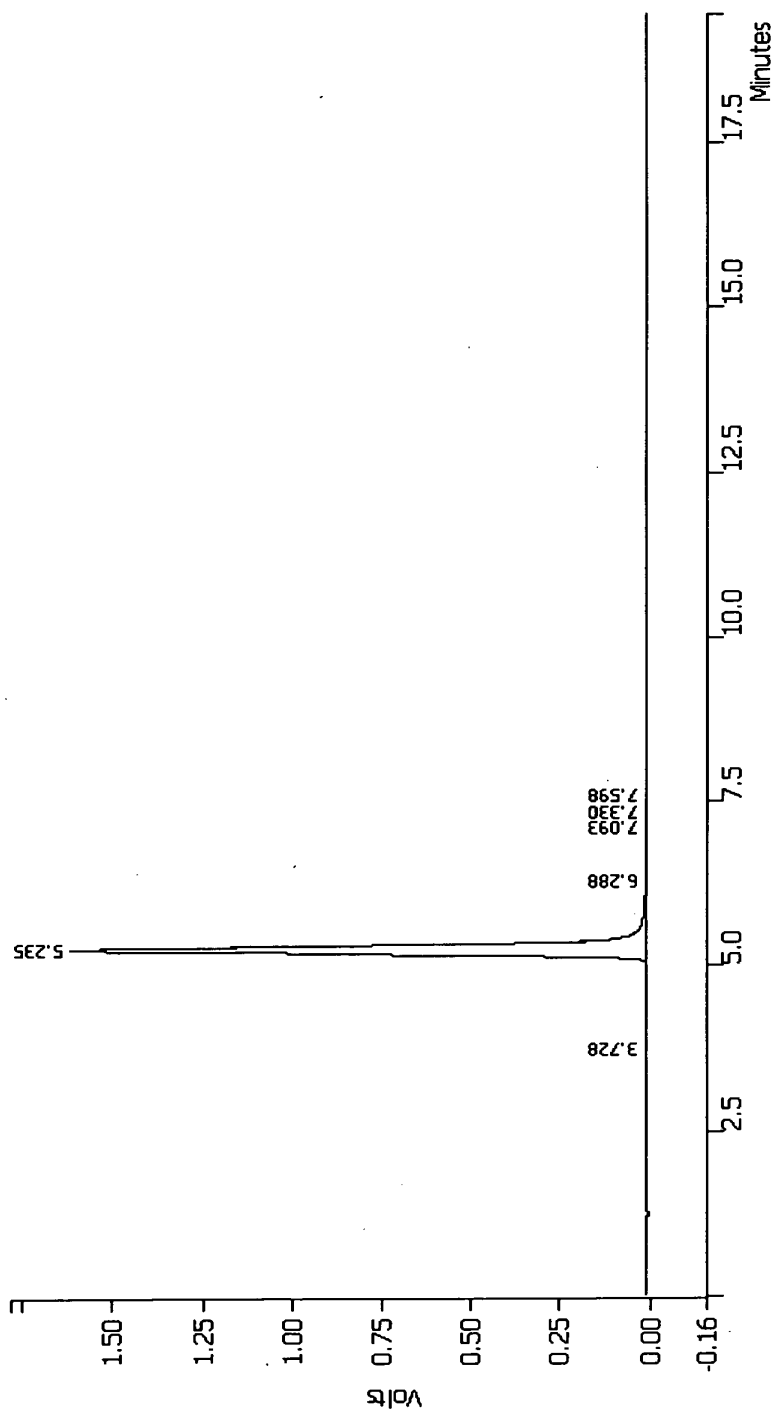


Fig. 1a: HPLC Chromatogram of 5'-DMT-ribo Guanosine (n-acetyl)

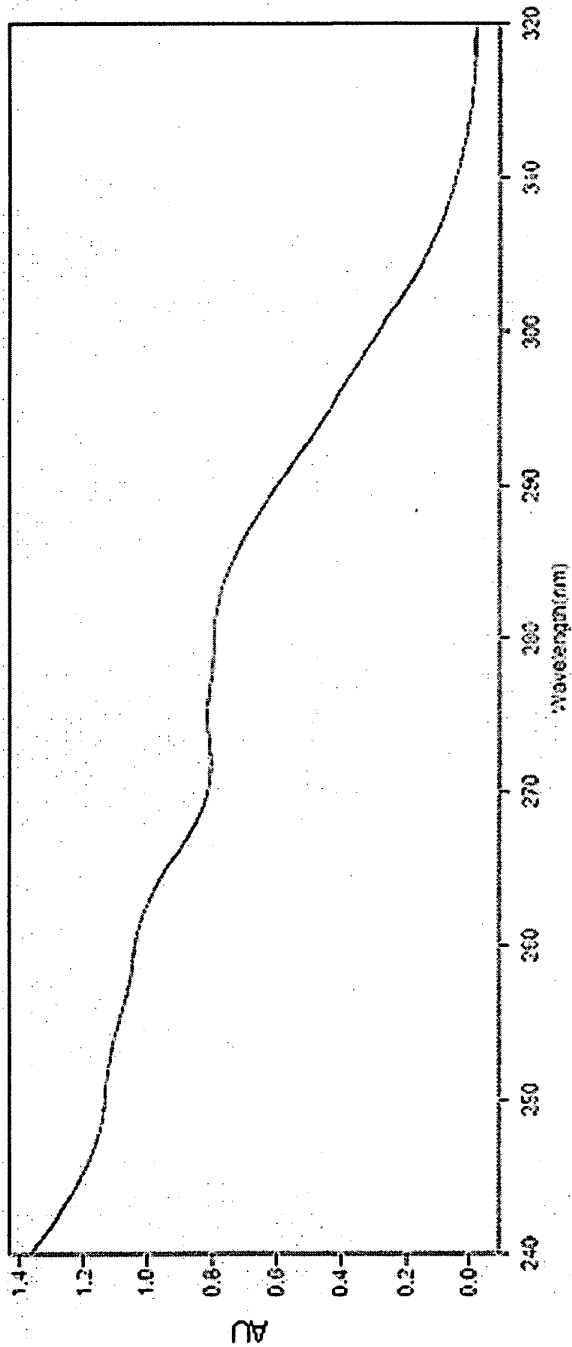


Fig.1b: UV Analysis of 5'-DMT –ribo Guanosine (n-acetyl)

Batch : 105361.sre

	A	B	C	D	E	F	G	H
1	105361.000		1	2	3	5	6	E _{max}
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280	250.0
3	Manual	A	1.133	1.042	0.794	1.087	1.312	17667

Fig.1c: Table of the UV Analysis of 5'-DMT–ribo Guanosine (n-acetyl)

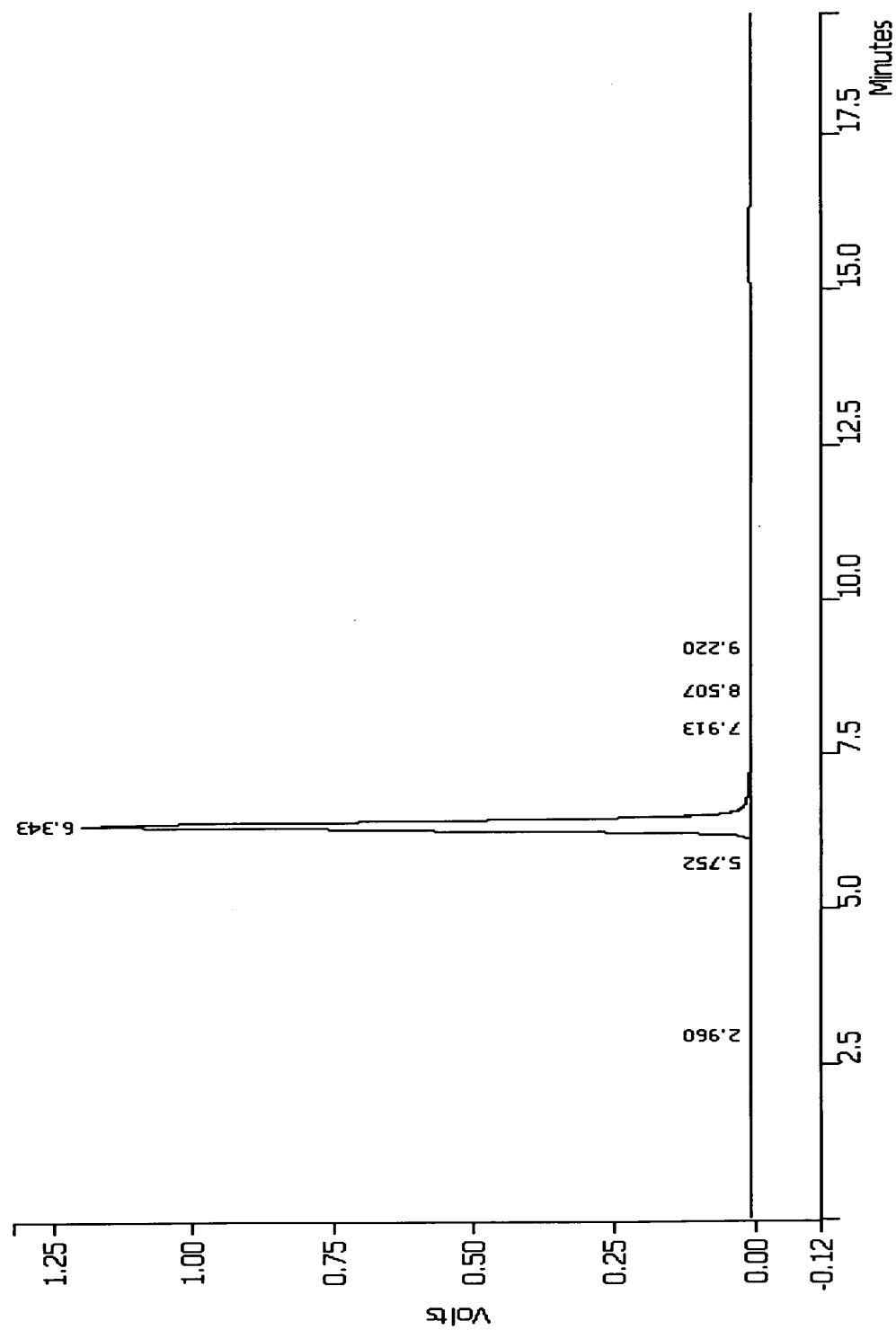


Fig.2a: HPLC Chromatogram of 5'-DMT-2'-TBDMS-ribo Guanosine (n-acetyl)

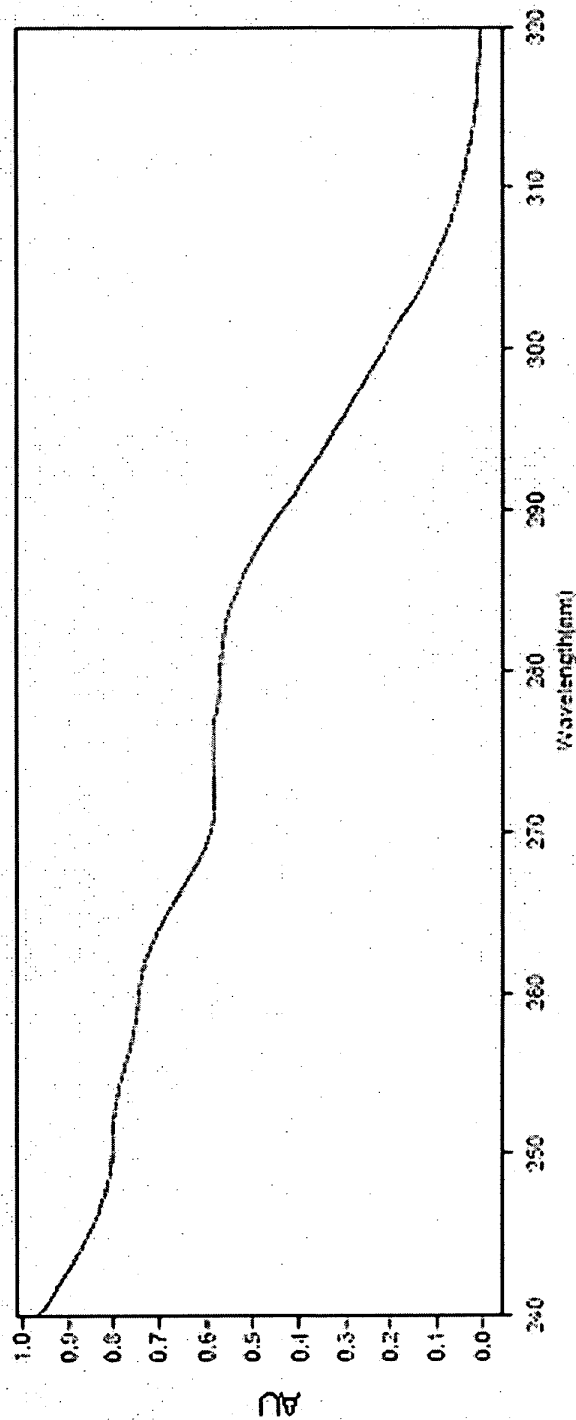


Fig.2b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

Batch : PS105-17.sre 1 / 1

	A	B	C	D	E	F	G	H
1	PS105-17		1	2	3	4.0	5.0	E _{max}
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280	250.0
3	Manual	A	0.803	0.745	0.569	1.078	1.310	22695
4	Cycle02	nm	250.0	260.0	280.0			
5	Manual	A	0.803	0.745	0.569	1.077	1.310	22695
6	Cycle03	nm	250.0	260.0	280.0			
7	Manual	A	0.803	0.745	0.569	1.078	1.309	22695
8	Ave. Value					1.078	1.310	22695

Fig.2c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

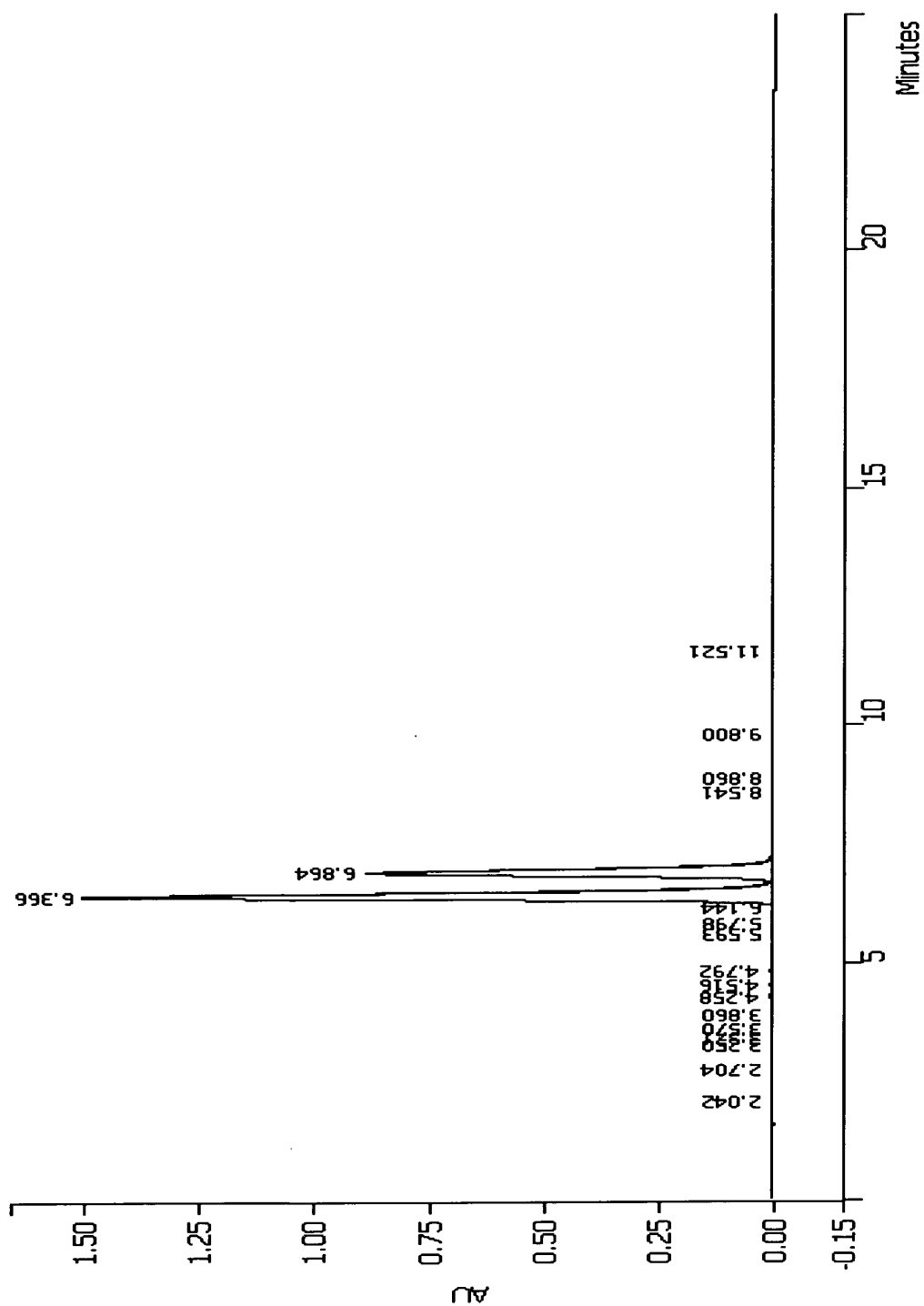


Fig.3a: HPLC Chromatogram of 5'-DMT-2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

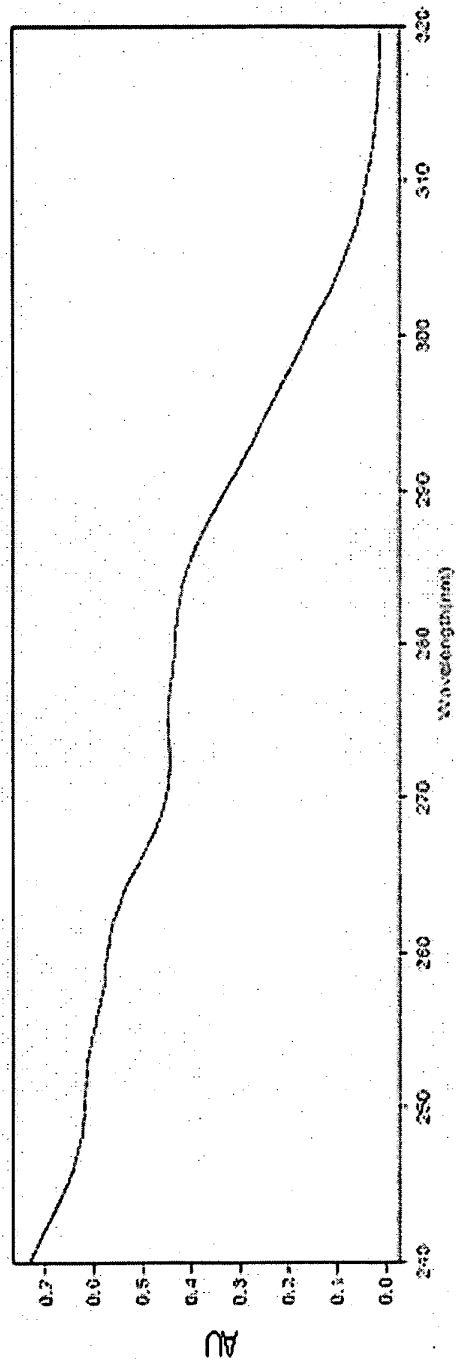


Fig.3b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

Batch : KP114-14.sre

	A	B	C	D	E	F	G	H
1	KP114-14		1	2	3	4.0	5.0	E _{max}
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280	250.0
3	Manual	A	0.620	0.574	0.435	1.081	1.319	20142
4	Cycle02	nm	250.0	260.0	280.0			
5	Manual	A	0.620	0.573	0.434	1.081	1.320	20142

Fig.3c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

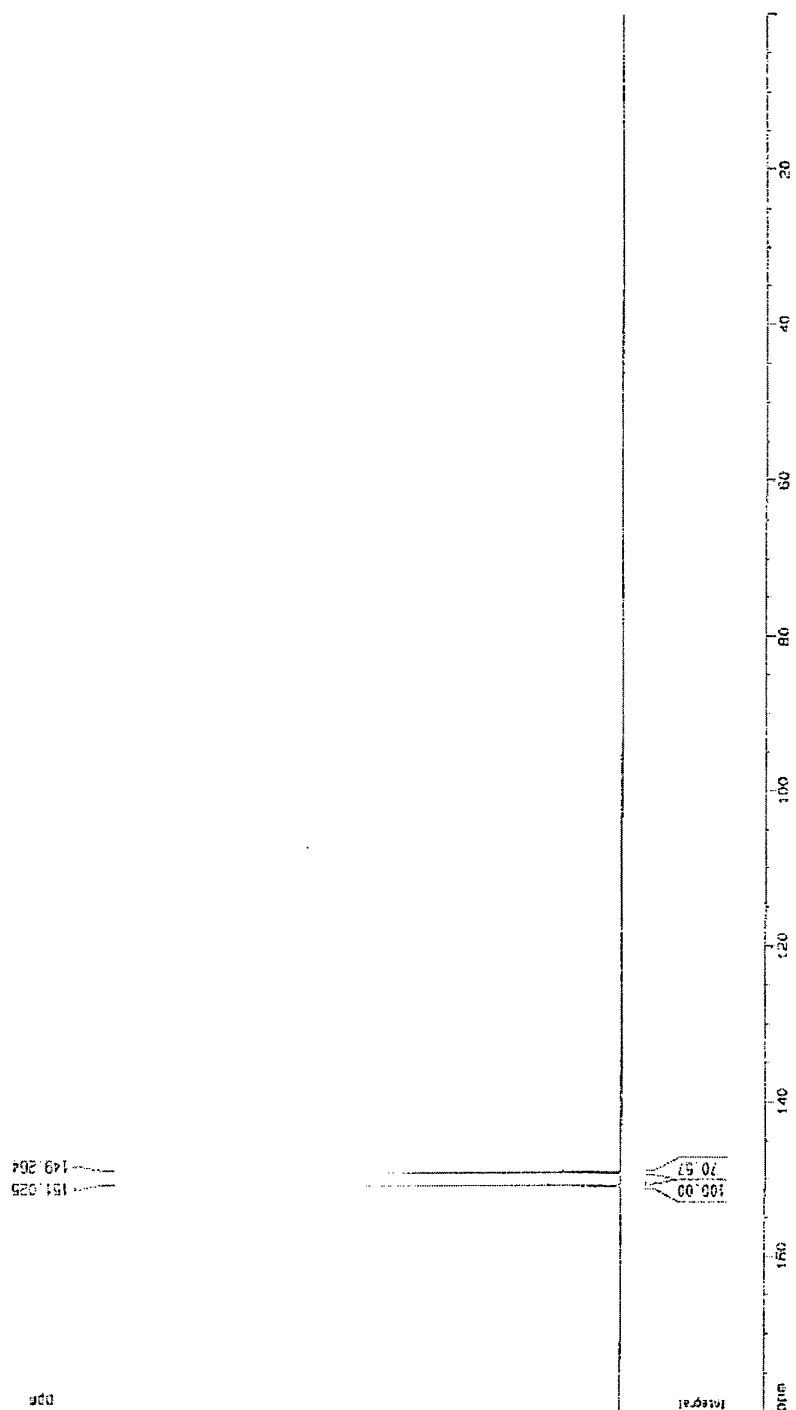


Fig.3d: 31P NMR Spectrum of 5'-DMT -2'- TBDMS -ribo Guanosine (n-acetyl)-phosphoramidite

Example of RNA synthesis #1:

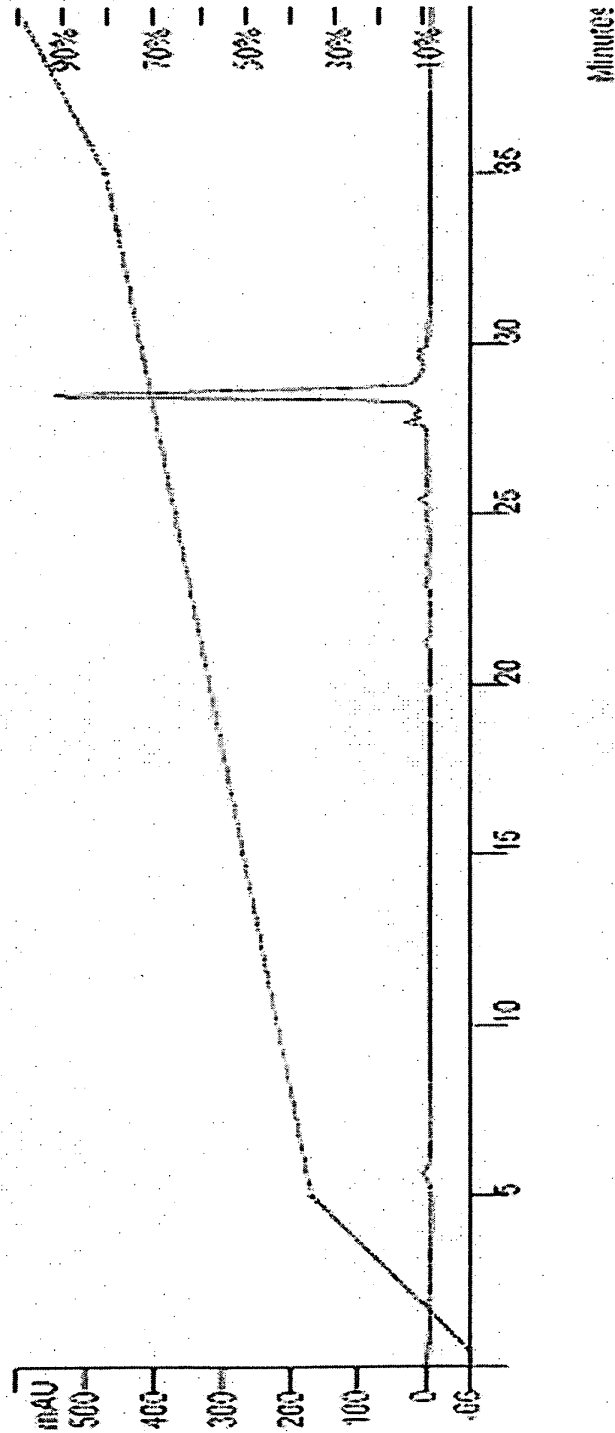


Fig 4a: HPLC Chromatogram of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01

After purification purity: 91.3%

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

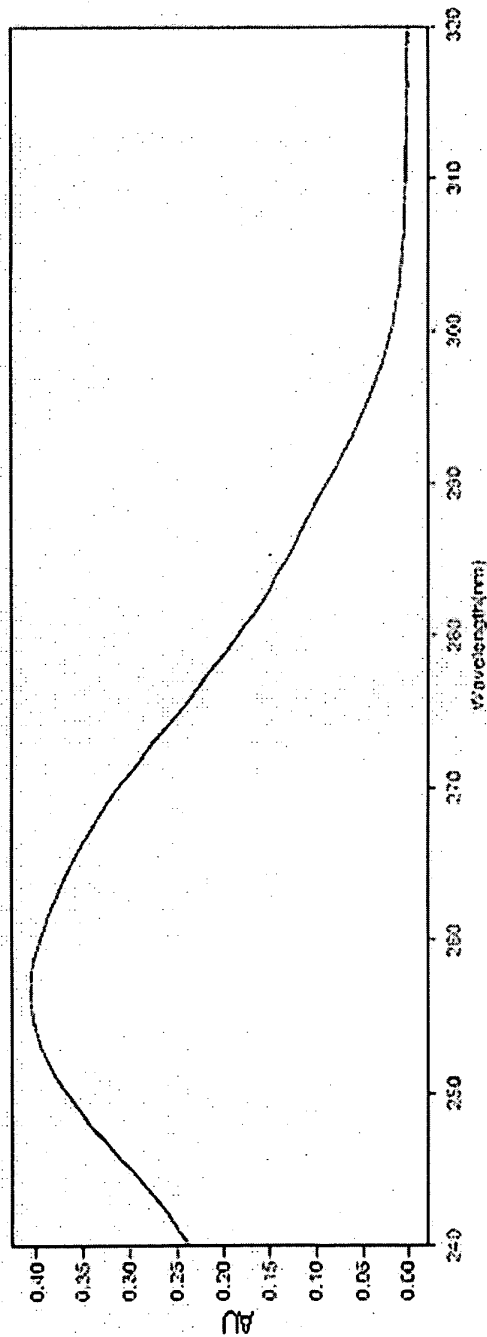


Fig.4b: UV Analysis of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Batch : 041109-E.sre

	A	B	C	D	E	F	G
1	041109-E		1	2	3	5	6
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280
3	Manual	A	0.367	0.397	0.185	0.925	2.140

Fig.4c: Table of UV Analysis of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

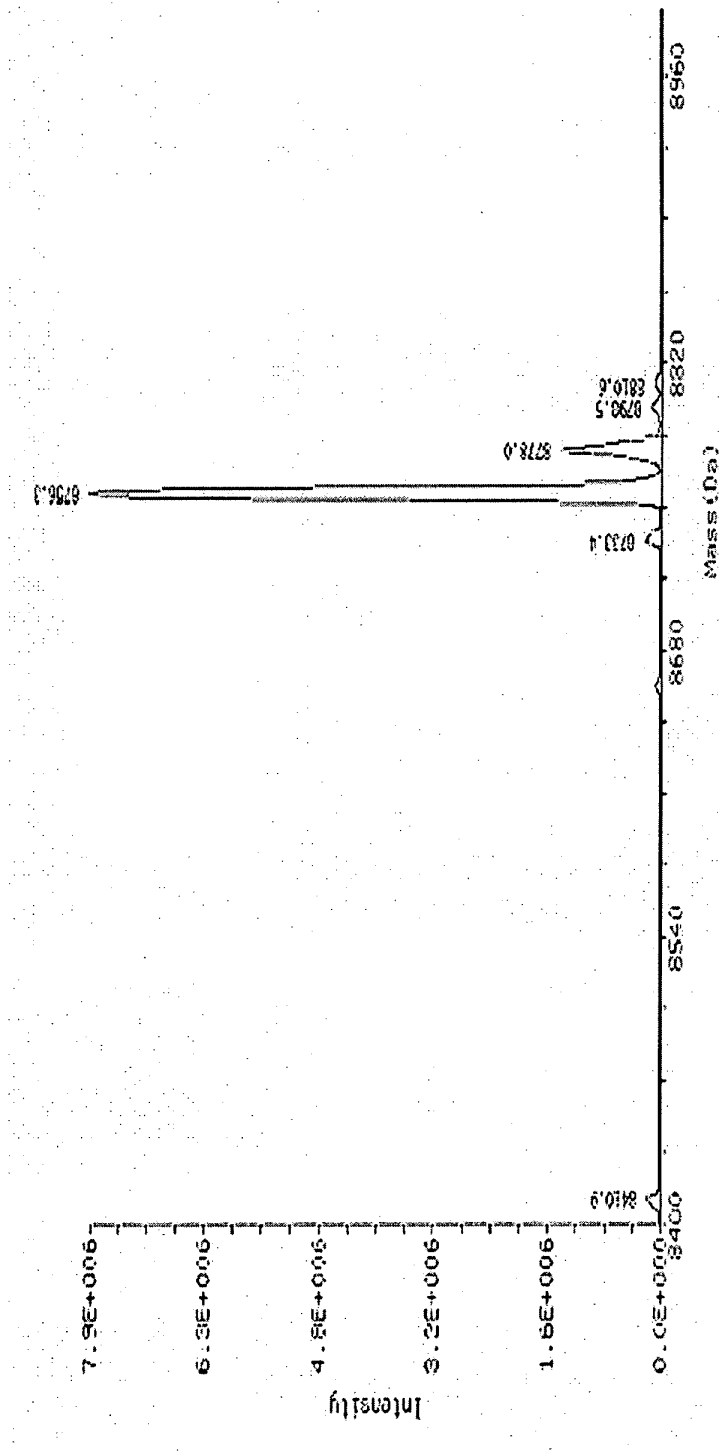


Fig.4d: ESI-MS Analysis of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).

Lot No. CH5-9R-45-01

Targeted mass: 8757.5

Observed Mass: 8756.3

Note:1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

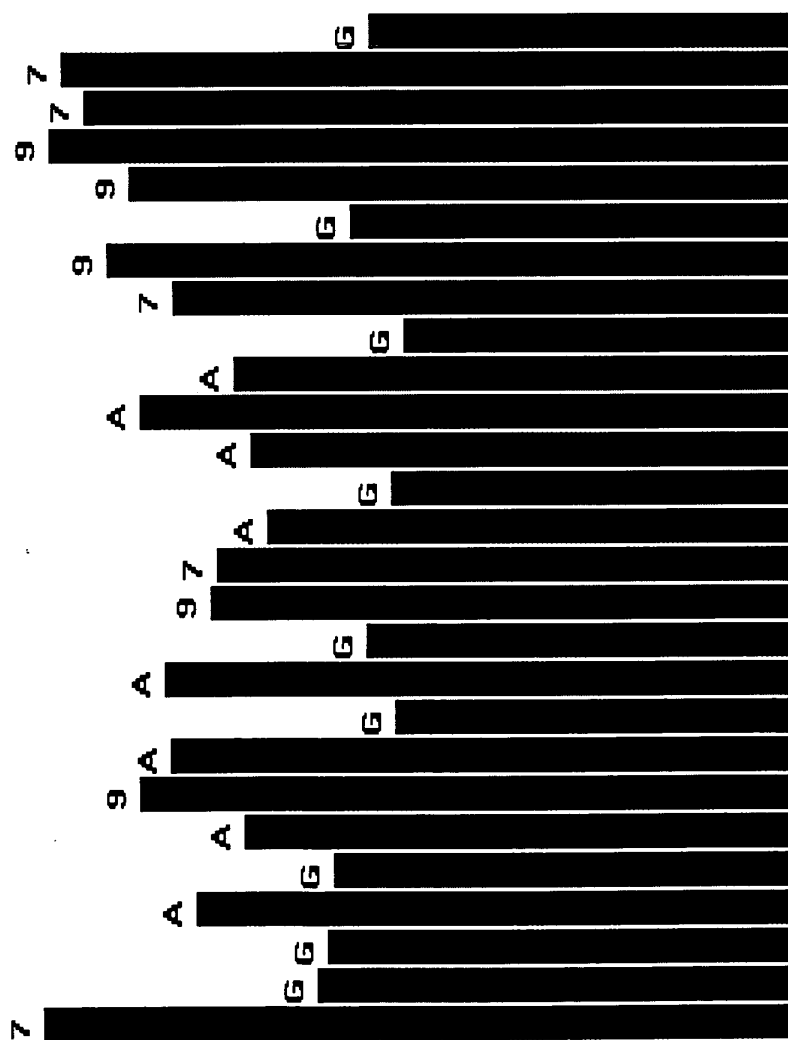


Fig.4e: Synthesis Report of RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).

Lot No. CH5-9R-45-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Example of RNA synthesis #2:

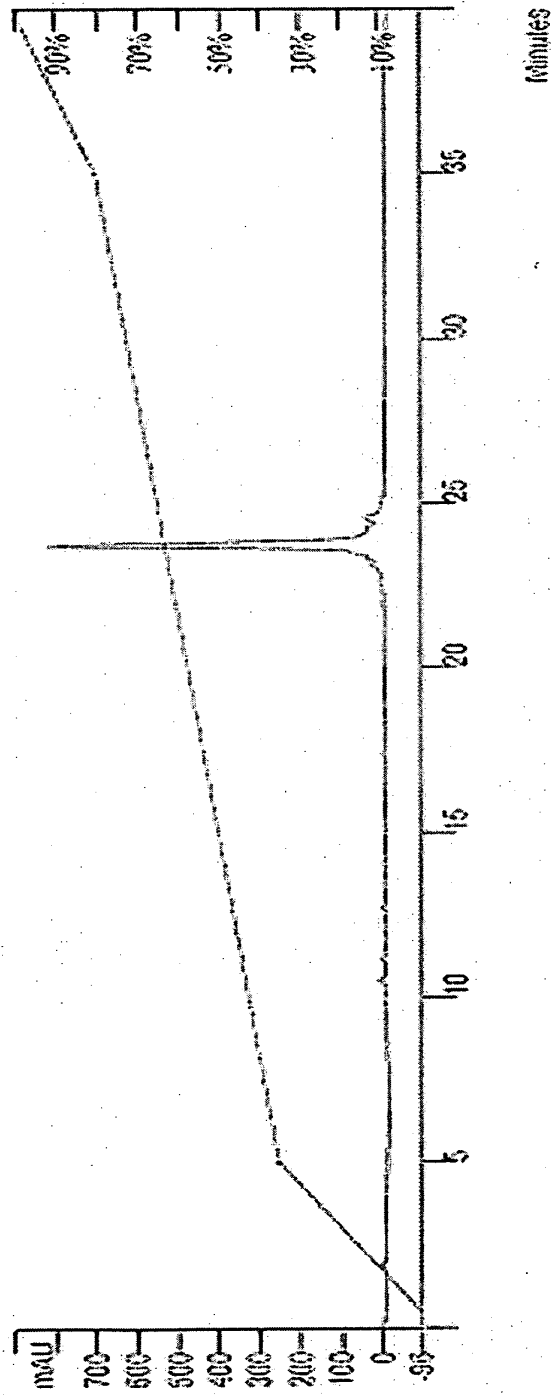


Fig. 5a: HPLC Chromatogram of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GGG7A7G9AGAG).
Lot No. CH5-10R-31-01
After purification purity: 90.53%
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

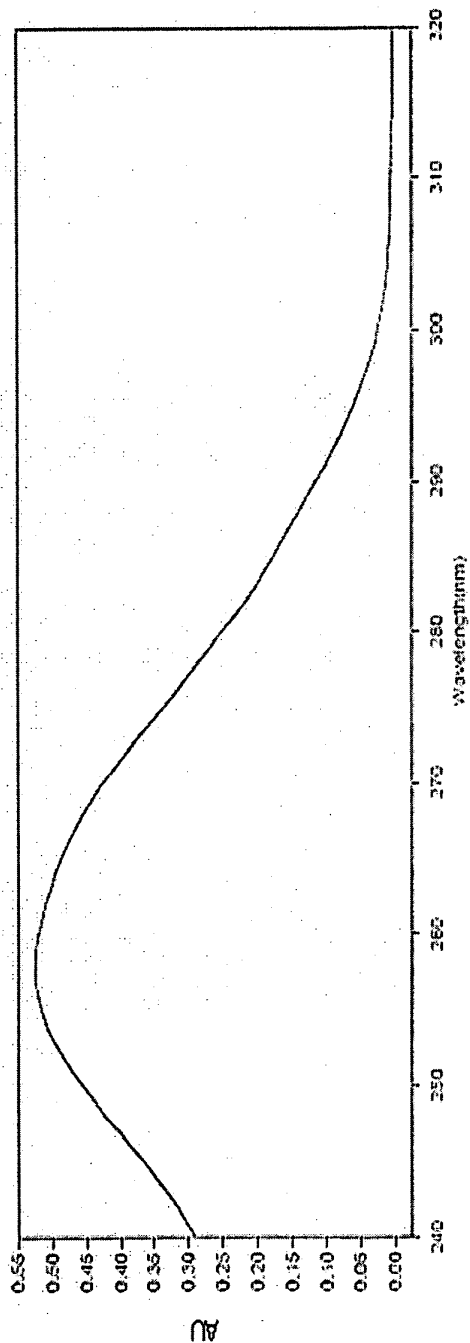


Fig.5b: UV Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GGG7A7G9AGAG).
Lot No. CH5-10R-31-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Batch : 041109-K.sre

	A	B	C	D	E	F	G
1	041109-K		1	2	3	5	6
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280
3	Manual	A	0.455	0.520	0.251	0.874	2.069

Fig.5c: Table of the UV Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GGG7A7G9AGAG).
Lot No. CH5-10R-31-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

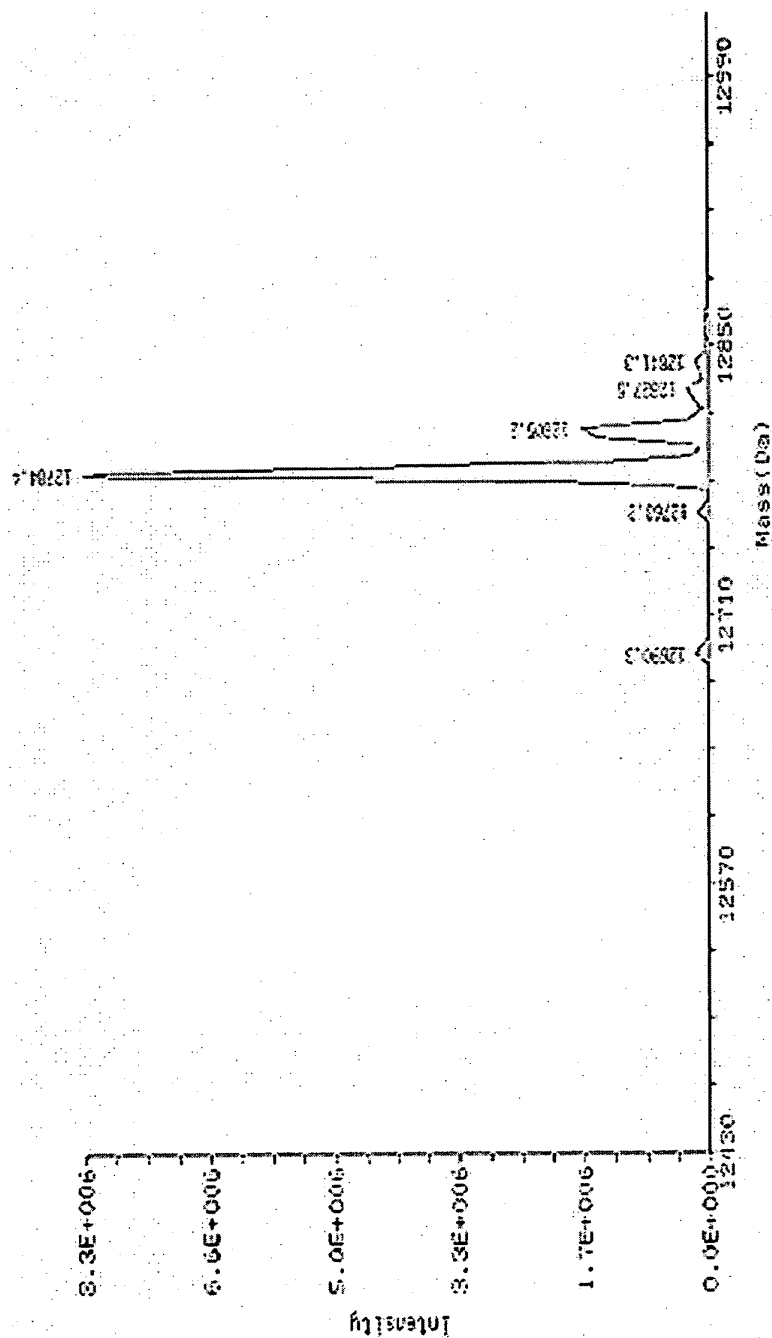


Fig.5d: ESI-MS Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GGG7A7G9AGAG).
 Lot No. CH5-10R-31-01
 Targeted mass: 12785.2
 Observed Mass: 12784.4
 Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
 #7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

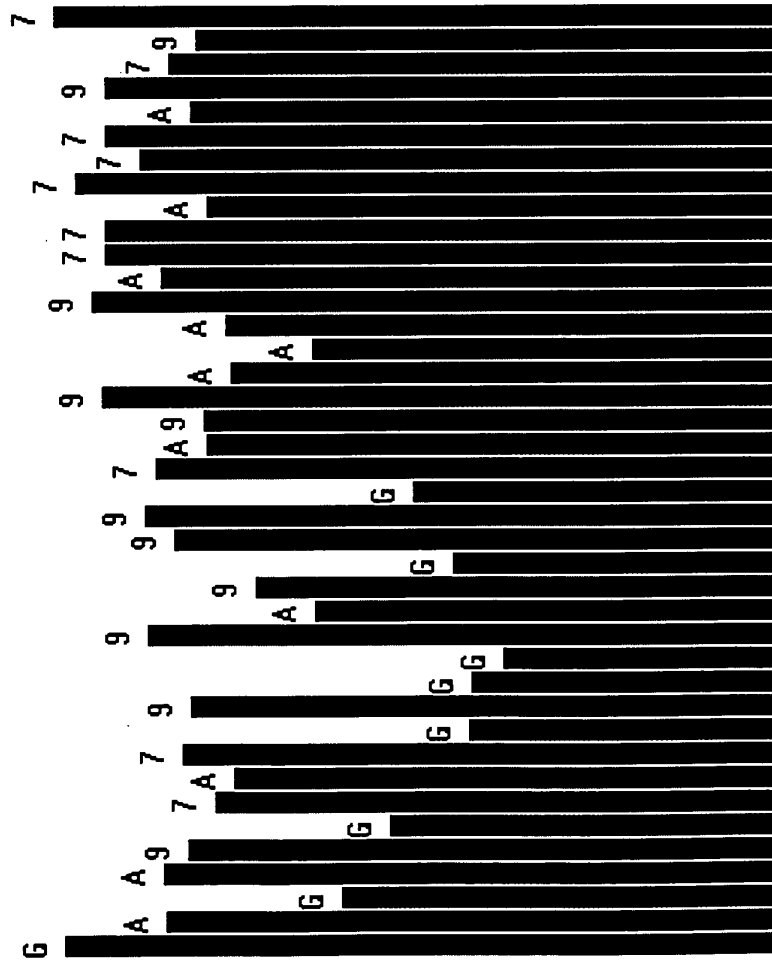


Fig.5e: Synthesis Report of RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).
 Lot No. CH5-10R-31-01
 Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
 #7 denotes 2'-Fluoro C base and #9 denotes 2'-Fluoro U base.

Example of RNA synthesis #3:

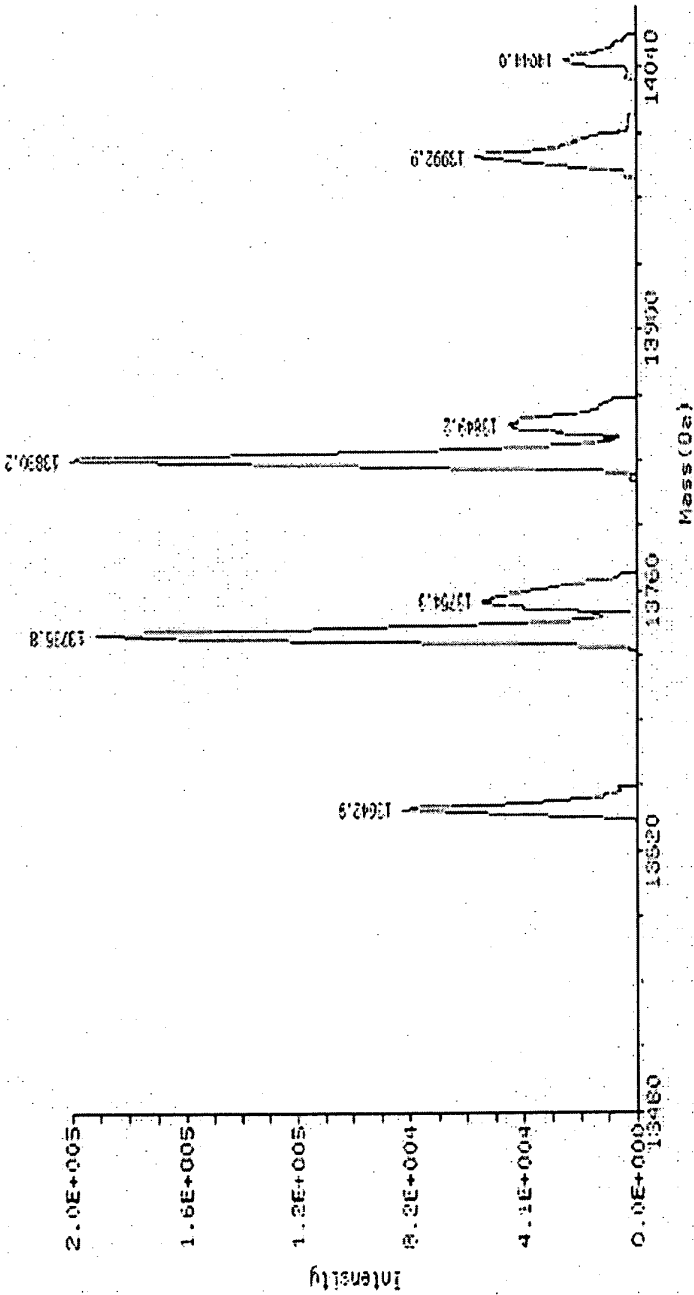


Fig.6a: ESI-MS Analysis of purified RNA Sequence (57A7GAGAG9GG97G9777AGGGGAGAA797G9G7979GG5).

Lot No. 092608

Targeted mass: 13831.7

Observed Mass: 13830.2, 13735.8, 13642.9

Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

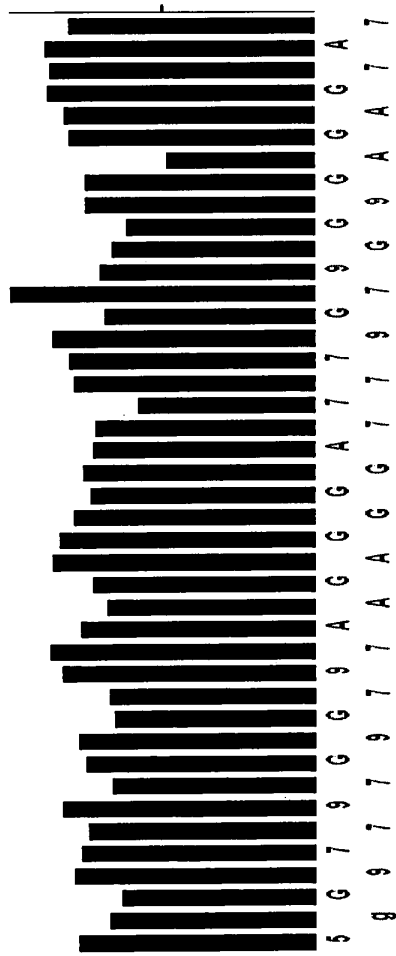


Fig.6b: Synthesis Report of RNA Sequence (57A7GAGAG9GG97G9777AGGGGAGAA797G9G79779GG5).
Lot No. 092608
Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2010/001494

International filing date: 19 May 2010 (19.05.2010)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 61/216,491
Filing date: 18 May 2009 (18.05.2009)

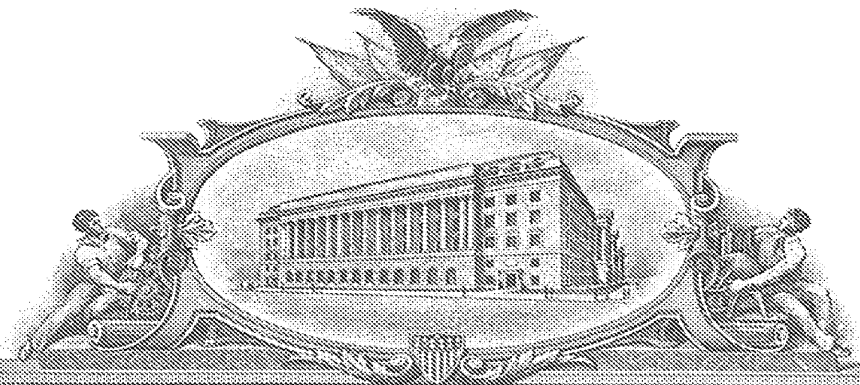
Date of receipt at the International Bureau: 06 June 2010 (06.06.2010)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)



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APPLICATION NUMBER: 61/216,491

FILING DATE: May 18, 2009

RELATED PCT APPLICATION NUMBER: PCT/US10/01494

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS US61/216,491



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U.S. PTO
61/216491
05/18/2009

PTO/SB/16 (12-08)

Approved for use through 06/30/2010. OMB 0651-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EB 739819121 US

INVENTOR(S)		
Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
Suresh C.	Srivastava	Burlington, Massachusetts
Naveen P.	Srivastava	Burlington, Massachusetts

Additional inventors are being named on the _____ separately numbered sheets attached hereto.

TITLE OF THE INVENTION (500 characters max):

SYNTHESIS OF N-2-ACETYL GUANINE-DEOXY NUCLEOSIDES, N-2-ACETYL GUANINE RIBO NUCLEOSIDES, N-2-ACETYL GUANINE-MODIFIES DEOXY & RIBO NUCLEOSIDES, THE CORRESPONDING PHOSPHORAMIDITES AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ The address corresponding to Customer Number: _____

OR

☒ Firm or Individual Name **Indu M. Anand, Esq.**

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City **Chelmsford** State **Massachusetts** Zip **01824**

Country **U.S.A.** Telephone **(978)250-9003** Email **indu_m_anand@yahoo.com**

ENCLOSED APPLICATION PARTS (check all that apply)

☐ Application Data Sheet. See 37 CFR 1.76 ☐ CD(s), Number of CDs _____

☒ Drawing(s) Number of Sheets **Seventeen** ☐ Other (specify) _____

☒ Specification (e.g. description of the invention) Number of Pages **Thirty seven**

Fees Due: Filing Fee of \$220 (\$110 for small entity). If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is \$270 (\$135 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).

METHOD OF PAYMENT OF THE FILING FEE AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27. **\$110**

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PROVISIONAL APPLICATION COVER SHEET
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Indu M. Anand

Date _____

5/18/09

TYPED or PRINTED NAME Indu M. Anand

REGISTRATION NO. 52,557
(if appropriate)

TELEPHONE (978) 250-9003

Docket Number: ChG 00309

Attorney Docket No.: ChG_00309

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

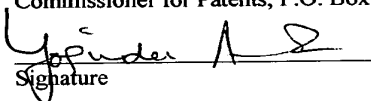
Inventors: Suresh C. Srivastava and Naveen P. Srivastava
Application: Provisional Application
Filed: May 18, 2009

Title: SYNTHESIS OF N-2-ACETYL GUANINE-DEOXY NUCLEOSIDES, N-2-ACETYL GUANINE RIBO NUCLEOSIDES, N-2-ACETYL GUANINE-MODIFIED DEOXY & RIBO NUCLEOSIDES, THE CORRESPONDING PHOSPHORAMIDITES AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

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Sir:

Please find enclosed for filing the Provisional Application for Patent pursuant to 37 CFR 1.53(c), with the Title and Inventors named above.

Please find enclosed in this mailing the following:

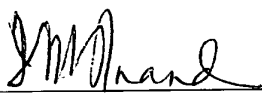
- Provisional Application Cover Sheet, Form PTO/SB/16
- Specification in accordance with 35 U.S.C. 112, 37 pages
- Drawings in accordance with 35 U.S.C. 113, 17 sheets
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EB 739819121 US Srivastava et al., SYNTHESIS OF N-2-ACETYL GUANINE- ... Attorney Docket No.: ChG_00309

In the event of a deficiency in fees and compliance, you are requested to kindly contact the undersigned representative.

Dated: May 18, 2009

Respectfully submitted,

By 

Indu M. Anand

Registration Number: 52,557

15 Green Way

Chelmsford, MA 01824

(978) 250-9003/ (617) 930-5000

**Synthesis of N-2-Acetyl guanine –deoxy nucleosides, N-2- Acetyl
guanine ribo nucleosides, N-2-Acetyl guanine –modified deoxy & ribo
nucleosides, the corresponding phosphoramidites and their use in high
purity oligonucleotide synthesis.**

Suresh C. Srivastava and Naveen P. Srivastava

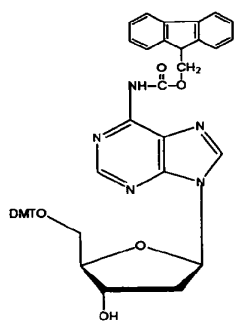
FIELD OF THE INVENTION

This invention relates to synthesis of novel N-2-acetyl protected deoxy and ribo-guanosine, –N-acetyl protected modified guanosine, their succinates, phosphoramidites, corresponding solid supports that are suitable for high purity DNA and RNA synthesis, and it leads to a novel approach to obtain highest purity oligonucleotides.

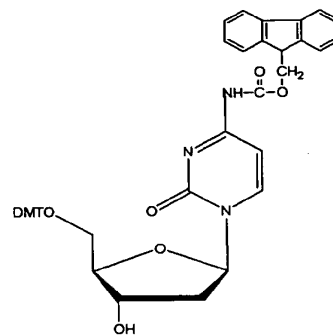
BACKGROUND OF THE INVENTION

The chemical synthesis of oligonucleotides of DNA fragments is performed efficiently by the phosphoramidite chemistry, and the coupling reaction gives excellent yield on various solid supports (Oligodeoxy nucleotide synthesis, Phosphoramidite Approach, Serge L. Beaucage in Protocols For OLigonucleotide s and Analogs, Synthesis and Properties, Editor, Sudhir Agarwal, Humana Press, 1993). Similarly excellent protocols have been developed for the synthesis of RNA, and various biologically active tRNA molecules (Oligoribonucleotide synthesis, The Silyl Phosphoramidite Method, Masad J. Damha and Kevin K. Ogilvie in Protocols For Oligonucleotides and Analogs, Synthesis and Properties, Editor, Sudhir Agarwal, Humana Press, 1993). A large number of such biologically functional DNA and RNA molecules carry base labile and modified nucleosides which cannot sustain prolonged basic conditions, generally required during deprotection. Thus dihydrouridine present in tRNA requires very mild deprotection conditions, otherwise it is completely decomposed and the quality of synthetic tRNA will be compromised. (C.Chaix, D. Molko and R. Teoule,

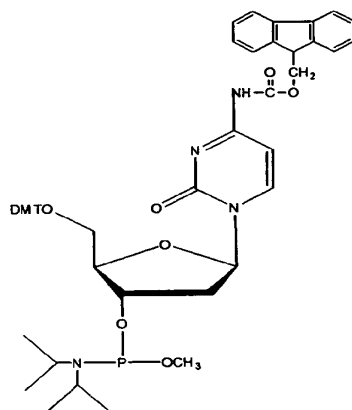
Tetrahedron Letters, 30, 1, 711-74, 1989). In order to develop protecting groups which are milder in nature have been developed in recent past. Thus 2-(acetoxymethyl)benzoyl (AMB) group has been reported which uses potassium carbonate as mild deprotecting group for their removal (W.H.A. Kuipers, J. Huskens and C.A.A. Van Boeckel, Tetrahedron Lett., 31, 6729-6732, 1990) & W.H.A. Kuipers, E. Kuyl-Yeheskiely, J.H. Van Boom and C.A.A. Van Boeckel, Nucl. Acids Res., 21, 3493-3500, 1993). The AMB group seems attractive, however there are many practical problems in their use. Fmoc group was reported for the protection of amino function of 2'-deoxycytidine, 2'-deoxy adenosine and 2'-deoxy guanosine and for the corresponding ribonucleosides (H. Heikkila and J. Chattopadhyaya, Acta Chem. Scand. B 37, No.3, 263-265, 1983). Fmoc as *n*-protecting group as pointed out by these authors for their capability to get cleaved under very mild alkaline deprotection condition, or by bases capable to carry out selective deprotection via B-elimination of Fmoc group (scheme 1). It is therefore not surprising that other attempts to synthesis of N-Fmoc protected nucleoside and phosphoramidites have been carried out. The publication (R.K. Gaur, V. Bobde, M. Atreyi and K.C. Gupta, Indian Journal of Chemistry, 29B, 108-112, 1990), reports preparation of 5'-DMT-n-Fmoc-dA (structure 1) and 5'-DMT-n-Fmoc-dC (structure 2). However these authors could not synthesize 5'-DMT-N-Fmoc-dG (structure 5). Further only *p*-methoxy phosphoramidites of 5'-DMT-n-Fmoc-dC (structure 3) and 5'-DMT-n-Fmoc-dA (structure 4) were synthesized by these authors. The *p*-methoxy phosphoramidites have only limited application in oligonucleotide synthesis. Further, no N-Fmoc protected solid supports were reported.



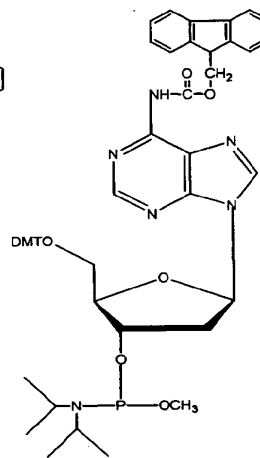
5'-DMT-N6-Fmoc-dA
 (Structure 1)



N-2-FMOC-5'-DMT-dC
 (Structure 2)

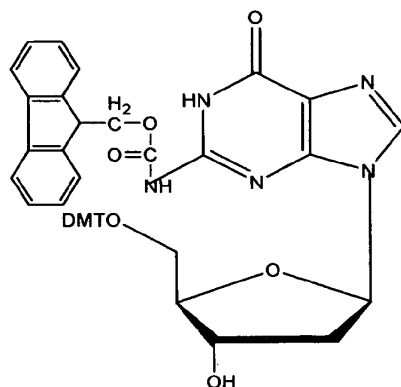


5'-DMT-N4-Fmoc-dC-
 p-methoxy-phosphoramidite
 (Structure 3)



N-6-FMOC-5'-DMT-dA-
 p-methoxy - phoshoramidite
 (Structure 4)

The synthesis of N-FMOC-5'-DMT-dG (structure 5) had eluded so far till our present invention.



5'-DMT-N2-Fmoc-dG

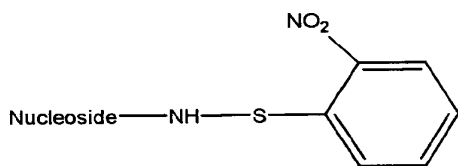
(Structure 5)

Similarly no solid supports or the succinates of the N-FMOC -5'-DMT-deoxy bases (dA and dC) revealed by these other authors. Hence there is no information as to the applicability of DMT-N-6-FMOC-dA -3'- succinyl-support, which would validate the concept that the solid support containing N-6-Fmoc-dA solid supports are expected to minimize or dramatically reduce formation of N-1, i.e. depurination of 3'- dA base products during oligo synthesis and hence about the quality of the synthesized 2'-deoxy oligonucleotides. These products are therefore required to improve the quality of the terminal 3'- dA containing oligonucleotides.

There seem to be no further attempts to make 5'- DMT-N-FMOC dG or the ribonucleoside containing N- Fmoc protected RNA synthesis synthons and the corresponding cyanoethyl phosphoramidites. The cyanoethyl phosphoramidite chemistry in DNA and RNA are currently used in present state of the art in this technology.

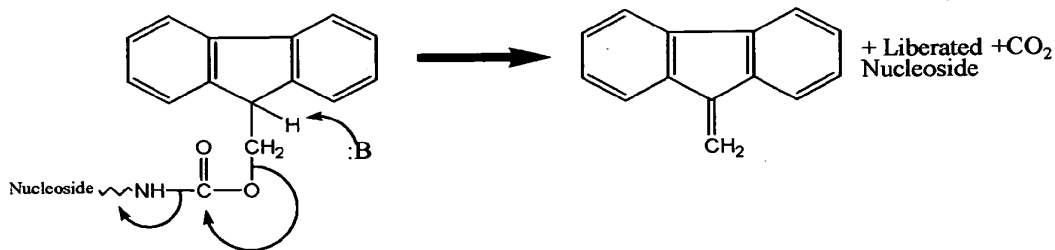
It was demonstrated by the authors (J. Heikkila and J. Chattopadhyaya, Acta Chem. Scand. B 37, No.3, 263-265, 1983) that deprotection of FMOC protecting group can be carried out under various very mild basic reaction conditions. It is possible to utilize either aq ammonia condition deprotection, which results in nucleophilic displacement of FMOC protecting group, or by a Non -nucleophilic base such as

triethylamine, which causes B- elimination of Fmoc – active hydrogen group (scheme 1). These authors however similarly did not pursue the n- Fmoc protecting group for further exploration and carried out investigation of other protecting groups such as ortho-nitro phenyl sulfenyl protected nucleosides(Structure 6). The Fmoc protecting group is very well established in peptide synthesis and one of the preferred reagents for amino group protection of alpha- amino group of amino acids for step wise peptide synthesis (Carpino, L.A., and Han, G. Y., J.Amer.Chem.Soc., 92 , 5748, 1970). In fact the authors (J. Heikkila and J. Chattopadhyaya, Acta Chem. Scand. B 37, No.3, 263-265, 1983), who initially synthesized the Fmoc deoxy and ribo nucleosides switched to (J. Heikkila, N. Balgobin and J. Chattopadhyaya, Acta Chem. Scand B 37, 857-864, 1983) to another N- protecting group, 2- nitrophenyl sulfenyl (Nps) for the protection of amino function of cytidine, adenosine, guanosine and the corresponding 2'- deoxy ribo nucleosides (structure 6).



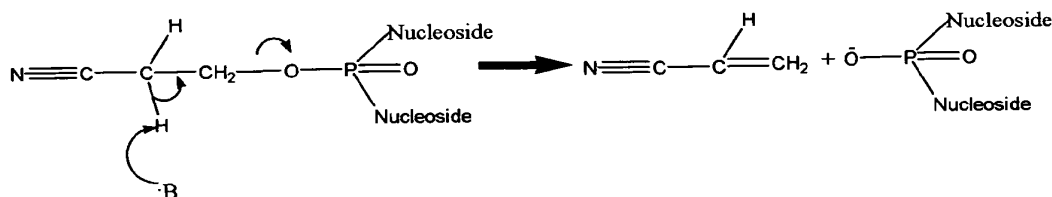
(Structure 6)

O-nitrophenylsulfenyl protecting group



Scheme1. Fmoc-B-Elimination scheme

It is well known that cyanoethyl protecting group for internucleotide phosphate is eliminatyed by B- elimination mechanism leading to acrylonitrile and phosphodiester oligonucleotides.(scheme 2).



Scheme2. Elimination of cyanoethyl phosphate group

It is therefore possible to modulate the Fmoc protecting group removal conditions from oligonucleotides, and the Fmoc as base protecting group can be removed by the process of B-elimination, just like the B- elimination process to remove cyanoethyl group.

This process therefore offers very attractive potential to use ammonia free oligo synthesis. This process, furthermore, has potential to offer deoxyoligonucleotides for complete deprotection of oligos on solid supports. This technology or process has the potential to offer ribonucleotides such as those required for chip based technology as well high purity oligonucleotides for microRNA, Si RNA, RNA chips

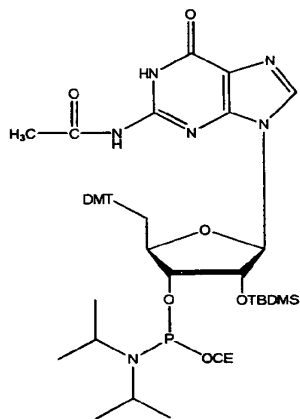
This group, in conjunction with cyanoethyl phosphate protecting group, therefore offer opportunity to remove both Fmoc and cyanoethyl groups from the synthesized deoxy and ribo oligonucleotides on the support cleanly, preferably with non aq bases, and on support for many diagnostics application. Our present invention is revealed by structures such as 7-10 below.

The present inventors recently proposed to utilize N- Fmoc protected purine and pyrimidine bases for the Sythesis of protected Deoxy nucleosides, ribonucleosides, phosphoramidites and their use in the synthesis of oligonucleotides. Although the Fmoc protecting group present tremendous advantage, practical large scale synthesis is inconvenient and difficult to achieve in order to produce large quantities of therapeutic grade RNA or RNA chimeras having sensitive groups such as 2'- fluoro group. It is also significantly labile so that this group has a tendency to fall off and

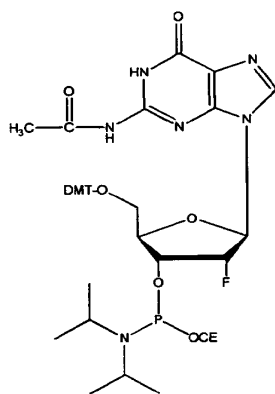
lead to by products or impurity. We therefore turn our attention to N-2- acetyl as guanine base protecting group. This group is significantly more stable than FMOC protecting group. Yet is quite labile as compared to isobutyryl group at N-2 position. Our results of RNA synthesis show that quality of RNA's suffer heavily if in the automated RNA synthesis on DNA/RNA synthesizer, DMT-N-2 –isobutyryl guanosine-2'- TBDMS-3'- Cyanoethyl phosphoramidite is utilized. The currently utilized, most popular and industry standard N-2-amino protecting group for guanine bases is isobutyryl. On the other hand, if DMT-N-2 –acetyl guanosine-2'- TBDMS-3'- Cyanoethyl phosphoramidite (structure 6) is used, high quality of RNA's are obtained. This has been substantiated by oligonucleotide Mass spectral data presented in the present invention.

The deprotection kinetics of N-2 acetyl guanine in a nucleoside or oligonucleotide is significantly faster as compared to standard N-2 isobutyryl group on guanine residue, so that the quality of oligonucleotides especially RNA and modified RNA increases dramatically.

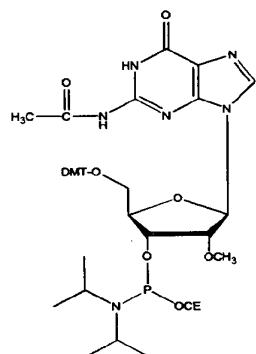
Synthons for RNA Synthesis:



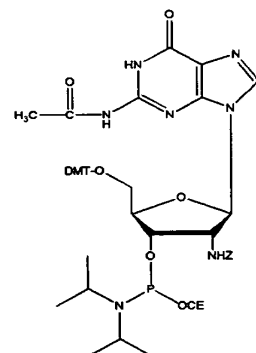
(Structure 6)
N-2-acetyl-guanosine-2'-TBDMS-3'-
CED Phosphoramidite



(Structure 7a)
 N-2-acetyl-guanosine-2'-fluoro-3'-
 CED Phosphoramidite

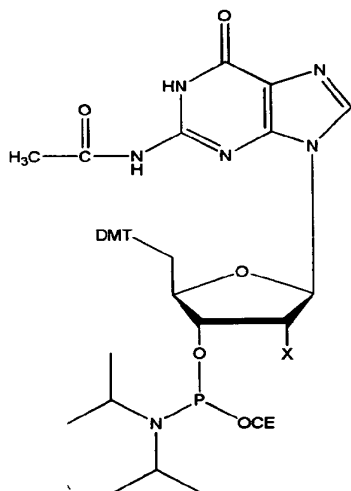


(Structure 8)
 N-2-acetyl-guanosine-2'-O-methyl-3'-
 CED Phosphoramidite



(structure 9)
 (N-2-acetyl-guanosine-2'-amino-3'-

CED Phosphoramidite); where Z is protecting group

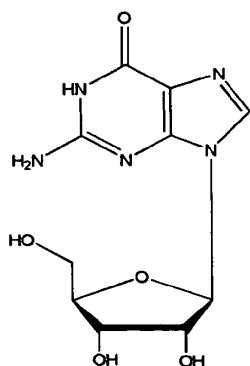


(Structure 7b)

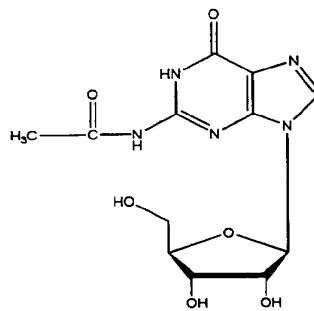
N-2-acetyl-guanine-2'-modified -3'-
 CED Phosphoramidite
 (Where X, F, OCH₃, NH₂ Protected)

Scheme 1: Step wise synthesis of Synthons (structures 6) starting from compound 10, followed by 11, followed by compound 12 & 13, for RNA Synthesis:

The synthesis of phosphoramidites, structures 6 was carried out using nucleosides 10, 11, 12 & 14 as depicted by the following structures:

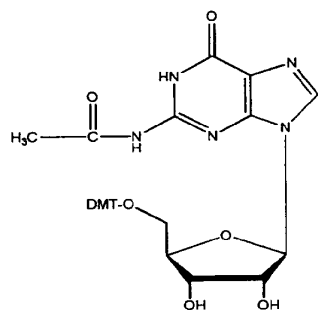


Structure 10 (Guanosine)

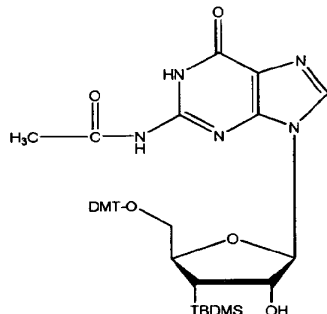


Structure 11 (N-2- acetyl-Guanosine)

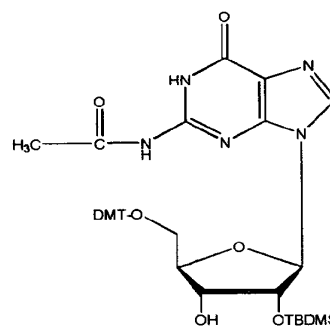
Note: compound (structure 12) is achieved by transient N-2 protected with acetyl chloride in presence of TMS Chloride/ pyridine as standard reaction conditions.



Structure 12
 (N-2 – acetyl guanosine-5' - DMT)

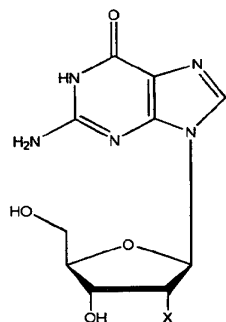


(Structure 13)
 (N-2 – acetyl guanosine-5' - DMT-
 3' - TBDMS)

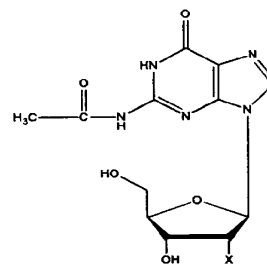


(Structure 14)
 (N-2 – acetyl guanosine-5' - DMT-
 2' -TBDMS)

Scheme 2: Stepwise synthesis of Synthons (structures 7a, 8 &9) for RNA Synthesis:



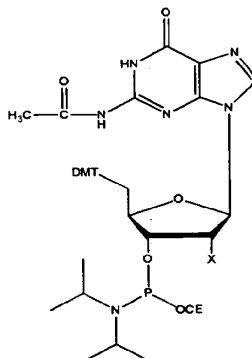
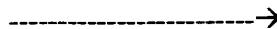
(Structure 15)
 (modified guanosine-
 2' - X; where X;F, OCH3, NH-protected)



(Structure 16)
 (N-2 – acetyl guanosine-
 2' -X; where X; F, OCH3 and NH-protected)

Note: Compound (structure 16) is produced by transient N-2 protected with acetyl chloride in presence of TMS Chloride/ pyridine as standard reaction conditions.

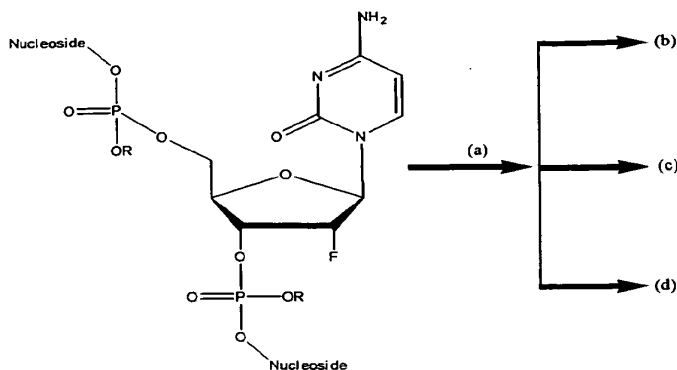
(N-2 – acetyl guanosine-5' - DMT-
 2' - X; where X;F, OCH₃, NH-protected)
 (structure 16)



(structure 7b)

(N-2 – acetyl guanosine-5' - DMT-
 2' - X; where X;F, OCH₃, NH-protected-
 3'-phosphoramidite)

The utility of N-FMOC protected nucleoside was discovered by the present inventors and they showed it to possess additional significance and importance. When oligo ribonucleotide chimeras comprise of mixed bases composed of 2' - fluoro and 2' - ribo bases they present a challenge in obtaining pure chimera oligonucleotides. It has been well documented by several recent reports that oligonucleotide chimeras having 2' - fluoro-2','-deoxy bases along with natural ribo bases present difficulty in obtaining pure oligos. It has been shown that with strongly basic conditions, there is significant loss of fluorine as loss of Hydrogen Fluoride ("HF") is seen as M-20 peak in Mass spectral analysis. Besides it has also been shown that uracil and cytosine are eliminated to a significant extent, when oligo chimeras containing 2'-fluoro-2'-deoxy uridine and 2'-fluoro-2'- deoxy cytidine are part of chimeras (see scheme 3).



Scheme3. Graphic Representation of effect on quality of oligonucleotides containing 2'- fluoro nucleosides: (a) deprotection using methyl amine, the usual deprotection condition of protecting groups of bases, (b) loss of fluorine leading to loss of HF, generating significant amount of M-20, (c) loss of cytosine and uracil, the pyrimidine bases is observed quite frequently, d) with the loss of pyrimidine , subsequent cleavage of chain occurs.

The studies as shown in scheme 3 were carried out independently by two groups recently. Ken Hill, Agilent Technologies, Boulder, Colorado; Identification of Process Related Impurities – Understanding Oligonucleotide Production, TIDES 2007, Las Vegas. Nevada. The author showed depyrimidation of chimera oligonucleotides carrying 2'- fluoro-2'- deoxy pyrimidine in RNA's; and, Nanda D. Sinha, Avecia Biotechnologies Inc., Massachusetts- Depyrimidation, as well as loss of HF and chain cleavage in chimeras having 2'- fluoro-2'- deoxy pyrimidines in RNA sequences. Eurotides , 2005, Munich, Germany.

Our data shows that by utilizing n- acetyl – guanine protected ribonucleoside phosphoramidites, used in oligo with 2'- fluoro substitution, high quality full length RNA were obtained.

It is therefore imperative to utilize 2'- fluoro-2'- deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups having N-2 acetyl guanine for mild and shorter base deprotection protocol. Although there is no B- elimination pathway for N-2-

acetyl guanosine protecting group, still high purity and integrity oligo chimeras is obtained and RNA high quality for therapeutic and diagnostic applications, such as for applications in SiRNA synthesis.

Besides the 2'-fluoro nucleosides, 2'-O-alkyl nucleoside phosphoramidites are extensively used in the design of biologically active oligonucleotides for therapeutic and diagnostic applications as fully alkylated or as chimeras. Amongst the 2'-O-alkyl nucleosides and phosphoramidites the most common are 2'-O-Methyl oligonucleotides which have shown enormous promise in drug design and specific diagnostics applications. Thus 2'-OMethyl oligoribonucleotides- RNA complexes have higher T_m than corresponding oligo-deoxy ribonucleoside - RNA duplexes, Iribarren, A.M., Sproat, B.S., Neuner, P., Sulston, I., Ryder, U., and Lamond, A.I., Proc. Natl. Acad. Sci. USA 87, 7747-7751, 1990. Various 2'-OMethyl-N-FMOC protected nucleosides and phosphoramidites offer great advantage to produce high quality of DNA- RNA oligonucleotides and chimera for biological applications.

Defined sequence RNA synthesis is now well established and currently in use for synthesis and development of vast variety of therapeutic grade RNA aptamers, tRNA's, Si RNA and biologically active RNA molecules. This approach utilizes a ribonucleoside with suitable N- protecting group, 5'- Protecting group, generally, and most popular being dimethoxytriphenyl, commonly called DMT group, 2'- protecting group, out of which most popular is t-Butyldimethylsilyl ether and a 3'- phosphoramidite, wherein the most popular still is cyanoethyl diisopropyl (component 1). This component is then coupled with a nucleoside with a suitable N- protecting group, 2' or 3' succinate of a ribonucleoside attached to a solid support. The coupling of component 1 and 5'- OH-n-protected -2',3'-protected-nucleoside are also achieved in solution phase in the presence of an activator to lead to dimers and oligoribonucleotides, followed by oxidation (3'→5' direction synthesis), also lead to protected dinucleoside having a 3'-5'- internucleotide linkage, Ogilvie, K.K., Can. J. Chem., 58, 2686, 1980.

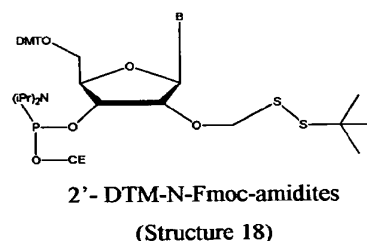
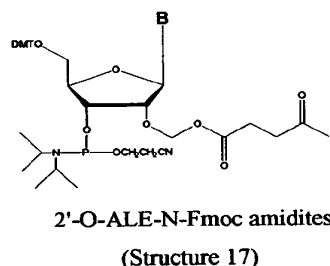
The N- acetyl guanine protecting group offers great potential in RNA synthesis of defined sequence based on our invention as outlined here.

This group can be utilized in conjunction with various 2'- protecting groups required for RNA synthesis. The most widely utilized 2'- protecting, tert- butyl-dimethylsilyl, which has been extensively developed by Ogilvie and coworkers as 2'- hydroxy protecting group for oligo ribonucleotide synthesis (Ogilvie, K.K., Sadana, K.L, Thompson, E.A., Quilliam, M.A., and Westmore, J.B *Tetrahedron Letters*, 15, 2861-2864, 1974; Ogilvie, K.K., Beaucage, S.L, Entwistle, D.W., Thompson, E.A., Quilliam, M.A., and Westmore, J.B. *J. Carbohydrate Nucleosides Nucleotides*, 3, 197-227, 1976 ; Ogilvie, K.K. Proceedings of the 5th International Round Table on Nucleosides, Nucleotides and Their Biological Applications, Rideout, J.L., Henry , D.W., and Beacham L.M., III, eds., Academic, London, pp. 209-256,1983).

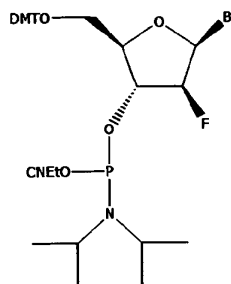
These studies subsequently led to continued developments of methods which were amenable to both solution and solid phase oligonucleotide synthesis, and the first chemical synthesis of RNA molecules of the size and character of tRNA (Usman, N., Ogilvie, K.K., Jiang, M.-Y.,and Cedergren, R.J. *J. Am. Chem. Soc.* 109, 7845-7854, 1987; Ogilvie, K.K., Usman, N., Nicoghossian, K, and Cedergren, R.J. *Proc. Natl. Acad. Sci. USA*, 85, 5764-5768, 1988 ; Bratty, J., Wu, T., Nicoghossian, K., Ogilvie, K.K., Perrault, J.-P., Keith, G. and Cedergren, R., *FEBS Lett.* 269, 60-64, 1990). The literature has been amply reviewed in subsequent excellent publication: Gait, M.J., Pritchard, C. and Slim, G., *Oligonucleotides and Their Analogs: A Practical Approach* (Gait, M.J., ed.), Oxford University Press Oxford, England, pp 25-48, 1991. Other protecting groups which have been lately employed for RNA synthesis are; bis (2- acetoxyethyl-oxy) methyl (ACE), Scaringe, S.A., Wincott, F.E., Caruthers, M.H., *J. Am. Chem. Soc.*, 120: 11820-11821, 1998; triisopropylsilyloxy methyl (TOM), Pitsch, S., Weiss, P.A., Jenny, L., Stutz, A., Wu, X., *Helv. Chim. Acta.* 84, 3773-3795, 2001 and t- butyldithiomethyl (DTM) (structure 16), Semenyuk, A., Foldesi, A., Johansson, T., Estmer-Nilsson , C., Blomgren, P., Brannvall, M., Kirsebom, L.A., Kwiatkowski, M., *J. Am. Chem. Soc.*, 128: 12356-12357, 2006 have been introduced. Recently another invention by the scientists at our company have submitted a patent application for synthesis of RNA in reverse direction (5'→3'direction), for efficient incorporation of many ligands and chromophores conveniently and efficiently at the 3'- end of RNA molecules and a recent publication, Srivastava, S.C., Pandey, D.P., Srivastava, N., Bajpai, S.P., *Nucleic Acids*

Symposium Series No. 52, 103-104, 2008 (structure 20, 21 & 22). Appropriately N-acetyl protected guanine can nucleosides, deoxy and ribo are envisaged to be synthesized and DNA and RNA synthesis is proposed to utilize the benefits which reverse DNA and RNA synthesis offer.

A novel 2'- protecting group, acetal levulinyl ester (ALE) (structure 15 has been recently proposed (J.G.Lackey and M.J.Damha, Nucleic Acids Symposium Series, No. 52, 35-36, 2008). Similar to this protecting group another 2'- labile protecting group based on similar chemical nature, 2'- O-acetal ester, pivaloyloxy methyl which has been found mild 2'- O protecting group, T. Laverne, A. Martin, F. Debart, J-J Vasseur, Nucleic Acids Symposium Series No. 52, , 51-52, 2008. The base protecting group used by these authors was n- acetyl and tbPAC. This gives additional credence to our process. And n- acetyl for RNA synthesis with other 2'- protecting groups or 2'- modification would be an ideal group for deprotection under mild basic condition in shorter period of time.

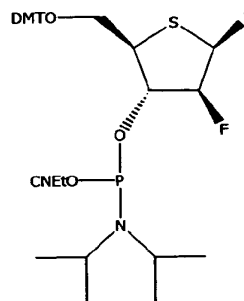


Chemically modified RNA have been synthesized having modified arabinosugars, 2'-deoxy-2'- fluoro- beta-D_arabinonucleic acid (FANA; structure 17)) and 2'-deoxy-4'-thio-2'- fluoro- beta-D_arabinonucleic acid (4'-Thio-FANA; structure 18) into sequences for SiRNA activities, Dowler, T., Bergeron, D., Tedeschi, Anna-Lisa, Paquet, L., Ferrari, N., Damha, M.J., Nucl. Acids Res., 34, 1669-1675, 2006. Amongst several new 2' -protecting group chemistry which have been developed , the 2'- protecting 2-cyanoethoxymethyl (CEM) (structure 19) has been shown for producing very long RNA also carries out RNA synthesis in conventional (3'→5' direction). However the quality of these long RNA remain in question.



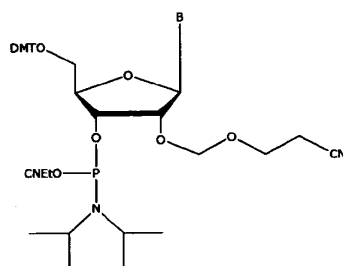
(structure 19)

2'- F-ANA modified phosphoramidites



(structure 20)

4'-Thio-2'- F-ANA modified

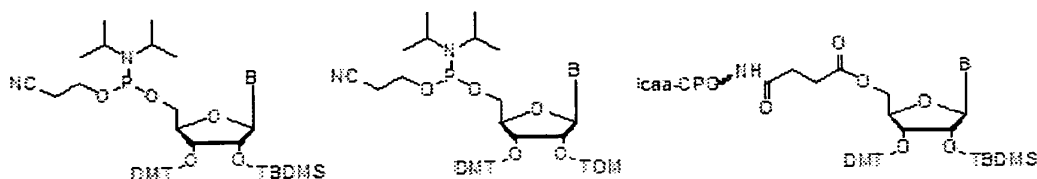


(Structure 21)

2'- CEM Protected RNA Intermediates

The N- acetyl protected guanine as nucleoside base having the 2'- protecting group discussed above can be combined and utilized in high purity RNA synthesis. The N-acetyl guanine protected nucleoside offers great potential in RNA synthesis of defined sequence. This applies to RNA synthesis in the conventional direction ($3' \rightarrow 5'$ direction as well as using our newly discovered $5' \rightarrow 3'$ direction synthons; structures 21, 22 & 23).

Structures of reverse phosphoramidites and solid supports:



Where B = A (N-Bz), C (N-Bz), G (N-Ac), U.

Reverse RNA synthon-2'- tBDSilyl-3'-DMT-5'- CED amidite (Structure 22)	Reverse RNA synthon-2'- TOM-3'-DMT-5'-CED amidite (Structure 23)	Reverse RNA synthon 2'-tBDSilyl-3'-DMT- 5'- succinyl Support (Structure 24)
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Chemical synthesis of RNA is desirable because it avoids the inefficiencies and limitation of scale of synthesis such as by in vitro transcription by T7 RNA polymerase, Helm, M., Brule, H., Giege, R., Florence, C., RNA, 5:618-621, 1999. Chemical synthesis of RNA is desirable for studies of RNA structure and function, and many useful modifications can be achieved selectively, such as site specific introduction of functional groups; viz., disulphide cross linking as a probe of RNA tertiary structures, Maglott, E.J., Glick, G.D., Nucl. Acids Res., 26: 1301-1308, 1999. Synthesis of long RNA is very important for biologically active molecules such as tRNA, and such synthesis have been achieved, Persson, T., Kutzke, U., Busch, S., Held, R., Harmann, R.K., Bioorgan. Med. Chem., 9:51-56, 2001; Oglvie, K.K., Usman, N., Nicoghiosian, K., Cedrgren, R.J., Proc. Natl. Acad. Sci., USA, 85:5764-5768, 1988; Bratty, J., Wu, T., Nicoghiosian, K., Oglvie, K.K., Perreault, J.-P., Keith, G., Cedergren, R.J., F.E.B.S. Lett., 269:60-64, 1990; Gasparutto, D., Livache, T., Bazin, H., Duplaa, A.M., Guy, A., Khorlin, A., Molko, D., Roget, A., Teoule, R., Nucl. Acids. Res., 20:5159-5166, 1992; Goodwin, J.T., Stanick, W.A., Glick, G.D., J.Org. Chem., 59:7941-7943, 1994. The aforementioned techniques, employ synthesis of RNA in reverse direction (5'→3' direction), and hence introduction of a number of groups required for selective introduction at 3'- end is practical and convenient. We have observed higher coupling efficiency per step during automated oligo synthesis with our reverse RNA amidites (structures 21, 22, 23), and therefore they have

greater ability to get higher purity and produce very long oligos. We also demonstrated that the process of our invention leads oligonucleotide free of M+1 species. Such species lead to closer impurities as shoulder of desired peak during HPLC analysis or purification or Gel purification. Such reverse RNA structures replacing the standard n- protecting group with n- Fmoc protecting group offer additional advantages not previously foreseen.

This invention relates to novel synthesis utilizing N- acetyl guanine protected nucleosides, succinates, phosphoramidites, corresponding solid supports that are suitable for oligo deoxy nucleosides and RNA oligonucleotide synthesis. Our discovery using N- acetyl as nucleoside base protecting group, which is more base labile protecting group as compared to n- isobutyryl group is a novel approach to obtain highest purity oligonucleotides. This approach is designed to lead to very high purity and very clean oligonucleotide, after removal of the protecting groups and efficiently in order to produce high purity and therapeutic grade DNA oligonucleotides, RNA oligonucleotides, diagnostic DNA, diagnostic RNA for microarray platform. The deprotection of acetyl protecting groups of the natural deoxy and ribonucleosides occurs under the mild deprotection and shorter contact time deprotection conditions and removal of such groups under very mild conditions would allow synthesis of various DNA and RNA of highest purity for diagnostics and therapeutic application. This approach is further designed to use acetyl guanine protecting group on various base sensitive nucleoside, and for use in oligo peptide synthesis.

Defined sequences RNA synthesis is now well established and currently in use for synthesis and development of vast variety of therapeutic grade RNA aptamers, tRNA's, siRNA and biologically active RNA molecules. This approach utilizes a ribonucleoside with suitable N- protecting group, 5'- Protecting group, generally and most popular being dimethoxytriphenyl, commonly called DMT group, 2'- protecting group, out of which most popular being t-Butyldimethylsilyl ether and a 3'- phosphoramidite, the most popular being cyanoethyl diisopropyl (component 1). This

component is then coupled with a nucleoside with a suitable N- protecting group, 2' or 3' succinate of a ribonucleoside attached to a solid support (component 2). The coupling of component 1 and 5'- OH-n-protected -2',3'-protected-nucleoside (component 3) are also achieved in solution phase in presence of an activator to lead to dimers and oligoribonucleotides, followed by oxidation (3'→5' direction synthesis), also lead to protected dinucleoside having a 3'-5'- internucleotide linkage, Ogilvie, K.K., Can. J. Chem., 58, 2686, 1980.

For the N- acetyl guanine nucleoside protecting group the widely utilized 2'- protecting group, viz.; TBDMS group, which has been extensively developed by Ogilvie and coworkers as 2'- hydroxy protecting group for oligo ribonucleotide synthesis (Ogilvie, K.K., Sadana, K.L, Thompson, E.A., Quilliam, M.A., and Westmore, J.B *Tetrahedron Letters*, 15, 2861-2864, 1974; Ogilvie, K.K., Beaucage, S.L, Entwistle, D.W., Thompson, E.A., Quilliam, M.A., and Westmore, J.B. *J. Carbohydrate Nucleosides Nucleotides*, 3, 197-227, 1976 ; Ogilvie, K.K. Proceedings of the 5th International Round Table on Nucleosides, Nucleotides and Their Biological Applications, Rideout, J.L., Henry , D.W., and Beacham L.M., III, eds., Academic, London, pp. 209-256,1983).

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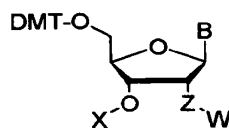
Pitsch, S., Weiss, P.A., Jenny, L., Stutz, A., Wu, X., *Helv. Chim. Acta.* 84, 3773-3795, 2001 and t- butyldithiomethyl (DTM) (structure 1), Semenyuk, A., Foldesi, A., Johansson, T., Estmer-Nilsson, C., Blomgren, P., Brannvall, M., Kirsebom, L.A., Kwiatkowski, M., *J.Am. Chem. Soc.*, 128: 12356-12357, 2006 have been introduced. However none of these are amenable to carry out the synthesis in reverse direction (5'→3'direction), and hence lack the capability of introduction of many ligands and chromophores conveniently and efficiently at the 3'- end of RNA molecules.

Our present invention is directed towards the synthesis of high purity RNA's and specifically to introduce nucleosidic or non – nucleosidic bases, which are labile in nature for synthesis of synthetic RNA's. Such RNA's will have vast application in therapeutics, diagnostics, drug design and selective inhibition of an RNA sequence within cellular environment, on demand blocking a function of different types of RNA present inside cell. Silencing gene expression at mRNA level with nucleic acid based molecules is a fascinating approach. Among these RNA interference (RNAi) has become a proven approach which offers great potential for selective gene inhibition and showing great promise for application in control and management of various biochemical and pharmacological processes. Early studies by Fire et al., Fire, A., Xu, S., Montgomery, M.K., Kostas, S.A., Driver, S.E., and Mello, C.C, *Nature*, 391, 806-811, 1998, showed that RNA interference in *Caenorhabditis elegans* is mediated by 21 and 22 nucleotide RNA sequences. This was further confirmed as general phenomenon of specific inhibition of gene expression by small double stranded RNA's being mediated by 21 and 22 nucleotide RNA's, *Genes Dev.*, 15, 188-200, 2001. Simultaneous studies by Capie, N.J., Parrish, S., Imani, F., Fire, A., and Morgan, R.A., confirmed such phenomenon of specific gene expression by small double stranded (ds) RNAs in invertebrates and vertebrates alike. Subsequently a vast amount of research led to confirmation of above studies and established RNAi as a powerful tool for selectively and very specific gene inhibition and regulation, Nishikura, K., *Cell*, 107, 415-418, 2001; Nykanen, A., Haley, B., Zamore, P.D., *Cell*, 107, 309-321, 2001; Tuschl, T., *Nat. Biotechnol.*, 20, 446-448, 2002; Mittal, V., *Nature Rev.*, 5, 355-365, 2004; *Proc. Natl. Acad. Sci. USA*, 99, 6047-6052, 2002;

Donze, O. & Picard, D., Nucl. Acids. Res., 30, e46,2002; Sui, G., Soohoo, C., Affar el, B., Gay, F., Shi, Y., Forrester, W.c., and Shi, Y., Proc. Natl. Acad. Sci. USA, 99, 5515-5520, 2002; Paddison, P.J., Caudy, A.A., Bernstein, E., Hannon, G.J., and Conklin, D.S., Genes Dev., 16, 948-959, 2002.

SUMMARY OF THE INVENTION

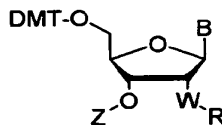
The invention provides a novel method of RNA synthesis utilizing N-2- acetyl guanosine-5'- DMT-2'-TBDMS- protected nucleoside phosphoramidites outlined in Formula 1 below. The synthetic route that has been developed allows obtaining desired nucleosides without any contamination with unwanted impurities. The N- 2- acetyl protected guanosine nucleosides having various 2'- protecting group discussed or 2'- modification, such as 2'- fluoro or 2'- amino groups can be combined with cyanoethyl phosphate protecting group and utilized in high purity RNA synthesis



Formula 1

Where B = a) Adenine (*N-bz*), b) Cytosine (*N-acetyl*), c) Guanine (*N-acetyl*), d) 5-methyl cytosine(*N- Fmoc*), e) 5- bromocytidine(*N-Fmoc*), i) 5- iodo cytosine(*N-Fmoc*), j) 5- fluorocytosine(*N-Fmoc*), k) 2,6-diaminopurine(*N-Fmoc*), l) 2- amino purine(*N-Fmoc*), Z= Oxygen & W is H, ; Z=Oxygen and W= *t*Butyldimethyl silyl, TOM (triisopropylloxymethylene), acetal levuliny ester (ALE), pivaloyloxy; cyanoethylmethylene (CEM); dithiomethylene (DTM); Z= oxygen and W is methyl and other higher alkyls, alkenes and alkynes; Z=W= ribo Fluorine; Z=W=ara fluorine; Z= amino, W= amino protecting group ;X = a) cyanoethyl-dialkyl phosphoramidite.

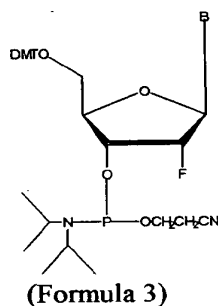
The nucleic base in our invention protected with N-2 acetyl guanosine (Acetyl; Ac). The solid support having protected nucleosides containing 5'- DMT group and 3' terminus is attached to solid support (Formula 2).



(Formula 2)

Where B = a) Adenine (*N-bz*), b) Cytosine (*N-acetyl*), c) Guanine (*N-acetyl*), d) 5-methyl

cytosine(N- Fmoc), e) 5- bromocytidine(N-Fmoc), i) 5- iodo cytosine(N- Fmoc), j) 5- fluorocytosine(N-Fmoc), k) 2,6-diaminopurine(N-Fmoc), l) 2- amino purine(N-Fmoc), Z= Oxygen & W is H, ; Z=Oxygen and W= tButyldimethyl silyl, TOM (triisopropyloxymethylene), acetal levuliny l ester (ALE), pivaloyloxy; cyanoethylmethylene (CEM); dithiomethylene (DTM); Z= oxygen and W is methyl and other higher alkyls, alkenes and alkynes; Z=W= ribo Fluorine; Z=W=ara fluorine; Z= amino, W= amino protecting group ;Z = a) succinimido long chain attached to a solid support, b) hydroquinione succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support.



Where B = a) Adenine (*N-bz*), b) Cytosine (*N-acetyl*), c) Guanine (*N-acetyl*), d) 5-methyl cytosine(N- Fmoc), e) 5- bromocytidine(N-Fmoc), i) 5- iodo cytosine(N- Fmoc), j) 5- fluorocytosine(N-Fmoc), k) 2,6-diaminopurine(N-Fmoc), l) 2- amino purine(N-Fmoc)

Z=W=ara fluorine; Z= amino, W= amino protecting group ;Z = a) succinimido long chain attached to a solid support, b) hydroquinione succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support.

The nucleosides can be used in oligonucleotide synthesis. The base deprotection step can be performed in mild basic conditions or a tertiary amine, secondary amines, such as piperidine capable of removal of Fmoc protecting group via B- elimination in solution phase or on solid support without oligonucleotide detachment. The invention provides for kits that contain one of the disclosed nucleoside compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawing figures display the experimental results as follows:

Fig. 1a: HPLC Chromatogram of 5'-DMT -ribo Guanosine (n-acetyl)

Fig. 1b: UV Analysis of 5'-DMT -ribo Guanosine (n-acetyl)

Fig. 1c: Table of the UV Analysis of 5'-DMT-ribo Guanosine (n-acetyl)

Fig. 2a: HPLC Chromatogram of 5'-DMT-2'-TBDMS-ribo Guanosine (n-acetyl)

Fig. 2b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

Fig. 2c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

Fig. 3a: HPLC Chromatogram of 5'-DMT-2'-TBDMS-ribo Guanosine (n-acetyl)-
phosphoramidite

Fig. 3b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-
phosphoramidite

Fig. 3c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-
phosphoramidite

Fig. 3d: ³¹P NMR Spectrum of 5'-DMT -2'- TBDMS -ribo Guanosine (n-acetyl)-
phosphoramidite

**Fig. 4a: HPLC Chromatogram of purified RNA Sequence
(G7799G97GAAAGA79GA9A9AGAGG7).**

Lot No. CH5-9R-45-01

After purification purity: 91.3%

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

**Fig. 4b: UV Analysis of purified RNA Sequence
(G7799G97GAAAGA79GA9A9AGAGG7).**

Lot No. CH5-9R-45-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

**Fig. 4c: Table of UV Analysis of purified RNA Sequence
(G7799G97GAAAGA79GA9A9AGAGG7).**

Lot No. CH5-9R-45-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

**Fig. 4d: ESI-MS Analysis of purified RNA Sequence
(G7799G97GAAAGA79GA9A9AGAGG7).**

Lot No. CH5-9R-45-01

Targeted mass: 8757.5

Observed Mass: 8756.3

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig.4e: Synthesis Report of RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig. 5a: HPLC Chromatogram of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).
Lot No. CH5-10R-31-01
After purification purity: 90.53%
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig. 5b: UV Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).
Lot No. CH5-10R-31-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig. 5c: Table of the UV Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).
Lot No. CH5-10R-31-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig. 5d: ESI-MS Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).
Lot No. CH5-10R-31-01
Targeted mass: 12785.2
Observed Mass: 12784.4
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig. 5e: Synthesis Report of RNA Sequence
(7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).

Lot No. CH5-10R-31-01

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig. 6a: ESI-MS Analysis of purified RNA Sequence
(57A7GAGAG9GG97G97777AGGGGAGAA797G9G79779GG5).

Lot No. 092608

Targeted mass: 13831.7

Observed Mass: 13830.2, 13735.8, 13642.9

Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Fig. 6b: Synthesis Report of RNA Sequence
(57A7GAGAG9GG97G97777AGGGGAGAA797G9G79779GG5).

Lot No. 092608

Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to synthesis of novel N-2-acetyl protected deoxy and ribo-guanosine, -N-acetyl protected modified guanosine, their succinates, phosphoramidites, corresponding solid supports that are suitable for high purity DNA and RNA synthesis. Our discovery using N- acetyl as guanine purine base protecting group, which is more base labile protecting group as compared to traditional N-2-isobutyryl guanine, is a novel approach to obtain highest purity oligonucleotides. This approach is designed to lead to high purity and very clean oligonucleotide, after efficient removal of the protecting groups and to produce high purity therapeutic grade DNA oligonucleotides, RNA oligonucleotides, diagnostic DNA, diagnostic RNA for microarray platform and high purity oligonucleotides in general.. The deprotection of N-acetyl protecting groups of the natural deoxy and ribonucleosides and modified deoxy and ribonucleotides occurs during a shorter period of base treatment conditions and removal of acetyl group from guanine moieties under such conditions allows synthesis of various DNA and RNA of highest purity for diagnostics and therapeutic application, RNA synthesis and high quality SiRNA in general. This approach is further designed to use N- acetyl guanine protecting group on various base sensitive nucleoside such as sugar fluorinated oligo nucleotides synthesis.

The nucleic bases in our invention protected with N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- tert butyl dimethyl silyl and 3'-cyanoethylphosphoramidite (CED) (group 1), N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- fluoro group and 3'-cyanoethylphosphoramidite (CED) (group 2) , N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- Omethyl group and 3'-cyanoethylphosphoramidite (CED) (group 3) , N-2 acetyl guanine and sugar moiety in the nucleosides carry a 5'- DMT group in deoxyribonucleosides, 2'- amino (appropriately protected) group and 3'-cyanoethylphosphoramidite (CED) (group 4) , 5'-DMT-3'-succinyl-Icaa CPG-N-acetyl guanine protected nucleosides or 5'- DMT-2'-tBDSilyl (tBDSi) -3'-cyanoethylphosphoramidite (CED) . N-2 acetyl guanine and sugar moiety in the

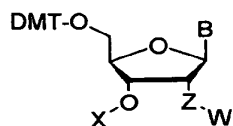
nucleosides carry a 5'-DMT group in deoxyribonucleosides (group 5), 5'-DMT-3'-succinyl-Icaa CPG-N-acetyl guanine protected nucleosides (group 6) .5'-DMT-2'-TBDMS -N- acetyl protected- guanosine -3'-amidites The invention also contemplates method for preparing the disclosed compositions. The starting base protection with transient protection with TMSChloride/ pyridine at low temperature affording N-acetyl protected nucleoside. The products are invariably crystallized. Following tritylation reaction (with DMT-Chloride) of the nucleoside with DMT chloride in pyridine gave desired nucleoside in high yields for rG, 2'- fluoro-rG, 2'- Omethyl-rguanosine. In the case of 2'- amino, the amino group is protected first with trifluoro methyl group.

Based on the foregoing disclosure and experimental results obtained,

We claim:

CLAIMS

1. Derivatized nucleoside and phosphoramidites of general formula 1.

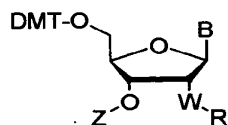


Formula 1

Where B = a) Guanine (*N-acetyl*), Z= Oxygen & W is H, ; Z=Oxygen and W= tButyldimethyl silyl, TOM (triisopropylloxymethylene), acetal levulinyl ester (ALE), pivaloyloxy; cyanoethylmethylene (CEM); dithiomethylene (DTM); Z= oxygen and W is methyl and other higher alkyls, alkenes and alkynes; Z=W= ribo Fluorine; Z=W=ara fluorine; Z= amino, W= amino protecting group ;X = a) cyanoethyl-dialkyl phosphoramidite.

And ; Where B = Z=W=H

2. Derivatized nucleoside and phosphoramidites of general formula 2.

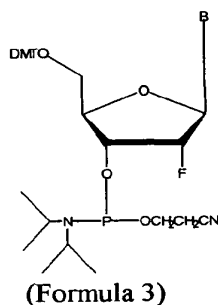


(Formula 2)

Where B = a) Guanine (*N-acetyl*), Z= Oxygen & W is H, ; Z=Oxygen and W= tButyldimethyl silyl, TOM (triisopropylloxymethylene), acetal levulinyl ester (ALE), pivaloyloxy; cyanoethylmethylene (CEM); dithiomethylene (DTM); Z= oxygen and W is methyl and other higher alkyls, alkenes and alkynes; Z=W= ribo Fluorine; Z=W=ara fluorine; Z= amino, W= amino protecting group ;Z = a) succinimido long chain attached to a solid support, b) hydroquinone succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support.

And; where Z=W=H

3. Derivatized nucleoside and solid supports of general formula 3.



Where B = a) Guanine (*N-acetyl*)

4. Derivatized nucleoside and phosphoramidites of general formula 1.

Where in

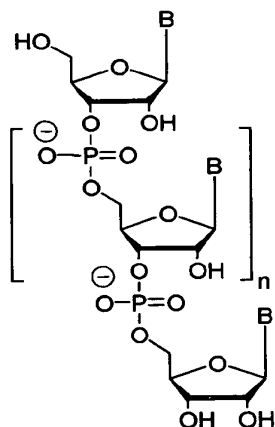
Z is, sulfur or selenium; W is H

5. Derivatized nucleoside and solid supports of general formula 2.

Where in;

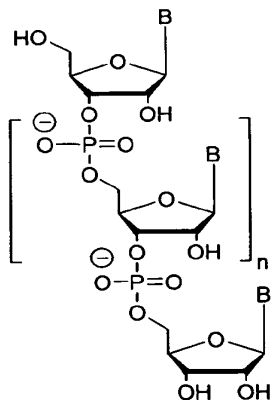
Z is sulfur or selenium; W is H

6. A method for 3' to 5' direction of oligonucleotide bond formations shown in formula 4 in synthetic RNA oligomers. The RNA could consist of natural or modified nucleobases as described in claim 1 to synthesize gapmers, phosphodiester, phosphorothiates, phosphoselenate. One of the nucleoside components will have N-acetyl guanosine base. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.



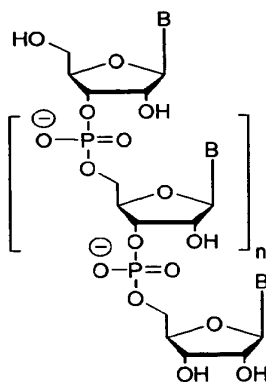
Formula 4.

7. A method for DNA & RNA synthesis using mild amine, secondary or tertiary amine for removal of N-acetyl protecting group of guanosine and cyanoethyl phosphate protecting group for RNA synthesis via 3' to 5' direction of oligonucleotide bond formations shown in formula 4 in synthetic RNA oligomers. The RNA could consist of natural or modified nucleobases, gapmers, phosphodiester, phosphorothiate, phosphoselenate. The nucleoside components will have N- Fmoc as protecting group. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.



Formula 4.

8. A method for DNA & RNA synthesis using mild basic conditions, such as methyl amine solution, alkylamines, secondary or tertiary amine for removal of N-acetyl guanosine protecting group and cyanoethyl phosphate protecting group for RNA synthesis via 3' to 5' direction of oligonucleotide bond formations shown in formula 4 in synthetic RNA oligomers. This is followed by wash of liberated protecting groups. The RNA could consist of natural or modified nucleobases, gapmers, phosphodiester, phosphorothiates, phosphoselenate. The nucleoside components will have N-Fmoc as protecting group. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.



Formula 4.

9. A method for DNA & RNA synthesis using mild basic conditions, such as methyl amine solution, alkylamines, secondary or tertiary amine for removal of N-acetyl guanosine as the solid support base and cyanoethyl phosphate protecting group for solid support attached DNA and RNA synthesis via 3' to 5' direction of oligonucleotide bond formations. This is followed by wash of liberated protecting groups. The support bound DNA and RNA could consist of natural or modified nucleobases, gapmers, phosphodiester, phosphorothiates, phosphoselenate. The nucleoside components during such oligo synthesis will have N-Fmoc as protecting group. The synthesis could be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.

10. The modified nucleosides incorporated by this method could consists of one or more of purine or pyrimidine modifications such as but not limited to , 5- Fluoro-U, 5-Fluoro dU, 5-fluoro-dC, 5-Fluro-rC, pseudouridine, 5-methyl-dU, 5-methyl-rU, 5-methyl-dC, 5-methyl-rC, 5-bromo-dU, 5-bromo-rU, 5-bromo-dC, 5-bromo-rC, 5-iodo-dU, 5-iodo-rU, 5-vinyl-dU, 5-vinyl-rU, 5-vinyl thymidine, N-3 methyldeoxy uridine, N-3 methyl-ribouridine, N-3 methyl thymidine, 4-thio uridine, 4-thio-2'-deoxyuridine, 2,6-diaminopurine deoxy riboside, N-3 methyl ribothymidine, 2, 6-diaminopurine riboside, 8-bromo 2'- deoxy adenosine, 8-bromo-r-adenosine, 8-oxo-deoxy adenosine, 8-oxo-riboadenosine, 8-oxo-2'-deoxy- adenosine, 8-oxo-riboadenosine, 8-oxo-deoxy inosine, 8-oxo-ribo inosine, 8-bromo-deoxy inosine, 8-bromo-ribo-inosine, N-1 methyl-riboadenosine, N-1 methyl-2'- deoxy adenosine, N-1 methyl 2'-deoxy inosine, N-1 methyl riboadenosine, N-1 methyldeoxy guanosine, N-1-methyl- riboguanosine, etheno adenosine, etheno 2'- deoxy adenosine, purine 2'- deoxy riboside, purine-ribonucleoside, 2-aminopurine-2'-deoxyriboside, 2-aminopurine-ribonucleoside,
11. Labelling of internal positions of an RNA synthesized by this methods with chromophores such as , but not limited to Fluorescein-C-5 dT, Dabcyl- C-5 thymidine, internal carboxyl group 5-dU-methylacrylate, biotin dT (biotin wattached via spacer to C-5 of dU), amino-dT (terminal amino attached via C-6 spacer to C-5 dU).
12. The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-fluoro ribo nucleosides (2'-F-ANAs) such as A, C, G, U , Inosine and modified nucleosides containing 2'- Fluoro, in one or more positions of an RNA or DNA sequence synthesized by this method.
13. The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-methoxy ribo nucleosides (2'-OMe-) such as A, C, G, U , Inosine and modified nucleosides containing 2'- methoxy, in one or more positions of an RNA or DNA sequence synthesized by this method.
14. The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-amino ribo nucleosides (2'-NH2) such as A, C, G, U , Inosine and modified nucleosides containing 2'- amino, in one or more positions of an RNA or DNA sequence synthesized by this method.

15. The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-terminal amino ribo nucleosides (2'-terminal NH₂), attached via spacer from 2-10 atoms on nucleosides such as A, C, G, U , Inosine and modified nucleosides containing 2'-terminal amino, in one or more positions of an RNA or DNA sequence synthesized by this method.
16. The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-methoxy ethoxy ribo nucleosides (2'-MOE), such as A, C, G, U , Inosine and modified nucleosides containing 2'- MOE, in one or more positions of an RNA or DNA sequence synthesized by this method.
17. The sugar modification of modified nucleosides could consist of other 2'- O-alkyl groups, such as 2'- deoxy-2'-ethoxy, propargyl, butyne ribo nucleosides (2'-OEt, O-Propargyl, 2'-O-Butyne), such as A, C, G, U , Inosine and modified nucleosides containing 2'- 2'-OEt, O-Propargyl, 2'-O-Butyne, in one or more positions of an RNA or DNA sequence synthesized by this method.
18. The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-fluoro arabino nucleosides (2'-F-ANAs) such as A, C, G, U , Inosine and modified nucleosides containing 2'-F-ANAs), in one or more positions of an RNA or DNA sequence synthesized by this method.
19. The sugar modification of modified nucleosides could consist of 2'- deoxy-2'-fluoro 4'-thioarabino nucleosides (4'-S-FANAs) such as A, C, G, U, Inosine and modified nucleosides containing 4'-S-FANAs in one or more positions of an RNA or DNA sequence synthesized by this method.
20. The RNA comprising one or more 2'-5'- linkage within the sequence , at the 3'- end of the sequence or at the 5'- end of the sequence.
21. The RNA having a 3'- end, synthesized by the method of this invention containing reverse attached deoxy nucleosides such as dT, dC, dG , thymidine, attached via their 3'-hydroxyl function.
22. The RNA having a 3'- end synthesized by the method of this invention containing reverse attached ribonucleosides such as rA, rC, rG, rU, attached via their 2' or 3'-hydroxyl function.
23. The RNA synthesis comprising 2'- triisopropylsilyloxy methyl (TOM), protecting group.

24. The RNA synthesis comprising 2'-t-butylthiomethyl (DTM) protecting group.
25. The reverse RNA synthesis comprising the modified base comprising 2'-deoxy-2'-fluoro-beta-D-arabinonucleic acid (FANA).
26. The RNA synthesis comprising the modified base comprising 4'-thio-2'-deoxy-2'-fluoro-beta-D-arabinonucleic acid (4'-Thio-FANA).
27. The RNA synthesis comprising the modified sugar comprising 2'-OMethyl modification.
28. The RNA synthesis comprising the modified sugar comprising Bicyclic locked nucleic acids (LNA's).
29. The RNA synthesis comprising the modified sugar comprising altritol sugar modified oligonucleotides (ANA).
30. The RNA synthesis comprising the step of conjugation of peptides, such as cell penetrating peptides (CPPs) or membrane permeant peptide (MPPs) utilizing either the free amine function of such peptides and a 3'-terminal carboxylic function on the reverse synthesized RNA. The CPPs and MPPs having an appropriate carboxyl function can be coupled to the free terminal amino function of an FMOC protected nucleotide or an oligonucleotide.
31. The DNA and RNA synthesis comprising the 2'-5'-linked DNA units or 2'-5'-RNA units within the sequence, at the 3'-end of the sequence or at the 5'-end of the sequence.

ABSTRACT

This invention relates to novel method of synthesis of RNA utilizing N-2-acetyl protected guanine as nucleoside base, nucleosides, succinates, phosphoramidites, corresponding solid supports that are suitable for oligo deoxy nucleosides and RNA oligonucleotide synthesis. Our discovery using N-acetyl protected guanine as nucleoside base protecting group, which is significantly faster base labile protecting group, yet significantly more stable than commonly utilized -2- isobutyryl guanosine is a novel approach to obtain highest purity oligonucleotides. This approach is designed to lead to very high purity and very clean oligonucleotide, after efficient removal of the protecting groups, including acetyl group from guanine and to produce high purity therapeutic grade DNA oligonucleotides, RNA oligonucleotides, diagnostic DNA, diagnostic RNA for microarray platform. The deprotection of acetyl protecting groups of the natural deoxy and ribonucleosides occurs under substantially reduced time in contact with mild deprotection conditions such as mild bases, secondary amines for removal of such groups under such conditions would allows synthesis of various DNA and RNA of highest purity for diagnostics and therapeutic application. This approach is further designed to use acetyl guanine protecting group when other bases are sensitive nucleoside, and for use in oligo peptide synthesis and for support bound oligo nucleotides.

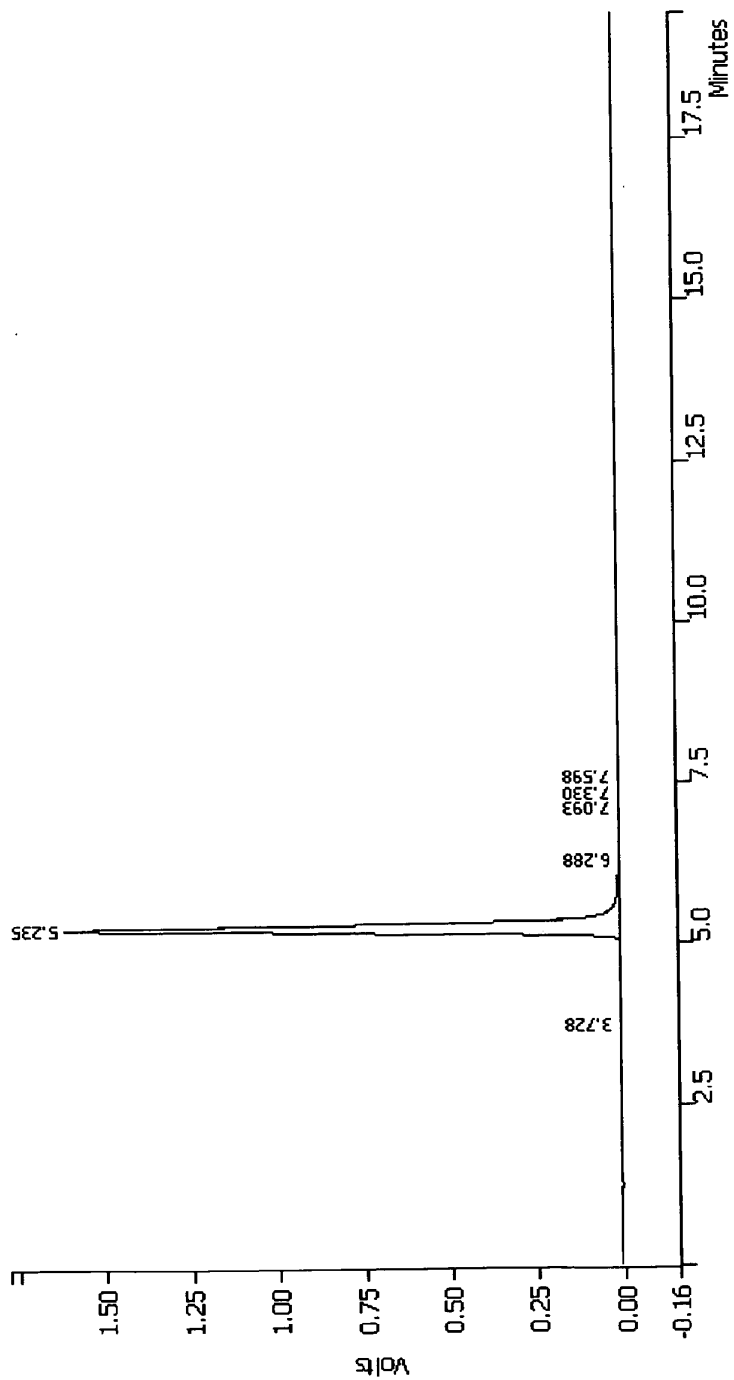


Fig.1a: HPLC Chromatogram of 5'-DMT-ribo Guanosine (n-acetyl)

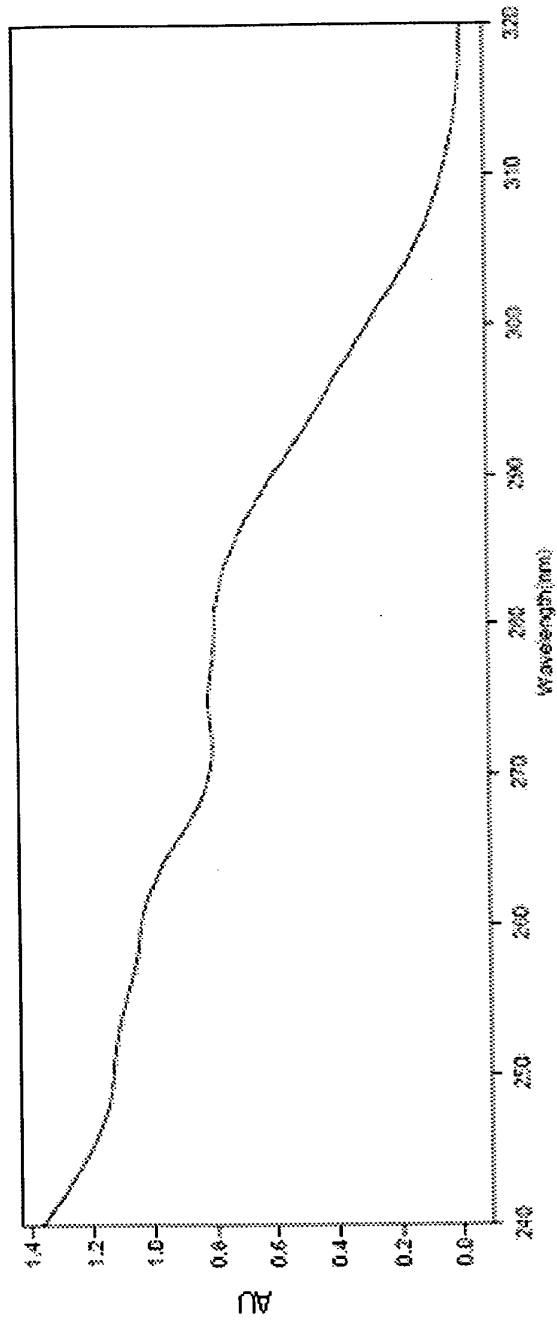


Fig.1b: UV Analysis of 5'-DMT -ribo Guanosine (n-acetyl)

Batch : 105361.sre

	A	B	C	D	E	F	G	H
1	105361.000		1	2	3	5	6	E _{max}
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280	250.0
3	Manual	A	1.133	1.042	0.794	1.087	1.312	17667

Fig.1c: Table of the UV Analysis of 5'-DMT-ribo Guanosine (n-acetyl)

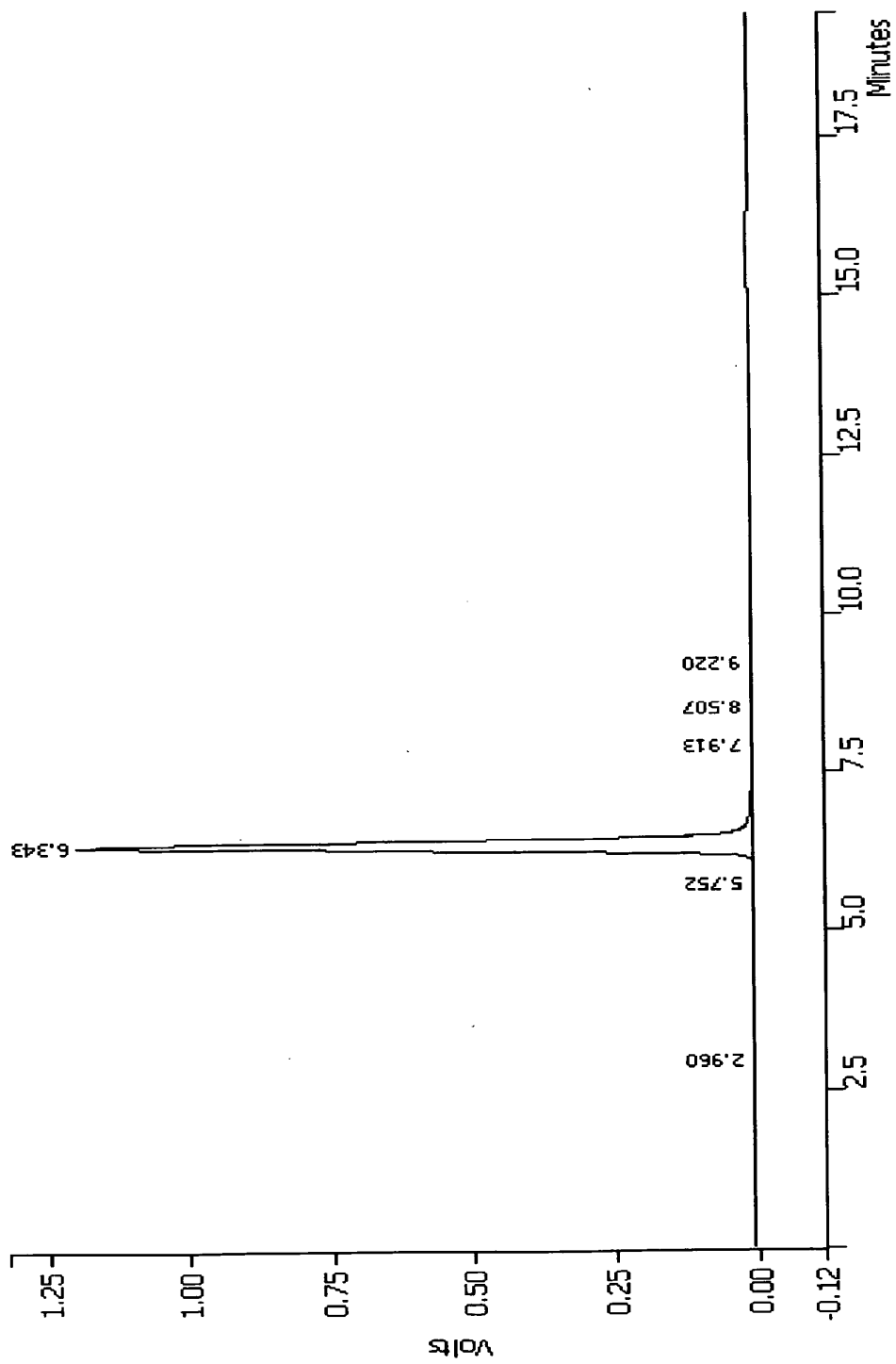


Fig.2a: HPLC Chromatogram of 5'-DMT-2'-TBDMS-ribo Guanosine (n-acetyl)

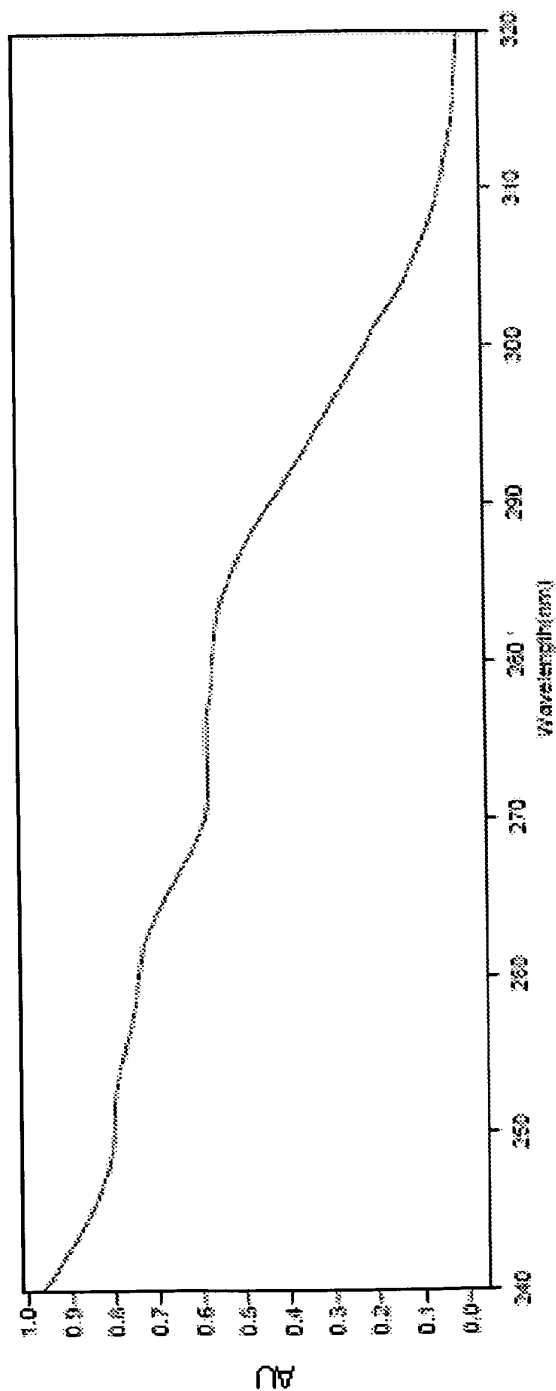


Fig.2b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

Batch : PS105-17.sre 1 / 1

	A	B	C	D	E	F	G	H
1	PS105-17		1	2	3	4.0	5.0	E _{max}
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280	250.0
3	Manual	A	0.803	0.745	0.569	1.078	1.310	22695
4	Cycle02	nm	250.0	260.0	280.0			
5	Manual	A	0.803	0.745	0.569	1.077	1.310	22695
6	Cycle03	nm	250.0	260.0	280.0			
7	Manual	A	0.803	0.745	0.569	1.078	1.309	22695
8	Ave. Value					1.078	1.310	22695

Fig.2c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)

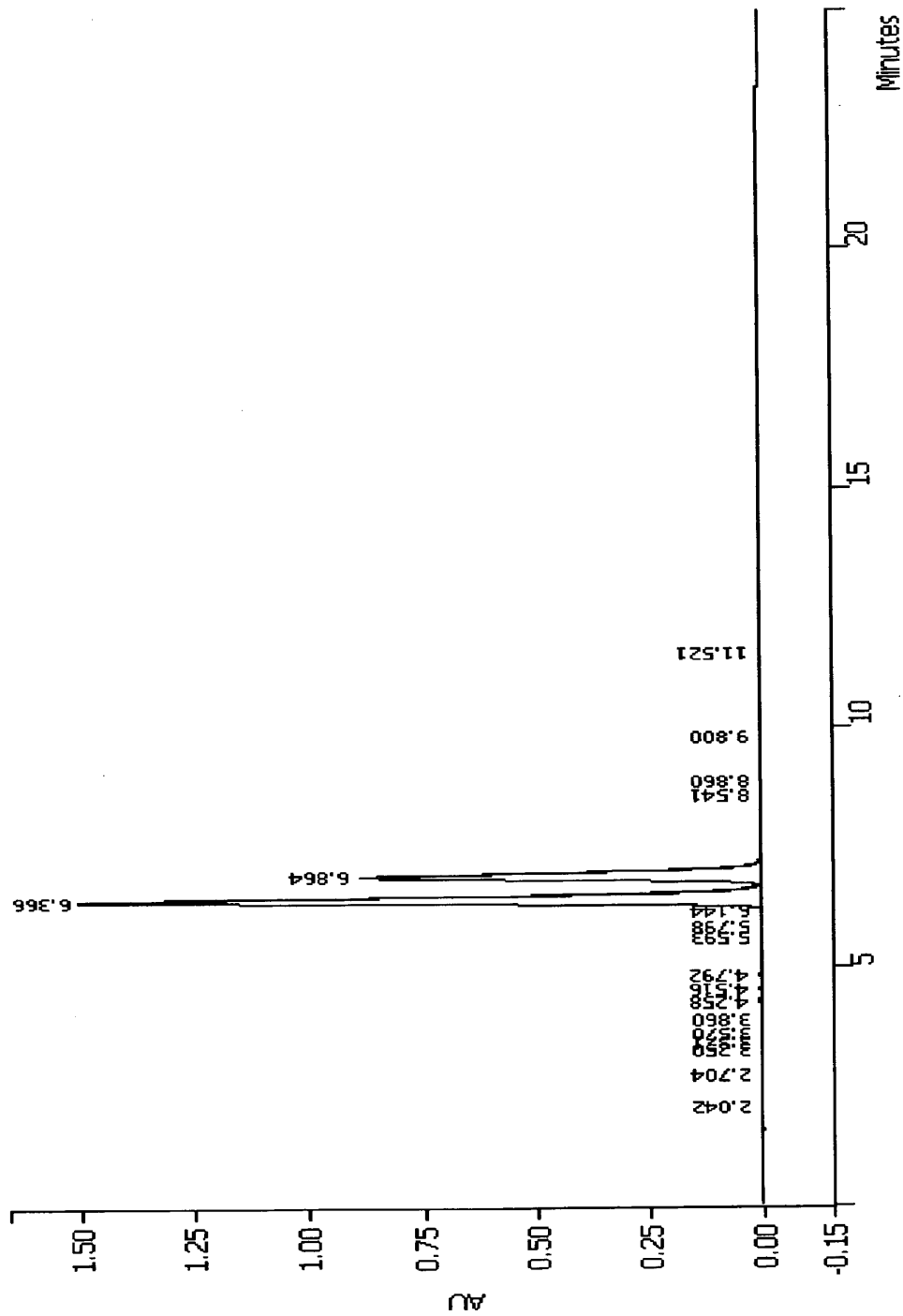


Fig.3a: HPLC Chromatogram of 5'-DMT-2'-TBDMMS-ribo Guanosine (n-acetyl)-phosphoramidite

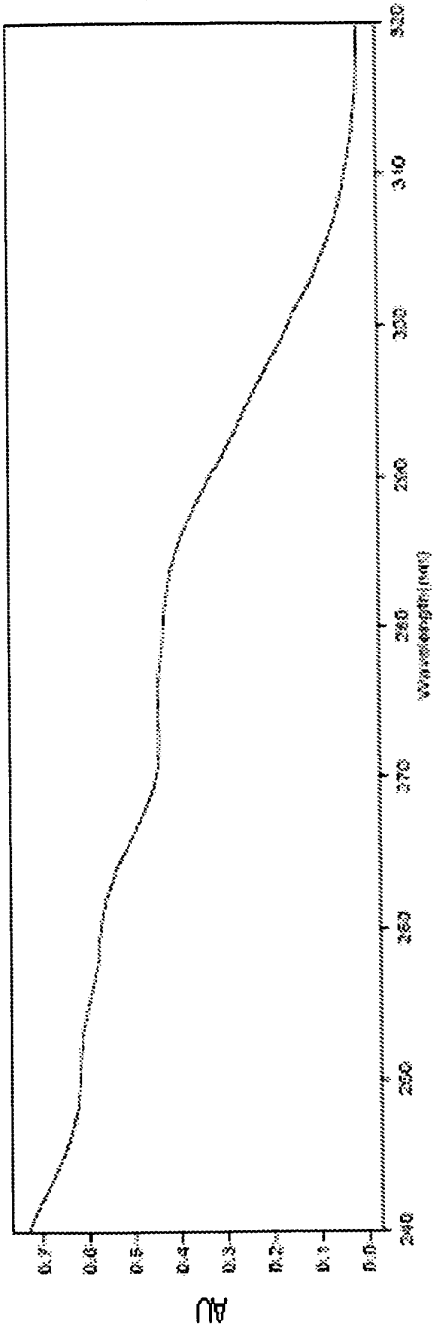


Fig.3b: UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

Batch : KP114-14.sre

	A	B	C	D	E	F	G	H
1	KP114-14		1	2	3	4.0	5.0	E _{max}
2	Cycle01	nm	250.0	260.0	280.0	250/260	260/280	250.0
3	Manual	A	0.620	0.574	0.435	1.081	1.319	20142
4	Cycle02	nm	250.0	260.0	280.0			
5	Manual	A	0.620	0.573	0.434	1.081	1.320	20142

Fig.3c: Table of the UV Analysis of 5'-DMT -2'-TBDMS-ribo Guanosine (n-acetyl)-phosphoramidite

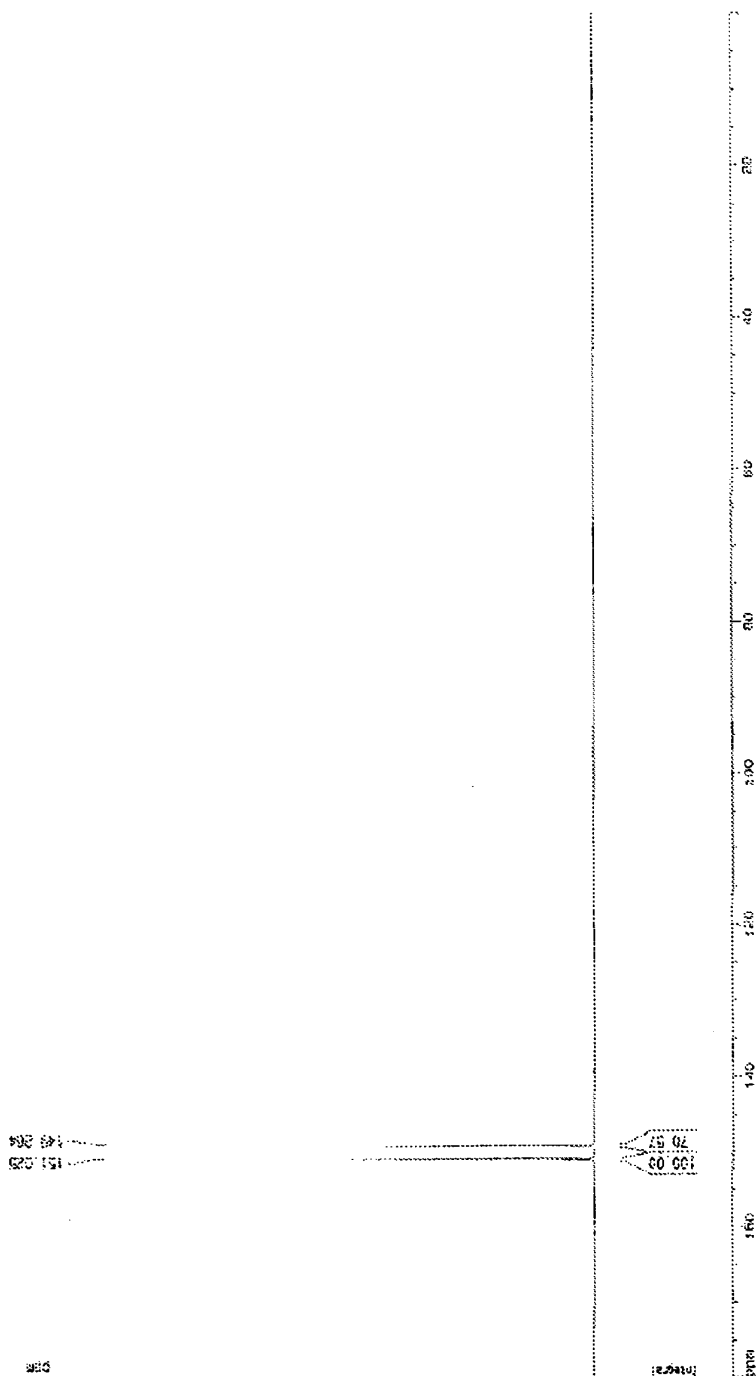


Fig.3d: 31P NMR Spectrum of 5'-DMT -2'- TBDMS -ribo Guanosine (n-acetyl)-phosphoramidite

Example of RNA synthesis #1:

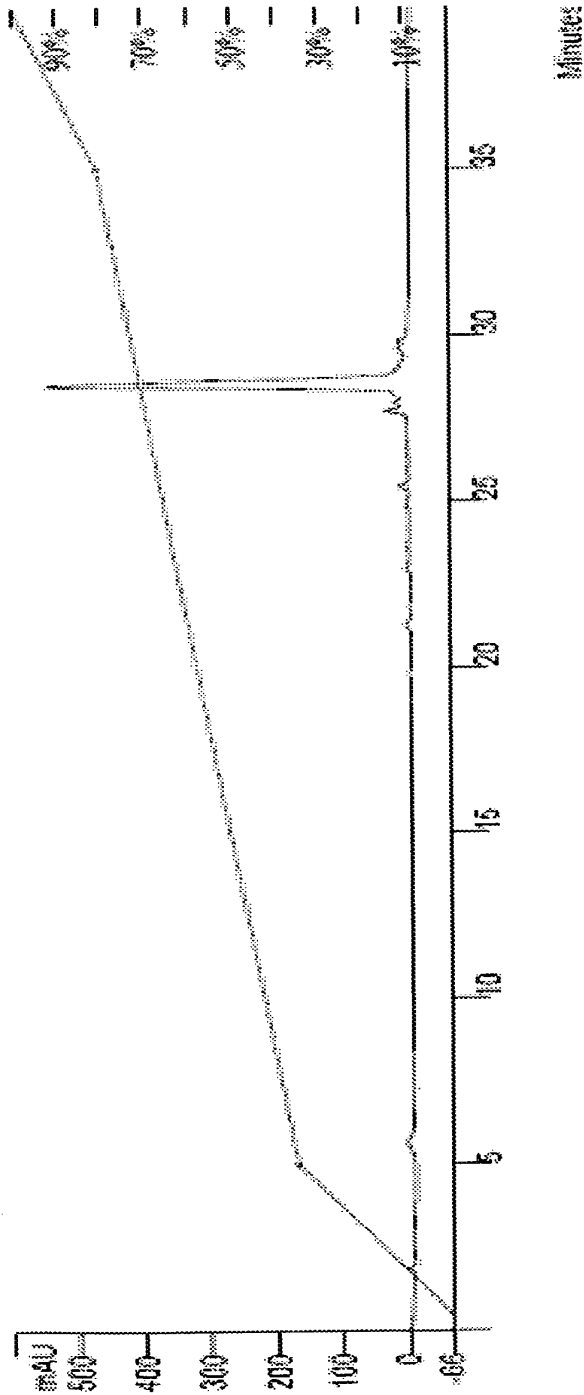


Fig. 4a: HPLC Chromatogram of purified RNA Sequence (G7799G97GAAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01
After purification purity: 91.3%
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

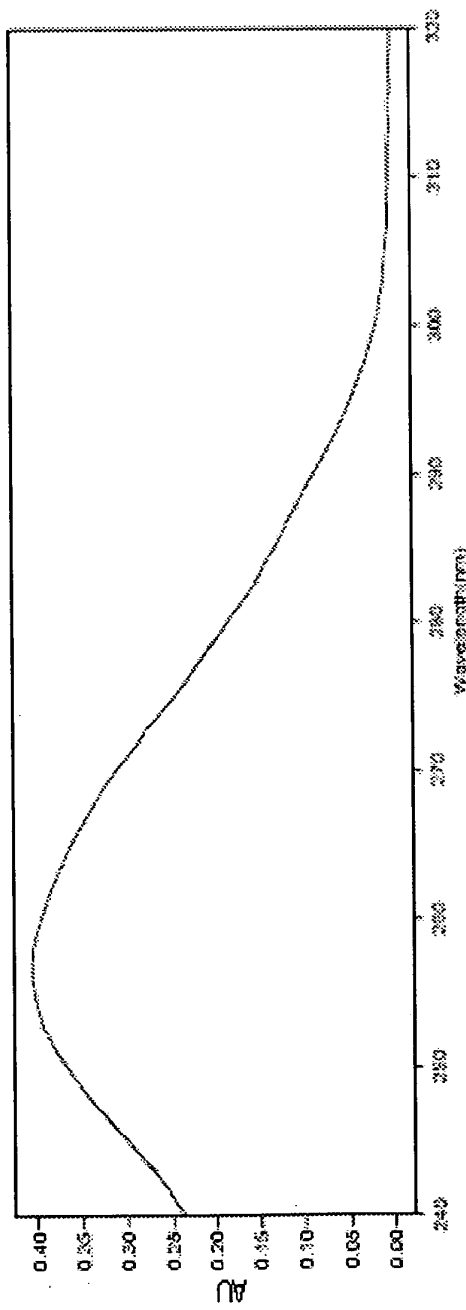


Fig.4b: UV Analysis of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Batch : 041109-E sre

	A	B	C	D	E	F	G
1	041109-E		1	2	3	5	6
2	Cycle01 nm		250.0	260.0	280.0	250/260	260/280
3	Manual A		0.367	0.397	0.185	0.925	2.140

Fig.4c: Table of UV Analysis of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

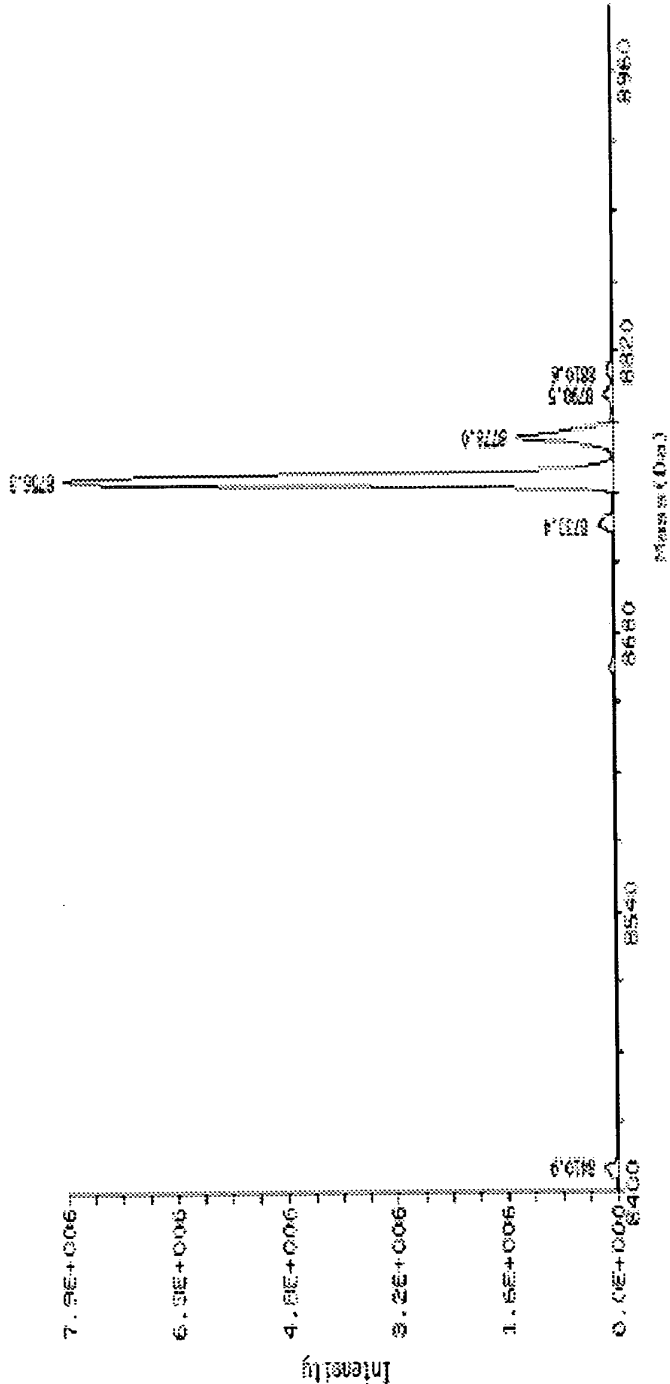


Fig.4d: ESI-MS Analysis of purified RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
Lot No. CH5-9R-45-01
Targeted mass: 8757.5
Observed Mass: 8756.3
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

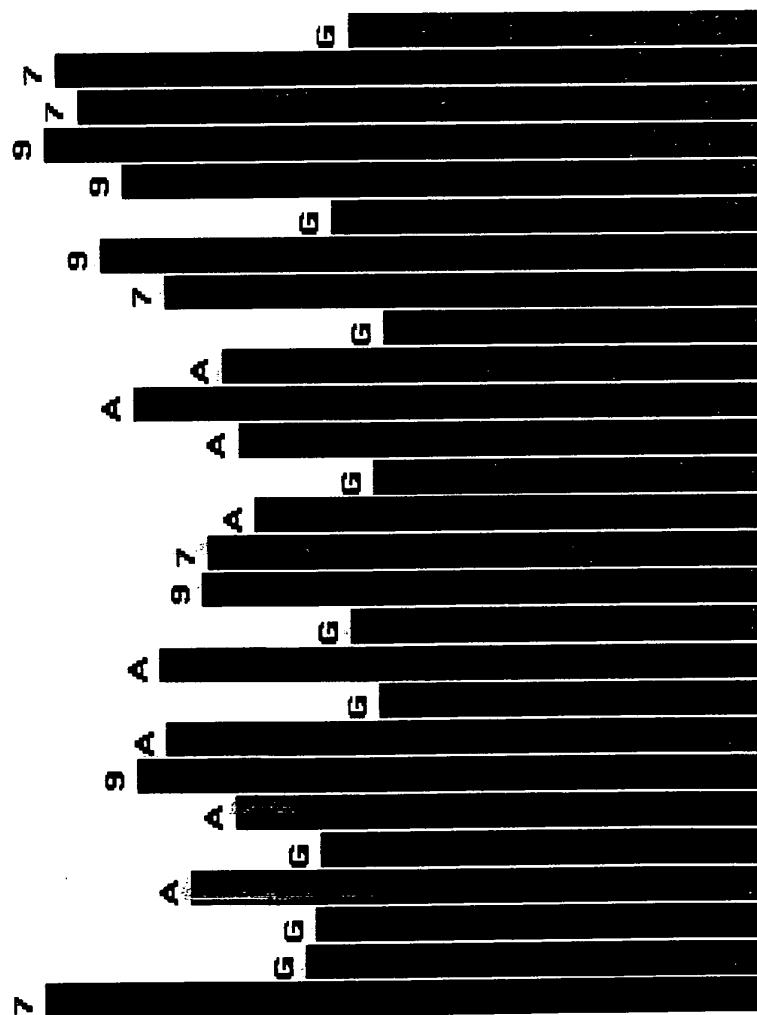


Fig.4e: Synthesis Report of RNA Sequence (G7799G97GAAAGA79GA9A9AGAGG7).
 Lot No. CH5-9R-45-01
 Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
 #7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Example of RNA synthesis #2:

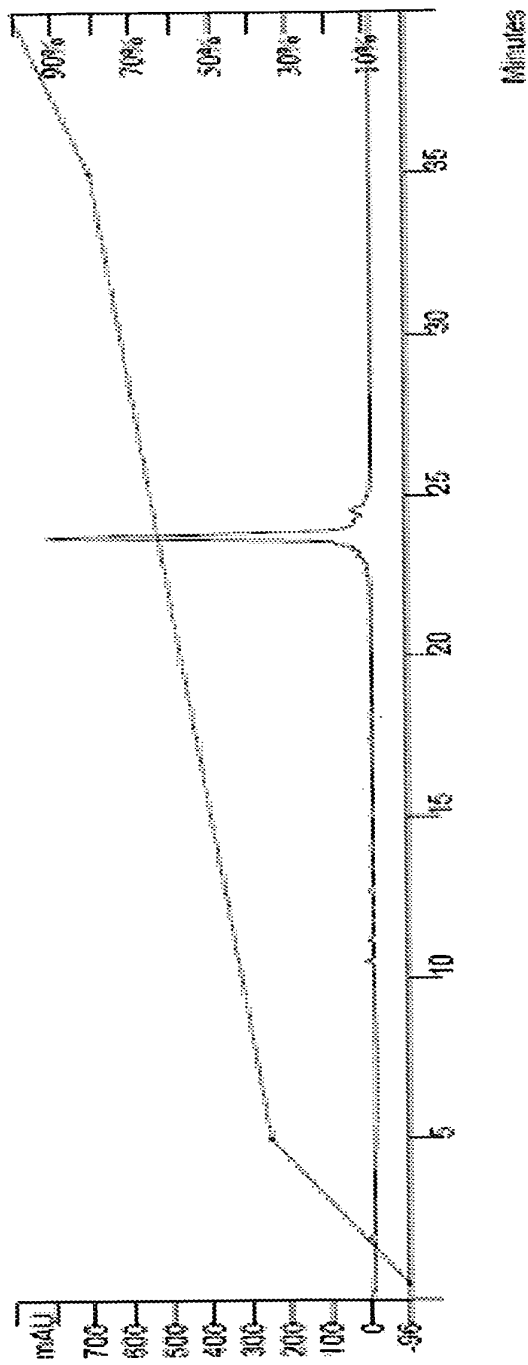


Fig. 5a: HPLC Chromatogram of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GGG9G7A7G9AGAG).
 Lot No. CH5-10R-31-01
 After purification purity: 90.53%
 Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
 #7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

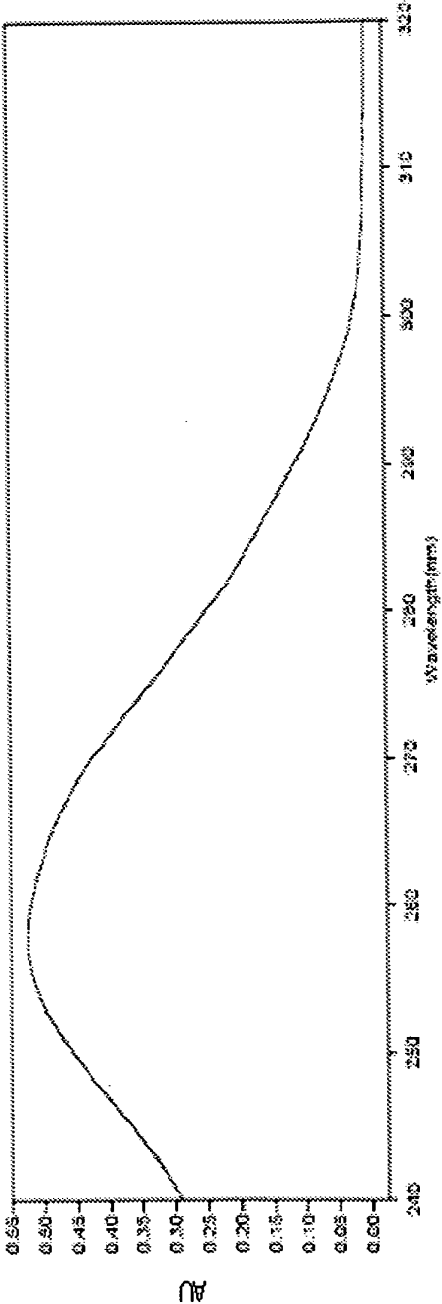


Fig. 5b: UV Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).
Lot No. CH5-10R-31-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Batch : 041109-K.sre						
	A	B	C	D	E	F
1	041109-K		1	2	3	5
2	Cycle01	nm	250.0	260.0	280.0	250/260
3	Manual	A	0.455	0.520	0.251	0.874
						2.069

Fig. 5c: Table of the UV Analysis of purified RNA Sequence (7979A777A77A9AAA99A7G99G9A9GG9G7A7G9AGAG).
Lot No. CH5-10R-31-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Drawing Sheet 14

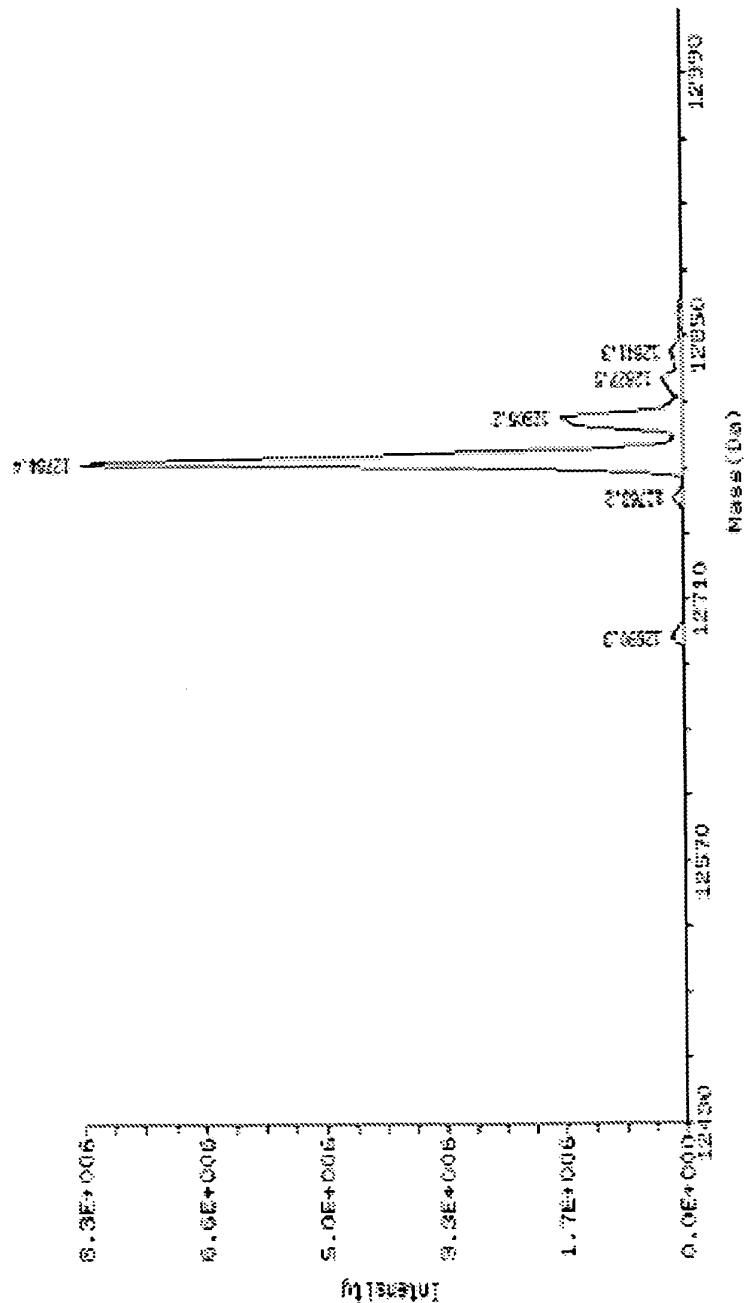


Fig.5d: ESI-MS Analysis of purified RNA Sequence (7979A777A77A9AA99A7G99G9A9GGG9G7A7G9AGAG).

Lot No. CH5-10R-31-01

Targeted mass: 12785.2

Observed Mass: 12784.4

Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.

2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.

#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.



Fig. 5c: Synthesis Report of RNA Sequence (7979A777A77A9AAA99A7G99G9A9GGG7A7G9AGAG):
Lot No. CH5-10R-31-01
Note: 1. N-2-acetyl-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
 #7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Example of RNA synthesis #3:

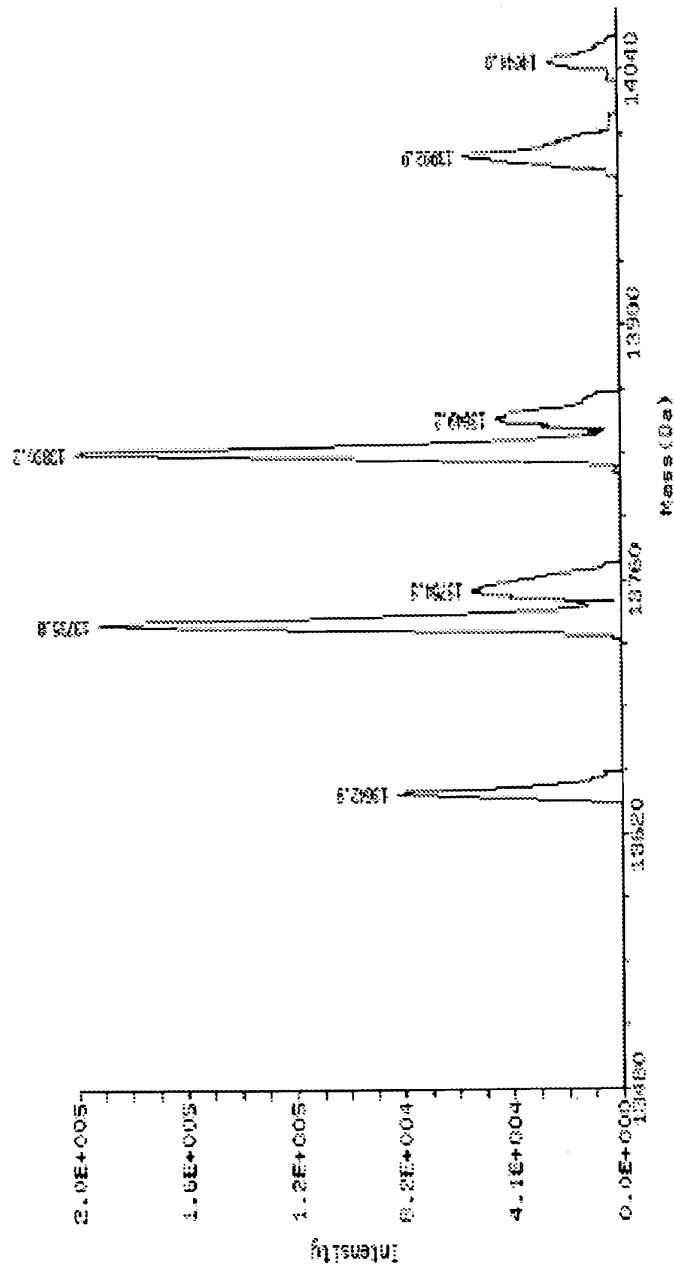


Fig. 6a: ESI-MS Analysis of purified RNA Sequence (57A7GAGAG9GG97G9777AGGGGAGAA797G97979GG5).
 Lot No. 092608
 Targeted mass: 13831.7
 Observed Mass: 13830.2, 13735.8, 13642.9
 Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
 2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
 #7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

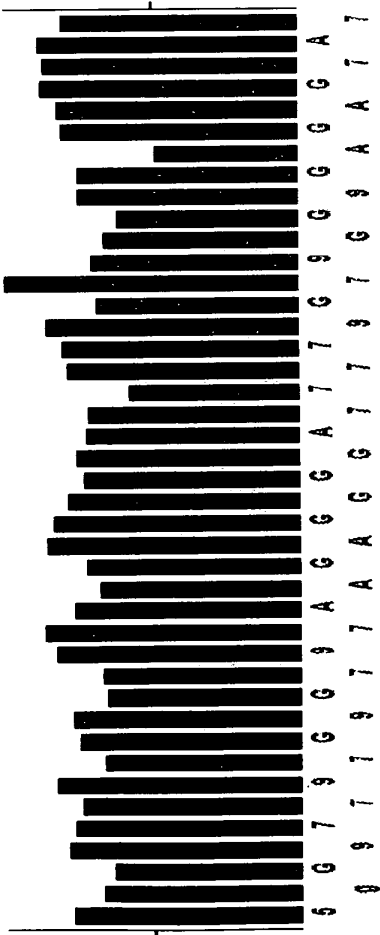


Fig.6b: Synthesis Report of RNA Sequence (57A7GAGAG9GG97G9777AGGGGAGAA797G97979GG5).
Lot No. 092608
Note: 1. N-2-ibu-ribo-Guanosine-2'-TBDMS-3'-CNET Phosphoramidite was utilized in the chimera RNA Synthesis.
2. The sequence contains 2'-Fluoro C and 2'-Fluoro-U.
#7 denotes 2'-Fluoro C base and #9 denote 2'-Fluoro U base.

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:
in relation to [this] international application,
ChemGenes Corporation is entitled to apply for and be granted a patent by virtue of the following:

ChemGenes Corporation is entitled as employer of the inventor, ... Suresh C. Srivastava,
ChemGenes Corporation is entitled as employer of the inventor, ... Naveen P. Srivastava.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

Box No. VIII (iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY

The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (iii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)):

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)):

in relation to this international application,
ChemGenes Corporation is entitled to claim priority of all earlier applications
by virtue of the following:

ChemGenes Corporation is entitled as employer of the
inventor, Suresh C. Srivastava;

ChemGenes Corporation is entitled as employer of the
inventor, Naveen P. Srivastava.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iii)".



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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
13/261,029	11/18/2011		610	ChG_00611	8	8

CONFIRMATION NO. 4149

83687

Indu M. Anand, Esq
15 Green Way
Chelmsford, MA 01824

FILING RECEIPT



OC000000051253444

Date Mailed: 12/02/2011

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**

Applicant(s)

Suresh C. Srivastava, Burlington, MA;
Naveen P. Srivastava, Burlington, MA;

Assignment For Published Patent Application

CHEMGENES CORPORATION

Power of Attorney: The patent practitioners associated with Customer Number 83687

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US2010/001494 05/19/2010
which claims benefit of 61/216,491 05/18/2009

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.)

If Required, Foreign Filing License Granted: 12/01/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/261,029**

Projected Publication Date: 03/15/2012

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO
NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE
IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

Preliminary Class**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.

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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 (1-866-999-4158).

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
13/261,029	Suresh C. Srivastava	ChG_00611
83687 Indu M. Anand , Esq 15 Green Way Chelmsford, MA 01824		INTERNATIONAL APPLICATION NO. PCT/US2010/001494
		I.A. FILING DATE 05/19/2010
		PRIORITY DATE 05/18/2009

CONFIRMATION NO. 4149
371 FORMALITIES LETTER



Date Mailed: 12/02/2011

Notification of Insufficient Fees (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as a Designated Office (37 CFR 1.494):

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 11/18/2011
- Copy of the International Search Report filed on 11/18/2011
- Oath or Declaration filed on 11/18/2011
- Request for Immediate Examination filed on 11/18/2011
- U.S. Basic National Fees filed on 11/18/2011
- Priority Documents filed on 11/18/2011
- Power of Attorney filed on 11/18/2011

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Additional claim fees of **\$625** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fees required for this application is **\$575** for a Small Entity:

Total additional claim fee(s) for this application is **\$625**

- **\$625** for **5** independent claims over 3.

(A previous payment of **\$50** will be applied to the additional fees indicated above.)

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

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ANITA D JOHNSON

Telephone: (571) 272-0386

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 13/261,029				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	190		N/A				
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	245		N/A				
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A				
TOTAL CLAIMS (37 CFR 1.16(j))	8	minus 20 = *	x 30 =	0.00	OR					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	8	minus 3 = *	x 125 =	625						
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).			0.00						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00						
				TOTAL		TOTAL				
* If the difference in column 1 is less than zero, enter "0" in column 2.				1185						
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	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))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	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))							OR		
	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.										

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)							Application Number 13261029		Filing Date				
							Applicant(s) Suresh Srivastava						
							* May be used for additional claims or amendments						
CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend		Indep	Depend	Indep	Depend	Indep	Depend
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Total Indep	8		0		0								
Total Depend	0		0		0								
Total Claims	8		0		0								

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/261,029	11/18/2011	Suresh C. Srivastava	ChG_00611

CONFIRMATION NO. 4149

83687

Indu M. Anand , Esq
15 Green Way
Chelmsford, MA 01824

PUBLICATION NOTICE



OC000000053144506

Title:SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

Publication No.US-2012-0065386-A1

Publication Date:03/15/2012

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 publicly 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 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

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
13/261,029	Suresh C. Srivastava	ChG_00611
83687 Indu M. Anand , Esq 15 Green Way Chelmsford, MA 01824		INTERNATIONAL APPLICATION NO. PCT/US2010/001494
		I.A. FILING DATE 05/19/2010
		PRIORITY DATE 05/18/2009

CONFIRMATION NO. 4149
371
ABANDONMENT/TERMINATION
LETTER



OC000000056223705

Date Mailed: 08/29/2012

NOTIFICATION OF ABANDONMENT

The United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495) has made the following determination:

- Applicant has failed to respond to the notification of MISSING REQUIREMENTS (Form PCT/DO/EO/905), mailed 12/02/2011 within the time period set therein.

Therefore, the above identified application failed to meet the requirements of 35 U.S.C. 371 and 37 CFR 1.495, and is ABANDONED AS TO THE UNITED STATES OF AMERICA.

ANITA D JOHNSON

Telephone: (571) 272-0386

Nov 17 12:02:59p

Law Offices of Indu Anand

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p.4

IAP01Rec'd PCT 19 NOV 2012

Attorney Docket No.: ChG_00611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Suresh C. Srivastava and Naveen P. Srivastava

Application: Serial No. 13/261,029

Filed: November 18, 2011

Title: **Synthesis of labile base protected – modified deoxy & modified ribo nucleosides, corresponding phosphoramidites and supports and their use in high purity oligonucleotide synthesis**

**STATEMENT REGARDING UNINTENTIONAL DELAY
ACCOMPANYING PETITION FOR REVIVAL OF APPLICATION ABANDONED UNINTENTIONALLY**

Attention: Office of Petitions
MAIL STOP PETITION
Commissioner for Patents
P.O.Box 1450
Alexandria, VA-22313-1450

Re: Notification of Abandonment dated 8/29/2012

Sir:

Due to clerical errors in the office of the representative, payment of additional fees communicated in the Notification of Insufficient Fees dated 12/2/2011 was missed for the US National Stage Patent Application with the Title and Inventors named above.

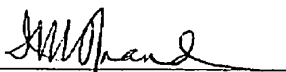
Please find payment by credit card, on two separate PTO-2038 forms, enclosed herewith for the following fees, along with the petition Form PTO/SB/64:

- Petition fee for revival of application for patent abandoned unintentionally under 37 CFR 1.137(b)
- Additional claims fee in the amount of \$ 575.

The Notification of Insufficient Fees and Notification of Abandonment are also enclosed. In the event of further deficiency in fees, you are hereby authorized to charge it to Deposit Account No. 505404. Kindly contact the undersigned representative for any other deficiency.

Dated: November 16, 2012

Respectfully submitted,

By 

Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824
(978) 250-9003/ (617) 930-5000

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Nov 17 12:02:58p

Law Offices of Indu Anand

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NOV 19 2012

15 Green Way, Chelmsford, MA 01824, USA; Tel: 978-250-9003; FAX: 978-250-7404

Indu M. Anand, Esq.

Fax

To:	Office of Petitions/USPTO	From:	Indu M. Anand
Fax:	1-571-273-8300	Pages:	<i>Nine</i> Eight, including this page
Phone:		Date:	16 November 2012
Re:	App. Serial #: 13/261,029		

Please find in this transmission:

Petition for Revival; Statement regarding unintentional delay; Notification of Abandonment;
Notification of Insufficient Fees; 2 Forms PTO-2038 for payment by credit card

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NOV 21 2012

Nov 17 12 02:59p

Law Offices of Indu Anand

NOV 19 2012

(978) 250-7404

p.2

Doc Code: PET.OP

Document Description: Petition for Revival by the Office of Petitions

PTO/SB/64 (07-09)

Approved for use through 07/31/2012. OMB 0851-0031

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.

**PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT
ABANDONED UNINTENTIONALLY UNDER 37 CFR 1.137(b)**Docket Number (Optional)
ChG_00611First named inventor: Suresh C. SrivastavaApplication No.: 13/261,029

Art Unit: _____

Filed: November 18, 2011

Examiner: _____

Title: Synthesis of labile base protected - modified deoxy & modified ribo nucleosides, corresponding phosphoramidites

Attention: Office of Petitions

Mail Stop Petition

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

FAX (571) 273-8300

NOTE: If information or assistance is needed in completing this form, please contact Petitions
Information at (571) 272-3282.

The above-identified application became abandoned for failure to file a timely and proper reply to a notice or action by the
United States Patent and Trademark Office. The date of abandonment is the day after the expiration date of the period set
for reply in the office notice or action plus any extensions of time actually obtained.

APPLICANT HEREBY PETITIONS FOR REVIVAL OF THIS APPLICATION

NOTE: A grantable petition requires the following items:

- (1) Petition fee;
- (2) Reply and/or issue fee;
- (3) Terminal disclaimer with disclaimer fee - required for all utility and plant applications filed
before June 8, 1995; and for all design applications; and
- (4) Statement that the entire delay was unintentional

1. Petition Fee

- ☒ Small entity-fee \$ 945 (37 CFR 1.17(m)). Application claims small entity status. See 37 CFR 1.27.
- ☐ Other than small entity-fee \$ _____ (37 CFR 1.17(m))

2. Reply and/or fee

- A. The reply and/or fee to the above-noted Office action in
the form of \$575 additional fees by credit card payment (identify type of reply):

- ☐ has been filed previously on 11/23/2012 LLANDGRA 00000009 13261029
01 FC:2453 945.00 OP
- ☒ is enclosed herewith.

- B. The issue fee and publication fee (if applicable) of \$ _____

- ☐ has been paid previously on _____
- ☐ is enclosed herewith.

(Page 1 of 2)

This collection of information is required by 37 CFR 1.137(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 1.0 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: Mail Stop Petition, 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.

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PTO/SB/64 (07-09)

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 displays a valid CMB control number

3. Terminal disclaimer with disclaimer fee

- ☒ Since this utility/plant application was filed on or after June 8, 1995, no terminal disclaimer is required.
- ☐ A terminal disclaimer (and disclaimer fee (37 CFR 1.20(d)) of \$ _____ for a small entity or \$ _____ for other than a small entity) disclaiming the required period of time is enclosed herewith (see PTO/SB/63).

4. STATEMENT: The entire delay in filing the required reply from the due date for the required reply until the filing of a grantable petition under 37 CFR 1.137(b) was unintentional. [NOTE: The United States Patent and Trademark Office may require additional information if there is a question as to whether either the abandonment or the delay in filing a petition under 37 CFR 1.137(b) was unintentional (MPEP 711.03(c), subsections (III)(C) and (D)).]

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.

Indu M. Anand
Signature
Indu M. Anand
Type or Printed name
On file - customer no. 83687
Address
Address

11/17/2012
Date
52,557
Registration Number, If applicable
Telephone Number

Enclosures:

- ☒ Fee Payment
- ☐ Reply
- ☐ Terminal Disclaimer Form
- ☒ Additional sheets containing statements establishing unintentional delay
- ☒ Other: Notification of Abandonment, Notification of Insufficient Fees

CERTIFICATE OF MAILING OR TRANSMISSION [37 CFR 1.8(a)]

I hereby certify that this correspondence is being:

☐ Deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Mail Stop Petition, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

☒ Transmitted by facsimile on the date shown below to the United States Patent and Trademark Office at (571) 273-8300.

11/17/2012
Date

Indu M. Anand
Signature

Indu M. Anand

Typed or printed name of person signing certificate

(Page 2 of 2)

Nov 17 12 03:00p

Law Offices of Indu Anand

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
13/261,029	Suresh C. Srivastava	ChG_00611
INTERNATIONAL APPLICATION NO.		
PCT/US2010/001494		
I.A. FILING DATE	PRIORITY DATE	
05/19/2010	05/18/2009	

83687

Indu M. Anand, Esq

15 Green Way

Chelmsford, MA 01824

CONFIRMATION NO. 4149

371 FORMALITIES LETTER



0000000051253445

Date Mailed: 12/02/2011

Notification of Insufficient Fees (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as a Designated Office (37 CFR 1.494):

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 11/18/2011
- Copy of the International Search Report filed on 11/18/2011
- Oath or Declaration filed on 11/18/2011
- Request for Immediate Examination filed on 11/18/2011
- U.S. Basic National Fees filed on 11/18/2011
- Priority Documents filed on 11/18/2011
- Power of Attorney filed on 11/18/2011

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Additional claim fees of \$625 as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fees required for this application is \$575 for a Small Entity:

Total additional claim fee(s) for this application is \$625

- \$625 for 5 independent claims over 3.

(A previous payment of \$50 will be applied to the additional fees indicated above.)

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

Adjustment date: 11/23/2012 LLANDGRA
11/21/2011 LLANDGRA 00000003 13261029
04 FC:1206 -50.00 OP

page 1 of 2 11/23/2012 LLANDGRA 00000009 13261029

02 FC:2614

625.00 OP

FOR: PCT/DO/EO/923 (371 Formalities Notice)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
<https://portal.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.

ANITA D JOHNSON

Telephone: (571) 272-0386

page 2 of 2

FORM PCT/DOE/523 (371 Form) (Notice)

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
13/261,029	Suresh C. Srivastava	ChG_00611
83687 Indu M. Anand, Esq 15 Green Way Chelmsford, MA 01824		
INTERNATIONAL APPLICATION NO. PCT/US2010/001494		
LA. FILING DATE	PRIORITY DATE	
05/19/2010	05/18/2009	

CONFIRMATION NO. 4149

371

ABANDONMENT/TERMINATION
LETTER



OC000000056223705

Date Mailed: 08/29/2012

NOTIFICATION OF ABANDONMENT

The United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495) has made the following determination:

- Applicant has failed to respond to the notification of MISSING REQUIREMENTS (Form PCT/DO/EO/905), mailed 12/02/2011 within the time period set therein.

Therefore, the above identified application failed to meet the requirements of 35 U.S.C. 371 and 37 CFR 1.495, and is ABANDONED AS TO THE UNITED STATES OF AMERICA.

ANITA D JOHNSON

Telephone: (571) 272-0386

page 1 of 1

FORM PCT/DO/EO/905 (371 Abandonment Notice)

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www.uspto.gov

Indu M. Anand , Esq
15 Green Way
Chelmsford MA 01824

MAILED

DEC 19 2012

PCT LEGAL ADMINISTRATION

In re Application of :
SRIVATAVA, et al. :
Application No.: 13/261,029 :
PCT No.: PCT/US2010/001494 : **DECISION ON PETITION**
Int. Filing Date: 19 May 2010 :
Priority Date: 18 May 2009 : **UNDER 37 CFR 1.137(b)**
Atty. Docket No.: ChG_00611 :
For: SYNTHESIS OF LABILE BASE PROTECTED - :
MODIFIED DEOXY & MODIFIED RIBO :
NUCLEOSIDES, CORRESPONDING :
PHOSPHORAMIDITES AND SUPPORTS AND :
THEIR USE IN HIGH PURITY :
OLIGONUCLEOTIDE SYNTHESIS :

The petition to revive under 37 CFR 1.137(b) filed 19 November 2012 in the above-captioned application is hereby **GRANTED** as follows:

Applicant's statement that "the entire delay in filing the required reply from the due date for the required reply until the filing of a grantable petition under 37 CFR 1.137(b) was unintentional" satisfies the requirement of 37 CFR 1.137(b)(3).

A review of the application file reveals that applicant has now provided payment of the remaining, additional claim fees. Therefore, the request to revive the application abandoned under 35 U.S.C. 371(d) is granted as to the National stage in the United States of America.

This application is being forwarded to the United States Designated/Elected Office (US/DO/EO) for continued processing.

Derek A. Putonen
Attorney Advisor
Office of PCT Legal Administration
Tel: (571) 272-3294

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 13/261,029	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	195		N/A	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	250		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	8	minus 20 = *	x 31 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	8	minus 3 = *	x 125 =	625			
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).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
				TOTAL		TOTAL	
* If the difference in column 1 is less than zero, enter "0" in column 2.				1195			
APPLICATION AS AMENDED - PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		OTHER THAN SMALL ENTITY
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		RATE(\$)
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		ADDITIONAL FEE(\$)
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
				TOTAL ADD'L FEE		TOTAL ADD'L FEE	
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		OTHER THAN SMALL ENTITY
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		RATE(\$)
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		ADDITIONAL FEE(\$)
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
				TOTAL ADD'L FEE		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
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www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
13/261,029	Suresh C. Srivastava	ChG_00611

83687
Indu M. Anand , Esq
15 Green Way
Chelmsford, MA 01824

INTERNATIONAL APPLICATION NO.	
PCT/US2010/001494	

I.A. FILING DATE	PRIORITY DATE
05/19/2010	05/18/2009

CONFIRMATION NO. 4149
371 ACCEPTANCE LETTER



0000000058324078

Date Mailed: 12/27/2012

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

11/18/2011
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1),
(c)(2) and (c)(4) REQUIREMENTS

11/18/2011
DATE OF COMPLETION OF ALL
35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 11/18/2011
- Copy of the International Search Report filed on 11/18/2011
- Oath or Declaration filed on 11/18/2011
- Request for Immediate Examination filed on 11/18/2011
- U.S. Basic National Fees filed on 11/18/2011
- Priority Documents filed on 11/18/2011
- Power of Attorney filed on 11/18/2011

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

ANITA D JOHNSON

Telephone: (571) 272-0386



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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
13/261,029	11/18/2011	1623	1185	ChG_00611	8	8

CONFIRMATION NO. 4149

UPDATED FILING RECEIPT



OC000000058324077

83687
Indu M. Anand, Esq
15 Green Way
Chelmsford, MA 01824

Date Mailed: 12/27/2012

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)

Suresh C. Srivastava, Burlington, MA;
Naveen P. Srivastava, Burlington, MA;

Applicant(s)

Suresh C. Srivastava, Burlington, MA;
Naveen P. Srivastava, Burlington, MA;

Assignment For Published Patent Application

CHEMGENES CORPORATION

Power of Attorney: The patent practitioners associated with Customer Number 83687

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US2010/001494 05/19/2010
which claims benefit of 61/216,491 05/18/2009

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: 12/01/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/261,029**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO
NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE
IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

Preliminary Class

536

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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.

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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>.

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Indu M. Anand, Esq 15 Green Way Chelmsford, MA 01824			EXAMINER LEWIS, PATRICK T	
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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.

Office Action Summary	Application No. 13/261,029	Applicant(s) SRIVASTAVA 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) 1-8 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) 1-8 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 11/18/2011 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) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____ | 4) ☐ Other: _____ |

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

Claim Rejections - 35 USC § 112

2. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-8 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Regarding claim 1, the parenthetical phrase “(Guanine-N-acetyl...5-fluoro uracil)” renders the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 1, the text “Z=W= ribo Fluorine or ara fluorine” renders the claim indefinite as the chemical structure is not clearly set forth.

Regarding claim 2, the parenthetical phrases “(Guanine-N-acetyl...5-fluoro uracil)” and “(tButyldimethyl silyl...dithiomethylene (DTM))” render the claim indefinite

because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 3, the parenthetical phrases “(Guanine-N-acetyl...5-fluoro uracil)” and “(methyl and other higher alkyls, alkenes and alkynes)” render the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 4, the parenthetical phrase “(Guanine-N-acetyl...5-fluoro uracil)” renders the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 5, the parenthetical phrases “(Guanine-N-acetyl...5-fluoro uracil)” and “(succinimido long chain...oxalyl amido long chain spacer)” render the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 5, the text “W==R= ribo Fluorine or ara fluorine” renders the claim indefinite as the chemical structure is not clearly set forth.

Regarding claim 5, the term “long chain” is a relative term that renders the claim indefinite. The term “long chain” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Regarding claim 6, the parenthetical phrases “(Guanine-N-acetyl...5-fluoro uracil)”, “(tButyldimethyl silyl...dithiomethylene (DTM))” and “(succinimido long chain...oxalyl amido long chain spacer)” render the claim indefinite because it is unclear

whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 6, the term "long chain" is a relative term that renders the claim indefinite. The term "long chain" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Regarding claim 7, the parenthetical phrases "(Guanine-N-acetyl...5-fluoro uracil)", "(methyl and other higher alkyls, alkenes and alkynes)" and "(succinimido long chain...oxalyl amido long chain spacer)" render the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 7, the term "long chain" is a relative term that renders the claim indefinite. The term "long chain" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Regarding claim 8, the parenthetical phrases "(Guanine-N-acetyl...5-fluoro uracil)" and "(succinimido long chain...oxalyl amido long chain spacer)" render the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 8, the term "long chain" is a relative term that renders the claim indefinite. The term "long chain" is not defined by the claim, the specification does not

provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

4. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

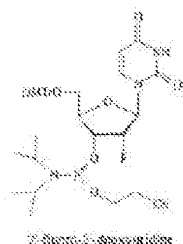
5. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

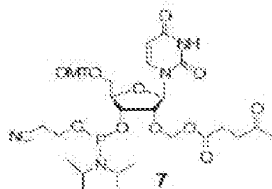
6. Claim(s) 1 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Scherr et al. Bioorganic & Medicinal Chemistry Letters (1997), Vol. 7, pages 1791-1796 (Scherr).

Scherr discloses 2'-fluoro-2'-deoxyuridine (Figure 2). 2'-Fluoro-2'-deoxyuridine is embraced by instant general formula 1.



7. Claim(s) 2 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey).

Lackey discloses compound **7** (Scheme 1). Compound **7** is embraced by instant general formula 1.



8. Claim(s) 2-3 are is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ashley JACS (1992), Vol. 114, pages 9731-9736 (Ashley).

Ashley discloses 5'-O-(4,4'-dimethoxytrityl)-2'-deoxy-(L)-uridine 3'-O-cyanoethyl N, N-diisopropylphosphoramidite and 5'-O-(4,4'-dimethoxytrityl)-2'-O-(tert-butyl dimethylsilyl)-(L)-uridine 3'-O-cyanoethyl N, N-diisopropylphosphoramidite which are embraced by instant formula 1 (page 9732).

9. Claim(s) 2-3 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu).

Ohkubu teaches that until date, a number of artificial oligonucleotides containing functional groups have been reported as powerful tools for the suppression of specific genes, the exhaustive analysis of gene expression, and the detection of single nucleotide polymorphisms (SNPs) (page 1952). However, when the standard phosphoramidite approach was used for these syntheses, base-labile functional groups could not be incorporated into DNA derivatives since ammonia treatment was required for removal of the base protecting groups and for release of DNA oligomers from the polymer supports.

Ohkubu proposes a different strategy to eliminate the problematic concentrated ammonia treatment using adenine and cytosine analogs having an acyl group on their amino groups in place of the corresponding N-free natural nucleobases (page 1953). The N-acylated adenine and cytosine analogs were designed in such a manner that the acyl groups can not only work as the protecting groups during the oligonucleotide synthesis but can also preserve the sites of Watson–Crick base pairing of these modified bases with thymine and guanine, respectively, even without removal of the acyl groups. To examine the possibility of a protected DNA probes (PDP) strategy, Ohkubu used 4-N-acetylcytosine (ac^4C) and 6-N-acylated adenine derivatives, as shown in Figure 1.

First, Ohkubo carried out the synthesis of DNA oligomers having an N-acylated adenine, i.e. 6-N-acetyladenine (ac^6A) and 6-N-benzoyladenine (bz^6A), to examine their base pairing properties. The phosphoramidite unit **3** of ac^6A was synthesized in 65% yield by acetylation of the N-unprotected dA phosphoramidite with acetyl chloride, as

shown in Figure 2. The phosphoramidite unit of bz⁶A was commercially available. Ohkubu tried to synthesize these modified DNA oligomers using the activated phosphite method and a silyl linker, as shown in Figure 3. After chain elongation, the selective removal of the cyanoethyl groups of the internucleotidic phosphates was carried out by treatment with 10% DBU in CH₃CN for 1 min and the successive release of the 5'-terminal DMTr group was carried out by treatment with 3% trichloroacetic acid in CH₂Cl₂. Finally, the modified DNA oligomers **5** and **6** were released from the resin by treatment with 0.2M Et₃N-3HF in THF at room temperature for 4 h.

Compound **3** is embraced by instant formula 1 (Fig. 2).

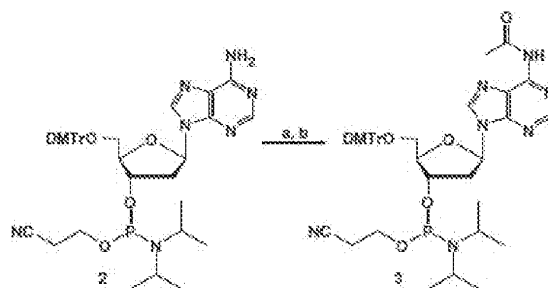


Figure 2. Synthesis of bz⁶A phosphoramidite unit **3**. Reagents and conditions: (a) AcCl, Et₃NPr₂, THF, rt; (b) pyridine-NH₃, aq. (2:1, v/v), rt, 10 min.

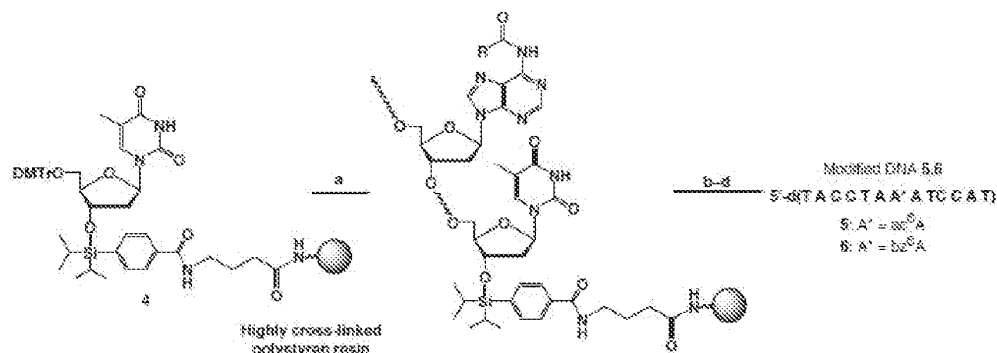


Figure 3. Synthesis of modified DNA **5** and **6**. Reagents and conditions: (a) protocol of the activated phosphite method on ABI392 DNA synthesizer; (b) DBU, CH₃CN, rt, 1 min; (c) 3% CH₂COOH, CH₂Cl₂, rt, 1 min; (d) Et₃N-3HF, THF, rt, 4 h.

Claim Rejections - 35 USC § 103

10. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

11. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

14. Claims 1 and 4 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Usman et al. US 2006/0142557 A1 (Usman) and Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) as applied to claims 2-3 above in combination.

Claims 1 and 4 are drawn to a compound of formula 1.

Usman teaches compounds **3-5** which are embraced by instant formula 1 (Fig. 6).

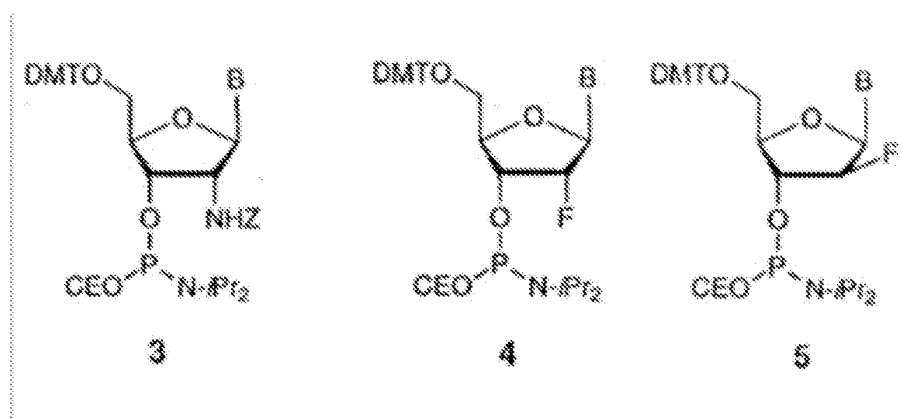


FIG. 6 shows the structures of various 2'-alkyl modified nucleotides which exemplify those of this invention. B is protected A, C, G, U, T, 2AP, I, DIAP, P etc. R groups are alkyl groups; Z is a protecting group.

Usman differs from the instantly claimed invention in that Usman does not teach a compound of structure **3**, **4** or **5** wherein B is explicitly selected from a group consisting of guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, 5-methyl cytosine-N-isobutyryl, uracil, 5-methyl uracil and 5-fluoro uracil; however, this deficiency would have been obvious in view of the teachings of Ohkubu.

As set forth supra, Ohkubu teaches N-acetylated adenosine derivatives.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

In the instant case, the simple substitution of one known element (nucleobase) for another to obtain predictable results is prima facie obvious. In the absence of unexpected results, a compound of structure **3**, **4** or **5** wherein B is uracil, adenine-N-acetyl or cytosine-N-acetyl would have been obvious to one of ordinary skill in the art at the time of the invention. The protection of adenine and cytosine bases with conventional, well-known protection groups such as acetyl using conventional, well-known methods would have been prima facie obvious. Indeed, Usman explicitly teaches compounds comprising uracil and cytosine-N-acetyl (see Examples).

15. Claims 5-8 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Scherr et al. *Bioorganic & Medicinal Chemistry Letters* (1997), Vol. 7, pages 1791-

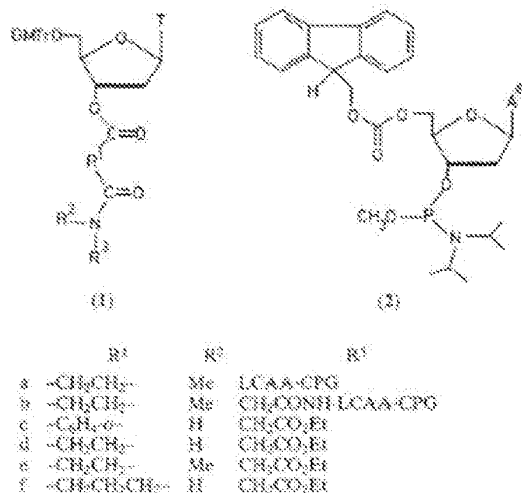
1796 (Scherr) as applied to claim 1 above; Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey) as applied to claim 2 above; Ashley JACS (1992), Vol. 114, pages 9731-9736 (Ashley) as applied to claims 2-3 above; Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) as applied to claims 2-3 above; Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey) as applied to claim 2 above; and Usman et al. US 2006/0142557 A1 (Usman) and Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) as applied to claims 2-3 above in combination and further in view of Brown et al. J. Chem. Soc., Chem. Commun. (1989), pages 891-893 (Brown).

Scherr, Lackey, Ashley, Ohkubu, Lackey, and Usman (prior art) differ from the instantly claimed invention in that prior art does not teach nucleosides comprising the instantly claimed spacer (i.e., a 3'-succinimido long chain spacer) attached to a solid support; however, this deficiency would have been obvious in view of the teachings of Brown.

Brown teaches that the obvious incompatibility of base-labile 5'-protecting groups and **(1a)** prompted us to design a resin-oligonucleotide linker that is resistant to DBU (page 892). Brown found that the linker **(1b)** suffers less than 5% cleavage after overnight treatment with a 10% solution of DBU in dry dichloromethane or toluene. Under the same conditions scission of **(1a)** is complete in less than 1 h, presumably owing to a mechanism involving deprotonation of the amide nitrogen followed by intramolecular nucleophilic displacement at the ester carbonyl group. Although **(1b)** is stable to DBU, it is hydrolyzed in less than 1 h

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at room temperature by concentrated aqueous ammonia, the standard reagent for removal of an oligonucleotide from the solid support.



Solid-phase DNA synthesis was carried out using the linker (**1b**) and 5'-DMTr-β-cyanoethyl phosphoramidite monomers. The oligonucleotides produced were indistinguishable in terms of purity and yield from those synthesized using linker (**1a**). Solid-phase oligonucleotide synthesis was carried out on an Applied Biosystems 380B DNA-synthesizer, using the standard 0.2 μmol β-cyanoethyl or methyl phosphoramidite cycle. The following sequences were prepared using oligonucleotide-resin-linkers (**1a**) and (**1b**) and DMTr monomers.

d(T)₁₅

d(GAAGAACTGT AGAGTCGGT)

d(TCGACAGTTCAGA TCGCGAT)

d(A)₈

Brown demonstrated the value of the sarcosyl linker in conjunction with the 5'-Fmoc protected monomer (**2**) by synthesizing d(A)₈. The reverse-phase h.p.l.c. chromatograms of the crude product and a sample of d(A)₈ prepared by standard methodology (Figure 1) indicate that both methods produce excellent quality DNA.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

In the instant case, the simple substitution of one known element (spacer/linker group) for another to obtain predictable results is *prima facie* obvious. In the absence of unexpected results, it would have been obvious to one of ordinary skill in the art employ a 3'-succinimido long chain spacer to connect a nucleoside unit of the prior art in order to synthesize desired oligonucleotides. As set forth *supra*, Brown teaches that the obvious incompatibility of base-labile 5'-protecting groups and (**1a**) prompted the design of a resin-oligonucleotide linker that is resistant to DBU (page 892). Brown found that the linker (**1b**) suffers less than 5% cleavage after overnight treatment with a 10% solution of DBU in dry dichloromethane or toluene. Under the same conditions scission of (**1a**) is complete in less than 1 h, presumably owing to a mechanism involving deprotonation of the amide nitrogen followed by intramolecular nucleophilic displacement at the ester carbonyl group. Although (**1b**) is stable to DBU, it is hydrolyzed in less than 1 h at room temperature by concentrated

aqueous ammonia , the standard reagent for removal of an oligonucleotide from the solid support. Thus, it would have been obvious to employ a linker such as depicted in 1b due to its enhanced stability to DBU.

Conclusion

16. Claims 1-8 are pending. Claims 1-8 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 Maxi-Flex.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. 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/

Notice of References Cited	Application/Control No. 13/261,029	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1672	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2006/0142557 A1	06-2006	Usman; Nassim	C07H19/04	536/23.1
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	C	US-				
	D	US-				
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	H	US-				
	I	US-				
	J	US-				
	K	US-				
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	M	US-				

FOREIGN PATENT DOCUMENTS

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	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Scherr et al. Bioorganic & Medicinal Chemistry Letters (1997), Vol. 7, pages 1791-1796.
	V	Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36.
	W	Ashley JACS (1992), Vol. 114, pages 9731-9736.
	X	Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001)

Notice of References Cited

Part of Paper No. 20161011

Notice of References Cited	Application/Control No. 13/261,029	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1672	Page 2 of 2

U.S. PATENT DOCUMENTS

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	S					
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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Brown et al. J. Chem. Soc., Chem. Commun. (1989), pages 891-893.
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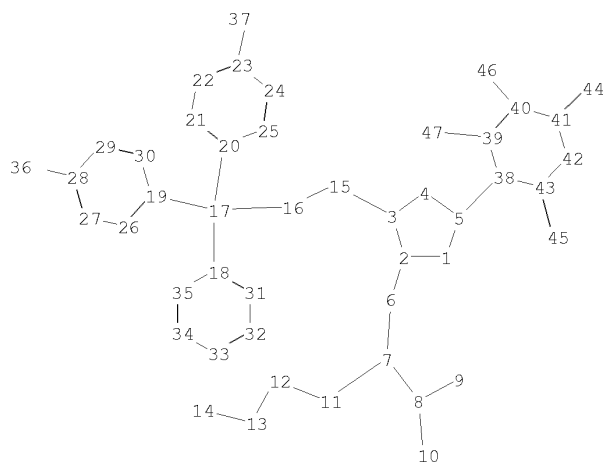
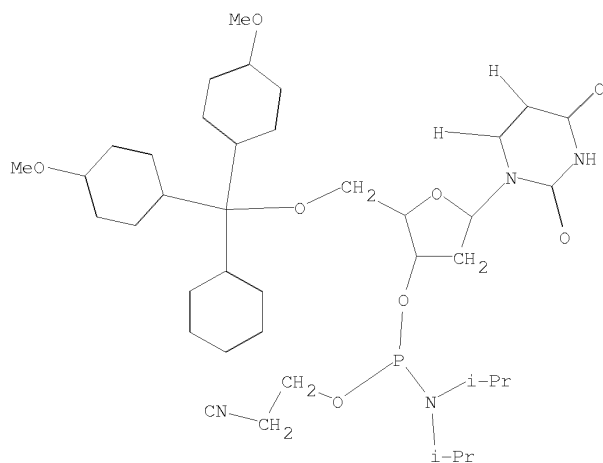
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chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 44 45 46 47

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 38 39
40 41 42 43

chain bonds :

2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18 17-19
17-20 23-37 28-36 39-47 40-46 41-44 43-45

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 38-39 38-43 39-40 40-41 41-42
42-43

exact/norm bonds :

1-2 1-5 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 16-17 38-39 38-43 39-40 40-41 41-42
41-44 42-43 43-45

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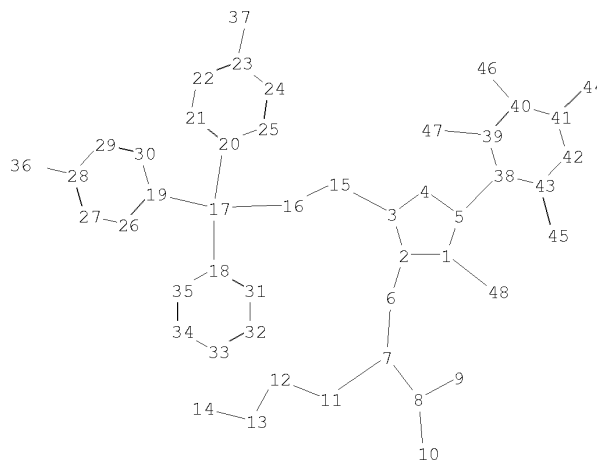
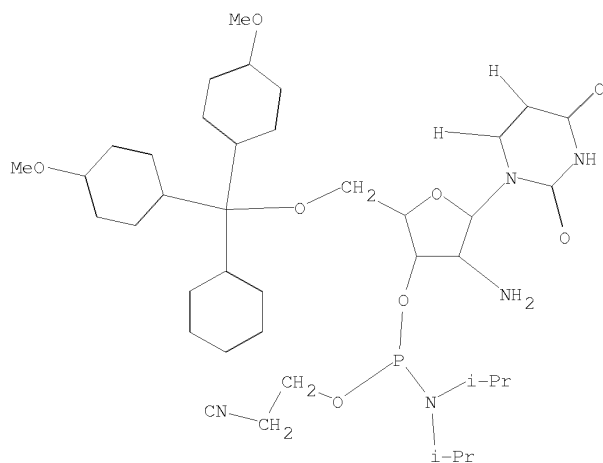
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normalized bonds :

18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25 26-27 27-28 28-29
29-30 31-32 32-33 33-34 34-35

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom
32:Atom 33:Atom 34:Atom 35:Atom 36:CLASS 37:CLASS 38:Atom 39:Atom 40:Atom 41:Atom
42:Atom 43:Atom 44:CLASS 45:CLASS 46:CLASS 47:CLASS



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 44 45 46 47 48

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 38 39
40 41 42 43

chain bonds :

1-48 2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
17-19 17-20 23-37 28-36 39-47 40-46 41-44 43-45

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 38-39 38-43 39-40 40-41 41-42
42-43

exact/norm bonds :

1-2 1-5 1-48 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 16-17 38-39 38-43 39-40 40-41
41-42 41-44 42-43 43-45

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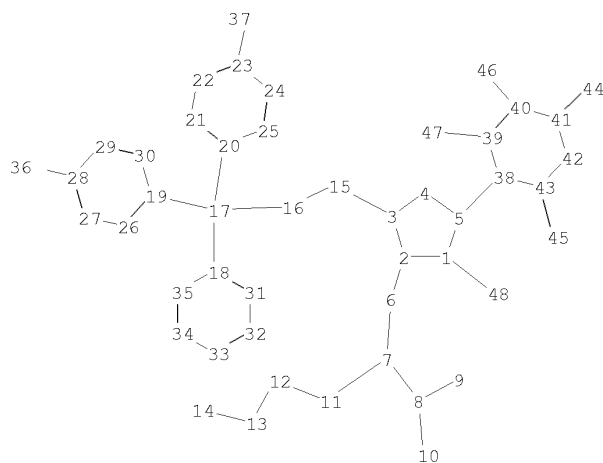
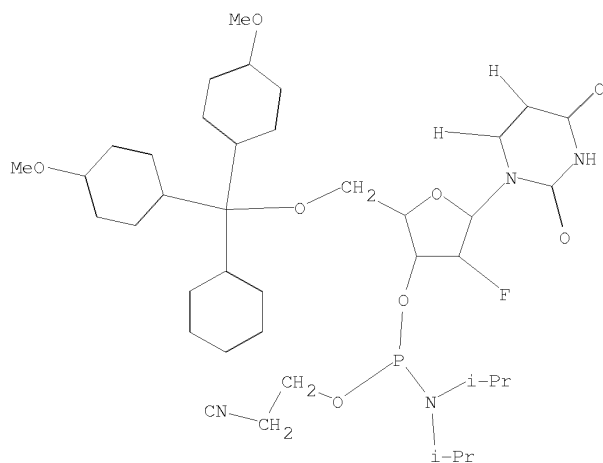
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normalized bonds :

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29-30 31-32 32-33 33-34 34-35

Match level :

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42:Atom 43:Atom 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 44 45 46 47 48

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 38 39
40 41 42 43

chain bonds :

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17-19 17-20 23-37 28-36 39-47 40-46 41-44 43-45

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 38-39 38-43 39-40 40-41 41-42
42-43

exact/norm bonds :

1-2 1-5 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 16-17 38-39 38-43 39-40 40-41 41-42
41-44 42-43 43-45

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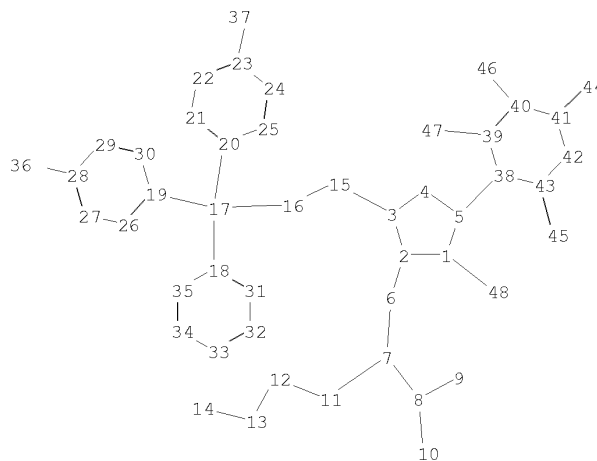
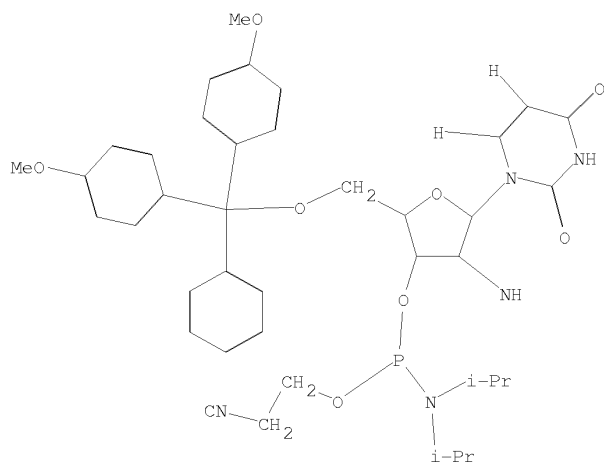
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40-46

normalized bonds :

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42:Atom 43:Atom 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS



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6 7 8 9 10 11 12 13 14 15 16 17 36 37 44 45 46 47 48

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1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 38 39
40 41 42 43

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17-19 17-20 23-37 28-36 39-47 40-46 41-44 43-45

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 38-39 38-43 39-40 40-41 41-42
42-43

exact/norm bonds :

1-2 1-5 1-48 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 16-17 38-39 38-43 39-40 40-41
41-42 41-44 42-43 43-45

exact bonds :

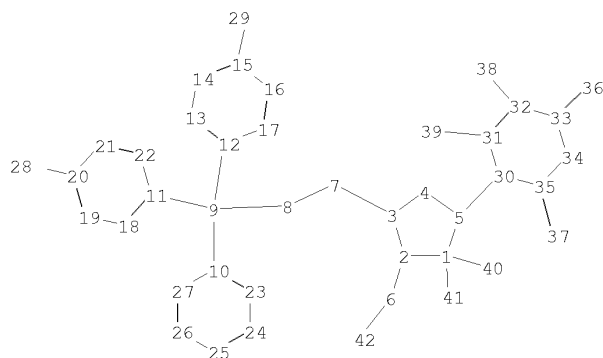
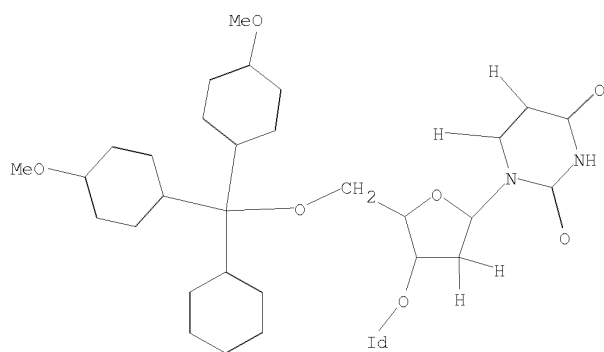
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normalized bonds :

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29-30 31-32 32-33 33-34 34-35

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42:Atom 43:Atom 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS



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chain nodes :
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ring nodes :
  1 2 3 4 5 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 30 31
  32 33 34 35
chain bonds :
  1-40 1-41 2-6 3-7 5-30 6-42 7-8 8-9 9-10 9-11 9-12 15-29 20-28 31-39 32-38 33-36
  35-37
ring bonds :
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  34-35
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  35-37
exact bonds :
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normalized bonds :
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42:CLASS

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<i>Index of Claims</i> 	Application/Control No. 13261029	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.
	Examiner PATRICK LEWIS	Art Unit 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								
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	5	✓								
	6	✓								
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	8	✓								

<i>Search Notes</i> 	Application/Control No. 13261029	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.
	Examiner PATRICK LEWIS	Art Unit 1672

CPC- SEARCHED		
Symbol	Date	Examiner

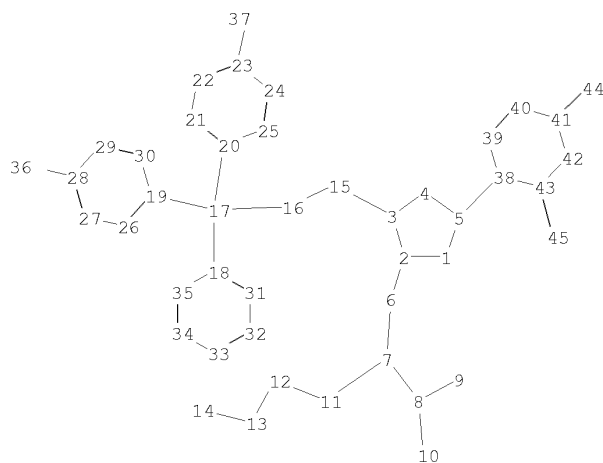
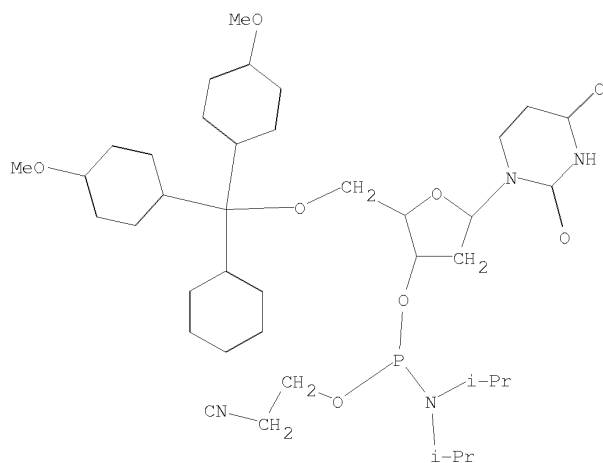
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US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	10/12/2016	/PL/

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 44 45

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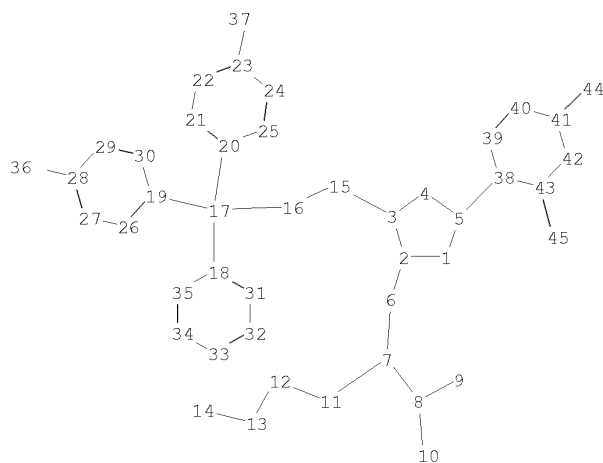
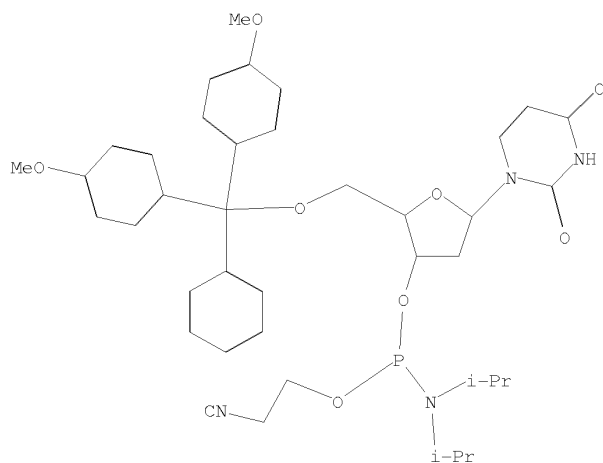
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BIB DATA SHEET

CONFIRMATION NO. 4149

SERIAL NUMBER 13/261,029	FILING or 371(c) DATE 11/18/2011 RULE	CLASS 536	GROUP ART UNIT 1672	ATTORNEY DOCKET NO. ChG_00611		
APPLICANTS INVENTORS Suresh C. Srivastava, Burlington, MA; Naveen P. Srivastava, Burlington, MA; ** CONTINUING DATA ***** This application is a 371 of PCT/US2010/001494 05/19/2010 which claims benefit of 61/216,491 05/18/2009 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 12/01/2011						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and /PATRICK T LEWIS/ Acknowledged Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY MA	SHEETS DRAWINGS 17	TOTAL CLAIMS 8	INDEPENDENT CLAIMS 8
ADDRESS Indu M. Anand , Esq 15 Green Way Chelmsford, MA 01824 UNITED STATES						
TITLE SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS						
FILING FEE RECEIVED 1185	FEES: Authority has been given in Paper 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		

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MAR 14 2017

Attorney Docket No.: ChG_00611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Inventor: Suresh C. Srivastava and Naveen Srivastava
Application Serial No.: 13/261,029
File Date: November 18, 2011
Title: SYNTHESIS OF LABILE BASE PROTECTED-
MODIFIED DEOXY & MODIFIED RIBONUCLEOSIDES CORRESPONDING
PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH
PURITY OLIGONUCLEOTIDE SYNTHESIS

Examiner: LEWIS, PATRICK T.
Art Unit: 1672

Certificate of Facsimile Transmission Under 37 CFR 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via facsimile to the United States Patent and Trademark Office at (571) 283-8300 on the date signed.

Name: _____ Signature: _____ Dated: _____

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MAIL STOP AMENDMENT

Commissioner for Patents

P. O. Box 1450

Alexandria, VA 22313 -1450

RE: Office Action of October 13, 2016

Dear Sir:

This amendment is in reply to the office action dated October 13, 2016, with the request to amend the above-identified U.S. patent application as follows:

Amendments to claims are reflected in the listing of claims starting on page 3, that follows this cover letter.

Remarks and arguments begin on page 8.

No new matter is introduced by this amendment.

03/14/2017 JVONG1 00000014 13261029

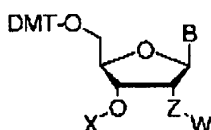
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300.00 0P

Please find included herein PTO-2038, payment by credit card to cover the fee for 2-month Extension of Time to reply. Further, authorization is hereby provided to charge any *additional* fee occasioned by this submission to Deposit account No. 505404.

CLAIMS

1. (Currently amended) Derivatized nucleoside and phosphoramidites of general formula 1[[.]],



Formula 1

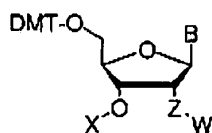
[[W]]where B is a member of selected from the group consisting of [[(]]Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5 fluoro uracil);

~~Z=W=riboFluorincorarafluorine;~~

Z is Oxygen and W is a member of selected from the group consisting of [[(]]tButyldimethyl silyl, acetal levuliny ester (ALE), and pivaloyloxy;[[.]] and.

X is cyanoethyl dialkyl phosphoramidite.

2. (Currently amended) Derivatized nucleoside and phosphoramidite[[s]] of general formula 1[[.]].



Formula 1

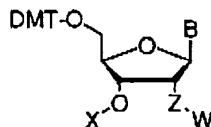
[[W]]where B is a member of selected from the group consisting of [[(]]Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5 fluoro uracil);

~~ZisHydrogenorOxygen; ifZisHydrogenthenWisnotused,andif~~

Z is Oxygen ~~then and~~ W is methyl a member of the group ((~~t~~Butyldimethylsilyl, triisopropylloxymethylene(TOM), acetallevulinylester(ALE), pivaloyloxy, cyanoethylmet
hylene(CEM), dithiomethylene(DTM)); and

X is cyanoethyl dialkyl phosphoramidite.

3. (Currently amended) Derivaized nucleoside and phosphoramidite[[s]] of general formula 1[[.]],



Formula 1

[[W]]where B is ~~a member of the group (Guanine-N-acetyl, or adenine-N-acetyl, inosine, cytosine N-acetyl, cytosine N-isobutyryl, 5-methyleytosine N-acetyl, 5-methyleytosine N-isobutyryl, uracil, 5-methyluracil, 5-fluorouracil);~~

Z is

~~Hydrogen or Oxygen, if Z is Hydrogen then W is not used, and if Z is Oxygen then W is a member of the groups consisting of (methyl and other higher alkyls, alkenes and alkynes)~~

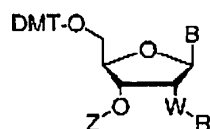
Z= ribo Fluoro or ara fluoro, and

W is absent; and

X is cyanoethyl dialkyl phosphoramidite.

4. (Canceled)

5. (Currently amended) Derivatized nucleosides, succinates and solid supports of general formula 2[[.]],



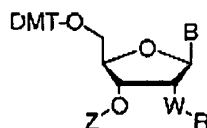
(Formula 2)

[[W]]where B is ~~a member of the group (Guanine-N-acetyl, or adenine-N-acetyl, cytosine N-acetyl, cytosine N-isobutyryl, 5-methyl cytosine-N-acetyl, 5-methyl cytosine N-isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);~~

W=R= ~~riboFluoro[[ine]]orarafluoro[[ine]]~~; Z represents ~~a member of the group (succinimido long chain, hydroquinone succinimido long chain spacer andoxalyl amido long chain spacer)~~ attached to a solid support.

Z is C(O)-M-C(O)-NH, where ~~Misselected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of~~ C1-C20 alkyl, ethoxyglycol, and a combination of alkyl and ethylene glycoxy.

6. (Currently amended) Derivatized nucleosides, succinates and solid supports of general formula 2[[.]],



(Formula 2)

wherein, B is selected from ~~a member of the group consisting of [[(]] Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);~~

~~W is Hydrogen or Oxygen; if W is Hydrogen then R is not used, and if~~

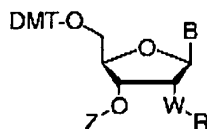
W is Oxygen then and R is a member of selected from the group consisting of [(t-Butyldimethyl silyl, triisopropylloxymethylene(TOM)-acetal levuliny ester (ALE), pivaloyloxy, cyanoethylmethylene(CEM), dithiomethylene(DTM)); and

Z represents a member of the group (succinimido long chain, hydroquinone succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support

is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethylene glycoxy.

7. (Currently amended)

Derivatized nucleosides, succinates and supports of general formula 2.



(Formula 2)

[[W]] wherein B is a member of selected from the group consisting of [(Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);

W is Hydrogen or Oxygen; if W is Hydrogen then R is not used, and if and R is the group consisting of methyl and other higher alkyls, alkenes and alkynes and

Z represents a member of the group (succinimido long chain, hydroquinone succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support

is $C(O)-M-C(O)-NH$, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of $C1-C20$ alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

8. (Canceled)

MAR 14 2017

Srivastava, Application No. 13/261,029, Filed: 11/18/2011, ...LABILEBASEPROTECTED ..., Ref: ChG_00611

REMARKS

The present reply answers below the many issues raised by the office action of 10/13/2016 and the examination of the present application under the pre-AIA first to invent provisions. Specific answers are provided below by reference to the paragraph numbering of the office action.

Claim Rejections-35 USC § 112

Claims 1-8 stand rejected (paragraph 3) under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor(s)/applicant regards as the invention.

Applicant responds as follows:

Claims 4 and 8 are canceled by this amendment, rendering moot all issues raised with regard to these two claims.

Applicant has removed the parentheses and clarified the language in claims 1, 2, 3, 5, 6 and 7. Also, the claim segment text "Z=W=riboFluorine or arafluorine" has been deleted from claims 1 and 5.

Additionally, the claim language has been amended and groups of compounds redefined in claims 5, 6 and 7, so as to address "long chain" related indefinite limitations.

Claim Rejections under 35 USC Section 102

Several references have been cited with special relevance in the office action:

The office action rejects:

claims 1 (paragraph 6)

as being anticipated by Scherr et al. Bioorganic & Medicinal Chemistry Letters (1997), Vol. 7, pages 1791-1796 (Scherr);

claim 2 (paragraph 7) as being anticipated

by Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey);

claims 2 and 3 (paragraph 8) as being anticipated by Ashley JAGS (1992), Vol. 114, pages 9731-9736 (Ashley); and

claims 2 and 3 (paragraph 9) as being anticipated by

Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964, (Ohkubu).

Without agreeing with these rejections in the context of the present invention, Applicant nevertheless has narrowed the scope of the claims to overcome potential grounds of conflict with the cited art of Scherr, Lackey, Ashley and Ohkubu.

Specifically,

- All claims referring to 2'-deoxy (DNA) have been withdrawn, by removing W=H.
- As to the rejection of claim 1 (para 6), Scherr discloses 2'-fluoro-2'-deoxyuridine (Figure 2), being embraced by the general formula 1 of the present invention, in order to avoid potential conflict, the scope of claim 1 has been narrowed by deleting 2'-fluoro-2'-deoxyuridine from it.
- As to the rejection of claim 2 (para 7), as being anticipated by Lackey et al., 2'-ALE with Uracil has been withdrawn from the amended claim to avoid potential conflict.
- As to the rejection of claim(s) 2-3 (para 8) as being anticipated by Ashley, Uridine -3'-phosphoramidite has been withdrawn from the amended claims

to avoid this potential conflict.

- As to the rejection of claim(s) 2-3 (para 9) as being anticipated by Ohkubu, we note that they carried out post synthesis modification of adenine to create adenine (N-acetyl)

2'-deoxy phosphoramidite, for the purpose of keeping the adenine compound intact, *not* for oligo synthesis, which would anticipate such acetyl protecting group to be cleaved for pure unprotected RNA molecules. Thus, Ohkubu's teachings *cannot* be applied to the present invention.

Even post synthetically, Ohkubu et al. synthesized deoxy adenine (N-acetyl) in order to avoid inherent instability of N- acetyl. They did not carry out any work on ribonucleosides generally, or on riboadenosine-N-acetyl 3'-phosphoramidite of present invention, specifically.

As a result, Ohkubu's invention refers to 2'-deoxy nucleosides while instant invention refers to 2'- tBDSilyl or other 2'- modifications.

As indicated in the disclosure of the present invention, in the absence of labile base protection, such as G-N-acetyl, there was substantial chain cleavage during oligo synthesis.

The novel process disclosed by Ohkubu et al. for introduction of N- acetyl in nucleoside phosphoramidites, however, supports the principal argument behind the subject invention: N- acetyls are unstable in nature.

Therefore, for the sensitive oligonucleotide synthesis protecting groups *are* required.

But, there is a *sharp* distinction between the technology alternatives proposed by Ohkubu and the present inventors to address the instability of N-acetyls: The present inventors *remove* these unstable protecting groups; in contrast Ohkubu et al. *retain* such groups in their application for oligonucleotides.

Claim Rejections under 35 USC Section 103

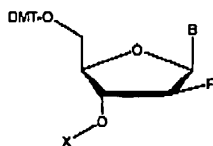
Claims 1 and 4 are rejected under pre-

AIA 35 U.S.C. 103(a) as being unpatentable over Usman et al. US 2006/0142557 A1 (Usman) and Ohkubet al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubet) as applied to claims 2-3 above in combination.

Claims 1 and 4 are drawn to a compound of formula 1.

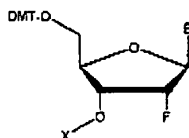
Structures of 2'- Ara fluoro and ribo fluoro compounds of our claims:

Examiner has correctly pointed out that our claims clearly do not distinguish ara fluoro and ribo fluoro of our claims. The two structures (A and B) are therefore drawn to represent these class of compounds respectively.



(Structure A)

2'- Ara fluoro-2'-deoxy
phosphoramidites and solid
supports



(Structure B)

2'-Ribo fluoro-2'-deoxy
phosphoramidites and solid
supports

Usman teaches compounds 3-5 which are embraced by instant formula 1 of Fig. 6, which shows the structures of various 2'-alkyl modified nucleotides which

exemplify those of this invention,

where B is protected A, C, G, U, T, 2AP, I, DIAP, etc. R groups are alkyl groups; and

Z is a protecting group.

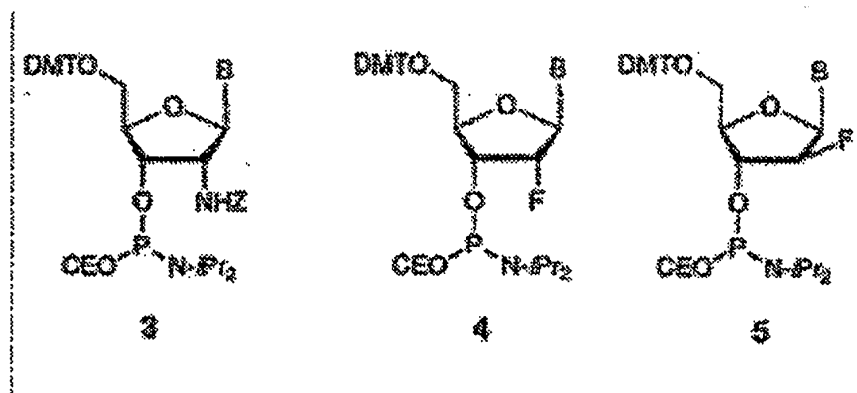


FIG.6

Applicants have considerably narrowed the claims in view of Usman.

Specifically:

- 2'-fluoro Uridine, inosine, Uracil, 5-methyl uracil, 5-fluoro uracil, 2'- alkenes and alkynes have been withdrawn in view of Usman et al.
- Additional compounds withdrawn from the amended claims include: W= Triisopropylloxymethylene (TOM), W= cyanoethylmethylene (CEM), W= dithiomethylene (DTM).
- In some claims, Z= Hydrogen is withdrawn (in which case W becomes mute). This is tantamount to withdrawal of 2'- deoxy nucleosides or phosphoramidites.

As noted in the office action, Usman differs from the instantly claimed invention in that Usman does not teach a compound of structure 3, 4 or 5 wherein B is explicitly selected from a group consisting of guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methylcytosine-N-acetyl, 5-methylcytosine-N-isobutyryl, uracil, 5-methyluracil and 5-fluorouracil.

However, it states that this deficiency would have been obvious in view of the teachings of Ohkubu.

Further, the office action notes that Scherr, Lackey, Ashley, Ohkubu, Lackey, and Usman (prior art) differ from the instantly claimed invention in that prior art does not teach nucleosides comprising the instantly claimed spacer (i.e., a 3'-succinimidolong chain spacer) attached to a solid support; however, this deficiency would have been obvious in view of the teachings of Brown.

Regarding Brown et al.; J. Chem. Soc., Chem. Commun. (1989), 891-893, they have reported synthesis of sarcosyl and other linker spacers for base labile protecting groups and synthesized a number of DNA oligonucleotides. However, Brown et al., carried out DNA synthesis and did not report any support which are compatible with RNA synthesis. Further, Brown et al. reported Thymidine and deoxy adenosine (N-Bz) protecting group based supports and phosphoramidites. They *did not* carry out any RNA based nucleosides and RNA synthesis with base labile protecting groups.

Srivastava, Application No. 13/261,029, Filed: 11/18/2011, ...LABILEBASEPROTECTED ..., Ref: ChG_00611

Additionally, the Applicants believe that in view of the considerable narrowing of the claims and deletions the anticipation rejections due to the cited references should be withdrawn. Furthermore, if the conflict with those cited references no longer applies, then the obviousness rejections should be withdrawn as well.

Conclusion

In view of the foregoing claim amendments, analysis and arguments, a Notice of Allowance is respectfully requested.

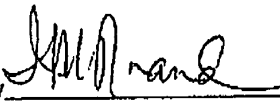
In case of any remaining issues or deficiency, you are requested to contact the undersigned representative.

Dated: March 13, 2017

Respectfully submitted,

*Suresh C. Srivastava and Naveen P.
Srivastava,*

Applicants

By 

Indu M. Anand

Registration Number: 52,557

15 Green Way
Chelmsford, MA 01824

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MAR 14 2017



Phone Number: 1.978.694.4500

Fax: 1.978.694.4502

ssrivastava@chemgenes.com

33 Industrial Way Wilmington, MA 01887

Fax

To:	Office of Petitions / USPTO	From:	Suresh C. Srivastava
Fax:	1-571-273-8300	Pages:	Seventeen (17), including this cover
	1-978-694-4500		
Phone:		Date:	03/13/2017
Re:	Patent Appl No. 13/261,029	For:	Petition to Revive & Reply with Amendment

Please find attached in this transmission: Petition to revive unintentionally abandoned application; Transmittal Cover letter; Amendment Cover describing amendment to Claims and detailed Remarks and arguments for the amendment.

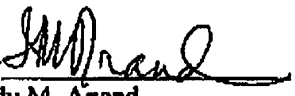
I. Suresh C. Srivastava

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For any further deficiency you are requested to contact the undersigned representative.

Dated: March 13, 2017

Respectfully submitted,

By 
Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824

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.

PATENT APPLICATION FEE DETERMINATION RECORD				Application or Docket Number		Filing Date		☐ To be Mailed	
Substitute for Form PTO-875				13/261,029		11/18/2011			
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO									
APPLICATION AS FILED – PART I									
(Column 1)		(Column 2)							
FOR	NUMBER FILED	NUMBER EXTRA		RATE (\$)		FEE (\$)			
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A					
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A					
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A					
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		X \$ =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		X \$ =					
☐ 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).								
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL					
APPLICATION AS AMENDED – PART II									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	03/14/2017	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 6	Minus	** 20	= 0	X \$40 =		0	
	Independent (37 CFR 1.16(h))	* 6	Minus	***8	= 0	X \$210 =		0	
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
TOTAL ADD'L FEE						0			
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =			
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
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 number found in the appropriate box in column 1.									

This collection of information is required by 37 CFR 1.16. 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 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Inventor: Suresh C. Srivastava and Naveen Srivastava
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File Date: November 18, 2011
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PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH
PURITY OLIGONUCLEOTIDE SYNTHESIS

Examiner LEWIS, PATRICK T.
Art Unit: 1672

Certificate of Electronic Transmission under 37 CFR Sec. 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being electronically transmitted on the date signed via USPTO's electronic filing system in accordance with 37 CFR Sec. 1.6(a)(4).

Name: I. Anand Signature: /Indu M. Anand/ Dated: April 15, 2017

RESUBMISSION - AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MAIL STOP AMENDMENT

Commissioner for Patents

P. O. Box 1450

Alexandria, VA 22313 -1450

RE: Office Action of October 13, 2016

Dear Sir:

The attached papers were submitted for the above noted application via facsimile from the Applicant's fax machine on March 13, 2017, in reply to the office action dated October 13, 2016, with the request to amend the above-identified U.S. patent application. These papers included: Cover letter; Amendments to the claims; Remarks and arguments; and, Payment by credit card to cover the fee for 2-month Extension of Time to reply.

Unfortunately, the transmission appears to have been sub-optimal, with the documents becoming difficult to decipher in part. During a telephone call by the undersigned representative, Examiner Lewis requested a better copy, entailing the current resubmission.

It is believed that no fee is required for this submission, but authorization is hereby provided to charge any *additional* fee occasioned by this submission to Deposit account No. 505404.

For any further deficiency you are requested to contact the undersigned representative.

Dated: April 15, 2017

Respectfully submitted,

By /Indu M. Anand/
Indu M. Anand
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15 Green Way
Chelmsford, MA 01824
Tel: (978)250-9003 / (617)930-5000
Fax: (978)250-7404

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Inventor: Suresh C. Srivastava and Naveen Srivastava
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Art Unit: 1672

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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via facsimile to the United States Patent and Trademark Office at (571) 283-8300 on the date signed.

Name: _____ Signature: _____ Dated: _____

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Dear Sir:

This amendment is in reply to the office action dated October 13, 2016, with the request to amend the above-identified U.S. patent application as follows:

Amendments to claims are reflected in the listing of claims starting on page 3, that follows this cover letter.

Remarks and arguments begin on page 8.

No new matter is introduced by this amendment.

Please find included herein PTO-2038, payment by credit card to cover the fee for 2-month Extension of Time to reply. Further, authorization is hereby provided to charge any *additional* fee occasioned by this submission to Deposit account No. 505404.

For any further deficiency you are requested to contact the undersigned representative.

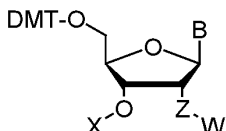
Dated: March 13, 2017

Respectfully submitted,

By /Indu M. Anand/
Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824

CLAIMS

1. (Currently amended) Derivatized nucleoside and phosphoramidites of general formula 1[[.]],



Formula 1

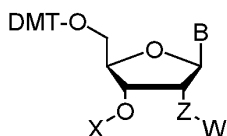
[[W]]where B is ~~a member of~~ selected from the group consisting of [[(]]Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, ~~uracil, 5-methyl uracil, 5-fluoro uracil~~);

~~Z=W=ribo-Fluorine or ara-fluorine;~~

Z is Oxygen and W is a member of selected from the group consisting of [[(]]tButyldimethyl silyl, acetal levulinyl ester (ALE), and pivaloyloxy;[[,]] and,

X is cyanoethyl dialkyl phosphoramidite.

2. (Currently amended) Derivatized nucleoside and phosphoramidite[[s]] of general formula 1[[.]],



Formula 1

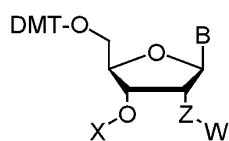
[[W]]where B is ~~a member of~~ selected from the group consisting of [[(]]Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, ~~uracil, 5-methyl uracil, 5-fluoro uracil~~);

~~Z is Hydrogen or Oxygen; if Z is Hydrogen then W is not used, and if~~

Z is Oxygen ~~then and~~ and W is methyl ~~a member of the group ((tButyldimethyl silyl, triisopropylloxymethylene (TOM), acetal levuliny ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and~~

X is cyanoethyl dialkyl phosphoramidite.

3. (Currently amended) Derivaized nucleoside and phosphoramidite[[s]] of general formula 1[[.]],



Formula 1

[[W]]where B is ~~a member of the group (Guanine-N-acetyl, or adenine-N-acetyl, inosine, cytosine N acetyl, cytosine N isobutyryl, 5 methyl cytosine N acetyl, 5 methyl cytosine N isobutyryl, uracil, 5 methyl uracil, 5 fluoro uracil);~~

Z is Hydrogen or Oxygen; if Z is Hydrogen then W is not used, and if Z is Oxygen then W is a member of the group consisting of (methyl and other higher alkyls, alkenes and alkynes)

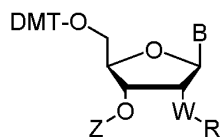
Z= ribo Fluoro or ara fluoro, and

W is absent; and

X is cyanoethyl dialkyl phosphoramidite.

4. (Canceled)

5. (Currently amended) Derivatized nucleosides, succinates and solid supports of general formula 2[[.]],



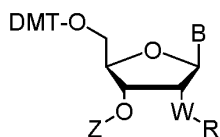
(Formula 2)

[[W]]where B is ~~a member of the group (Guanine-N-acetyl, or adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, 5-methyl cytosine-N-isobutyryl, uracil, 5-methyl uracil, 5-fluoro uracil);~~

W=R= ribo Fluoro~~[[ine]]~~ or ara fluoro~~[[ine]]~~; ~~Z represents a member of the group (succinimido long chain, hydroquinone succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support.~~

Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1- C20 alkyl, ethoxyglycol, and a combination of alkyl and ethyleneglycoxy.

6. (Currently amended) Derivatized nucleosides, succinates and solid supports of general formula 2~~[[.]]~~,



(Formula 2)

wherein, B is selected from ~~a member of~~ the group consisting of ~~[[()]]~~ Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, ~~uracil, 5-methyl uracil, 5-fluoro uracil);~~

~~W is Hydrogen or Oxygen; if W is Hydrogen then R is not used, and if~~

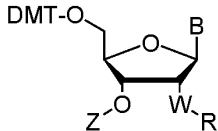
W is Oxygen ~~then~~ and R is ~~a member of~~ selected from the group consisting of ~~[[()]]~~t-Butyldimethyl silyl, ~~triisopropylloxymethylene (TOM)~~, acetal levuliny ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and

Z ~~represents a member of the group (succinimido long chain, hydroquinione succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support~~

is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1- C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

7. (Currently amended)

Derivatized nucleosides, succinates and supports of general formula 2,



(Formula 2)

[[W]]wherein B is ~~a member of~~ selected from the group consisting of ~~[[()]]~~Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl, ~~uracil, 5-methyl uracil, 5-fluoro uracil~~);

W is ~~Hydrogen or Oxygen; if W is Hydrogen then R is not used, and if~~ and R is ~~the group consisting of methyl and other higher alkyls, alkenes and alkynes and~~

Z ~~represents a member of the group (succinimido long chain, hydroquinione succinimido long chain spacer and oxalyl amido long chain spacer) attached to a solid support~~

is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1- C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

8. (Canceled)

REMARKS

The present reply answers below the many issues raised by the office action of 10/13/2016 and the examination of the present application under the pre-AIA first to invent provisions. Specific answers are provided below by reference to the paragraph numbering of the office action.

Claim Rejections - 35 USC § 112

Claims 1-8 stand rejected (paragraph 3) under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor(s)/applicant regards as the invention.

Applicant responds as follows:

Claims 4 and 8 are canceled by this amendment, rendering moot all issues raised with regard to these two claims.

Applicant has removed the parentheses and clarified the language in claims 1, 2, 3, 5, 6 and 7. Also, the claim segment text "Z=W= ribo Fluorine or ara fluorine" has been deleted from claims 1 and 5.

Additionally, the claim language has been amended and groups of compounds redefined in claims 5, 6 and 7, so as to address "long chain" related indefinite limitations.

Claim Rejections under 35 USC Section 102

Several references have been cited with special relevance in the office action:

The office action rejects:

claims 1 (paragraph 6) as being anticipated by Scherr et al. Bioorganic & Medicinal Chemistry Letters (1997), Vol. 7, pages 1791-1796 (Scherr);

claim 2 (paragraph 7) as being anticipated by Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey);

claims 2 and 3 (paragraph 8) as being anticipated by Ashley JAGS (1992), Vol. 114, pages 9731-9736 (Ashley); and

claims 2 and 3 (paragraph 9) as being anticipated by Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964, (Ohkubu).

Without agreeing with these rejections in the context of the present invention, Applicant nevertheless has narrowed the scope of the claims to overcome potential grounds of conflict with the cited art of Scherr, Lackey, Ashley and Ohkubu.

Specifically,

- All claims referring to 2'- deoxy (DNA) have been withdrawn, by removing W=H.
- As to the rejection of claim 1 (para 6), Scherr discloses 2'-fluoro-2'-deoxyuridine (Figure 2), being embraced by the general formula 1 of the present invention, in order to avoid potential conflict, the scope of claim 1 has been narrowed by deleting 2'-fluoro-2'-deoxyuridine from it.
- As to the rejection of claim 2 (para 7), as being anticipated by Lackey et al., 2'- ALE with Uracil has been withdrawn from the amended claim to avoid potential conflict.
- As to the rejection of claim(s) 2-3 (para 8) as being anticipated by Ashley, Uridine -3'—phosphoramidite has been withdrawn from the amended claims

to avoid this potential conflict.

- As to the rejection of claim(s) 2-3 (para 9) as being anticipated by Ohkubu, we note that they carried out post synthesis modification of adenine to create adenine (N-acetyl) 2'-deoxy phosphoramidite, for the purpose of keeping the adenine compound intact, *not* for oligo synthesis, which would anticipate such acetyl protecting group to be cleaved for pure unprotected RNA molecules. Thus, Ohkubu's teachings *cannot* be applied to the present invention.

Even post synthetically, Ohkubu et al. synthesized deoxy adenine (N-acetyl) in order to avoid inherent instability of N- acetyl. They did not carry out any work on ribonucleosides generally, or on riboadenosine-N-acetyl 3'-phosphoramidite of present invention, specifically.

As a result, Ohkubu's invention refers to 2'-deoxy nucleosides while instant invention refers to 2'- tBDSilyl or other 2'- modifications.

As indicated in the disclosure of the present invention, in the absence of labile base protection, such as G-N-acetyl, there was substantial chain cleavage during oligo synthesis.

The novel process disclosed by Ohkubu et al. for introduction of N- acetyl in nucleoside phosphoramidites, however, supports the principal argument behind the subject invention: N- acetyls are unstable in nature.

Therefore, for the sensitive oligonucleodide synthesis protecting groups *are* required.

But, there is a *sharp* distinction between the technology alternatives proposed by Ohkubu and the present inventors to address the instability of N-acetyls: The present inventors *remove* these unstable protecting groups; in contrast Ohkubu et al. *retain* such groups in their application for oligonucleotides.

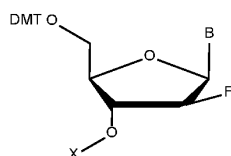
Claim Rejections under 35 USC Section 103

Claims 1 and 4 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Usman et al. US 2006/0142557 A1 (Usman) and Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) as applied to claims 2-3 above in combination.

Claims 1 and 4 are drawn to a compound of formula 1.

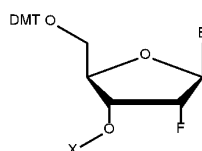
Structures of 2'- Arafluoro and ribo fluoro compounds of our claims:

Examiner has correctly pointed out that our claims clearly do not distinguish ara fluoro and ribo fluoro of our claims. The two structures (A and B) are therefore drawn to represent these class of compounds respectively.



(Structure A)

2'- Ara fluoro-2'-deoxy
phosphoramidites and solid
supports



(Structure B)

2'-Ribo fluoro-2'-deoxy
phosphoramidites and solid
supports

Usman teaches compounds 3-5 which are embraced by instant formula 1 of Fig. 6, which shows the structures of various 2'-alkyl modified nucleotides which

exemplify those of this invention, where B is protected A, C, G, U, T, 2AP, I, DIAP, P etc. R groups are alkyl groups; and Z is a protecting group.

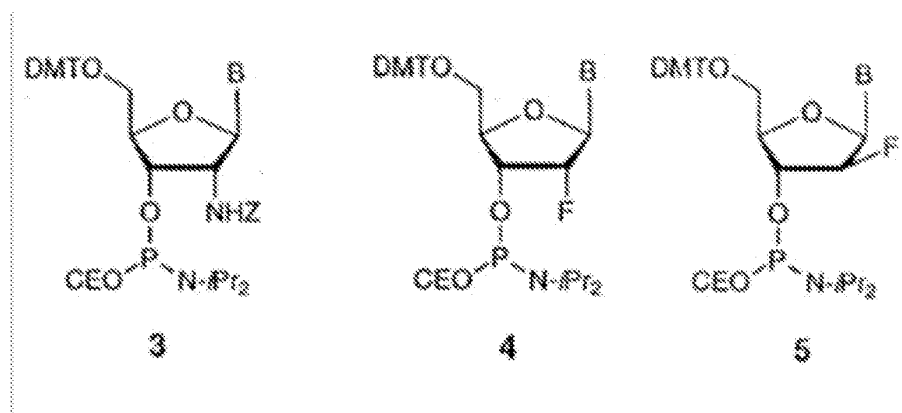


FIG. 6

Applicants have considerably narrowed the claims in view of Usman.

Specifically:

- 2'-fluoro Uridine, inosine, Uracil, 5-methyl uracil, 5-fluoro uracil, 2'- alkenes and alkynes have been withdrawn in view of Usman et al.
- Additional compounds withdrawn from the amended claims include: W= Triisopropylxymethylene (TOM), W= cyanoethylmethylene (CEM), W= dithiomethylene (DTM).
- In some claims, Z= Hydrogen is withdrawn (in which case W becomes mute). This is tantamount to withdrawal of 2'- deoxy nucleosides or phosphoramidites.

As noted in the office action, Usman differs from the instantly claimed invention

in that Usman does not teach a compound of structure 3, 4 or 5 wherein B is explicitly selected from a group consisting of guanine-N-acetyl, adenine-N-acetyl, inosine, cytosine-N-acetyl, cytosine- N-isobutyryl, 5-methyl cytosine-N-acetyl, 5-methyl cytosine-N-isobutyryl, uracil, 5-methyl uracil and 5-fluoro uracil.

However, it states that this deficiency would have been obvious in view of the teachings of Ohkubu.

Further, the office action notes that Scherr, Lackey, Ashley, Ohkubu, Lackey, and Usman (prior art) differ from the instantly claimed invention in that prior art does not teach nucleosides comprising the instantly claimed spacer (i.e., a 3'-succinimido long chain spacer) attached to a solid support; however, this deficiency would have been obvious in view of the teachings of Brown.

Regarding Brown et al.; J. Chem.Soc., Chem. Commun. (1989), 891-893, they have reported synthesis of sarcosyl and other linker spacers for base labile protecting groups and synthesized a number of DNA oligonucleotides. However, Brown et al., carried out DNA synthesis and did not report any support which are compatible with RNA synthesis. Further, Brown et al. reported Thymidine and deoxy adenosine (N-Bz) protecting group based supports and phosphoramidites. They *did not* carry out any RNA based nucleosides and RNA synthesis with base labile protecting groups.

Additionally, the Applicants believe that in view of the considerable narrowing of the claims and deletions the anticipation rejections due to the cited references

should be withdrawn. Furthermore, if the conflict with those cited references no longer applies, then the obviousness rejections should be withdrawn as well.

Conclusion

In view of the foregoing claim amendments, analysis and arguments, a Notice of Allowance is respectfully requested.

In case of any remaining issues or deficiency, you are requested to contact the undersigned representative.

Dated: March 13, 2017

Respectfully submitted,

*Suresh C. Srivastava and Naveen P.
Srivastava,*

Applicants

By /Indu M. Anand/
Indu M. Anand

Registration Number: 52,557

15 Green Way
Chelmsford, MA 01824

Electronic Acknowledgement Receipt	
EFS ID:	28936626
Application Number:	13261029
International Application Number:	
Confirmation Number:	4149
Title of Invention:	SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	83687
Filer:	Indu Mati Anand
Filer Authorized By:	
Attorney Docket Number:	ChG_00611
Receipt Date:	16-APR-2017
Filing Date:	18-NOV-2011
Time Stamp:	01:02:16
Application Type:	U.S. National Stage under 35 USC 371

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	LBP-Reply-ReSubmission-Cover_15Apr17.pdf	147430 80468986ef2dee6831d422f3496d487e12b43db9	no	2
Warnings:					

Information:					
2	Miscellaneous Incoming Letter	LBP-ReplyCover-of_13Mar17.pdf	146091	no	2
			e64113018fa7c511770a6dd2c272d5ba7c5611c2		
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	LBP-AmendedCLAIMS-Remarks_13Mar17.pdf	407348	no	12
			b0a3dd2025ca3d3ee6bd99b443a2fae575d9d69		
Warnings:					
Information:					
Total Files Size (in bytes):			700869		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.					

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.

PATENT APPLICATION FEE DETERMINATION RECORD					Application or Docket Number		Filing Date		☐ To be Mailed	
Substitute for Form PTO-875					13/261,029		11/18/2011			
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO										
APPLICATION AS FILED – PART I										
(Column 1) (Column 2)										
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)		
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A				
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))		N/A		N/A		N/A				
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A				
TOTAL CLAIMS (37 CFR 1.16(j))		minus 20 =		*		X \$ =				
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$ =				
☐ 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).								
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL				
APPLICATION AS AMENDED – PART II										
(Column 1) (Column 2) (Column 3)										
AMENDMENT	04/16/2017	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	* 6	Minus	** 20	= 0	X \$40 =		0		
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X \$210 =		0		
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE		0		
(Column 1) (Column 2) (Column 3)										
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =				
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =				
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						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 number found in the appropriate box in column 1.										

This collection of information is required by 37 CFR 1.16. 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 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.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/261,029	11/18/2011	Suresh C. Srivastava	ChG_00611	4149
83687	7590	06/05/2017		
Indu M. Anand, Esq 15 Green Way Chelmsford, MA 01824			EXAMINER LEWIS, PATRICK T	
			ART UNIT 1673	PAPER NUMBER
			MAIL DATE 06/05/2017	DELIVERY MODE PAPER

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.

Office Action Summary	Application No. 13/261,029	Applicant(s) SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1673	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 4/16/2017.
☐ 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) 1-3 and 5-7 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☒ Claim(s) 2,3,6 and 7 is/are allowed.
- 7) ☒ Claim(s) 1 and 5 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 11/18/2011 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 ____.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 4) ☐ Other: ____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

Applicant's Response Dated April 16, 2017

2. In the Response dated April 16, 2017, claims 1-3 and 5-7 were amended; claims 4 and 8 were canceled. Claims 1-3 and 5-7 are pending. An action on the merits of claims 1-3 and 5-7 is contained herein.

3. The rejection of claims 1-3 and 6-7 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, has been rendered moot in view of applicant's amendment dated April 16, 2017.

4. The rejection of claim 5 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, is maintained for the reasons of record as set forth in the Office Action dated October 13, 2016.

5. The rejection of claim 1 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Scherr et al. Bioorganic & Medicinal Chemistry Letters (1997), Vol. 7, pages 1791-1796 (Scherr) has been rendered moot in view of applicant's amendment dated April 16, 2017.

6. The rejection of claim 2 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey) has been rendered moot in view of applicant's amendment dated April 16, 2017.

7. The rejection of claims 2-3 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ashley JACS (1992), Vol. 114, pages 9731-9736 (Ashley) has been rendered moot in view of applicant's amendment dated April 16, 2017.

8. The rejection of claims 2-3 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) has been rendered moot in view of applicant's amendment dated April 16, 2017.

9. The rejection of claim 1 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Usman et al. US 2006/0142557 A1 (Usman) and Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) as applied to claims 2-3 above in combination has been rendered moot in view of applicant's amendment dated April 16, 2017.

10. The rejection of claims 5-7 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Scherr et al. Bioorganic & Medicinal Chemistry Letters (1997), Vol. 7, pages 1791-1796 (Scherr) as applied to claim 1 above; Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey) as applied to claim 2 above; Ashley JACS (1992), Vol. 114, pages 9731-9736 (Ashley) as applied to claims 2-3 above; Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) as applied to claims 2-3 above; Lackey et al. Nucleic Acids Symposium Series No. 52 (2008), pages 35-36 (Lackey) as applied to claim 2 above; and Usman et al. US 2006/0142557 A1 (Usman) and Ohkubu et al. Nucleic Acids Research (2008), Vol. 2008, pages 1952-1964 (Ohkubu) as applied to claims 2-3 above in combination and further in view of Brown et al. J. Chem. Soc., Chem. Commun. (1989), pages 891-

893 (Brown) has been rendered moot in view of applicant's amendment dated April 16, 2017.

Rejections of Record Set Forth in the Office Action Dated October 13, 2016

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. Claim 5 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Regarding claim 5, the text "W=R= ribo Fluoro or ara fluoro" renders the claim indefinite as the chemical structure is not clearly set forth.

Claim Rejections - 35 USC § 102

13. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

14. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Art Unit: 1673

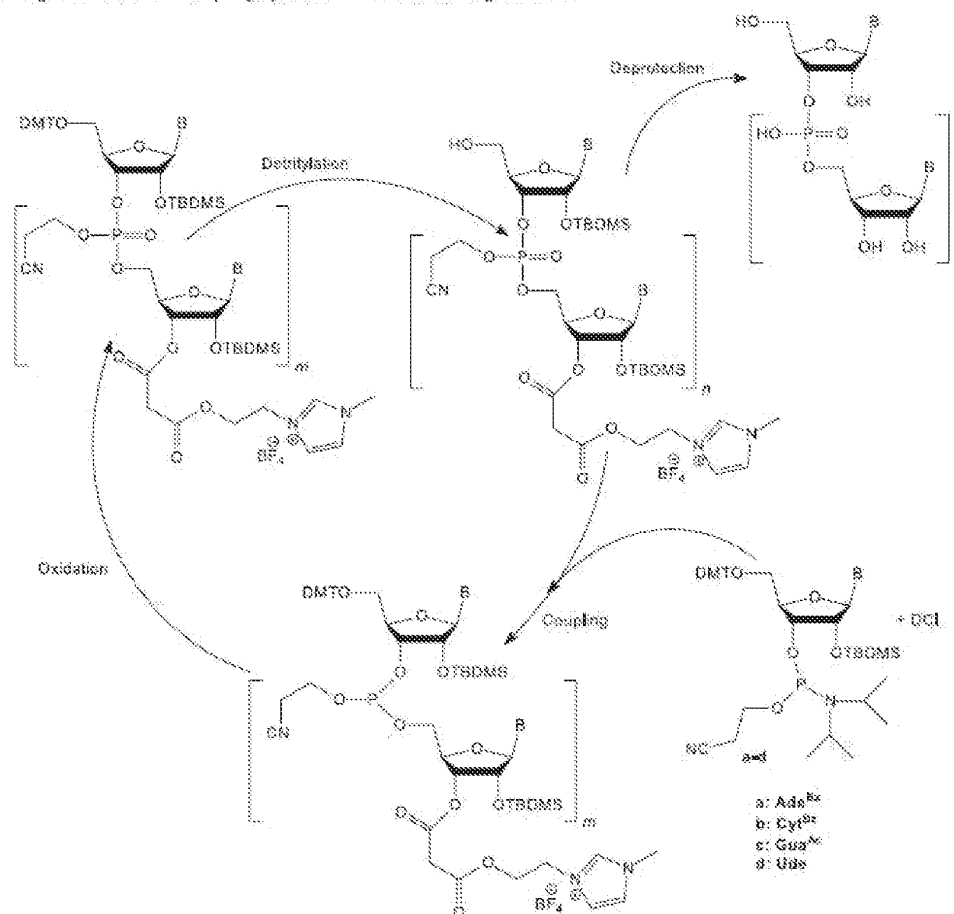
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim(s) 1 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Donga et al. Can. J. Chem. (2007), Vol. 85, pages 274-282 (Donga).

Donga teaches that since it was first introduced by Ogilvie and co-workers in 1974, the *tert*-butyl dimethylsilyl (TBDMS) group has become the standard 2'-protecting group in both solid- and solution-phase oligomerizations of ribonucleotides (page 274). Along with the phosphoramidite approach to ribonucleoside coupling, the TBDMS group remains one of the most widely used 2'-protecting groups for commercially available ribo-phosphoramidites. With the advent of RNAi and an increasing number of RNA-based therapeutics progressing toward clinical development, the TBDMS approach will continue to be an important resource as more commercially viable processes are developed for the large-scale synthesis of oligoribonucleotides.

Donga further teaches an oligonucleotide coupling cycle employing (2'-TBDMS-protected) 3'-cyanoethylphosphoramidite (Scheme 3). The 2'-TBDMS-protected 3'-cyanoethylphosphoramidite wherein B = Gua^{Ac} is embraced by instant Formula 1.

Scheme 3. Oligoribonucleotide coupling cycle (illustrated as one regioisomer).

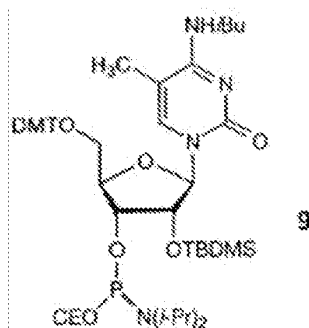


16. Claim(s) 1 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Usman et al. US 6,528,639 B2 (Usman).

Usman relates to enzymatic RNA molecules or ribozymes having a modified nucleotide base sequence (column 1, lines 15-16). Usman has determined that base modification within some catalytic core nucleotides maintains or enhances enzymatic activity compared to an unmodified molecule (column 3, lines 42-46). Base-modified nucleotides, in general, may also be used to enhance the nuclease resistance of the

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catalytic nucleic acids in which they are incorporated (column 4, lines 9-13). Usman teaches compound 9 which is embraced by instant Formula 1 (Fig. 10).



Conclusion

17. Claims 1-3 and 5-7 are pending. Claims 1 and 5 are rejected. Claims 2-3 and 6-7 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 Maxi-Flex.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. 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 1673

/PL/

Notice of References Cited	Application/Control No. 13/261,029	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1673	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-6,528,639 B2	03-2003	Usman; Nassim	C07H19/06	435/91.1
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Donga et al. Can. J. Chem. (2007), Vol. 85, pages 274-282.
	V	
	W	
	X	

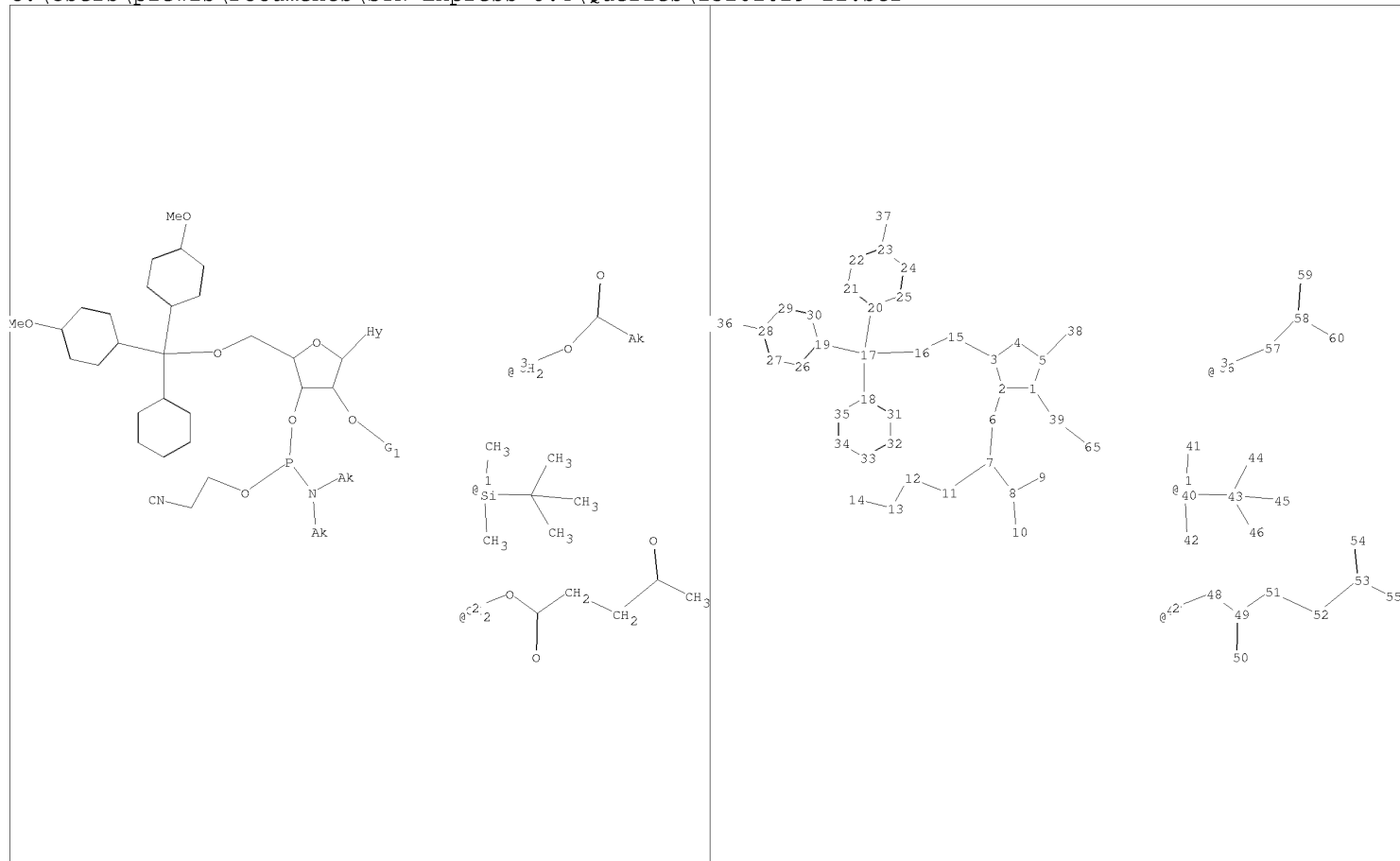
*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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L1 STRUCTURE UPLOADED

FILE 'REGISTRY' ENTERED AT 09:19:49 ON 31 MAY 2017
L2 STRUCTURE UPLOADED

L3	0	S	L2	SSS	SAM
L4	0	S	L2	SSS	FULL
L5	0	S	L1	SSS	SAM
L6	0	S	L1	SSS	FULL



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40 41 42 43 44 45 46 47 48
49 50 51 52 53 54 55 56 57 58 59 60 65

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35

chain bonds :

1-39 2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
17-19 17-20 23-37 28-36 39-65 40-41 40-42 40-43 43-44 43-45 43-46 47-48 48-49
49-50 49-51 51-52 52-53 53-54 53-55 56-57 57-58 58-59 58-60

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35

exact/norm bonds :

1-2 1-5 1-39 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 8-9 8-10 11-12 15-16 16-17 39-65
48-49 49-50 53-54 57-58 58-59 58-60

exact bonds :

3-15 12-13 13-14 17-18 17-19 17-20 23-37 28-36 40-41 40-42 40-43 43-44 43-45 43-46
47-48 49-51 51-52 52-53 53-55 56-57

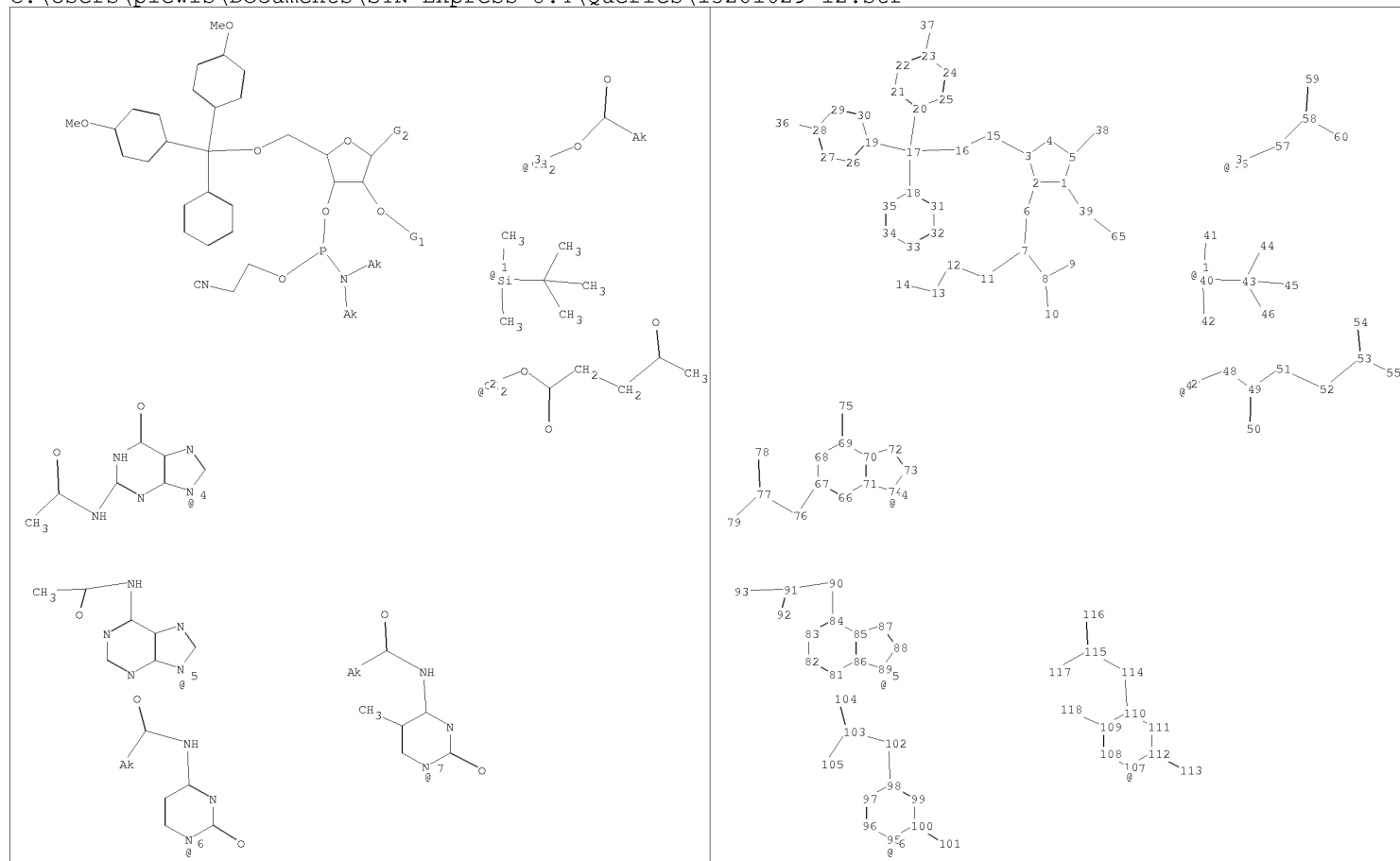
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29-30 31-32 32-33 33-34 34-35

G1: [@1], [@2], [@3]

Match level :

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12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom
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51:CLASS 52:CLASS 53:CLASS 54:CLASS 55:CLASS 56:CLASS 57:CLASS 58:CLASS 59:CLASS
60:CLASS 65:CLASS



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40 41 42 43 44 45 46 47 48
 49 50 51 52 53 54 55 56 57 58 59 60 65 75 76 77 78 79 90 91 92 93 101
 102 103 104 105 113 114 115 116 117 118

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 66 67
 68 69 70 71 72 73 74 81 82 83 84 85 86 87 88 89 95 96 97 98 99 100 107
 108 109 110 111 112

chain bonds :

1-39 2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
 17-19 17-20 23-37 28-36 39-65 40-41 40-42 40-43 43-44 43-45 43-46 47-48 48-49
 49-50 49-51 51-52 52-53 53-54 53-55 56-57 57-58 58-59 58-60 67-76 69-75 76-77
 77-78 77-79 84-90 90-91 91-92 91-93 98-102 100-101 102-103 103-104 103-105 109-118
 110-114 112-113 114-115 115-116 115-117

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
 26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 66-67 66-71 67-68 68-69 69-70
 70-71 70-72 71-74 72-73 73-74 81-82 81-86 82-83 83-84 84-85 85-86 85-87 86-89
 87-88 88-89 95-96 95-100 96-97 97-98 98-99 99-100 107-108 107-112 108-109 109-110
 110-111 111-112

exact/norm bonds :

1-2 1-5 1-39 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 8-9 8-10 11-12 15-16 16-17 39-65
 48-49 49-50 53-54 57-58 58-59 58-60 66-67 66-71 67-68 67-76 68-69 69-70 69-75
 70-71 70-72 71-74 72-73 73-74 76-77 77-78 84-90 85-87 86-89 87-88 88-89 90-91
 91-92 95-96 95-100 96-97 97-98 98-99 98-102 99-100 100-101 102-103 103-104 103-105
 107-108 107-112 108-109 109-110 110-111 110-114 111-112 112-113 114-115 115-116
 115-117

exact bonds :

3-15 12-13 13-14 17-18 17-19 17-20 23-37 28-36 40-41 40-42 40-43 43-44 43-45 43-46
 47-48 49-51 51-52 52-53 53-55 56-57 77-79 91-93 109-118

normalized bonds :

18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25 26-27 27-28 28-29
 29-30 31-32 32-33 33-34 34-35 81-82 81-86 82-83 83-84 84-85 85-86

G1: [@1], [@2], [@3]

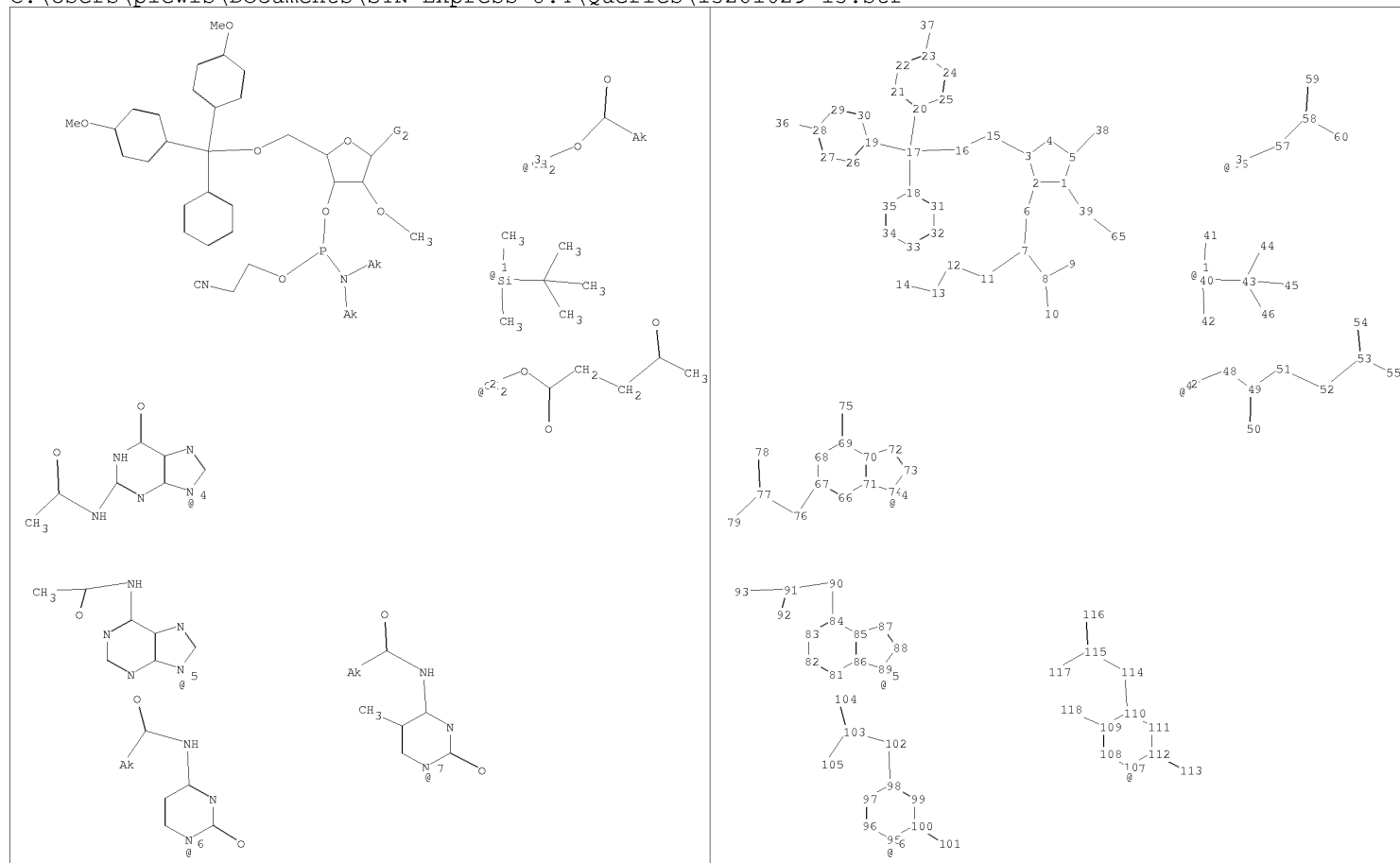
G2: [@4], [@5], [@6], [@7]

Match level :

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12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom
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105:CLASS 107:Atom 108:Atom 109:Atom 110:Atom 111:Atom 112:Atom 113:CLASS 114:CLASS
115:CLASS 116:CLASS 117:CLASS 118:CLASS

Generic attributes :

105:
Saturation : Saturated
Number of Carbon Atoms : less than 7
117:
Saturation : Saturated
Number of Carbon Atoms : less than 7



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40 41 42 43 44 45 46 47 48
 49 50 51 52 53 54 55 56 57 58 59 60 65 75 76 77 78 79 90 91 92 93 101
 102 103 104 105 113 114 115 116 117 118

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 66 67
 68 69 70 71 72 73 74 81 82 83 84 85 86 87 88 89 95 96 97 98 99 100 107
 108 109 110 111 112

chain bonds :

1-39 2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
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 110-111 111-112

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 107-112 108-109 109-110 110-111 110-114 111-112 112-113 114-115 115-116 115-117

exact bonds :

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G1: [@1], [@2], [@3]

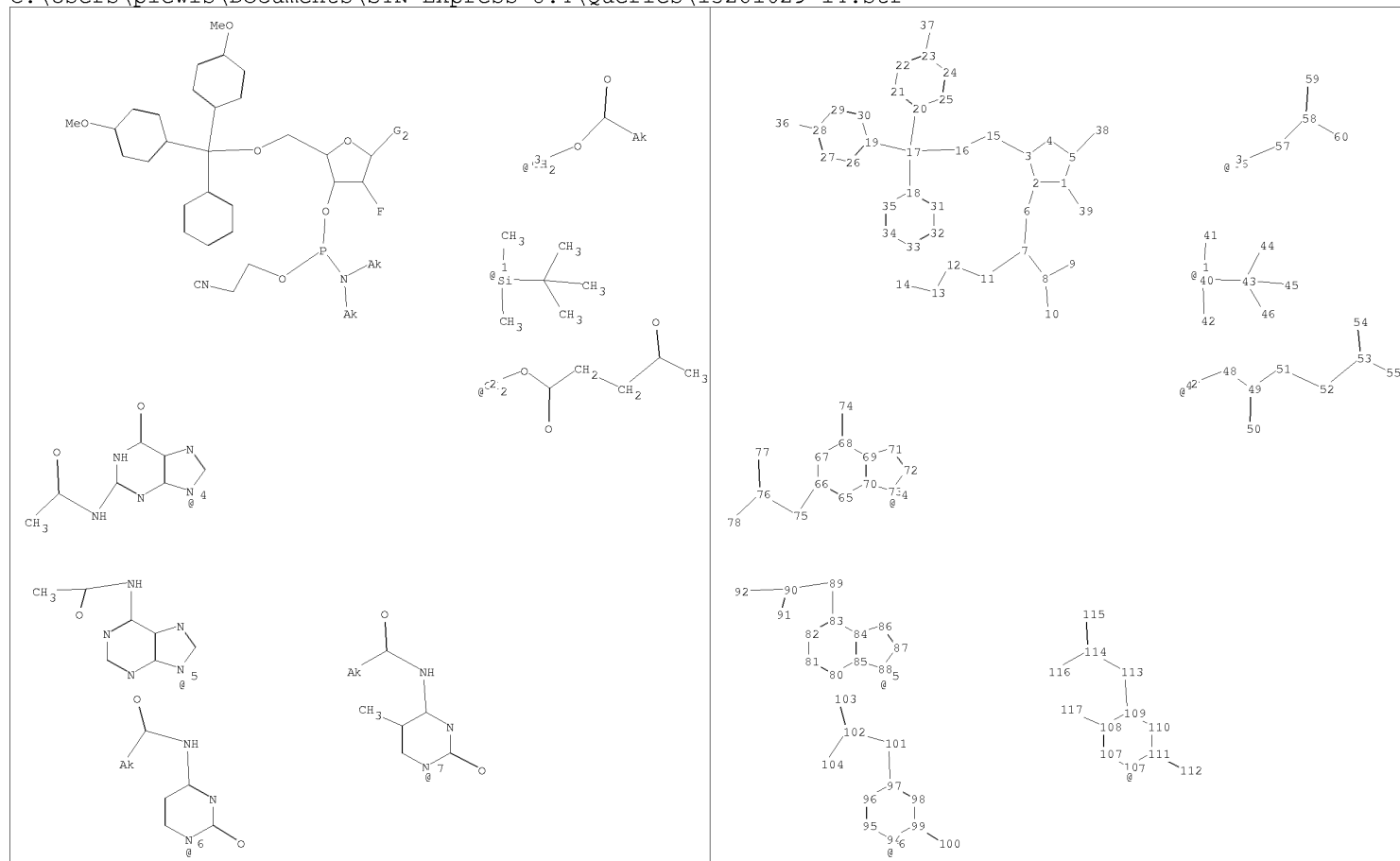
G2: [@4], [@5], [@6], [@7]

Match level :

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115:CLASS 116:CLASS 117:CLASS 118:CLASS

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105:
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Number of Carbon Atoms : less than 7
117:
Saturation : Saturated
Number of Carbon Atoms : less than 7



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40 41 42 43 44 45 46 47 48
 49 50 51 52 53 54 55 56 57 58 59 60 74 75 76 77 78 89 90 91 92 100 101
 102 103 104 112 113 114 115 116 117

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 65 66
 67 68 69 70 71 72 73 80 81 82 83 84 85 86 87 88 94 95 96 97 98 99 106
 107 108 109 110 111

chain bonds :

1-39 2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
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 109-110 110-111

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 106-111 107-108 108-109 109-110 109-113 110-111 111-112 113-114 114-115 114-116

exact bonds :

1-39 3-15 12-13 13-14 17-18 17-19 17-20 23-37 28-36 40-41 40-42 40-43 43-44 43-45
 43-46 47-48 49-51 51-52 52-53 53-55 56-57 76-78 90-92 108-117

normalized bonds :

18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25 26-27 27-28 28-29
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G1: [@1] , [@2] , [@3]

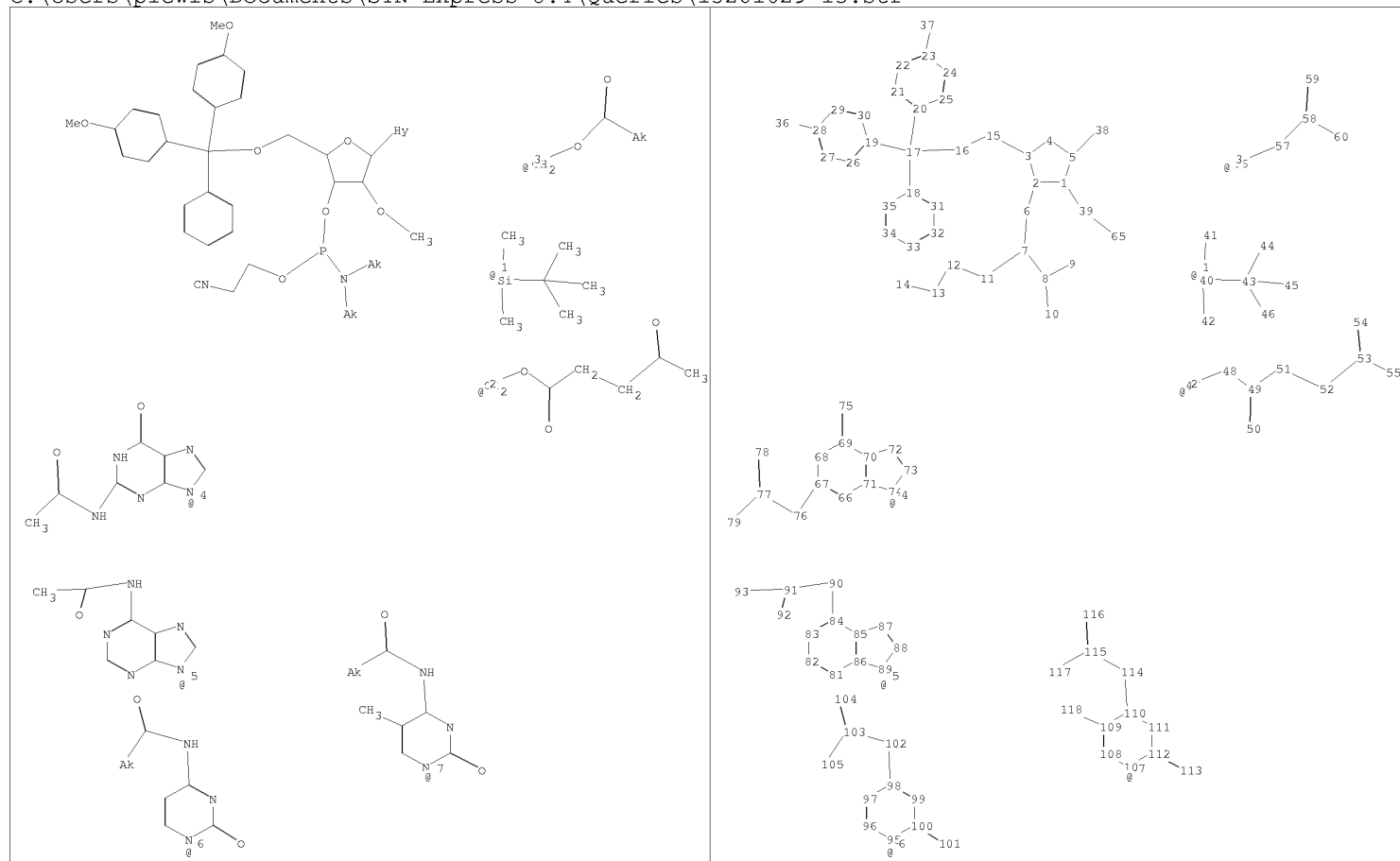
G2: [@4] , [@5] , [@6] , [@7]

Match level :

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51:CLASS 52:CLASS 53:CLASS 54:CLASS 55:CLASS 56:CLASS 57:CLASS 58:CLASS 59:CLASS
60:CLASS 65:Atom 66:Atom 67:Atom 68:Atom 69:Atom 70:Atom 71:Atom 72:Atom 73:Atom
74:CLASS 75:CLASS 76:CLASS 77:CLASS 78:CLASS 80:Atom 81:Atom 82:Atom 83:Atom 84:Atom
85:Atom 86:Atom 87:Atom 88:Atom 89:CLASS 90:CLASS 91:CLASS 92:CLASS 94:Atom 95:Atom
96:Atom 97:Atom 98:Atom 99:Atom 100:CLASS 101:CLASS 102:CLASS 103:CLASS 104:CLASS
106:Atom 107:Atom 108:Atom 109:Atom 110:Atom 111:Atom 112:CLASS 113:CLASS 114:CLASS
115:CLASS 116:CLASS 117:CLASS

Generic attributes :

104:
Saturation : Saturated
Number of Carbon Atoms : less than 7
116:
Saturation : Saturated
Number of Carbon Atoms : less than 7



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40 41 42 43 44 45 46 47 48
 49 50 51 52 53 54 55 56 57 58 59 60 65 75 76 77 78 79 90 91 92 93 101
 102 103 104 105 113 114 115 116 117 118

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 66 67
 68 69 70 71 72 73 74 81 82 83 84 85 86 87 88 89 95 96 97 98 99 100 107
 108 109 110 111 112

chain bonds :

1-39 2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
 17-19 17-20 23-37 28-36 39-65 40-41 40-42 40-43 43-44 43-45 43-46 47-48 48-49
 49-50 49-51 51-52 53-54 53-55 56-57 57-58 58-59 58-60 67-76 69-75 76-77
 77-78 77-79 84-90 90-91 91-92 91-93 98-102 100-101 102-103 103-104 103-105 109-118
 110-114 112-113 114-115 115-116 115-117

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
 26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 66-67 66-71 67-68 68-69 69-70
 70-71 70-72 71-74 72-73 73-74 81-82 81-86 82-83 83-84 84-85 85-86 85-87 86-89
 87-88 88-89 95-96 95-100 96-97 97-98 98-99 99-100 107-108 107-112 108-109 109-110
 110-111 111-112

exact/norm bonds :

1-2 1-5 1-39 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 8-9 8-10 11-12 15-16 16-17 48-49
 49-50 53-54 57-58 58-59 58-60 66-67 66-71 67-68 67-76 68-69 69-70 69-75 70-71
 70-72 71-74 72-73 73-74 76-77 77-78 84-90 85-87 86-89 87-88 88-89 90-91 91-92
 95-96 95-100 96-97 97-98 98-99 98-102 99-100 100-101 102-103 103-104 103-105 107-108
 107-112 108-109 109-110 110-111 110-114 111-112 112-113 114-115 115-116 115-117

exact bonds :

3-15 12-13 13-14 17-18 17-19 17-20 23-37 28-36 39-65 40-41 40-42 40-43 43-44 43-45
 43-46 47-48 49-51 51-52 52-53 53-55 56-57 77-79 91-93 109-118

normalized bonds :

18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25 26-27 27-28 28-29
 29-30 31-32 32-33 33-34 34-35 81-82 81-86 82-83 83-84 84-85 85-86

G1: [@1] , [@2] , [@3]

G2: [@4], [@5], [@6], [@7]

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom
32:Atom 33:Atom 34:Atom 35:Atom 36:CLASS 37:CLASS 38:Atom 39:CLASS 40:CLASS 41:CLASS
42:CLASS 43:CLASS 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS 49:CLASS 50:CLASS
51:CLASS 52:CLASS 53:CLASS 54:CLASS 55:CLASS 56:CLASS 57:CLASS 58:CLASS 59:CLASS
60:CLASS 65:CLASS 66:Atom 67:Atom 68:Atom 69:Atom 70:Atom 71:Atom 72:Atom 73:Atom
74:Atom 75:CLASS 76:CLASS 77:CLASS 78:CLASS 79:CLASS 81:Atom 82:Atom 83:Atom 84:Atom
85:Atom 86:Atom 87:Atom 88:Atom 89:Atom 90:CLASS 91:CLASS 92:CLASS 93:CLASS 95:Atom
96:Atom 97:Atom 98:Atom 99:Atom 100:Atom 101:CLASS 102:CLASS 103:CLASS 104:CLASS
105:CLASS 107:Atom 108:Atom 109:Atom 110:Atom 111:Atom 112:Atom 113:CLASS 114:CLASS
115:CLASS 116:CLASS 117:CLASS 118:CLASS

Generic attributes :

105:
Saturation : Saturated
Number of Carbon Atoms : less than 7
117:
Saturation : Saturated
Number of Carbon Atoms : less than 7

=> d his

(FILE 'HOME' ENTERED AT 14:21:48 ON 30 MAY 2017)

FILE 'REGISTRY' ENTERED AT 14:21:59 ON 30 MAY 2017

L1 STRUCTURE UPLOADED

L2 24 S L1 SSS SAM

L3 494 S L1 SSS FULL

FILE 'CAPLUS, MEDLINE' ENTERED AT 14:22:39 ON 30 MAY 2017

L4 439 S L3

Search Notes 	Application/Control No. 13261029	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.
	Examiner PATRICK LEWIS	Art Unit 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)	10/12/2016	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	5/31/2017	/PL/

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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<i>Index of Claims</i> 	Application/Control No. 13261029	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.
	Examiner PATRICK LEWIS	Art Unit 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	10/12/2016	05/31/2017												
	1	✓	✓												
	2	✓	=												
	3	✓	=												
	4	✓	-												
	5	✓	✓												
	6	✓	=												
	7	✓	=												
	8	✓	-												

(FILE 'HOME' ENTERED AT 15:58:16 ON 30 MAY 2017)

FILE 'REGISTRY' ENTERED AT 15:58:25 ON 30 MAY 2017

L1	STRUCTURE UPLOADED
L2	0 S L1 SSS SAM
L3	0 S L1 SSS FULL
L4	STRUCTURE UPLOADED
L5	0 S L4 SSS SAM
L6	0 S L4 SSS FULL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Inventor: Suresh C. Srivastava and Naveen Srivastava
Application Serial No.: 13/261,029
File Date: November 18, 2011
Title: SYNTHESIS OF LABILE BASE PROTECTED -MODIFIED DEOXY &
MODIFIED RIBO NUCLEOSIDES, CORRESPONDING
PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH
PURITY OLIGONUCLEOTIDE SYNTHESIS

Examiner: LEWIS, PATRICK T.
Art Unit: 1672

Certificate of Electronic Transmission Under 37 CFR 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being electronically transmitted on the date signed via the electronic filing system of the United States Patent and Trademark Office in accordance with 37 CFR Sec. 1.6(a)(4).

Name: Indu M. Anand Signature: /Indu M. Anand/ Date: 10/05/2017

RESPONSE TO OFFICE ACTION UNDER AFCP 2.0

MAIL STOP AF
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313 -1450
RE: Office Action of June 5, 2017

Dear Sir:

This amendment is filed in accordance with 37 CFR §1.116 under AFCP 2.0, in reply to the office action dated June 5, 2017, with the request to amend the above-identified U.S. patent application as follows:

Amendments to claims are reflected in the listing of claims starting on page 3, that follows this cover letter.

Amendments to the specification follow on page 6.

Remarks and arguments begin on page 8.

The certification and request form PTO/SB/434 is included.

No new matter is introduced by this amendment.

Authorization is hereby provided to charge any *additional* fee, required beyond the payment accompanying this submission, to Deposit account No. 505404. For any further deficiency you are requested to contact the undersigned representative.

Dated: October 5, 2017

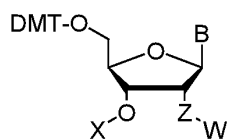
Respectfully submitted,

By /Indu M. Anand/
Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824

AMENDMENTS TO THE CLAIMS

1. (Canceled)

2. (Previously presented) Derivatized nucleoside and phosphoramidite of general formula 1,



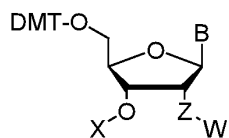
Formula 1

where B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl;

Z is Oxygen and W is methyl; and

X is cyanoethyl dialkyl phosphoramidite.

3. (Currently amended) ~~Derivaized~~Derivatized nucleoside and phosphoramidite of general formula 1,



(Formula 1)

where B is Guanine-N-acetyl, or adenine-N-acetyl;

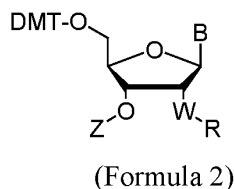
Z= ribo Fluoro or ara fluoro, and

W is absent; and

X is cyanoethyl dialkyl phosphoramidite.

4. (Canceled)

5. (Currently amended) Derivatized nucleosides, succinates and solid supports of general formula 2,



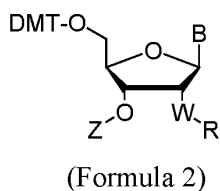
where B is Guanine-N-acetyl, or adenine-N-acetyl;

W= ribo fluoro or ara fluoro, and R is absent;

~~W=R= ribo Fluoro or ara fluoro;~~

Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1- C20 alkyl, ethoxyglycol, and a combination of alkyl and ethyleneglycoxy.

6. (Previously presented) Derivatized nucleosides, succinates and solid supports of general formula 2,



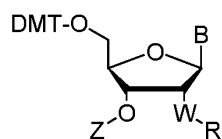
wherein, B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl;

W is Oxygen and R is selected from the group consisting of t-Butyldimethyl silyl, acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and

Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1- C20 alkyl, ethoxyglycol, and a combination of alkyl and ethyleneglycoxy.

7. (Currently amended)

Derivatized nucleosides, succinates and supports of general formula 2,



(Formula 2)

wherein B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N- isobutyryl, 5-methyl cytosine-N-acetyl, and 5- methyl cytosine-N- isobutyryl;

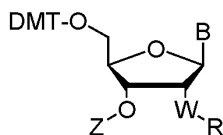
W is Oxygen and R is methyl ; and

Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is C1- C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

8. (Canceled)

AMENDMENTS TO THE SPECIFICATION

Please replace *with the text* submitted herebelow, the part of the *second* paragraph of “SUMMARY OF THE INVENTION” section of the specification as filed (on the page numbered 20), beginning with the *text following* the structure named as Formula 2 to the text immediately following the structure named as Formula 3 (the structures shown here are for reference, no change is made to the structures of formulas 2 and 3):



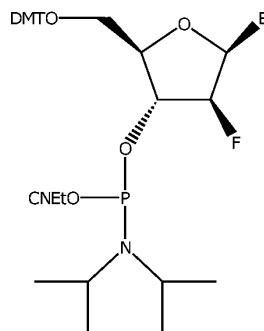
(Formula 2)

Where B = [[a]] Adenine (*N-bz*), [[b]] Cytosine (*N-acetyl*), [[c]] Guanine (*N-acetyl*), [[d]] 5-methyl cytosine(*N- Fmoc*), [[e]] 5- bromocytidine(*N-Fmoc*), [[i]] 5- iodo cytosine(*N- Fmoc*), [[j]] 5- fluorocytosine(*N-Fmoc*), [[k]] 2,6-diaminopurine(*N-Fmoc*), or [[l]] 2- amino purine(*N-Fmoc*)[[,]];

Z = [[a]] succinimido long chain attached to a solid support, [[b]] hydroquinone succinimido long chain spacer attached to solid support, or [[c]] oxalyl amido long chain spacer attached to solid support;

[[Z]]W= Oxygen & [[W]]R is H[[,]]; or, [[Z]]W=Oxygen and [[W]]R= tButyldimethyl silyl, TOM (triisopropyloxymethylene), acetal levulinyl ester (ALE), pivaloyloxy; cyanoethylmethylene (CEM); or dithiomethylene (DTM); or, [[Z]]W= oxygen and [[W]]R is methyl [[and]] or other higher alkyl[[s]], alkene[[s]] [[and]] or alkyne[[s]]; or, [[Z=]]W= ribo Fluorine, where the fluoro radical points downward in ribo configuration and R is absent; or [[Z=]]W=ara fluorine, where the fluoro radical poits upward in ara configuration (Formula 3) and R is absent; or, [[Z]]W= amino, and [[W]]R= amino protecting group. [[,]]

~~Z= a) succinimido long chain attached to a solid support, b) hydroquinone succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support;~~



(Formula 3)

Where B = a) Adenine (*N*-bz), b) Cytosine (*N*-acetyl), c) Guanine (*N*-acetyl), d) 5-methyl cytosine(*N*-Fmoc), e) 5-bromocytidine(*N*-Fmoc), i) 5-iodo cytosine(*N*-Fmoc), j) 5-fluorocytosine(*N*-Fmoc), k) 2,6-diaminopurine(*N*-Fmoc), l) 2-amino purine(*N*-Fmoc)

~~Z=W=ara-fluorine; Z= amino, W= amino-protecting group; Z= a) succinimido long chain attached to a solid support, b) hydroquinone succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support.~~

REMARKS

Amendments to the Claims

Applicant gratefully notes the Examiner's allowance of claims 2 - 3 and 6 -7, and that as indicated in paragraphs 3 – 10 of the Office Action, several previous rejections have been withdrawn in view of the claim amendment submitted in April 2017.

With the current amendment Applicant retains claims 2 - 3 and 6 -7 as allowed, except correcting minor typographical errors in claims 3 and 7, i.e., a spelling error in claim 3 and insertion of a missing semicolon in claim 7.

Further, in order to advance the prosecution, Applicant cancels claim 1.

Rejections of Record Set Forth in the Office Action Dated October 13, 2016

Claim 5 stands rejected (paragraph 12) under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor(s)/applicant regards as the invention.

In response, Applicant submits amended claim 5 with the erroneous claim segment "Z=W= ribo Fluorine or ara fluorine" rectified to clarify the parameters and the assigned values.

Claim Rejections under 35 USC Section 102

Applicant believes that cancelation of claim 1 renders this rejection moot.

Amendments to the Specification

Applicant notes with regret that some definitions of the parameters provided for Formula 2 were erroneous in the "SUMMARY OF THE INVENTION" section in the specification as filed. Specifically, these errors include: Absence of the definition of the variable R, notation of Variable Z in place of W in multiple places, and inappropriate placement of the definition of variable Z.

Therefore, Applicant submits a correction for these inadvertent errors in order to define Formula 2 correctly. The corrected text is included herewith on separate sheet, and includes other minor corrections to improve clarity of the description.

Since the corrections are numerous, though minor in nature, the corrected part of the text is provided below in clean form for convenience of comparison:

"Where B = Adenine (*N-bz*), Cytosine (*N-acetyl*), Guanine (*N-acetyl*), 5-methyl cytosine(*N- Fmoc*), 5- bromocytidine(*N-Fmoc*), 5- iodo cytosine(*N- Fmoc*), 5- fluorocytosine(*N-Fmoc*), 2,6-diaminopurine(*N-Fmoc*), or 2- amino purine(*N-Fmoc*);

Z = succinimido long chain attached to a solid support, hydroquinone succinimido long chain spacer attached to solid support, or oxalyl amido long chain spacer attached to solid support;

W= Oxygen & R is H ; or, W= Oxygen and R= tButyldimethyl silyl, TOM (triisopropylloxymethylene), acetal levuliny ester (ALE), pivaloyloxy; cyanoethylmethylene (CEM); or dithiomethylene (DTM); or, W= oxygen and R is methyl or other higher alkyl, alkene or alkyne; or, W= ribo Fluorine, where the fluoro radical points downward in ribo configuration and R is absent; or W=ara fluorine, where the fluoro radical poits upward in ara configuration (Formula 3) and R is absent; or, W= amino, and R= amino protecting group.

~~Z = a) succinimido long chain attached to a solid support, b) hydroquinone succinimido long chain spacer attached to solid support, c) oxalyl amido long chain spacer attached to solid support; ”~~

Conclusion

In view of the aforementioned amendment to claims, a Notice of Allowance is respectfully requested.

In case of any remaining issues or deficiency, you are requested to contact the undersigned representative.

Dated: October 5, 2017

Respectfully submitted,
*Suresh C. Srivastava and Naveen P.
Srivastava,
Applicants*

By /Indu M. Anand/
Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824

Doc Code: A.NE.AFCP

Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0		
Practitioner Docket No.: ChG_00611	Application No.: 13/261,029	Filing Date: November 18, 2011
First Named Inventor: Suresh C. Srivastava	Title: SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND TH	
APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116. 1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (<i>e.g.</i>, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c). 2. The above-identified application contains an outstanding final rejection. 3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect. 4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection. 5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response. 6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web). 7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, <i>e.g.</i>, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.] 8. By filing this certification and request, applicant acknowledges the following: • Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0. • The examiner will verify that the AFCP 2.0 submission is compliant, <i>i.e.</i>, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions: ○ The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, <i>e.g.</i>, by mailing an advisory action. ○ If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview. ▪ The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate. ▪ If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.		
Signature /Indu M. Anand/	Date 10/05/2017	
Name (Print/Typed) Indu M. Anand	Practitioner Registration No. 52,557	
Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.		
☐ * Total of <u>one</u> forms are submitted.		

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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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 Patent Application Fee Transmittal				
Application Number:		13261029		
Filing Date:		18-Nov-2011		
Title of Invention:		SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS		
First Named Inventor/Applicant Name:		Suresh C. Srivastava		
Filer:		Indu Mati Anand		
Attorney Docket Number:		ChG_00611		
Filed as Small Entity				
Filing Fees for U.S. National Stage under 35 USC 371				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 1 month with \$0 paid	2251	1	100	100
Miscellaneous:				
Total in USD (\$)				100

Electronic Acknowledgement Receipt	
EFS ID:	30581401
Application Number:	13261029
International Application Number:	
Confirmation Number:	4149
Title of Invention:	SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	83687
Filer:	Indu Mati Anand
Filer Authorized By:	
Attorney Docket Number:	ChG_00611
Receipt Date:	05-OCT-2017
Filing Date:	18-NOV-2011
Time Stamp:	18:43:31
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$100
RAM confirmation Number	100617INTEFSW18483600
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response After Final Action	LBP-Reply-5Oct17.pdf	261990	no	9
			4e41b7babfa89701179ee0516603b235c3145aeb		
Warnings:					
Information:					
2	After Final Consideration Program Request	13261029-2017-sb0434.pdf	226819	no	2
			86a13ebf54caa6f7ffe4858b0d7e56418710f9c8		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31062	no	2
			c4063c20d40dd4d08453b921a83c63b2760a1156		
Warnings:					
Information:					
Total Files Size (in bytes):			519871		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.					

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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 13/261,029		Filing Date 11/18/2011		☐ To be Mailed				
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO													
APPLICATION AS FILED – PART I													
(Column 1)			(Column 2)										
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)					
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A							
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))		N/A		N/A		N/A							
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A							
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 =		*		X \$ =							
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$ =							
☐ 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).											
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))													
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL							
APPLICATION AS AMENDED – PART II													
(Column 1)			(Column 2)			(Column 3)							
AMENDMENT	10/05/2017		CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))		* 5		Minus	** 20		= 0		X \$40 =		0	
	Independent (37 CFR 1.16(h))		* 5		Minus	***6		= 0		X \$210 =		0	
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
	TOTAL ADD'L FEE											0	
(Column 1)			(Column 2)			(Column 3)							
AMENDMENT			CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))		*		Minus	**		=		X \$ =			
	Independent (37 CFR 1.16(h))		*		Minus	***		=		X \$ =			
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
	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 number found in the appropriate box in column 1.											SLIE HELENA PAYTON		

This collection of information is required by 37 CFR 1.16. 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 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.

(FILE 'HOME' ENTERED AT 09:40:59 ON 07 NOV 2017)

FILE 'REGISTRY' ENTERED AT 09:41:04 ON 07 NOV 2017

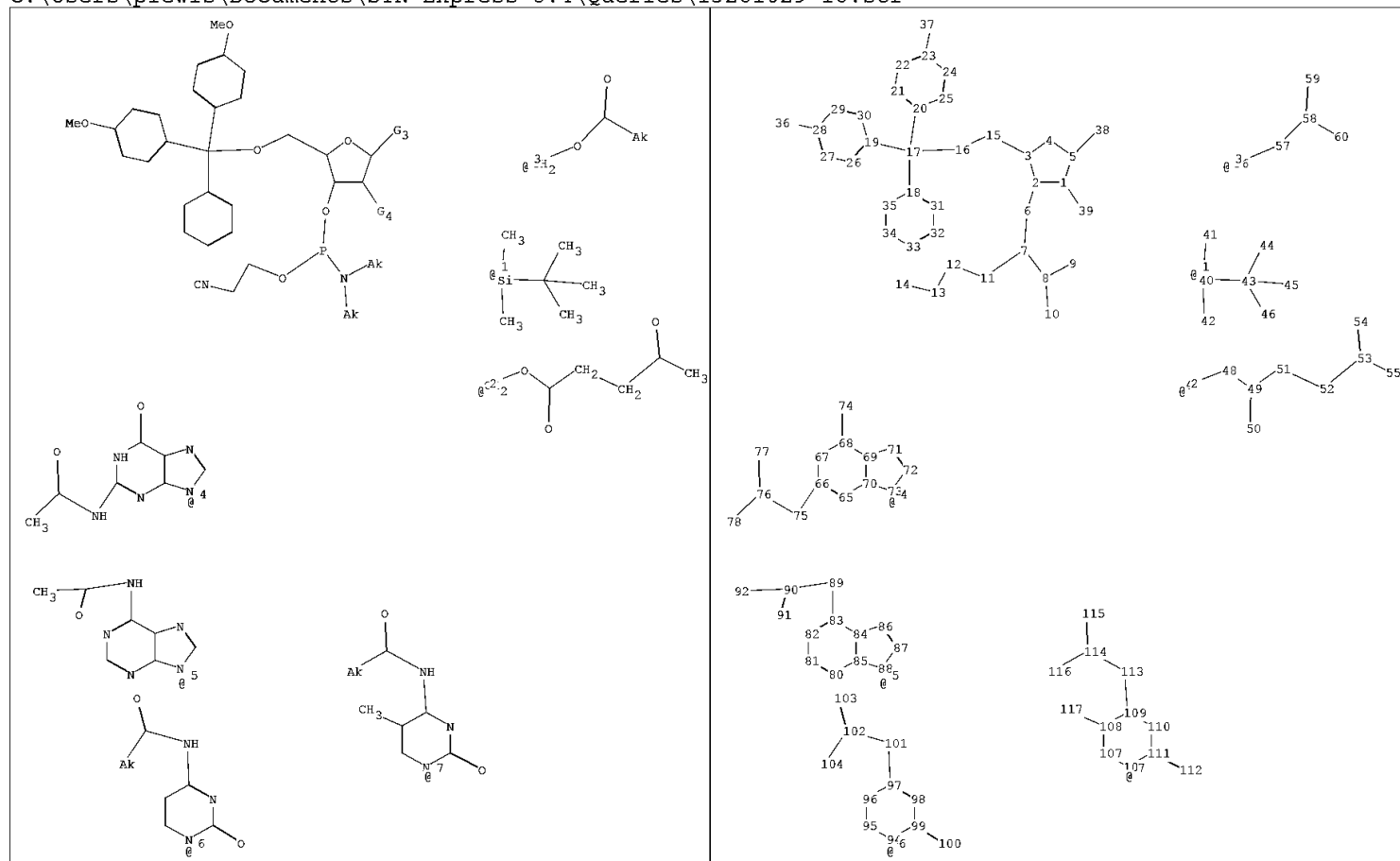
L1	STRUCTURE UPLOADED
L2	0 S L1 SSS SAM
L3	0 S L1 SSS FULL
L4	STRUCTURE UPLOADED
L5	0 S L4 SSS SAM
L6	0 S L4 SSS FULL

WEST Search History

DATE: Tuesday, November 07, 2017

Hide?	<u>Set</u> <u>Name</u>	<u>Query</u>	<u>Hit</u> <u>Count</u>
<i>Interference</i>			
<i>DB=PGPB,USPT; PLUR=YES; OP=ADJ</i>			
☐	L7	L6 and n acetyl	43
☐	L6	L5 and support	344
☐	L5	L4 and base labile	359
☐	L4	L3 and oligonucleotide synthesis	1914
☐	L3	L2 and phosphoramidite	2745
☐	L2	L1 SPACE~or ((C07H19/16 C07H19/06 C07H19/04).CPC.)	7710
☐	L1	(536/25.3 or 536/25.34 or 536/26.1 or 536/27.1 or 536/27.13 or 536/27.2 or 536/27.3 or 536/28.4)! [CCLS]	4175

END OF SEARCH HISTORY



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40 41 42 43 44 45 46 47 48
 49 50 51 52 53 54 55 56 57 58 59 60 74 75 76 77 78 89 90 91 92 100 101
 102 103 104 112 113 114 115 116 117

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 65 66
 67 68 69 70 71 72 73 80 81 82 83 84 85 86 87 88 94 95 96 97 98 99 106
 107 108 109 110 111

chain bonds :

1-39 2-6 3-15 5-38 6-7 7-8 7-11 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
 17-19 17-20 23-37 28-36 40-41 40-42 40-43 43-44 43-45 43-46 47-48 48-49 49-50
 49-51 51-52 52-53 53-54 53-55 56-57 57-58 58-59 58-60 66-75 68-74 75-76 76-77
 76-78 83-89 89-90 90-91 90-92 97-101 99-100 101-102 102-103 102-104 108-117 109-113
 111-112 113-114 114-115 114-116

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
 26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 65-66 65-70 66-67 67-68 68-69
 69-70 69-71 70-73 71-72 72-73 80-81 80-85 81-82 82-83 83-84 84-85 84-86 85-88
 86-87 87-88 94-95 94-99 95-96 96-97 97-98 98-99 106-107 106-111 107-108 108-109
 109-110 110-111

exact/norm bonds :

1-2 1-5 1-39 2-3 2-6 3-4 4-5 5-38 6-7 7-8 7-11 8-9 8-10 11-12 15-16 16-17 48-49
 49-50 53-54 57-58 58-59 58-60 65-66 65-70 66-67 66-75 67-68 68-69 68-74 69-70
 69-71 70-73 71-72 72-73 75-76 76-77 83-89 84-86 85-88 86-87 87-88 89-90 90-91
 94-95 94-99 95-96 96-97 97-98 97-101 98-99 99-100 101-102 102-103 102-104 106-107
 106-111 107-108 108-109 109-110 109-113 110-111 111-112 113-114 114-115 114-116

exact bonds :

3-15 12-13 13-14 17-18 17-19 17-20 23-37 28-36 40-41 40-42 40-43 43-44 43-45 43-46
 47-48 49-51 51-52 52-53 53-55 56-57 76-78 90-92 108-117

normalized bonds :

18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25 26-27 27-28 28-29
 29-30 31-32 32-33 33-34 34-35 80-81 80-85 81-82 82-83 83-84 84-85

G1: [@1], [@2], [@3]

G2: [@4], [@5], [@6], [@7]

G3: [@4], [@5], [@6], [@7]

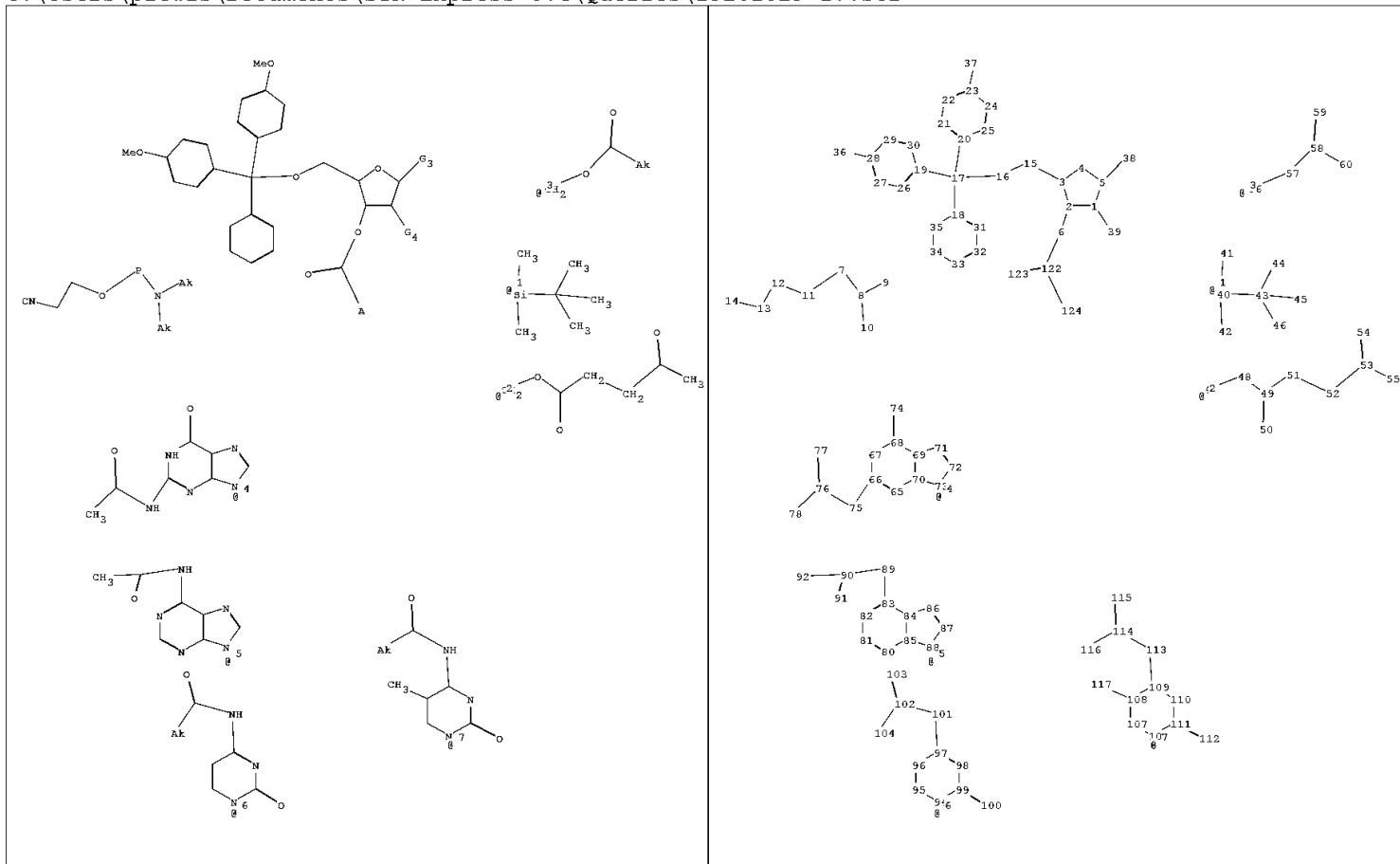
G4: MeO, EtO, n-PrO, i-PrO, n-BuO, i-BuO, s-BuO, t-BuO, F

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom
32:Atom 33:Atom 34:Atom 35:Atom 36:CLASS 37:CLASS 38:Atom 39:CLASS 40:CLASS 41:CLASS
42:CLASS 43:CLASS 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS 49:CLASS 50:CLASS
51:CLASS 52:CLASS 53:CLASS 54:CLASS 55:CLASS 56:CLASS 57:CLASS 58:CLASS 59:CLASS
60:CLASS 65:Atom 66:Atom 67:Atom 68:Atom 69:Atom 70:Atom 71:Atom 72:Atom 73:Atom
74:CLASS 75:CLASS 76:CLASS 77:CLASS 78:CLASS 80:Atom 81:Atom 82:Atom 83:Atom 84:Atom
85:Atom 86:Atom 87:Atom 88:Atom 89:CLASS 90:CLASS 91:CLASS 92:CLASS 94:Atom 95:Atom
96:Atom 97:Atom 98:Atom 99:Atom 100:CLASS 101:CLASS 102:CLASS 103:CLASS 104:CLASS
106:Atom 107:Atom 108:Atom 109:Atom 110:Atom 111:Atom 112:CLASS 113:CLASS 114:CLASS
115:CLASS 116:CLASS 117:CLASS

Generic attributes :

104:
Saturation : Saturated
Number of Carbon Atoms : less than 7
116:
Saturation : Saturated
Number of Carbon Atoms : less than 7



chain nodes :

6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40 41 42 43 44 45 46 47 48
 49 50 51 52 53 54 55 56 57 58 59 60 74 75 76 77 78 89 90 91 92 100 101
 102 103 104 112 113 114 115 116 117 122 123 124

ring nodes :

1 2 3 4 5 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 65 66
 67 68 69 70 71 72 73 80 81 82 83 84 85 86 87 88 94 95 96 97 98 99 106
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chain bonds :

1-39 2-6 3-15 5-38 6-122 7-11 7-8 8-9 8-10 11-12 12-13 13-14 15-16 16-17 17-18
 17-19 17-20 23-37 28-36 40-41 40-42 40-43 43-44 43-45 43-46 47-48 48-49 49-50
 49-51 51-52 52-53 53-54 53-55 56-57 57-58 58-59 58-60 66-75 68-74 75-76 76-77
 76-78 83-89 89-90 90-91 90-92 97-101 99-100 101-102 102-103 102-104 108-117 109-113
 111-112 113-114 114-115 114-116 122-123 122-124

ring bonds :

1-2 1-5 2-3 3-4 4-5 18-31 18-35 19-26 19-30 20-21 20-25 21-22 22-23 23-24 24-25
 26-27 27-28 28-29 29-30 31-32 32-33 33-34 34-35 65-66 65-70 66-67 67-68 68-69
 69-70 69-71 70-73 71-72 72-73 80-81 80-85 81-82 82-83 83-84 84-85 84-86 85-88
 86-87 87-88 94-95 95-96 96-97 97-98 98-99 106-107 106-111 107-108 108-109
 109-110 110-111

exact/norm bonds :

1-2 1-5 1-39 2-3 2-6 3-4 4-5 5-38 6-122 7-11 7-8 8-9 8-10 11-12 15-16 16-17
 48-49 49-50 53-54 57-58 58-59 58-60 65-66 65-70 66-67 66-75 67-68 68-69 68-74
 69-70 69-71 70-73 71-72 72-73 75-76 76-77 83-89 84-86 85-88 86-87 87-88 89-90
 90-91 94-95 94-99 95-96 96-97 97-98 97-101 98-99 99-100 101-102 102-103 102-104
 106-107 106-111 107-108 108-109 109-110 109-113 110-111 111-112 113-114 114-115
 114-116 122-123 122-124

exact bonds :

3-15 12-13 13-14 17-18 17-19 17-20 23-37 28-36 40-41 40-42 40-43 43-44 43-45 43-46
 47-48 49-51 51-52 52-53 53-55 56-57 76-78 90-92 108-117

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 29-30 31-32 32-33 33-34 34-35 80-81 80-85 81-82 82-83 83-84 84-85

G1: [@1], [@2], [@3]

G2: [@4], [@5], [@6], [@7]

G3: [@4], [@5], [@6], [@7]

G4: MeO, EtO, n-PrO, i-PrO, n-BuO, i-BuO, s-BuO, t-BuO, F

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom
32:Atom 33:Atom 34:Atom 35:Atom 36:CLASS 37:CLASS 38:Atom 39:CLASS 40:CLASS 41:CLASS
42:CLASS 43:CLASS 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS 49:CLASS 50:CLASS
51:CLASS 52:CLASS 53:CLASS 54:CLASS 55:CLASS 56:CLASS 57:CLASS 58:CLASS 59:CLASS
60:CLASS 65:Atom 66:Atom 67:Atom 68:Atom 69:Atom 70:Atom 71:Atom 72:Atom 73:Atom
74:CLASS 75:CLASS 76:CLASS 77:CLASS 78:CLASS 80:Atom 81:Atom 82:Atom 83:Atom 84:Atom
85:Atom 86:Atom 87:Atom 88:Atom 89:CLASS 90:CLASS 91:CLASS 92:CLASS 94:Atom 95:Atom
96:Atom 97:Atom 98:Atom 99:Atom 100:CLASS 101:CLASS 102:CLASS 103:CLASS 104:CLASS
106:Atom 107:Atom 108:Atom 109:Atom 110:Atom 111:Atom 112:CLASS 113:CLASS 114:CLASS
115:CLASS 116:CLASS 117:CLASS 122:CLASS 123:CLASS 124:CLASS

Generic attributes :

104:
Saturation : Saturated
Number of Carbon Atoms : less than 7
116:
Saturation : Saturated
Number of Carbon Atoms : less than 7

Search Notes 	Application/Control No. 13/261,029	Applicant(s)/Patent Under Reexamination Srivastava et al.
	Examiner PATRICK T LEWIS	Art Unit 1673

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	10/12/2016	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	5/31/2017	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	11/07/2017	/PL/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
536	25.3, 25.34, 26.1, 27.1, 27.13, 27.2, 27.3, 2.4	11/07/2017	/PL/
C07H	19/04, 19/06, 19/16	11/07/2017	/PL/

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1673	
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NOTICE OF ALLOWANCE AND FEE(S) DUE

83687 7590 11/29/2017
Indu M. Anand, Esq
15 Green Way
Chelmsford, MA 01824

EXAMINER

LEWIS, PATRICK T

ART UNIT

PAPER NUMBER

1673

DATE MAILED: 11/29/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/261,029	11/18/2011	Suresh C. Srivastava	CHG_00611	4149

TITLE OF INVENTION: SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	02/28/2018

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

83687 7590 11/29/2017
Indu M. Anand, Esq
15 Green Way
Chelmsford, MA 01824

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/261,029	11/18/2011	Suresh C. Srivastava	CHG_00611	4149

TITLE OF INVENTION: SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	02/28/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1673	536-026740

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



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.
13/261,029	11/18/2011	Suresh C. Srivastava	CHG_00611	4149
83687	7590	11/29/2017	EXAMINER	
Indu M. Anand , Esq 15 Green Way Chelmsford, MA 01824			LEWIS, PATRICK T	
			ART UNIT	PAPER NUMBER

1673

DATE MAILED: 11/29/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

Notice of Allowability	Application No. 13/261,029	Applicant(s) Srivastava et al.	
	Examiner PATRICK T LEWIS	Art Unit 1673	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to Amendment dated 10/5/2017 .
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2. ☐ 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.

3. ☒ The allowed claim(s) is/are 2-3 and 5-7 . As a result of the allowed claim(s), 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**.

4. ☐ 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)).

* Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)	5. ☐ Examiner's Amendment/Comment
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____	6. ☐ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____	7. ☒ Other <u>PTO 2323</u> .
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____	

	/PATRICK T LEWIS/ Primary Examiner, Art Unit 1673
--	--

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Inventor: Suresh C. Srivastava and Naveen Srivastava
Application Serial No.: 13/261,029
File Date: November 18, 2011
Title: SYNTHESIS OF LABILE BASE PROTECTED -MODIFIED DEOXY &
MODIFIED RIBO NUCLEOSIDES, CORRESPONDING
PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH
PURITY OLIGONUCLEOTIDE SYNTHESIS

Examiner: LEWIS, PATRICK T.
Art Unit: 1672

Certificate of Electronic Transmission Under 37 CFR 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being electronically transmitted on the date signed via the electronic filing system of the United States Patent and Trademark Office in accordance with 37 CFR Sec. 1.6(a)(4).

Name: Indu M. Anand Signature: /Indu M. Anand/ Date: 10/05/2017

RESPONSE TO OFFICE ACTION UNDER AFCP 2.0

MAIL STOP AF
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313 -1450
RE: Office Action of June 5, 2017

Dear Sir:

This amendment is filed in accordance with 37 CFR §1.116 under AFCP 2.0, in reply to the office action dated June 5, 2017, with the request to amend the above-identified U.S. patent application as follows:

Amendments to claims are reflected in the listing of claims starting on page 3, that follows this cover letter.

Amendments to the specification follow on page 6.

Remarks and arguments begin on page 8.

The certification and request form PTO/SB/434 is included.

No new matter is introduced by this amendment.

Authorization is hereby provided to charge any *additional* fee, required beyond the payment accompanying this submission, to Deposit account No. 505404. For any further deficiency you are requested to contact the undersigned representative.

Dated: October 5, 2017

Respectfully submitted,

By /Indu M. Anand/
Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824

Issue Classification 	Application/Control No. 13/261,029	Applicant(s)/Patent Under Reexamination Srivastava et al.
	Examiner PATRICK T LEWIS	Art Unit 1673

CPC						
Symbol					Type	Version
C07H	/	19	/	06	F	2013-01-01
C07H	/	19	/	16	I	2013-01-01
C07H	/	21	/	02	I	2013-01-01
C07H	/	23	/	00	I	2013-01-01
C07H	/	19	/	04	A	2013-01-01
Y02P	/	20	/	55	A	2015-11-01

CPC Combination Sets					
Symbol				Type	Set
	/		/		

NONE (Assistant Examiner)		Total Claims Allowed: 5	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1673 (Primary Examiner)		07 November 2017 (Date)	O.G. Print Claim(s) 1
			O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20171107

Issue Classification 	Application/Control No. 13/261,029	Applicant(s)/Patent Under Reexamination Srivastava et al.
	Examiner PATRICK T LEWIS	Art Unit 1673

INTERNATIONAL CLASSIFICATION			
CLAIMED			
C07H	/	19	/ 04
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
536	26.1

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
536	25.3	25.34	27.1	27.13	27.2	27.3
536	28.4					

NONE (Assistant Examiner)		Total Claims Allowed: 5	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1673 (Primary Examiner)		07 November 2017 (Date)	O.G. Print Claim(s) 1
			O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20171107

Issue Classification 	Application/Control No. 13/261,029	Applicant(s)/Patent Under Reexamination Srivastava et al.
	Examiner PATRICK T LEWIS	Art Unit 1673

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1														
	2														
	3														
	4														
	5														
	6														
	7														
	8														

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 5	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1673 (Primary Examiner) _____ (Date) _____		07 November 2017 O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20171107

AFCP 2.0 Decision

Application No.

13/261,029

Applicant(s)

Srivastava et al.

Examiner

PATRICK T LEWIS

Art Unit

1673

AIA Status

No

This is in response to the After Final Consideration Pilot request filed 05 October 2017.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

- ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.
- ☐ A non-broadening amendment to at least one independent claim was not submitted.
- ☐ A proper AFCP 2.0 request was submitted in response to the most recent final rejection.
- ☐ Other: _____

2. **Proper Request**

- A. After final amendment submitted with the request will not be treated under AFCP 2.0.

The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

- ☐ The after final amendment will be treated under pre-pilot procedure.

- B. Updated search and/or completed additional consideration.

The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

- ☒ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.
- ☐ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action.
See attached interview summary for further details.
- ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.
- ☐ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.
- ☐ 5. Other: _____

Examiner Note: Please attach an interview summary when necessary as described above.



15 Green Way, Chelmsford, MA 01824, USA; Tel: 978-250-9003; FAX: 978-250-7404

Indu M. Anand, Esq.**Fax**

To:	USPTO / Issue Fee	From:	Indu M. Anand
Fax:	1-571-273-2885	Pages:	Four, including this page
Phone:		Date:	December 22, 2017
Re:	App. #: 13/261,029		

Please find in this transmission for the above noted patent application number:

Form PTO-2938 for payment of issue fee and 20 copies of the patent; Two copies of form Part B
- Fee(s) Transmittal.

Confidentiality Note: This transmission is intended exclusively for the individual or the entity to which it is addressed, and may contain information that is proprietary, privileged, confidential or otherwise excepted from disclosure. If you are not the named addressee, you are not authorized to read, print, retain, copy or disseminate this transmission or any part of it. If you received this message in error, please destroy all copies of the message, and notify the sender of the error by email, fax or telephone together with any charges incurred by you to so notify us. Thank you.

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Dec 22 17 10:33p

Law Offices of Indu Anand

(978) 250-7404

p.3

rfw

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the **ISSUE FEE** and **PUBLICATION FEE** (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

83687 7590 11/29/2017
Indu M. Anand, Esq
15 Green Way
Chelmsford, MA 01824



Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

INDU M. ANAND	(Depositor's name)
<i>[Signature]</i>	(Signature)
22 December 2017	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/261,029	11/18/2011	Suresh C. Srivastava	CHG_00611	4149

TITLE OF INVENTION: SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

APPL. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	02/28/2018

12/26/2017 JVONGE 00000009 13261029

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1673	536-026740

01 FC:2501 480.00 OP

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form, PTO/SB/47, Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list:
 (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
 (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Law Offices of Indu M. Anand
 2. _____
 3. _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: **CHEMGENES CORPORATION**

(B) RESIDENCE (CITY and STATE OR COUNTRY): **Wilmington, Massachusetts**

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☒ Advance Order - # of Copies **Twenty**

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number **5054014** (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
 NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
 NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature: *Indu M. Anand*
 Typed or printed name: **INDU M. ANAND**

Date: **12/22/2017**
 Registration No. **52,557**

* Law Offices of Indu M. Anand

Page 2 of 3

PTO Form P (10-13) Approved for use through 10/31/2012

OMB 0651-0027

U.S. Patent and Trademark Office U.S. DEPARTMENT OF COMMERCE

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Law Offices of Indu Anand

(978) 250-7404

p.4

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
 or Fax **(571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

83687 7590 11/29/2017
 Indu M. Anand, Esq
 15 Green Way
 Chelmsford, MA 01824



Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

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Indu M. Anand	(Depositor's name)
Indu	(Signature)
22 December 2017	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/261,029	11/18/2011	Suresh C. Srivastava	CHG_00611	4149

TITLE OF INVENTION: SYNTHESIS OF LABILE BASE PROTECTED - MODIFIED DEOXY & MODIFIED RIBO NUCLEOSIDES, CORRESPONDING PHOSPHORAMIDITES AND SUPPORTS AND THEIR USE IN HIGH PURITY OLIGONUCLEOTIDE SYNTHESIS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	02/28/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1673	536-026740

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47, Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
 (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Law Offices of Indu M. Anand

2

3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

CHEMGENES CORPORATION

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Wilmington, Massachusetts

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☒ Advance Order - # of Copies Twenty

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 505404 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature Indu M. Anand
 Typed or printed name INDU M. ANAND

Date 12/22/2017
 Registration No. 52,557

* Law Offices of Indu M. Anand Page 2 of 3

PTOL 95-B (Rev. 12/13) Approved for use through 10/31/2017

OMB 0651-0023

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PAGE 4/4 * RCVD AT 12/22/2017 11:50:14 PM [Eastern Standard Time] * SVR:W-PTOFAX-002/19 * DNIS:2732885 * CSID:978 250 7404 * DURATION (mm:ss):02:28



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/261,029	02/06/2018	9884885	CHG_00611	4149

83687 7590 01/17/2018
Indu M. Anand , Esq
15 Green Way
Chelmsford, MA 01824

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 1723 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Suresh C. Srivastava, Burlington, MA;
Naveen P. Srivastava, Burlington, MA;

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AO 120 (Rev. 08/10)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Massachusetts on the following

☐ Trademarks or ☒ Patents. (☐ the patent action involves 35 U.S.C. § 292.)

DOCKET NO. 1:22-10290	DATE FILED 02/18/2022	U.S. DISTRICT COURT Massachusetts
PLAINTIFF ChemGenes Corporation		DEPENDANT Hongene Biotechnology Ltd.
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,309,707	11/13/2012	ChemGenes Corporation
2 8,541,569	Format m/d/yyyy 09/24/2013	ChemGenes Corporation
3 9,884,885	Format m/d/yyyy 02/08/2016	ChemGenes Corporation
4	Format m/d/yyyy	
5	Format m/d/yyyy	
	Format m/d/yyyy	

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED Format m/d/yyyy	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading
TRADEMARK NO.	HOLDER OF PATENT OR TRADEMARK
1	
2	Format m/d/yyyy
3	Format m/d/yyyy
4	Format m/d/yyyy
5	Format m/d/yyyy
	Format m/d/yyyy

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE Format m/d/yyyy
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