HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

UTILITY PATENT APPLICATION TRANSMITTAL *(Only for new nonprovisional applications under 37 CFR 1.53(b))*	Attorney Docket No.	4441.1001-002
	First Named Inventor	Suresh C. Srivastava
	Express Mail Label No.	

Title of Invention	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA		
Name of Assignee for Publication Purposes	ChemGenes Corporation	City and State for Publication Purposes	Wilmington, Massachusetts

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria, VA 22313-1450

1. ☐ Fee Transmittal Form
2. ☒ Specification **Total Pages 148**
   Both the claims and the abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
3. ☒ Drawing(s) (35 U.S.C. 113) **Total Sheets 32**
   ☐ Fig. of the Drawings for Publication [ ]
   ☒ No Figure to be Published
4. ☐ Oath or Declaration **Total Pages [ ]**
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 C.F.R. 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. ☐ CD-ROM or CD-R in duplicate ☐ Text file attached herewith
   Large table or Computer Program *(Appendix)*
6. ☐ Nucleotide and/or Amino Acid Sequence Submission
   (if applicable, items a.-c. are required)
   a. ☐ Computer Readable Form (CRF)
   i. ☐ Computer Readable Form (CRF)
   ii. ☐ Transfer Request (37 CFR 1.821(e))
   b. ☐ Specification Sequence Listing on:
   i. ☐ CD-ROM or CD-R (2 copies); or
   ii. ☐ Text file attached herewith *(electronic filing)*
   iii. ☐ Paper [ ] **Pages**
   c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers *(Do not submit when e-filing application)*
8. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
   (when there is an assignee)
9. ☐ English Translation Document *(if applicable)*
10. ☐ Information Disclosure Statement
    (Listing of References *(formerly PTO-1449)*)
    ☐ Copies of foreign patent docs., publications, and other info.
11. ☐ Preliminary Amendment
12. ☐ Return Receipt Postcard *(Check this box if going by express mail)*
13a. ☐ A Foreign Priority Claim under 35 U.S.C. § 119 or 365
    i. ☐ is made to [country], [app. #], filed [ ]
    ii. ☐ is presented in the attached
    ☐ Specification ☐ Preliminary Amendment
    ☐ Separate Sheet ☐ Declaration
13b. ☐ A Certified Copy of each Priority Document
    i. ☐ is enclosed
    ii. ☐ was filed in U.S. Application No. [ ]
14. ☐ Nonpublication Request under 35 U.S.C. 122(b)(2)(B)(i).
    Applicant must attach form PTO/SB/35 or equivalent.
15. ☐ Remarks [/ Change of Correspondence Address]
16. ☐ Small Entity Statement(s)
17. ☐ Other: _____

18. **If a CONTINUING APPLICATION,** check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title:
☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No.: PCT/US2009/005063
Prior application information: Examiner: Group Art Unit:

The entire disclosure of the prior application is considered a part of the disclosure of the accompanying application and is hereby incorporated by reference. ***(Add standard Related Applications section with incorporation by reference to specification or update same)***

19. **CORRESPONDENCE ADDRESS**

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Submitted by Typed or Printed Name	Alice O. Carroll	Reg. Number	33,542

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Date:_____Express Mail Label No._____

Inventors: Suresh C. Srivastava and Naveen P. Srivastava

Attorney's Docket No.: 4441.1001-002

PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

RELATED APPLICATIONS

This application is a continuation-in-part of International Application No. PCT/US2009/005063, which designated the United States and was filed on September 8, 2009, published in English, which claims the benefit of U.S. Provisional Application No. 61/191,065, filed on September 6, 2008.

The entire teachings of the above application(s) are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Defined sequence RNA synthesis in the 3' → 5' direction is now well established and currently in use for synthesis and development of a vast variety of therapeutic grade RNA aptamers, tRNAs, siRNA and biologically active RNA molecules. The 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 (See Helm, M., *et al.*, *RNA, 5*:618-621, 1999, the entire teachings of which are incorporated herein by reference). 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

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(See Maglott, E.J., Glick, G.D., *Nucl. Acids Res., 26*: 1301-1308, 1999, the entire teachings of which are incorporated herein by reference).

This approach utilizes a ribonucleoside with suitable N- protecting group: generally 5'- protecting group, the most popular being dimethoxytriphenyl, *i.e.,* the DMT group; 2'- protecting group, out of which most popular is t-Butyldimethylsilyl ether; and, a 3'- phosphoramidite, the most popular of which is cyanoethyl diisopropyl. 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 presence of an activator leading to dimers and oligoribonucleotides, followed by oxidation (3'→5' direction synthesis), also leads to a protected dinucleotide having a 3'→5'- internucleotide linkage, Ogilvie, K.K., *Can. J. Chem., 58*: 2686, 1980 (scheme 1).

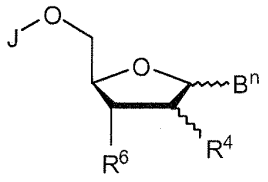
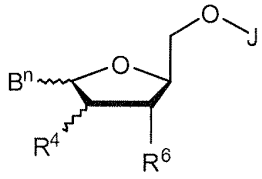
A number of such synthetic RNA require a modification or labeling of the 3'-end of an oligonucleotide. The synthesis of 3'- end modified RNA requiring lipophilic, long chain ligands or chromophores, using 3' → 5' synthesis methodology are challenging, difficult to synthesize and generally result in low coupling efficiency and lower purity of the final oligonucleotide, in general. Additional purifications are generally required. Therefore, new synthetic methodologies are needed to synthesize RNA molecules quickly, and cleanly and in a form that allows for modification at the 3' end.

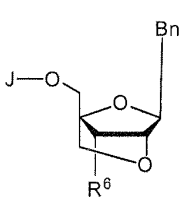
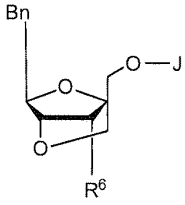
SUMMARY OF THE INVENTION

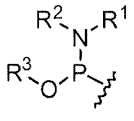
The present invention provides building blocks and methods for synthesizing very pure RNA in a form that can efficiently be modified at the 3' end. Reverse RNA monomer phosphoramidites have been developed for RNA synthesis in 5'→ 3' direction, leading to very clean oligo synthesis that allows for the introduction of various modifications at the 3'-end cleanly and efficiently.

Higher coupling efficiency per step have been observed during automated oligo synthesis with the reverse RNA amidites disclosed herein, resulting in a greater ability to achieve higher purity and produce very long oligonucleotides. The use of the reverse RNA phosphoramidites in the synthetic process of this invention leads to oligonucleotides free of N+1 species. The N+1 species leads to impurities that broaden out the desired peak during HPLC analysis/ purification or Gel purification. The N+1 species arise by addition of the two nucleobases within the same coupling cycle rather than just one nucleobase.

In one embodiment, the invention relates to a compound of Formula Ia, Ib, Ic, or Id:


(Ia) or

(Ib);


(Ic) or

(Id), or a salt thereof, wherein

J is H,  , or  , wherein ⦚ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or

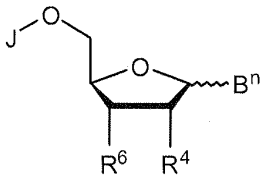
unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

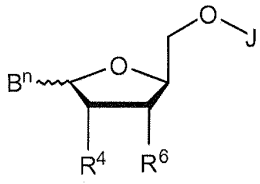
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

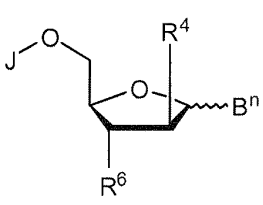
R^4 is a --halo, --R^5, --NR^7R^8, -OR^9, --SR^{10}, or 2'-blocking group,; or when Structural Formula Ia or Ib is:



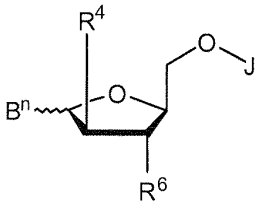
(II), or



(III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:



(IV), or



(V); R^4 is further selected from -OC(=O)R^{12};

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a

substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with $-NR^7R^8$, $(C_1$-$C_4)$alkylamino, di$(C_1$-$C_4)$alkylamino, $-OR^9$, $(C_1$-$C_6)$alkoxy, benzyl or substituted benzyl, $-SR^{10}$; or -S-$(C_1$-$C_6)$alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)$-phthalimide; $-C(=O)-(CH_2)_{1-16}-$phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted $(C_1$-$C_{12})$alkyl group, a substituted or unsubstituted $(C_2$-$C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2$-$C_{12})$alkynyl group;

each R^8 is H or a substituted or unsubstituted $(C_1$-$C_{12})$alkyl group, a substituted or unsubstituted $(C_2$-$C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2$-$C_{12})$alkynyl group;

each R^9 is independently $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted $(C_2$-$C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2$-$C_{12})$alkynyl group;

each R^{10} is independently $-S(C_1$-$C_6)$ alkyl, $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted $(C_2$-$C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2$-$C_{12})$alkynyl group;

each R^{11} is independently a substituted or unsubstituted $(C_1$-$C_{12})$alkyl group, a substituted or unsubstituted $(C_2$-$C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2$-$C_{12})$alkynyl group;

each R^{12} is independently a substituted or unsubstituted $(C_1$-$C_{12})$alkyl group, a substituted or unsubstituted $(C_2$-$C_{12})$alkenyl group, or a

substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

Z is an acid labile protecting group;

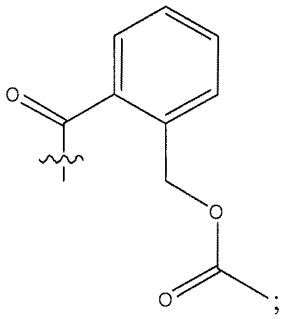
B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C$(CH_2)_{1\text{-}8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro

Shanghai Hongene Exhibit 1002

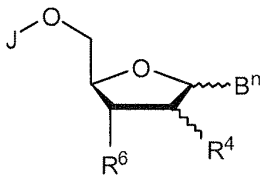
methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; -C(=O)$CH_2CH_2CH=CH_2$l; -C(=O)(C_1-C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; =CR^8N(C_1-C_6)alkyl)$_2$; -C(=O)-NR^8-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$NR^8(CH_2)_{1-16}NR^8$C(=O)-phthalimide; -C(=O)-$(CH_2)_{1-16}$-phthalimide; and

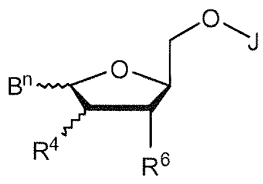


wherein any substitutable oxygen atom within the nucleobase is optionally substituted with –C(=O)N(C_1-C_6alkyl)$_2$ – C(=O)N(phenyl)$_2$.

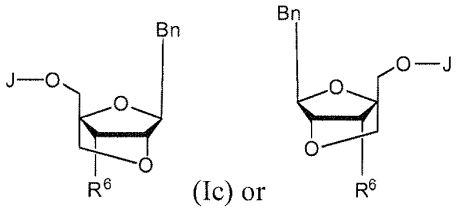
In another embodiment, the invention relates to a compound of Formula Ia, Ib, Ic, or Id:

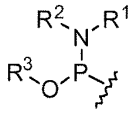


(Ia) or



(Ib);


(Ic) or
(Id), or a salt thereof, wherein

J is H,  , or  , wherein ⦚ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

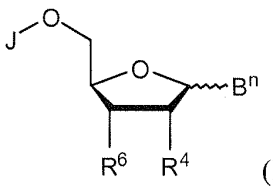
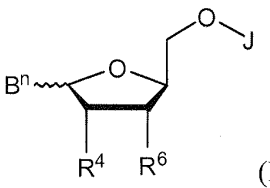
R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

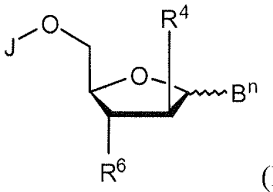
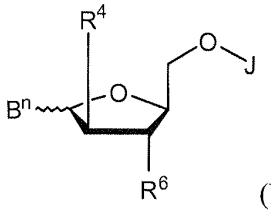
R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

R^4 is a --halo, $--R^5$, $--NR^7R^8$, $-OR^9$, $--SR^{10}$, or 2'-blocking group,; or when Structural Formula Ia or Ib is:


(II), or

(III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:


(IV), or

(V); R^4 is further selected from -OC(=O)R^{12};

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with –NR^7R^8, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, -OR^9, (C_1-C_6)alkoxy, -SR^{10}; or -S-(C_1-C_6)alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1-16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1\text{-}16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1\text{-}16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group; provided that if R^4 is –O-Si(R^{11})$_3$, and two R^{11} groups are both methyl, the other is not t-butyl or if R^4 is -O-CH_2-Si(R^{11})$_3$, then the three R^{11} groups cannot all be isopropyl;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing will be apparent from the following more particular description of example embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views.

The drawings are not necessarily to scale, emphasis instead being placed upon illustrating embodiments of the present invention.

FIGS. 1A-1C are graphs and tables demonstrating the purity of REV-2'-OMe-BTT- mArArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO: 1). (BTT is 5-Benzyl thio-1-H-tetrazole) synthesized with a coupling time of 2 minutes with the activator BTT. FIG. 1A is a graph of the trityl histogram; FIG. 1B is a graph of the capillary gel electrophoresis (CE) analysis of the crude RNA; and FIG 1C is a table containing the crude RNA-CE analysis report.

FIGS. 2A-2D are graphs and tables demonstrating the purity of REV-2'-OMe-phosphorothioate- Oligo mArArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO: 1) synthesized with a coupling time of 4 minutes with the activator (0.25M) ETT (ethyl thio tetrazole). FIG. 2A is a graph of the trityl histogram; FIG. 2B is a graph of the CE analysis of the crude RNA (desalted); FIG. 2C is a table containing the CE analysis report of crude RNA; and FIG. 2D is a graph of ESI/MS (crude) Actual MW: 6971.1; Found Value: 6972.0.

FIGS. 3A-3C are graphs and tables demonstrating the purity of REV-2'-OMe-phosphodiester – Oligo mArArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO: 1) synthesized with a coupling time of 4 minutes. FIG. 3A is a graph of the trityl histogram; FIG. 3B is a graph of the CE analysis of the crude oligo (desalted); and FIG. 3C is a table containing the CE analysis report of the crude RNA.

FIGS. 4A-4D are graphs and tables demonstrating the purity of REV-phosphodiester – Oligo rCrArCrArGrCrArUrArCrArUrCrUrCrGrArCrCrArU (SEQ ID NO: 2) synthesized with a coupling time of 4 minutes; FIG. 4A is a graph of the trityl histogram; FIG. 4B is a graph of the CE analysis crude (desalted); FIG. 4C is a table containing CE analysis report of the crude RNA; and FIG. 4D is a graph of ESI/MS Crude RNA (desalted); Calc.: MW: 6598.9.

FIGS. 5A-5C are graphs and tables demonstrating the purity of REV-phosphodiester – Oligo CrArCrArGrCrArUrArCrArUrCrUrCrGrArCrCrArU (SEQ ID NO: 2) (crude desalted) using a coupling time of 6 minutes; FIG. 5A is a graph of the

trityl histogram; FIG. 5B is a table of CE analysis crude (desalted); and FIG. 5C is a table of the CE analysis report crude RNA (desalted).

FIGS. 6A-6B is a graph and a picture of a gel demonstrating the purity of REV-phosphodiester – OLIGO-76 mer rArCrGrCrGrGrGrCrUrUrGrUrCrCrCrUrGrArArCrUrUrGrGrGrArCrCrUrGrGr GrArGrUrCrUrArUrUrUrUrUrCrArGrArCrUrArCrGrArGrArUrGrGrCrUrGrArCrUrC rGrArUrArGrGrCrCrCrG (SEQ ID NO: 3) synthesized with a coupling time of 6 minutes. FIG. 6A is a graph of the trityl histogram; and FIG. 6B is a picture of a gel of the page analysis of 76 mer phosphodiester; band #1; Bromo phenol blue; band #2; 76 mer with regular RNA; band #3; 76mer with reverse RNA; band #4; 76mer with reverse TOM RNA. TOM RNA reverse phosphoramidites: 2'-TOM-3'-O-DMT-adenosine(n-acetyl)5'-cyanoethylphosphoramidite; 2'-TOM-3'-O-DMT-cytidine(n-acetyl)5'-cyanoethylphosphoramidite; 2'-TOM-3'-O-DMT-guanosine(n-acetyl)5'-cyanoethylphosphoramidite; 2'-TOM-3'-O-DMT-uridine-5'-cyanoethylphosphoramidite.

FIG. 7 is the ^{31}P – NMR spectrum of 3'- DMT-2'-TBDMS-A(N-Bz)-5'-Phosphoramidite (lot # AL-300-2); 100% by analysis of region from 0-200 ppm.

FIG. 8 is the ^{31}P – NMR spectrum of 3'- DMT-2'-TBDMS-C-(N-Ac)-5'-Phosphoramidite (lot # NS-143-19); 100% by analysis of region from 0-200 ppm.

FIG. 9 is the ^{31}P – NMR spectrum of 3'- DMT-2'-TBDMS-U-5'-Phosphoramidite (lot # NS-147-19); 100% by analysis of region from 0-200 ppm.

FIG. 10 is the ^{31}P – NMR spectrum of 3'- DMT-2'-TBDMS-G-(N-iBu)-5'-Phosphoramidite (lot # NS-42-19); 100% by analysis of region from 0-200 ppm.

FIGS. 11A and 11B are (a) the HPLC chromatogram and (b) the table of peak retention times of the HPLC analysis for 3'- DMT-2'-TBDMS-A(N-Bz)-5'-Phosphoramidite (lot # AL-300-2).

FIGS. 12A and 12B are (a) the HPLC chromatogram and (b) the table of peak retention times for the HPLC analysis for 3'- DMT-2'-TBDMS-G(N-iBu)-5'-Phosphoramidite (lot # NS 42-19).

FIGS. 13A and 13B are (a) the HPLC chromatogram and (b) the table of peak retention times for the HPLC analysis for 3'- DMT-2'-TBDMS-C(N-Ac)-5'-Phosphoramidite (lot # NS 143-19).

FIGS. 14A and 14B are (a) the HPLC chromatogram and (b) the table of peak retention times for the HPLC analysis for 3'- DMT-2'-TBDMS- U-5'-Phosphoramidite (lot # NS 147-19).

FIGS. 15A – 15F are graphs and tables demonstrating the purity of REV-RNA-Me-THIO- mArArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO: 1) synthesized with a coupling time of 6 minutes. FIG. 15A is a graph of the trityl histogram; FIG. 15B is a graph of the CE crude; FIG. 15C is table of the CE analysis; FIG. 15D is a graph showing the migration time; FIG. 15E is table of the CE report; and FIG. 15F is a graph of Mass Spectrum; Actual Value: 6971.1; Found Value: 6971.7.

FIG. 16A is a graph of an electropherogram of the crude 21-mer RNA made by conventional method (3'→5'-direction). Expedite model 8909-1 umole scale. Crude purity; 70.73%.

FIG. 16B is a graph of an electropherogram of the purified 21-mer RNA made by conventional method (3'→5'-direction). Expedite model 8909-1 umole scale. Crude purity; 90.78%.

FIG. 17 is a graph of an electropherogram of the crude 21-mer RNA made by Reverse RNA synthesis method (5'→3'-direction). Expedite model 8909-1 umole scale. Crude purity; 78.55%.

FIG. 18 is a graph an electropherogram of the crude 21-mer RNA with 3'-cholesterol CPG, made by conventional method (3'→-5'-direction). Expedite model 8909-1 umole scale. Crude purity; 82.83%.

FIG. 19 is a graph of an electropherogram of the crude 21-mer RNA with 3'-Cholesterol CPG, made by Reverse RNA synthesis method (5'→ 3'-direction). Expedite model 8909-1 umole scale. Crude purity; 85.76%.

FIG. 20 is a graph of the 21-Mer RNA with 3'-Cholesterol-TEG linker. Reverse direction (5'→ 3') synthesis and HPLC purification. 1 umole scale. Purity; 99.9%.

FIGS. 21A and 21B are graphs of electropherograms. FIG. 21A is a graph of an electropherogram of the crude 21-mer RNA with 3'-HEG (Hexaethyloxyglycol) made by Reverse RNA synthesis method (5'→ 3'-direction). Expedite model 8909-1 umole scale. Crude purity; 56.60%. FIG. 21B is a graph of an electropherogram of 21-mer RNA synthesized by reverse direction (5'→3'), followed by HEG (Hexa-ethyloxyglycol) attachment. After HPLC purification, purity by CE; 94.39%.

FIG. 22 is a graph of an electropherogram of the crude 21-mer RNA with 3'-PEG(Polyethylene glycol; MW 2000) made by Reverse RNA synthesis method (5'→3'-direction). Expedite model 8909-1 umole scale. Crude purity; 91.87%.

FIG. 23 is a graph of the ESI Spectral analysis of 21-mer RNA with 3'-PEG-2000 attachment, purified RNA as shown in FIG. 24. The synthesis was carried out in reverse direction (5'→3' direction). The PEG-2000 was attached as last step via the corresponding phosphoramidite, ChemGenes catalog; CLP-3119; Calculated Molecular Weight: 8684.1; and Observed Molecular Weight: 8681.1.

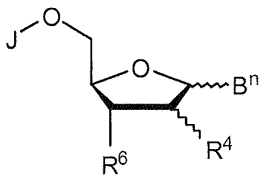
FIG. 24 is a graph of an electropherogram of the HPLC purified 21-mer RNA with 3'-PEG (Polyethyleneglycol; MW 2000). Made by Reverse RNA synthesis method (5'→3'-direction). Expedite model 8909-1 umole scale. Purity; 100%.

DETAILED DESCRIPTION OF THE INVENTION

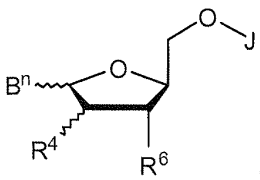
A description of example embodiments of the invention follows.

The teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

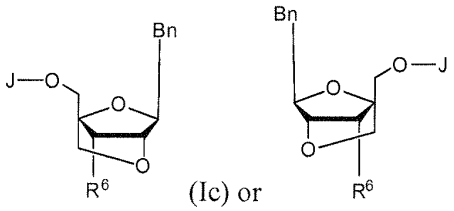
In a first embodiment, the invention relates to a compound of Formula Ia, Ib, Ic, or Id:

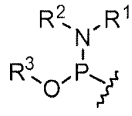
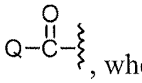


(Ia) or



(Ib);


(Ic) or
(Id), or a salt thereof, wherein

J is H,  , or  , wherein ≀ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

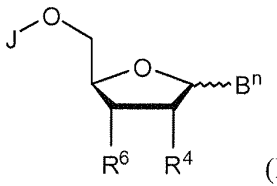
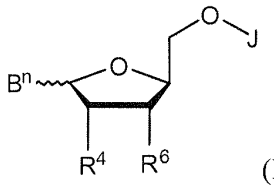
R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

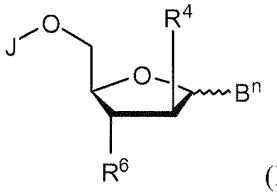
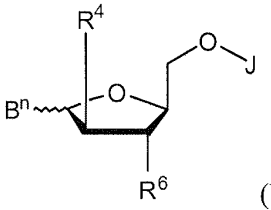
R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

R^4 is a --halo, --R^5, --NR^7R^8, -OR^9, --SR^{10}, or 2'-blocking group,; or when Structural Formula Ia or Ib is:


(II), or

(III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:


(IV), or

(V); R^4 is further selected from -OC(=O)R^{12};

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with –NR^7R^8, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, -OR^9, (C_1-C_6)alkoxy, benzyl or substituted benzyl, -SR^{10}; or -S-(C_1-C_6)alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; -C(=O)-(CH_2)$_{1-16}$$NR^8$C(=O)$CF_3$; -C(=O)-($CH_2$)$_{1-16}$$NR^8$C(=O)-phthalimide; -C(=O)-(CH_2)$_{1-16}$–phthalimide; NR^8C(=O)-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

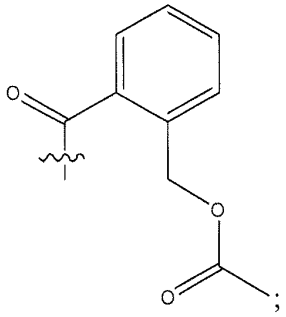
Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C$(CH_2)_{1-8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-

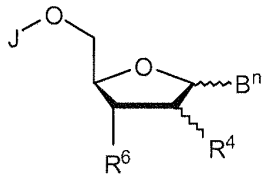
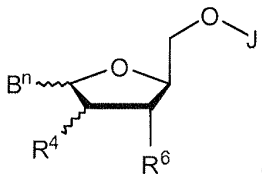
bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

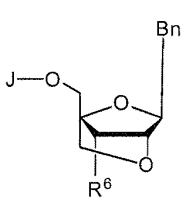
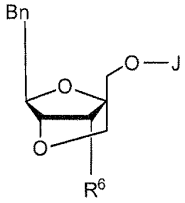
wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; -C(=O)$CH_2CH_2CH=CH_2$l; -C(=O)(C_1-C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; $=CR^8N(C_1$-$C_6)alkyl)_2$; -C(=O)-NR^8-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$NR^8(CH_2)_{1-16}NR^8$C(=O)-phthalimide; -C(=O)-$(CH_2)_{1-16}$-phthalimide; and

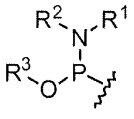


wherein any substitutable oxygen atom within the nucleobase is optionally substituted with $-C(=O)N(C_1\text{-}C_6alkyl)_2$ – $C(=O)N(phenyl)_2$.

In a second embodiment, the invention relates to a compound of Formula Ia, Ib, Ic, or Id:

 (Ia) or  (Ib);

 (Ic) or  (Id), or a salt thereof, wherein

J is H,  , or  , wherein ≀ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

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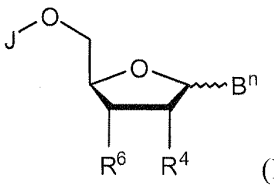
R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

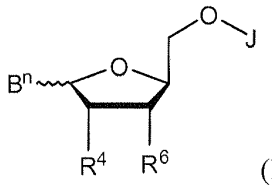
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

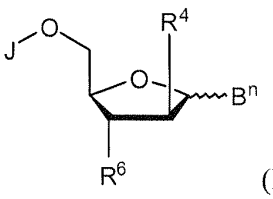
R^4 is a --halo, --R^5, --NR^7R^8, -OR^9, --SR^{10}, or 2'-blocking group,; or when Structural Formula Ia or Ib is:



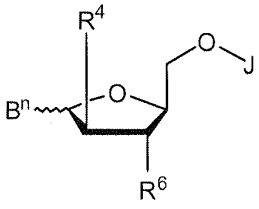
(II), or



(III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:



(IV), or



(V); R^4 is further selected from -OC(=O)R^{12};

Shanghai Hongene Exhibit 1002

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with $-NR^7R^8$, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, $-OR^9$, (C_1-C_6)alkoxy, benzyl or substituted benzyl, $-SR^{10}$; or -S-(C_1-C_6)alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)$-phthalimide; $-C(=O)-(CH_2)_{1-16}-$phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group; provided that

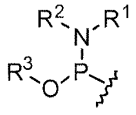
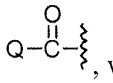
if R^4 is $-O-Si(R^{11})_3$, and two R^{11} groups are both methyl, the other is not t-butyl or if R^4 is $-O-CH_2-Si(R^{11})_3$, then the three R^{11} groups cannot all be isopropyl;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

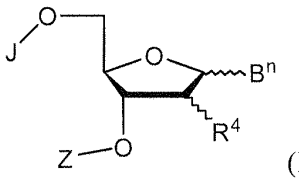
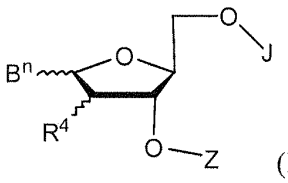
Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group.

In one aspect of either the first or second embodiment, wherein J is


, or

, wherein ≀ indicates where J is attached to the O atom.

In one aspect of either the first or second embodiment, wherein the compound is represented by Formula Ia or Ib:


(Ia);

(Ib) or a salt thereof.

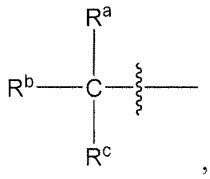
In another aspect of either the first or second embodiment, Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl.

In another aspect of either the first or second embodiment, Z is di-p-anisylphenyl methyl, p-fluorophenyl-1- naphthylphenyl methyl, p-anisyl-1-

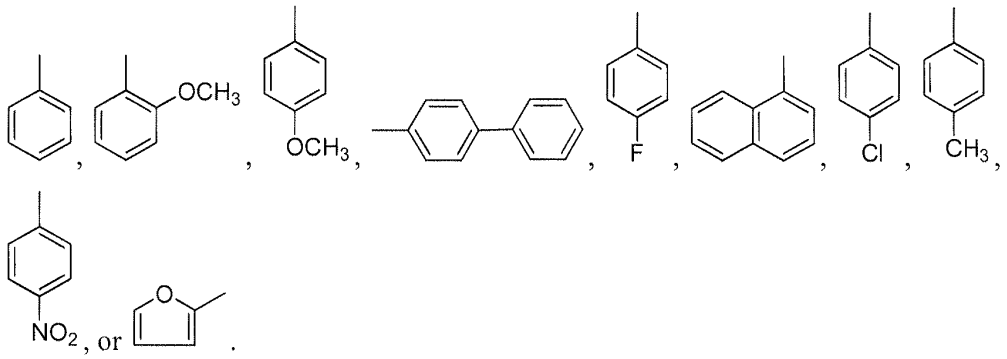
Shanghai Hongene Exhibit 1002

naphthylphenyl methyl, di-o-anisyl-1- naphthyl methyl, di-o-anisylphenyl methyl, p-tolyldiphenylmethyl, di-p-anisylphenylmethyl, di-o-anisyl-1- naphthylmethyl, di-p-anisylphenyl methyl, di-o-anisyl phenyl methyl, di-p-anisylphenyl methyl, or p-tolyldiphenylmethyl.

In yet another aspect of either the first or second embodiment, Z is represented by the following structural formula:



, wherein ≀ indicates attachment to the 3' oxygen atom and R^a, R^b, and R^c are independently selected from the following structural formulas:

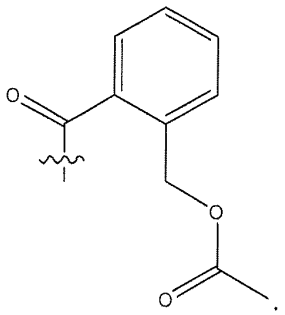


In one aspect of either the first or second embodiment, Z is 4-methoxytrityl, 4, 4'-dimethoxytrityl, or 4, 4', 4"-trimethoxytrityl.

In another aspect of either the first or second embodiment, the substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with $=CHN(CH_3)_2$; $C(=O)CH(CH_3)_2$; $-C(=O)CH_3$, $=C(CH_3)N(CH_3)_2$; $-C(=O)OPh$; $-C(=O)CH_2CH_2CH=CH_2$; $-C(=O)CH_2CH_2-C(=O)O(C_1-C_6)alkyl$; $-C(=O)-NR^8-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$;

Shanghai Hongene Exhibit 1002

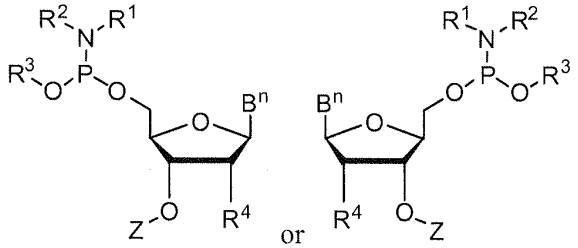
-C(=O)-$NR^8(CH_2)_{1-16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1-16}$-phthalimide and



In yet another aspect of either the first or second embodiment, R^3 is -CH_2CH_2CN, -CH_2CH_2-$Si(CH3)_2C_6H_5$, -CH_2CH_2-$S(O)_2$-CH_2CH_3, -CH_2CH_2-C_6H_4-NO_2, -CH_2CH_2-NH-C(O)-C_6H_5, or -CH_2CH_2-O-C_6H_4-$C(O)CH_3$, and R^4 is --O-$Si(R^{11})_3$.

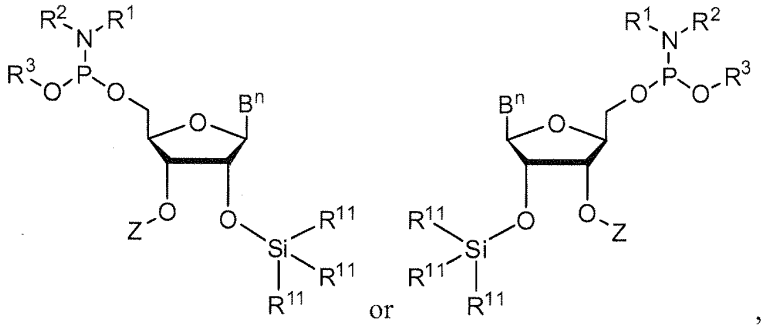
In yet another aspect of either the first or second embodiment, R^4 is –O-$Si(CH_3)_2(C(CH3)_3)$ or -O-CH_2-$Si(CH(CH_3)_2)_3$).

In one aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas :



or a salt thereof.

In another aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas:

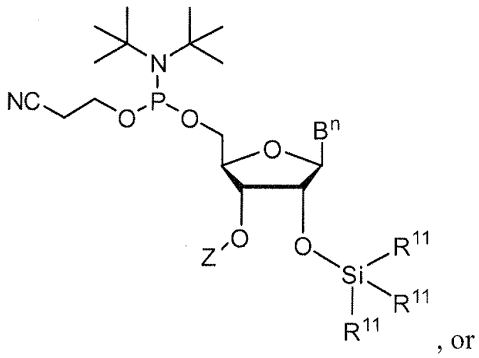


or

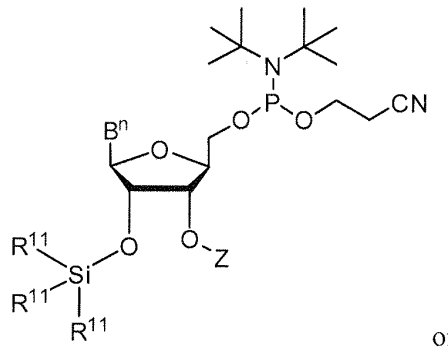
, or a salt thereof.

In yet another aspect of either the first or second embodiment, R^3 is -CH_2CH_2CN.

In one aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas:



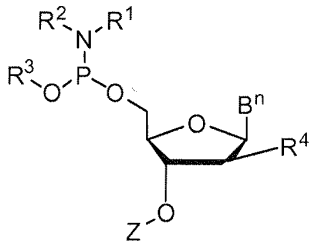
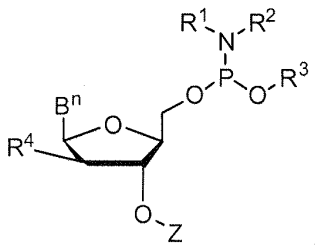
, or



or a salt thereof.

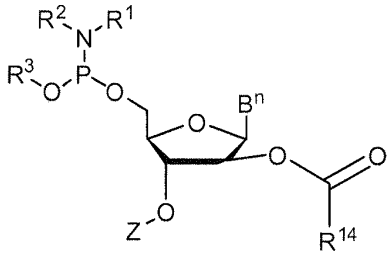
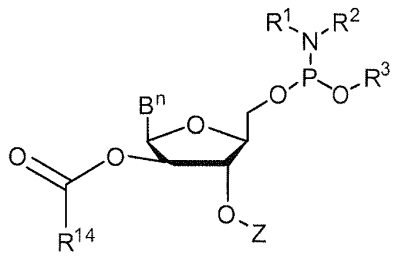
Shanghai Hongene Exhibit 1002

In one aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas:

or , or a salt thereof.

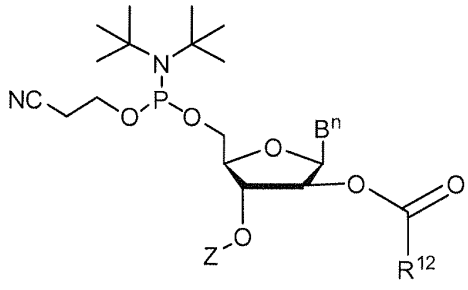
In another aspect of either the first or second embodiment, the compound is represented by one of the following structural formula:

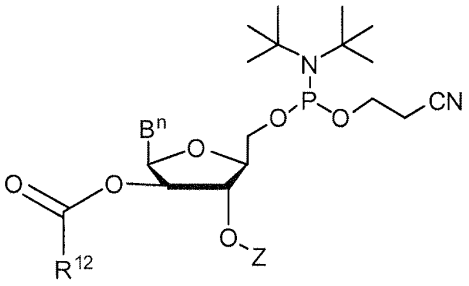
, or or a salt thereof.

In yet another aspect of either the first or second embodiment, R^3 is CH_2CH_2CN.

In one aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas:

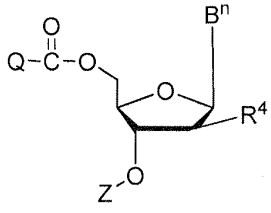


, or

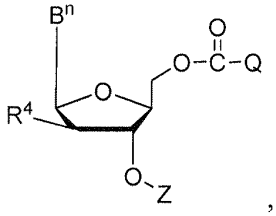


or a salt thereof.

In one aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas :

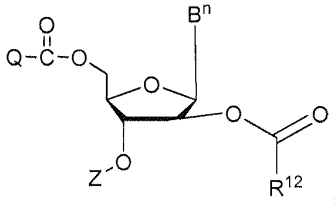


or

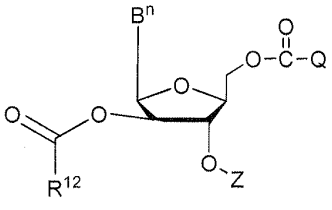


, or a salt thereof.

In one aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas:



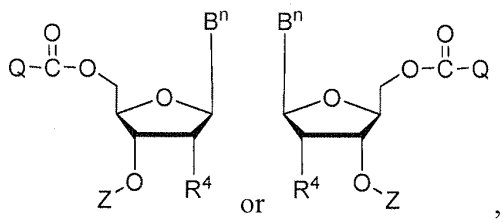
, or



or a salt thereof.

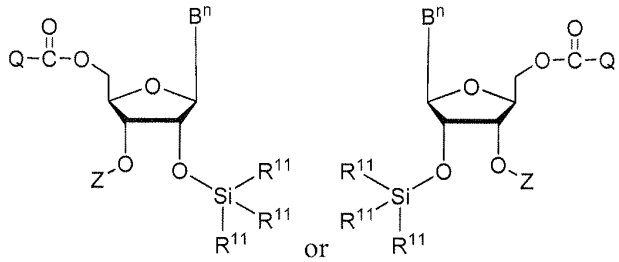
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In another aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas:



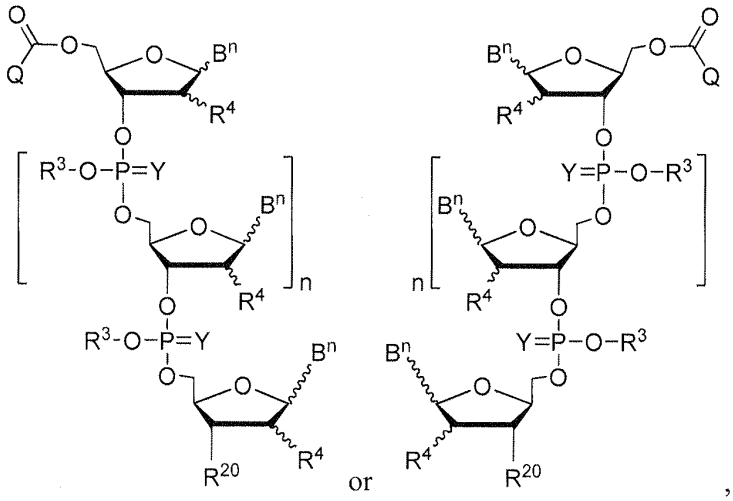
, or a salt thereof.

In another aspect of either the first or second embodiment, the compound is represented by one of the following structural formulas:



, or a salt thereof.

In a third embodiment, the invention relates to a compound represented by one of the following structural formulas:



, or salts thereof, wherein

each Y is independently oxygen or sulfur;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl;

R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

R^4 is a --halo, --R^5, --NR^7R^8, -OR^9, --SR^{10}, or 2'-blocking group; or when R^4 is in the ribose conformation , R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or R^4 is in the arabinose conformation, R^4 is further selected from -OC(=O)R^{12};

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with –NR^7R^8, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, -OR^9, (C_1-C_6)alkoxy, benzyl or substituted benzyl, -SR^{10}; or -S-(C_1-C_6)alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1-16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

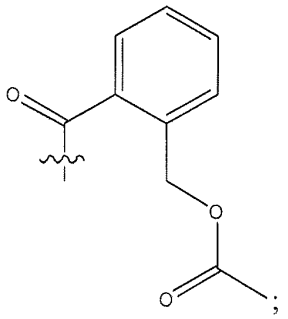
Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C$(CH_2)_{1-8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine,

8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5- methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; -C(=O)CH_2CH_2CH=CH_2l; -C(=O)(C_1-C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; =CR^8N(C_1-C_6)alkyl)$_2$; -C(=O)-NR^8-$(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$; -C(=O)-$NR^8(CH_2)_{1\text{-}16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1\text{-}16}$-phthalimide; and



;

wherein any substitutable oxygen atom within the nucleobase is optionally substituted with –C(=O)N(C_1-C_6alkyl)$_2$ –C(=O)N(phenyl)$_2$;

R^{20} is H, –O-Z, or R^{21};

R^{21} is 3' functional group;

Z is an acid labile protecting group; and

n is 0 to 150;

or a salt thereof.

In one aspect of the third embodiment, the compound of Claim 24, wherein R^{21} is

a) cyanoethyl phosphate-polyethylene glycols^{v}, where v is 2-100 and is number of glycol units;

b) cyanoethyl phosphate –linker attached with cholesterol, biotin, fluoresceins, cyanine dyes, psoralen, tetramethylrhodamine dye, dabcyl dye, C-3 disulfide, C-6 disulfide, symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}), symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}) with a terminal amino group protected with CF3C(=O) or phthalamido or FMOC, (C_1-C_{16})alkylene-amine protected with a amine protecting group, (C_1-C_5)alkylene- amine protected with an azide group; (C_1-C_5)alkylene- amine protected amine protected with an acetylene (C triple bond CH) group

c) cyanoethyl phosphate –ethane-2-ol- protected with DMT group or other acid labile groups, cyanoethyl phosphate –propane -3-ol- protected with DMT group or other acid labile groups,

d) (C_1-C_{50})alkylene with a terminal hydroxy;

e)lipids , carboxyl groups, or peptide; or

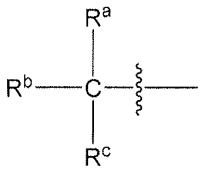
f) a branched phosphoramidite.

In another aspect of the third embodiment, the compound of Claim 24, wherein n is 5-75. Alternatively, n is 76-150. Alternatively, n is 10-25. Alternatively, n is 25-50. Alternatively, n is 50-75. Alternatively, n is 75-100.

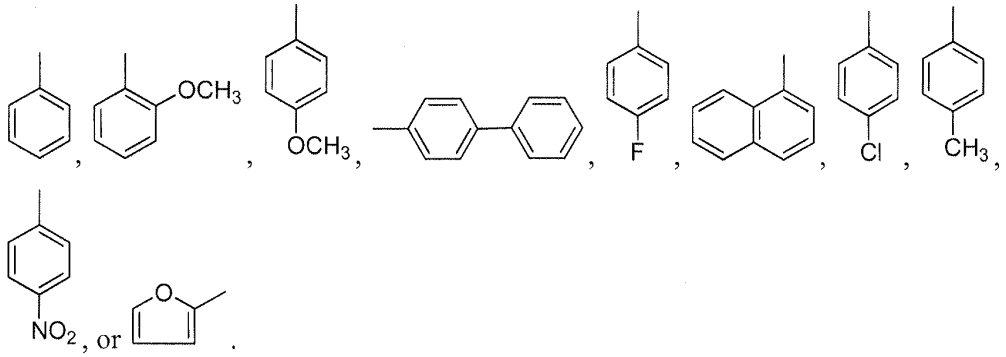
In another aspect of the third embodiment, Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl.

In another aspect of the third embodiment, Z is di-p-anisylphenyl methyl, p-fluorophenyl-1- naphthylphenyl methyl, p-anisyl-1- naphthylphenyl methyl, di-o-anisyl-1- naphthyl methyl, di-o-anisylphenyl methyl, p-tolyldiphenylmethyl, di-p-anisylphenylmethyl, di-o-anisyl-1- naphthylmethyl, di-p-anisylphenyl methyl, di-o-anisyl phenyl methyl, di-p-anisylphenyl methyl, or p-tolyldiphenylmethyl.

In yet another aspect of the third embodiment, Z is represented by the following structural formula:

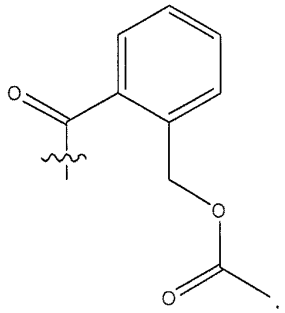


, wherein ≀ indicates attachment to the 3' oxygen atom and R^a, R^b, and R^c are independently selected from the following structural formulas:



In one aspect of the third embodiment, Z is 4-methoxytrityl, 4, 4'-dimethoxytrityl, or 4, 4', 4"-trimethoxytrityl.

In another aspect of the third embodiment, the substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with $=CHN(CH_3)_2$; $C(=O)CH(CH_3)_2$; $-C(=O)CH_3$, $=C(CH_3)N(CH_3)_2$; $-C(=O)OPh$; $-C(=O)CH_2CH_2CH=CH_2$; $-C(=O)CH_2CH_2-C(=O)O(C_1-C_6)$alkyl; $-C(=O)-NR^8-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-NR^8(CH_2)_{1-16}NR^8C(=O)$-phthalimide; $-C(=O)-(CH_2)_{1-16}$-phthalimide and



In yet another aspect of the third embodiment, R^3 is $-CH_2CH_2CN$, $-CH_2CH_2-Si(CH3)_2C_6H_5$, $-CH_2CH_2-S(O)_2-CH_2CH_3$, $-CH_2CH_2-C_6H_4-NO_2$, $-CH_2CH_2-NH-C(O)-C_6H_5$, or $-CH_2CH_2-O-C_6H_4-C(O)CH_3$, and R^4 is $--O-Si(R^{11})_3$.

In yet another aspect of the third embodiment, R^4 is $-O-Si(CH_3)_2(C(CH3)_3)$ or $-O-CH_2-Si(CH(CH_3)_2)_3$).

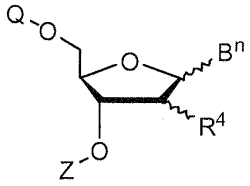
In yet another aspect of the third embodiment, R^3 is $-CH_2CH_2CN$.

A fourth embodiment of the invention is a synthetic RNA molecule with purity exceeding 97 % and synthesized from a 5'phosphoramidite nucleoside.

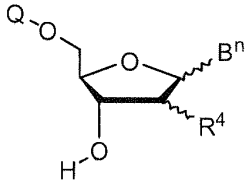
The compounds of the first and the second embodiments and aspest therof can be used in the following methods.

A fifth embodiment of the invention is a method of preparing an oligonucleotide by bond formations in the 5'- to 3'- direction for the synthesis of RNA oligomers and enantiomers thereof, said method comprises the following steps

a) cleavage of the Z protecting group from a compound attached to the support represented by the following structural formula:

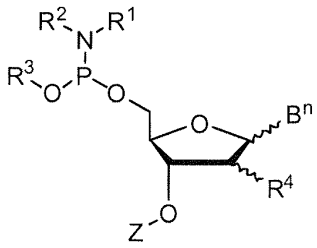


, thereby forming a compound represented by structural formula (XX):

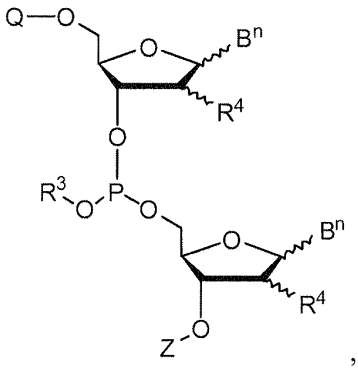


(XX);

b) reacting the compound represented by structural formula XX with a compound of structural formula XXI:



(XXI), thereby forming 2-mer compound represented by the following structural formula:

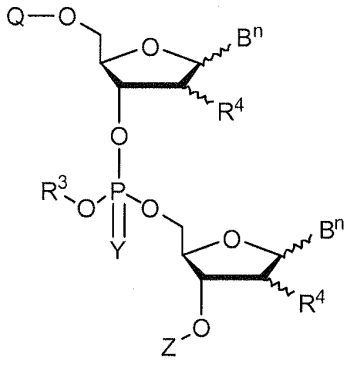


,

c) reacting the 2-mer with a capping agent; for example an acid anhydride to block the unreacted 3' hydroxy group

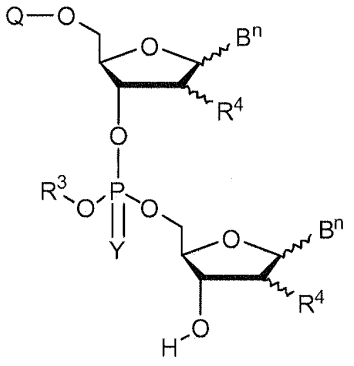
Shanghai Hongene Exhibit 1002

d) oxidizing or sulfurization of the trivalent phosphorous group of the 2-mer compound to form a compound of structural formula XXII:



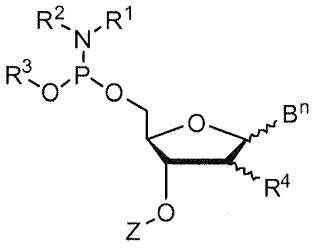
(XXII);

e) cleavage of the Z protecting group from a compound represented by the structural formula XXII, thereby forming a compound of structural formula XXIII:

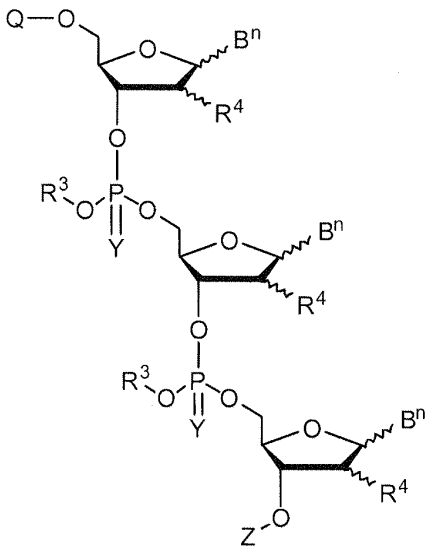


(XXIII);

f) reacting the compound represented by structural formula XXIII with a compound represented by the following structural formula:



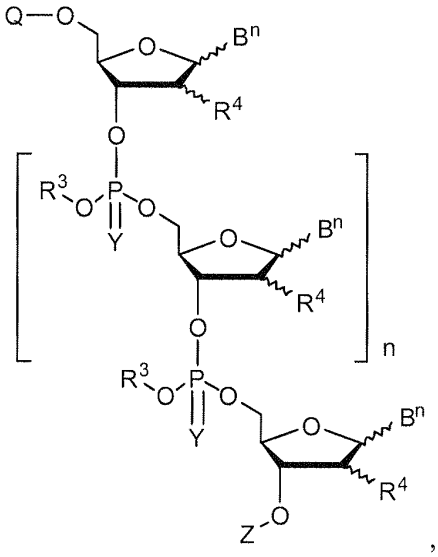
, thereby forming a 3-mer after oxidation or sulfurization, represented by the following structural formula XXIV:



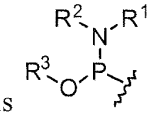
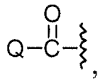
XXIV;

e) cleavage of the Z protecting group from a compound represented by structural formula XXIV;

g) repeating steps a) through e) n times, thereby forming a oligonucleotide represented by the following structural formula:



, or a salt thereof, wherein

J is  , or  , wherein ≀ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

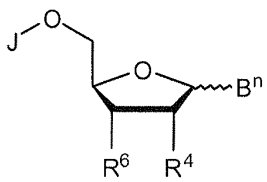
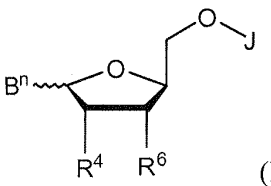
R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

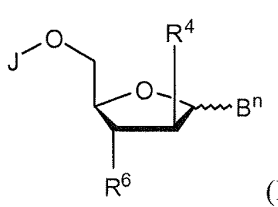
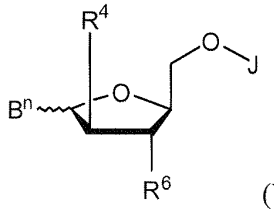
R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

R^4 is a --halo, $--R^5$, $--NR^7R^8$, $-OR^9$, $--SR^{10}$, or 2'-blocking group,; or when Structural Formula Ia or Ib is:

 (II), or  (III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:

(IV), or (V); R^4 is further selected from $-OC(=O)R^{12}$;

each R^5 is independently a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with $-NR^7R^8$, $(C_1\text{-}C_4)$alkylamino, di$(C_1\text{-}C_4)$alkylamino, $-OR^9$, $(C_1\text{-}C_6)$alkoxy, benzyl or substituted benzyl, $-SR^{10}$; or -S-$(C_1\text{-}C_6)$alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; $-C(=O)\text{-}(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$; $-C(=O)\text{-}(CH_2)_{1\text{-}16}NR^8C(=O)$-phthalimide; $-C(=O)\text{-}(CH_2)_{1\text{-}16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group;

each R^8 is H or a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group;

each R^9 is independently $-C(=O)\text{-}(CH_2)_{1\text{-}16}CH_3$; a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group;

each R^{10} is independently $-S(C_1\text{-}C_6)$ alkyl, $-C(=O)\text{-}(CH_2)_{1\text{-}16}CH_3$; a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group;

each R^{11} is independently a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

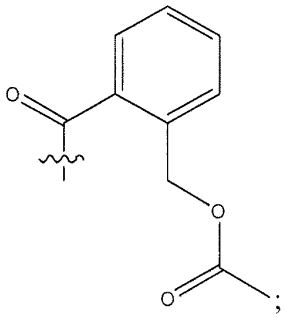
Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C(CH_2)$_{1\text{-}8$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5- methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; -C(=O)CH_2CH_2CH=CH_2l; -C(=O)(C_1-

C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; =CR^8N(C_1-C_6)alkyl)$_2$; -C(=O)-NR^8-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$NR^8(CH_2)_{1-16}NR^8$C(=O)-phthalimide; -C(=O)-$(CH_2)_{1-16}$-phthalimide; and



wherein any substitutable oxygen atom within the nucleobase is optionally substituted with –C(=O)N(C_1-C_6alkyl)$_2$ –C(=O)N(phenyl)$_2$; an

n is 1 to 150;

or a salt thereof.

In another aspect, each Y group is independently introduced via sulfurization to form a phosphorothioate linkage or via oxidation to form a phosphate linkage.

In another aspect, wherein the R^3 group is eliminated after oxidation to form a phosphate linkage.

In another aspect, the R^3 group is eliminated after sulfurazation to form a phosphorothioate linkage.

In another aspect, the nucleobase protecting groups are deprotected with a base.

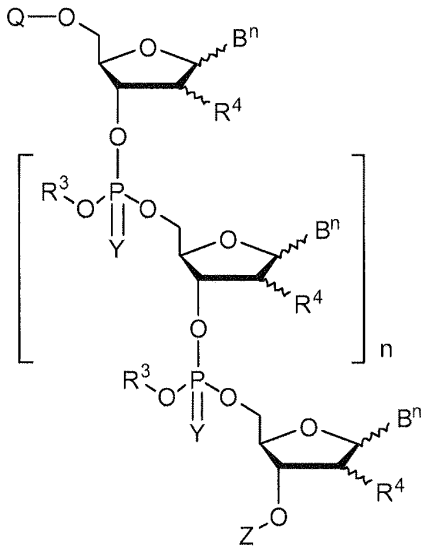
In another aspect, the base is selected from aq ammonia, methanolic ammonia, or ethanolic ammonia.

In another aspect, R^4 is –OSi(R^{11})$_3$.

In another aspect, the method further comprises the step of cleaving –$OSi(R^{11})_3$ with a fluoride salt.

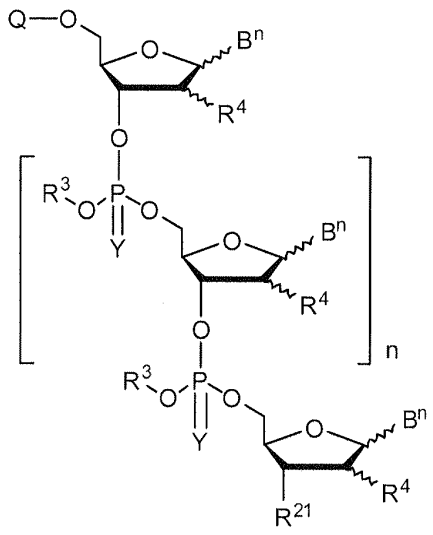
In another aspect, the fluoride salt is tetraethylammonium fluoride.

In another aspect, further comprising the step of reacting the compound represented by the following structural formula:



, with a 3' functional group, thereby forming a compound of represented by the following structural formula;

Shanghai Hongene Exhibit 1002



, wherein R^{21} is the 3'functional group or a salt thereof.

In another aspect, R^{21} is

a) cyanoethyl phosphate-polyethylene glycols^{v}, where v is 2-100 and is number of glycol units;

b) cyanoethyl phosphate –linker attached with cholesterol, biotin, fluoresceins, cyanine dyes, psoralen, tetramethylrhodamine dye, dabcyl dye, C-3 disulfide, C-6 disulfide, symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}), symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}) with a terminal amino group protected with CF3C(=O) or phthalamido or FMOC, (C_1-C_{16})alkylene-amine protected with a amine protecting group, (C_1-C_5)alkylene- amine protected with an azide group; (C_1-C_5)alkylene- amine protected amine protected with an acetylene (C triple bond CH) group

c) cyanoethyl phosphate –ethane-2-ol- protected with DMT group or other acid labile groups, cyanoethyl phosphate –propane -3-ol- protected with DMT group or other acid labile groups,

d) (C_1-C_{50})alkylene with a terminal hydroxy;

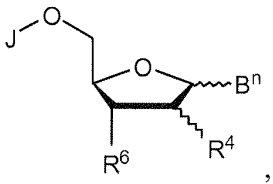
e) lipids, carboxyl groups, or peptide; or

f) a branched phosphoramidite.

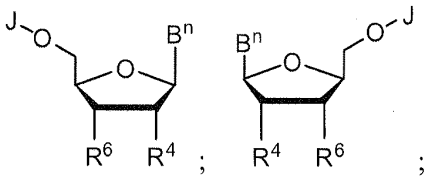
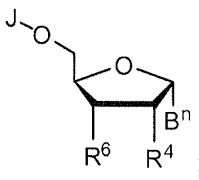
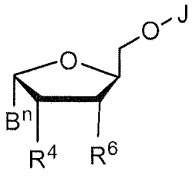
In another aspect, a RNA molecule made by the claimed method having a purity of 97% or greater following purification of the synthesized RNA molecule by HPLC, ion exchange, or reverse phase chromatography.

Abbreviation Summary:
mA = 2'-O-Methyl adenosine,
rA = adenosine,
rC = cytidine
rU = uridine
rG = guanosine,
2'-OMe = 2'- O-Methyl
BTT = 5- Benzyl thio-1-H-tetrazole,
phosphorothioate = phosphorus in the pentavalent oxidized state with sulfur as P=S
Me-THIO = phosphothioate
CE = Capillary-Electrophoresis
MW = Molecular Weight
ESI/MS = Electrospray Ionisation-Mass Spectrometry
DMT = 4,4'-dimethoxytrityl
TBDMS = tert-butyldimethylsilyl
Ac = acetyl ($-COCH_3$)
Bz = benzene
iBu = isobutyl (2-methylpropyl)
TOM = triisopropylsiloxymethyl
THIO = phosphorothioate, i.e., sulfur attached to phosphorus (V) (P=S)

The compounds of the invention are represented by

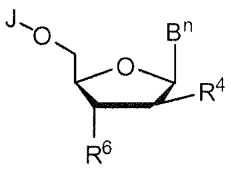
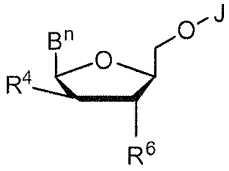
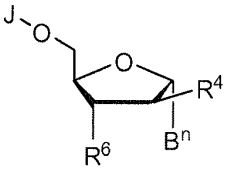
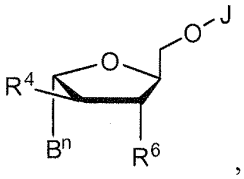

, or a salt thereof.

In a specific embodiment, the compound is represented by the following structural formulas:

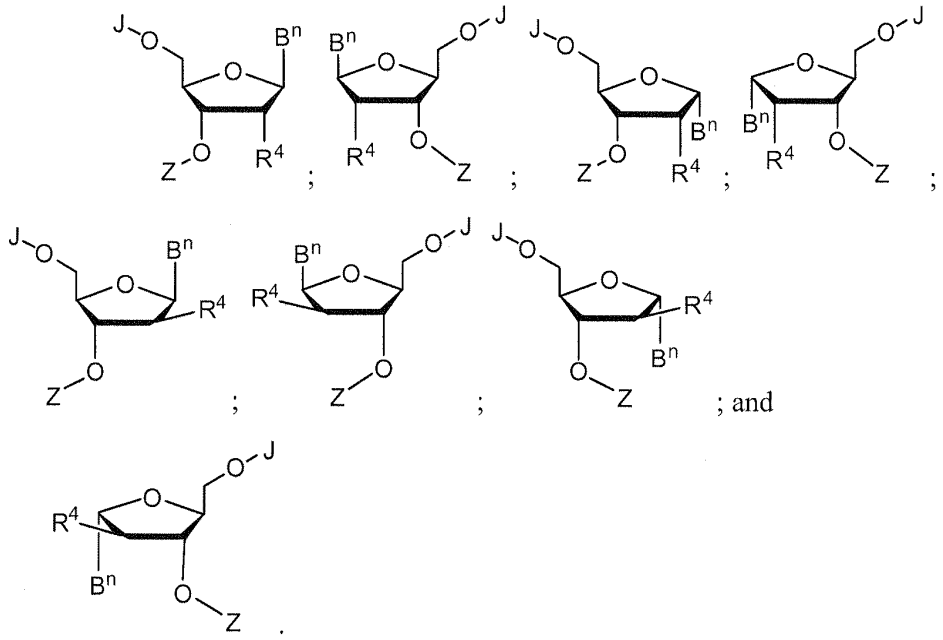

;
; 
; and 
.

β-D- ribose; β-L- ribose; α-D- ribose α-L- ribose

In another embodiment, the compound is represented by the following structural formulas:


; 
; 
; and 
, corresponding to β-D- arabinose; β-L- arabinose; α-D- arabinose; α-L- arabinose, respectively.

In one embodiment, R^6 is –H, or –O-Z. In a specific embodiment, R^6 is –O-Z and the compound is represented by the following structural formulas:

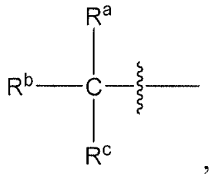


In one embodiment, Z is an acid labile protecting group. An acid labile protecting group is a protecting group which can be removed by contacting the group with a Bronsted or a Lewis acid. Acid labile protecting groups are known to those skilled in the art. Trityl groups are commonly substituted by electron donating substituents such as alkoxy groups. A preferred acid labile protecting group is a substituted or unsubstituted trityl, for example 4,4'-dimethoxytrityl (hereinafter "DMT").

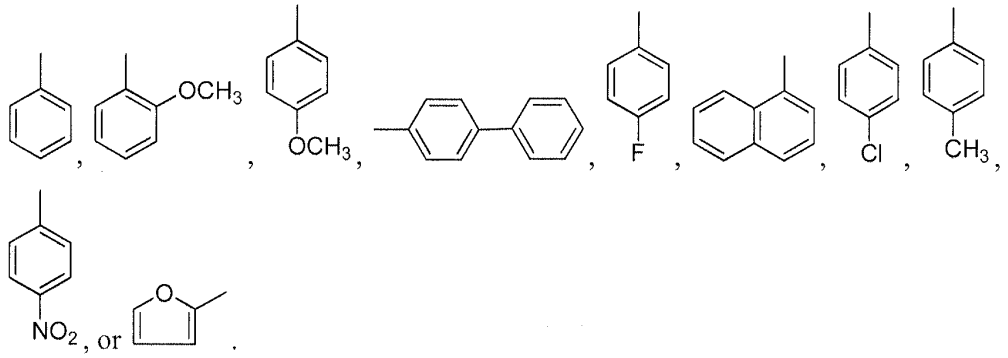
In a specific embodiment, Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl. In a more specific embodiment, Z is selected from the following group: Trityl (triphenylmethyl, Tr), Methoxytrityl [(4-methoxyphenyl)diphenylmethyl, MMT), Dimethoxytrityl [bis-(4-methoxyphenyl)phenylmethyl, DMT], 4, 4', 4"-trimethoxytrityl, and 9-phenylxanthy. In another specific embodiment, Z is 4-methoxytrityl, 4, 4'-dimethoxytrityl, or 4, 4', 4"-trimethoxytrityl.

In another embodiment, Z is di-p-anisylphenyl methyl, p-fluorophenyl-1-naphthylphenyl methyl, p-anisyl-1- naphthylphenyl methyl, di-o-anisyl-1- naphthyl methyl, di-o-anisylphenyl methyl, p-tolyldiphenylmethyl, di-p-anisylphenylmethyl, di-o-anisyl-1- naphthylmethyl, di-p-anisylphenyl methyl, di-o-anisyl phenyl methyl, di-p-anisylphenyl methyl, or p-tolyldiphenylmethyl.

In another specific embodiment, Z is represented by the following structural formula:



, wherein ≀ indicates attachment to the 3' oxygen atom and R^a, R^b, and R^c are independently selected from the following structural formulas:



An "alkyl ester" group refers to a C1-C18 carbon chain that attaches to the rest of the molecule through a –C(O)- moiety. The carbon chain may be linear or branched, saturated or unsaturated, and may contain intervening heteroatoms such as O, NH, NR^4, or S.

"Aliphatic groups", as used herein, include straight chained or branched C_1-C_{18} hydrocarbons which are completely saturated or which contain one or more unconjugated double bonds, or cyclic C_3-C_{18} hydrocarbons which are completely saturated or which contain one or more unconjugated double bonds. Alkyl groups are straight chained or branched C_1-C_8 hydrocarbons or C_3-C_8 cyclic hydrocarbons which are completely saturated. Aliphatic groups are preferably alkyl groups.

The term "alkyl", used alone or as part of a larger moiety such as "arylalkyl" or "cycloalkylalkyl" means a straight or branched hydrocarbon radical having 1-18 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl and the like.

The term "alkylene", means a straight or branched hydrocarbon di-radical having 1-18 carbon atoms and includes, for example, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$) and the like.

The term "alkenyl", means a straight or branched hydrocarbon radical having 1-18 carbon atoms and one or more double bonds.

The term "alkynyl", means a straight or branched hydrocarbon radical having 1-18 carbon atoms and one or more triple bonds.

The term "cycloalkyl" means a monocyclic, bicyclic or tricyclic, saturated hydrocarbon ring having 3-20 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, spiro [4.4]nonane, adamantyl and the like.

The alkyl, acetyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^5, O and S. The alkyl or cycloalkyl can have up to 10 intervening heteroatoms. Specifically, the number of intervening heteroatoms can be 1, 2, 3, or 4. Alkyl groups with intervening heteroatoms include, for example $-OCH_2CH_2-OH$, $-OCH_2CH_2-OCH_3$, $-OCH_2CH_2-OCH_2CH_3$, $-OCH_2CH_2-OCH_2CH_2OH$, $-OCH_2CH_2-OCH_2CH_2OCH_3$, $-OCH_2CH_2-OCH_2CH_2OCH_2CH_3$, $-CH_2CH_2-NH_2$, $-SCH_2CH_2-OCH_3$, and the like. Cycloalkyl groups that include intervening heteroatoms include, for example, piperidinyl, piperazinyl, dioxanyl, morpholinyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, thizaolidinyl, and the like.

"Aryl", used alone or as part of a larger moiety as in "arylalkyl", means a 6-10 membered carbocyclic aromatic monocyclic or polycyclic ring system. Examples include phenyl and naphthyl. The term "aryl" also includes phenyl rings fused to non-aromatic carbocyclic ring or to a heterocyclyl group. The term "aryl" may be used

interchangeably with the terms "aromatic group", "aryl ring" "aromatic ring", "aryl group" and "aromatic group".

"Hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O. A hetero ring may have 1, 2, 3, or 4 carbon atom members replaced by a heteroatom.

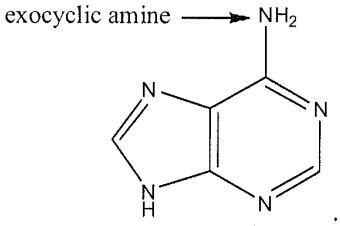
"Heterocyclyl" refers to a saturated or unsaturated, non-aromatic, monocyclic or polycyclic ring system of 3 to 20 atoms, 3 to 12 atoms, or 3 to 8 atoms, containing one to four ring heteroatoms chosen from O, N and S. Exemplary heterocyclyls include pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-2-one, piperidine, piperidin-2-one, 2-pyridone, 4-pyridone, piperazine, 1-(2,2,2-trifluoroethyl)piperazine, piperazin-2-one, 5,6-dihydropyrimidin-4-one, pyrimidin-4-one, tetrahydrofuran, tetrahydropyran, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, oxazolidin-2-one, imidazolidin-2-one, imidazolidine-2,4-dione, tetrahydropyrimidin-2(1H)-one, morpholine, N-methylmorpholine, morpholin-3-one, 1,3-oxazinan-2-one, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-1,2,5-thiaoxazole 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide and isothiazolidine 1,1-dioxide.

"Heterocyclyl" also includes heteroaryl groups. The term "heteroaryl" means a 5-10 membered monovalent heteroaromatic monocyclic and polycylic ring radical containing 1 to 4 heteroatoms independently selected from N, O, and S. The term "heteroaryl" also includes monocyclic heteroaryl ring fused to non-aromatic carbocyclic ring or to a heterocyclyl group. Heteroaryl groups include furyl, thienyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridinyl-N-oxide, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzo[b]furyl, benzo[b]thienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzodioxolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzoxazolyl,

benzothiazolyl, cinnolinyl, phthalzinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,5-thiadiazolyl-1-oxide, 1,2,5-thiadiazolyl-1,1-dioxide, 1,3,4-thiadiazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, tetrazolyl, and pteridinyl. The terms "heteroaryl", "heteroaryl ring", and "heteroaryl group" are used interchangeably herein.

Amine, hydroxy and thiol protecting groups are known to those skilled in the art. For examples of amine protecting groups see Greene, *et al.*, *Protective Groups in Organic Synthesis* (1991), John Wiley & Sons, Inc., pages 309-405, the teachings of which are incorporated herein by reference in their entirety. Preferably, amines are protected as amides or carbamates. For examples of hydroxy protecting groups see *Id.*, pages 10-142, the teachings of which are incorporated herein by reference in their entirety. A preferred hydroxy protecting group is t-butyldimethylsilyl group. For examples of thiol protecting groups see *Id.*, pages 277-308, the teachings of which are incorporated herein by reference in their entirety.

As used herein, an "exocyclic amine" refers to the amine attached to the base of the nucleoside. For example, the exocyclic amine of adenine is shown below:



. The exocylic amine can be either protected (for example, with benzoyl) or protected as formamidine (for example, -N=CH-$N(CH_3)_2$).

The term "oligonucleotide," as used herein, includes naturally occurring oligonucleotides, for example and ribonucleic acids (hereinafter "RNA") and nucleic acids containing modified sugar moieties, modified phosphate moieties, or modified nucleobases. Modification to the sugar moiety includes replacing the ribose ring with a hexose, cyclopentyl or cyclohexyl ring. Alternatively, the D-ribose ring of a naturally occurring nucleic acid can be replaced with an L-ribose ring or the β-anomer of a

naturally occurring nucleic acid can be replaced with the α-anomer. The oligonucleotide may also comprise one or more abasic moieties. Modified phosphate moieties include phosphorothioates, phosphorodithioates, methyl phosphonates, methyl phosphates, and phosphoramidates. Such nucleic acid analogs are known to those of skill in the art. Oligonuceotides comprising mixtures of two or more of the foregoing may be prepared, for example, oligonuceotides comprising mixtures of deoxyribo- and ribonucleosides, particularly mixtures of deoxyribonucleosides and 2'-O-substituted ribonucelosides, such as 2'-O-methyl or 2'-O-methoxyethyl ribonucleosides. Examples of oligonucleotides comprising mixtures of nucleosides include ribozymes.

A chimeric oligonucleotide is an oligonucleotide that has both phosphodiester and phosphorothioate linkages and/ or ribose or arabinose sugars or modified nucleoside/s within sequence such as 2'- fluoro, 2'- Omethyl,_2'-O-,4'-C-methylene ribonucleosides, reverse abasic, reverse thymidine either within sequence or terminally.

A synthetic oligonucleotide preferably has from 2 to about 150 nucleobases. More preferably, a synthetic oligonucleotide has 2 to about 75 nucleobases. Many synthetic oligonucleotides of current therapeutic interest comprise from 8 to 40 nucleobases.

Nucleoside Bases

The compound of the invention contain a nucleoside base, represented by B^n. B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group.

Nucleoside bases include naturally occurring bases, such as adenine, guanine, cytosine, thymine and uracil and modified bases such as

a) adenine or guanine substituted with one to 3 groups selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, $\text{-}(CH_2)_mC(=O)(C_1\text{-}C_6)$alkyl, $\text{-}(CH_2)_mC(=O)O(C_1\text{-}C_6)$alkyl, $\text{-}(CH_2)_mOC(=O)(C_1\text{-}C_6)$alkyl, $\text{-}(CH_2)_mNR^{10}C(=O)(C_1\text{-}C_6)$alkyl, $\text{-}(CH_2)_mC(=O)(C_2\text{-}C_6)$alkenyl, $\text{-}(CH_2)_mC(=O)O(C_2\text{-}C_6)$alkenyl,

$-(CH_2)_mOC(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mNR^{10}C(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mC(=O)(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mOC(=O)(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mC(=O)O(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mNR^{10}C(=O)(C_2\text{-}C_6)$alkynyl, $-Si((C_1\text{-}C_6)alkyl)_3$, $-O\text{-}Si((C_1\text{-}C_6)alkyl)_3$, aryl$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_6)$alkyl, amino, $(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, triazolyl, and aminoallyl, wherein the alkyl, alkenyl or alkynyl is optionally substituted with $-C(=O)NHR^{14}$; $-(CH_2)_m$-amino$(C_1\text{-}C_6)$alkyl, $-(CH_2)_m$-amino-halo$(C_1\text{-}C_6)$alkyl, $-(CH_2)_m$-phthalimide,

b) uracil or cytosine substituted with one to 3 groups selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, $-(CH_2)_mC(=O)(C_1\text{-}C_6)$alkyl, $-(CH_2)_mC(=O)O(C_1\text{-}C_6)$alkyl, $-(CH_2)_mOC(=O)(C_1\text{-}C_6)$alkyl, $-(CH_2)_mNR^{10}C(=O)(C_1\text{-}C_6)$alkyl, $-(CH_2)_mC(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mC(=O)O(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mOC(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mNR^{10}C(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mC(=O)(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mOC(=O)(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mC(=O)O(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mNR^{10}C(=O)(C_2\text{-}C_6)$alkynyl, $-Si((C_1\text{-}C_6)alkyl)_3$, $-O\text{-}Si((C_1\text{-}C_6)alkyl)_3$, aryl$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_6)$alkyl, oxo, amino, $(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, triazolyl, and aminoallyl, wherein the alkyl, alkenyl or alkynyl is optionally substituted with $-C(=O)NHR^{14}$; $-(CH_2)_m$-amino$(C_1\text{-}C_6)$alkyl, $-(CH_2)_m$-amino-halo$(C_1\text{-}C_6)$alkyl, or $-(CH_2)_m$-phthalimide,

c) thymine, pyrimidine or pyridone each optionally substituted with halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, $-(CH_2)_mC(=O)(C_1\text{-}C_6)$alkyl, $-(CH_2)_mC(=O)O(C_1\text{-}C_6)$alkyl, $-(CH_2)_mOC(=O)(C_1\text{-}C_6)$alkyl, $-(CH_2)_mNR^{10}C(=O)(C_1\text{-}C_6)$alkyl, $-(CH_2)_mC(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mC(=O)O(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mOC(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mNR^{10}C(=O)(C_2\text{-}C_6)$alkenyl, $-(CH_2)_mC(=O)(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mOC(=O)(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mC(=O)O(C_2\text{-}C_6)$alkynyl, $-(CH_2)_mNR^{10}C(=O)(C_2\text{-}C_6)$alkynyl, $-Si((C_1\text{-}$

C_6)alkyl)$_3$, -O-Si((C_1-C_6)alkyl)$_3$, aryl(C_1-C_4)alkyl, halo(C_1-C_6)alkyl, oxo, amino, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, triazolyl, and aminoallyl, wherein the alkyl, alkenyl or alkynyl is optionally substituted with –C(=O)NHR^{14}; -(CH_2)$_m$-amino(C_1-C_6)alkyl, -(CH_2)$_m$-amino-halo(C_1-C_6)alkyl, or -(CH_2)$_m$-phthalimide, provided that the nucleobase formed is not uracil or cytosine;

d) purine, optionally substituted with halogen, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, -(CH_2)$_m$C(=O)(C_1-C_6)alkyl, -(CH_2)$_m$C(=O)O(C_1-C_6)alkyl, -(CH_2)$_m$OC(=O)(C_1-C_6)alkyl, -(CH_2)$_m$NR^{10}C(=O)(C_1-C_6)alkyl, -(CH_2)$_m$C(=O)(C_2-C_6)alkenyl, -(CH_2)$_m$C(=O)O(C_2-C_6)alkenyl, -(CH_2)$_m$OC(=O)(C_2-C_6)alkenyl, -(CH_2)$_m$NR^{10}C(=O)(C_2-C_6)alkenyl, -(CH_2)$_m$C(=O)(C_2-C_6)alkynyl, -(CH_2)$_m$OC(=O)(C_2-C_6)alkynyl, -(CH_2)$_m$C(=O)O(C_2-C_6)alkynyl, -(CH_2)$_m$NR^{10}C(=O)(C_2-C_6)alkynyl, -Si((C_1-C_6)alkyl)$_3$, -O-Si((C_1-C_6)alkyl)$_3$, aryl(C_1-C_4)alkyl, halo(C_1-C_6)alkyl, oxo, amino, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, triazolyl, and aminoallyl, wherein the alkyl, alkenyl or alkynyl is optionally substituted with –C(=O)NHR^{14}; -(CH_2)$_m$-amino(C_1-C_6)alkyl, -(CH_2)$_m$-amino-halo(C_1-C_6)alkyl, or -(CH_2)$_m$-phthalimide; provided that the nucleobase formed is not adenine or guanidine; or

e) N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C(CH_2)$_{1-8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N3 methyl thymine, 5-acroxymethylcytosine, 5-azacytosine, isocytosine, N4(C_1-C_6)alkylcytosine,

N3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acroxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine; wherein each of which is optionally substituted with halogen, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, -$(CH_2)_m$C(=O)(C_1-C_6)alkyl, -$(CH_2)_m$C(=O)O(C_1-C_6)alkyl, -$(CH_2)_m$OC(=O)(C_1-C_6)alkyl, -$(CH_2)_m$NR[10]C(=O)(C_1-C_6)alkyl, -$(CH_2)_m$C(=O)(C_2-C_6)alkenyl, -$(CH_2)_m$C(=O)O(C_2-C_6)alkenyl, -$(CH_2)_m$OC(=O)(C_2-C_6)alkenyl, -$(CH_2)_m$NR[10]C(=O)(C_2-C_6)alkenyl, -$(CH_2)_m$C(=O)(C_2-C_6)alkynyl, -$(CH_2)_m$OC(=O)(C_2-C_6)alkynyl, -$(CH_2)_m$C(=O)O(C_2-C_6)alkynyl, -$(CH_2)_m$NR[10]C(=O)(C_2-C_6)alkynyl, -Si((C_1-C_6)alkyl)$_3$, -O-Si((C_1-C_6)alkyl)$_3$, aryl(C_1-C_4)alkyl, halo(C_1-C_6)alkyl, oxo, amino, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, triazolyl, and aminoallyl, wherein the alkyl, alkenyl or alkynyl is optionally substituted with –C(=O)NHR[14]; -$(CH_2)_m$-amino(C_1-C_6)alkyl, -$(CH_2)_m$-amino-halo(C_1-C_6)alkyl, or -$(CH_2)_m$-phthalimide;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine in groups a), b), c), d) or e) is optionally substituted with (isobutyryl, phenoxyacetyl, tert – butylphenoxy acetyl, isopropyl phenoxyacetyl, acetyl, -C(O)OCH_3, di(C_1-C_6)alkylformamidine, *p*-chlorobenzoyl, *o*-chlorobenzoyl, *o*-nitrobenzoyl, p- nitrobenzoyl,

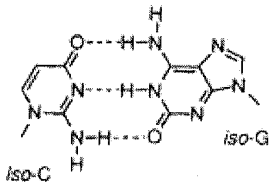
fluorenylmethyloxycarbonyl, nitrophenylethyl, phthaloyl, Benzyl (Bn) group, p-Methoxybenzyl (PMB), 3,4-Dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP) group and $=CR^{15}N((C_1\text{-}C_6)alkyl)_2$,

each R^{14} or R^{15} is a independently substituted or unsubstituted $(C_1\text{-}C_6)$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_6)$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_6)$alkynyl group; and

each m is independently 0-12.

A protected nucleoside base is a nucleoside base in which reactive functional groups of the base are protected. Similarly, a protected heterocycle is a heterocycle in which reactive substituents of the heterocycle are protected. Typically, nucleoside bases or heterocycles have amine groups which can be protected with an amine protecting group, such as an amide or a carbamate. For example, the amine groups of adenine and cytosine are typically protected with benzoyl and alkyl ester, respectively, protecting groups, and the amine groups of guanine is typically protected with an isobutyryl group, an acetyl group or t-butylphenoxyacetyl group. However, other protection schemes may be used. For example, for fast deprotection, the amine groups of adenine and guanine are protected with phenoxyacetyl groups and the amine group of cytosine is protected with an isobutyryl group or an acetyl group. Conditions for removal of the nucleobase or heterocycle protecting group will depend on the protecting group used. When an amide protecting group is used, it can be removed by treating the oligonucleotide with a base solution, such as a concentrated ammonium hydroxide solution, N-methylamine solution or a solution of t-butylamine in ammonium hydroxide.

Nucleoside bases also include isocytidine (isoC) and isoguanosine (IsoG). IsoC and IsoG can used to exploit Watson Crick base pairing mechanism, which allow three hydrogen bonds between isoC and isoG, as shown below:



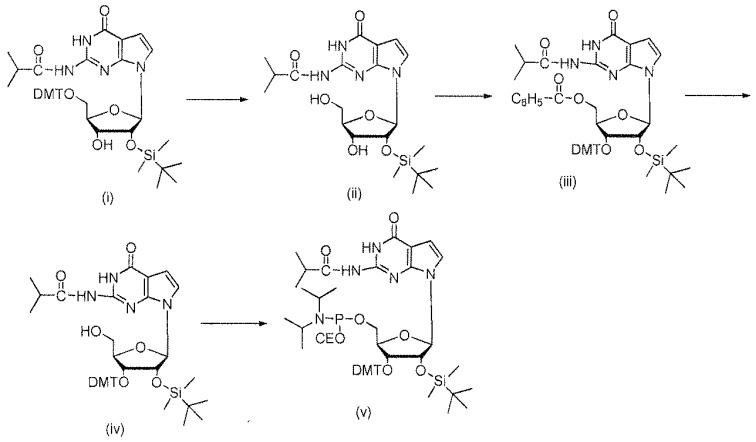
These bases can pair in both parallel and antiparallel duplex forms and as in DNA sequences they are recognized by DNA polymerases as well for chain extension, PCR etc. These molecules therefore have significant importance in as part of RNA sequences for diagnostics and therapeutic applications (See S.C.Jurczyk, *et al., Helvetica Chimica Acta., 81*, 793-811, 1998; and C. Roberts, *et al., Tetrahedron Lett., 36*, 21, 3601-3604, 1995, the entire teachings of which are incorporated herein by reference).

Nucleoside bases also include 7-deaza- ribonucleosides. These 7-deaza-ribonucleosides (including 7- deaza guanosine and adenosine and inosine) can be further modified at the 7 position by introducing various substituents. For example, modification can include attachment of halogen (such as fluoro, chloro, bromo, or iodo), alkynyl, trimethylsilylalkynyl, propynylaminotrifluoromethyl, or propynylamino phthalamido. (See Xiaohua Peng and Frank Seela, International Round Table on Nucleosides, Nucleotides and Nucleic Acids, IRT-XVII, Sep 3-7, 2006, page 82, Bern , Switzerland, the entire teachings of which are incorporated herein by reference).

Specially, 7- deaza-2'- deoxy nucleosides can be incorporated within the RNA sequence in place of a dGuanosine base to result in a decrease clamping of oligodeoxy nucleotide and hence better resolution in sequence analysis. This modification does not decrease the tm values of sequences during hybridization to complementary sequences. This modification has many significant biological properties for diagnostic and therapeutic field of DNA and RNA (See N. Ramazaeva, *et al.*, XIII International Round Table; Nucleosides, Nucleotides and Their Biological Application, Montpellier, France Sep. 6-10, 1998, poster 304; Ramazaeva, N., *et al.*, Helv. Chim. Acta 1997, 80, 1809 and references cited therein; Sheela, F. *et al., Helvetica Chimica Acta, 73*: 1879, 1990, the entire teachings of which are incorporated herein). In RNA, the effect of G-C base pairing is much more pronounced because RNA molecules have a strong tendency to

form secondary structures. Substitution of guanosine with 7- deaza-riboguanosine has great significance in RNA therapeutics and diagnostics. 7-substituted -7- deaza-ribonucleosides have significance due to possibility of various ligand and chromophore attachments at 7- position without disturbing G-C base pairing properties.

The synthesis of 7-deaza- ribonucleosides can be achieved through the proposed synthesis of 3'- DMT-2'- TBDMS-N- protected-β-D- 7-deaza-guanosine-5'-phosphoramidite (Scheme 1):



Scheme 1: Synthesis of 2'-TBDMS-3'-DMT- 7- deaza-r-G(n-ibu):

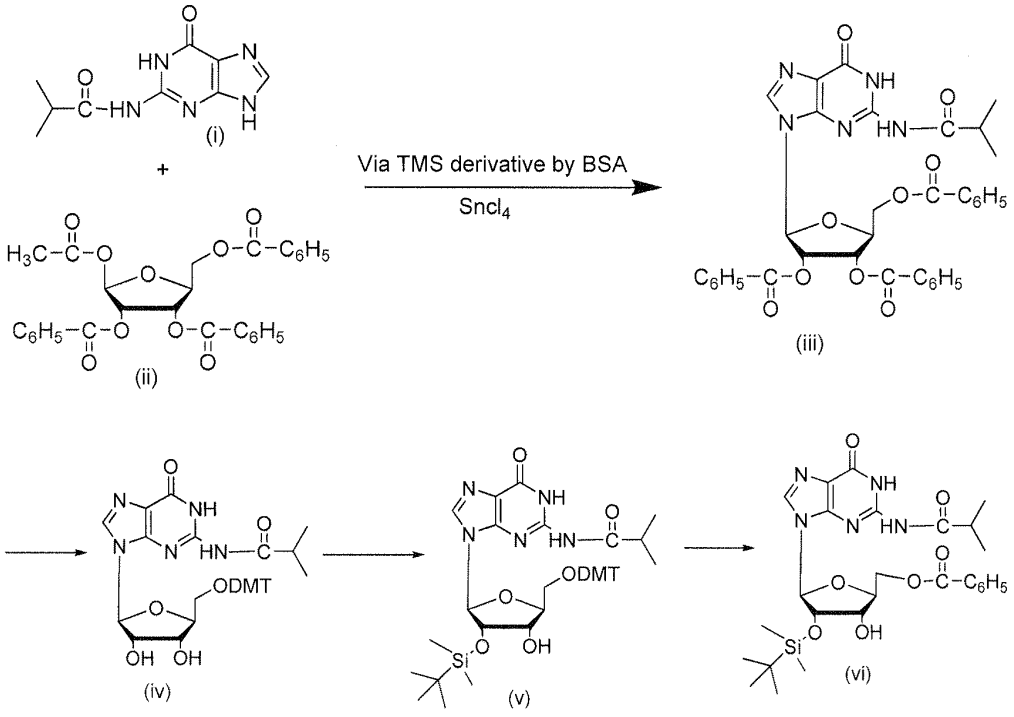
Synthesis of Compound (ii); selective DMT removal from compound (i) using trichloroacetic acid and dichloromethane as solvent to obtain (ii). Compound (iii); step a; selective 5'- benzoyalation with benzoyl chloride chloride (1.1 eq) / pyridine solvent (10 fold v/v) at 0-5 C temp. leads to 5'- benzoyl group; followed by work up and column purification; (iii; step b); subsequent DMT Chloride reaction in pyridine at room temperature for 24 hours, followed by work up; subsequent column chromatography leads to compound (iii). Compound (iv); selective removal of 5'-benzoyl is achieved by selective reaction with aq. 2 N NaOH reaction by reaction of iv with aq. 2 N NaOH in pyridine as solvent , followed by neurtalization with pyridinium Dowex cation exchange resin, followed by filtration to remove Dowex resin to get solution of crude iv, subsequent chromatography to get purified (iv). Compound (v).

Shanghai Hongene Exhibit 1002

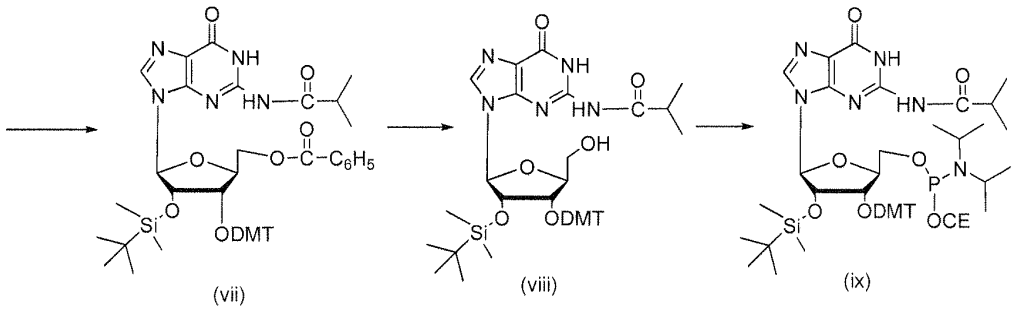
phosphitylation of (iv). with n, n- diisopropyl -2- cyanoethyl-chloro reagent (1.1 eq) in diisopropyl ethyl amine (2 eq,) in THF leads to crude vi, followed by chomatoghaphy to get pure phosphoramidite (v).

The synthesis of 3'- DMT- L –ribonucleoside oligonucleotides can be achieved through of L- ribonucleosides appropriately exocyclic amine protected. A typical example of 3'- DMT-L-r-G(n-ibu)-5'- phosphoramidite is illustrated below:

The synthesis of 7-deaza- ribonucleosides can be achieved through of 3'- DMT-2'- TBDMS-N- protected-β-L- 7-deaza-guanosine-5'- phosphoramidites (Scheme 2):



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Scheme 2:

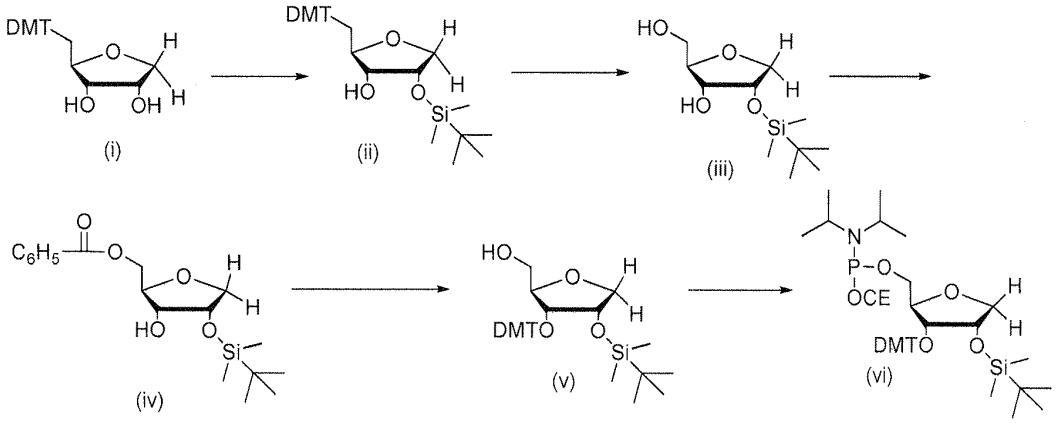
O-Acetyl –tri-O-benzoyl- L- ribose (ii) was synthesized similar to synthesis of 1- acetyl –tri-O-benzoyl-D- ribose. N- isobutyryl guanine is first converted into silyl derivative by treatment with bissilyl trimethyl acetamidite (BSA; 5 eq) The L- sugar (iii) was then fused with silylalated n- isobutyryl –guanine in presence of $SnCl_4$ (Sn(IV) chloride) to yield fully protected crude tri-O-benzoyl-N-isobutyryl- L- guanosine. This compound was purified by column chromatography on silica gel (70-230 mesh size; Merck silica gel). The pure fully protected intermediate compound was then hydrolyzed selectively under controlled hydrolysis conditions with 2 N NaOH in pyridine/ methanol (80:20) for 20 minutes at 5-10 C, followed by neutralization of reaction mixture with Dowex- pyridinium cation exchange resin to yield 5',3',2'-trihydoxy –L-guanosine (n-ibu). The crude compound was washed with ethyl acetate, followed by diethyl ether to removed solvents and benzoic acid by-products to get pure 5',3',2'-tri- hydoxy –L-guanosine (n-ibu). The dried compound subsequently treated with DMT-Chloride (DMT Chloride; 1.2 equivalent) in dry pyridine (10 fold with respect to 5',3',2'- tri hydroxy –L-guanosine (n-ibu) at 5 C for 3-4 hours to yield crude 5'- DMT-2',3'- dihydroxy-L-guanosine (n-ibu)(iv). This was purified on silica gel (70-230 mesh, Merck grade) column. The pure fractions were pooled to get pure 5'- DMT-2',3'- dihydroxy-L-guanosine (n-ibu)(iv; yield 70-75% yield from the trihydroxy compound). 2'- silylation was done to get a mixture of 2' and 3'- TBDMS protected nucleoside, from which pure 5'- DMT-2'- silyl-L-G(n-ibu) nucleoside (v) was separated by column chromatography. From this compound DMT group was selectively removed using trichloroacetic acid in dichloromethane (3% solution, v/v) at room

temperature for 10 minutes. The reaction mixture was quenched with 10% aq sodium bicarbonate at zero degrees to neutralize the reaction mixture to yield crude 5, 3'-dihydroxy -2'- TBDMS-L-G-(N-ibu). This compound was purified by column chromatography on silica gel (70-230 mesh; Merck grade) to provide pure 5', 3'-dihydroxy -2'- TBDMS-L-G-(N-ibu). Selective 5'- benzoylation of this compound with benzoyl chloride (1.1 eq; -10 to 0 C) for 1.5 hours to yield compound (vi). This compound was similarly purified to yield pure 5'- O-benzoyl - 3'- hydroxy -2'-TBDMS-L-G-(N-ibu) (compound vi). Subsequent reaction of well dried compound (vi) with DMT-chloride (2.5 eq; pyridine w/v; 1:10) was treated at room temperature for 24 hours to yield compound (vii). Purified (vii) was purified on silica gel column chromatography. The pure vii was then selectively hydrolyzed with 2 N NaOH at 5 C for 30 minutes , followed by neutralization of reaction mixture with Dowex- pyridinium cation exchange resin to yield to yield , 5'- OH, 3'- DMT-2'- TBDMS-L-rG- n-ibu (compound viii). The crude compound was purified by silica gel column (70-230 mesh , Merck silica gel) chromatography. subsequent chromatography to get purified viii was done by phosphitylation of viii. with n, n- diisopropyl -2- cyanoethyl chloro reagent (1 .1 eq) in diisopropyl ethyl amine (2 eq,) in THF leads to crude ix, followed by chromatography to get pure 5'- phosphoramidite (ix).

Nucleoside bases also include abasic nucleosides. Abasic sites in DNA are generated chemically or enzymatically by loss of glycolytic bond. The resulting a purinic/pyrimidinic sites lack coding information and lead to misincorporation of bases by polymerases and may play important role in mutagenesis. They eventually get converted to tetrahydrofuran derivative with a methylene group modifying the 1 position of 2'-deoxyribose. The CE phosphoramidites of both 2 deoxy and 2 – hydroxyl -D- ribose with an amidite have been synthesized. A reverse RNA modification will allow efficient synthesis of such RNA , RNA/DNA chimeras, modified RNA, (See Takeshitsa, M., *et al.*, *J. Biol. Chem.*, 1987, 262, 10171-10179;

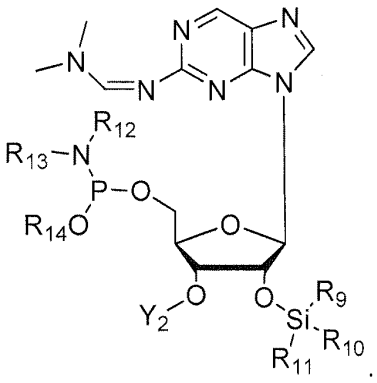
and Kalnik, M.W., *et. al.*, *Biochemistry*, 1988, 27, 924-931, the entire teachings of which are incorporated herein by reference).

Abasic nucleosides can be synthesized by a method similarly applicable for 3'-DMT-2'-TBDMS-N- protected nucleoside phosphoramidites and is shown in the scheme below:



Scheme: 1,1 Dihydro-D Ribose -3-DMT-2'-silyl-phosphoramidites. Compound (i) from ChemGenes Corp.; (ii) selective TBDMS chloride introduction is achieved under standard condition (isomer formed at this stage can be conveniently separated); (iii) and (iv) selective 5- DMT group removal, followed by selective 5-positiobn benzoylation, (v) DMT chloride reaction leads to 3- position DMT introduction; (vi) 5- position benzoyl removal , followed by phosphorylation and purification by chromatography.

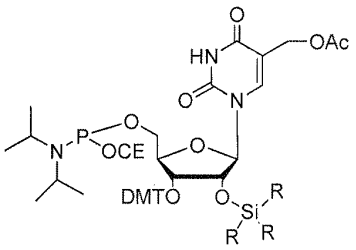
Nucleoside bases also include 2-Aminopurine nucleosides. 2-Aminopurine is a modified nucleobase analog incorporated in oligonucleotides for mutagenic studies, due to its fluorescence properties. Its structural homology to adenine and guanine make it an important tool in enzymological studies by substitution in place of adenosine or guanosine in a sequence (See Schmidt, S. *et al., Nucleosides & Nucleotides, 14(6)*, 1445-1452 ,1995; and McLaughlin, L.W. *et al., Nucleic Acids Res.,* 1988, 16, 5631, the entire teachings of which are incorporated herein by reference). A representative structure of a 2-aminopurine nucleoside is 2 aminopurine 3'-DMT-2'- silyl -5'-phosphoramidite, which is represented by the following structural formula:

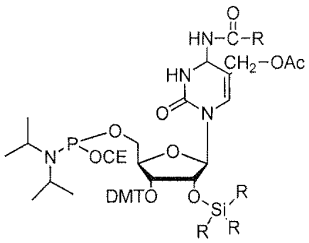


Nucleoside Modifications:

5- Hydroxymethyluridine & Cytidine are nucleoside modifications included in this invention. The 5' hydroxymethyl modification is protected with –OAc (-O-C(=O)CH_3) to yield 5-acetoxymethylcytosine and 5-acetoxymethyluracil.

Solid phase synthesis and restriction endonuclease cleavage of oligo deoxy nucleosides containing 5- hydroxyl methyl cytosine. has been described, see for example, "Cytosine methylation and study of its effect"; Severine Tardy – Planechaud, June Fujimoto, Susan S. Lin and Lawrence C. Sowers; *Nucleic Acids Research*, Vol. 25, No. 3, 553-558(1997), the entire teachings of which are incorporated herein by reference.

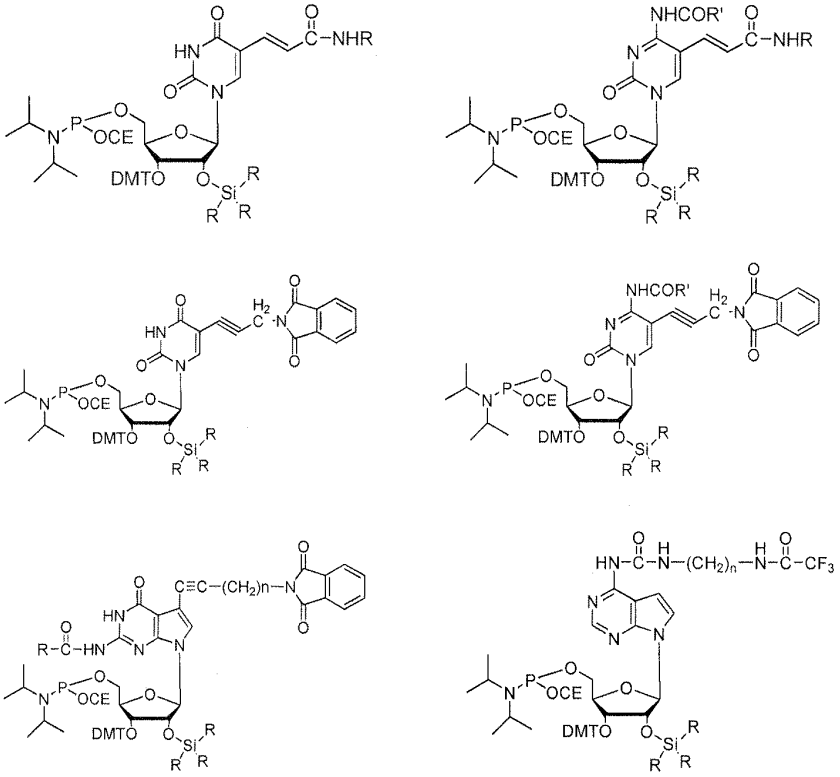




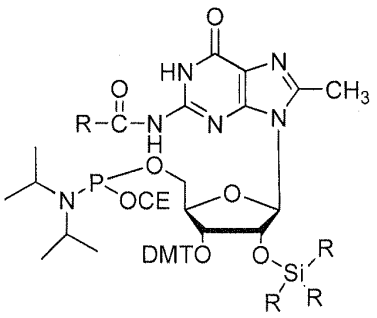
Other modified nucleobases include 1, N^6–ethenoadenosine, 3,N^4 – ethenocytidine, C-5 (rU and rC)Pyrene modification, C-5 (rU and rC) Perylene modification, C-5 (rU and rC) acrylate- C-6 amino linker (TFA protected , C-5 (rU & rC) acrylate- C-2 amino

linker (TFA protected), C-5 (rU and rC) acrylate- C-6 amino linker (FMOC protected), 5'- PT modifier supports, C-5 Pyrene-r-uridine, C-5 perylene-r-uridine, (5,6)-pyrrole-r-cytidine.

A representative compound of the invention including nucleobase modifications are shown below:

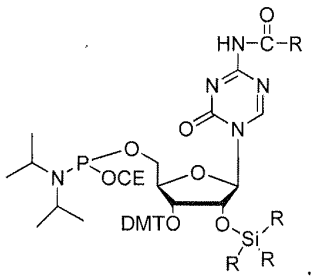


8- Methylguanosine: Several publications have reported 8- methyl guanosine as very useful modification for oligonucleotide aptamer design and Z DNA stabilizer. See for example, 8-Methylguanosine: A Powerful DNA Stabilizer; Yan Xu, Reiko Ikeda and Hiroshi Sugiyama, J.AM.Chem. Soc. 2003, 125, 13519-13524 -13519, the entire teachings of which are incorporated herein by reference. A representative compound of the invention including 8- methylguanosine is shown below:



5- Aza cytidine: 5- Azacytidine is proposed to be utilized as reverse RNA synthon . 5-aza-cytidine is an well known anticancer agent.

A representative compound of the invention including 5- Azacytidine is shown below:



2,6- Diaminopurine riboside; See, for example, Pasternak, A., Nucleic Acids Research 2007 35(12):4055-4063, the entire teachings of which are incorporated herein by reference. The article report use of 2'-O, 4'-C-methylene ribonucleosides bases in combination of 2,6-diaminopurine riboside, and the influence of 2,-O-methyl-2,6-diaminopurine and LNA-2,6-diaminopurine ribosides on the thermodynamic properties of 2'-O-methyl RNA-RNA heterodulplexes,

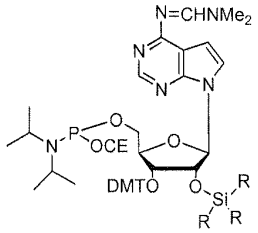
Nucleobase protecting groups.

Protecting groups for nucleobases are know in the art. See, for example:

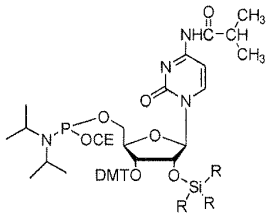
1. RNA synthesis using phosphoramidites with Labile Base Protection: Users Bulletin, Applied Biosystems, Number 69, Instructions for 380B, 392 and 394 synthesizers, the entire teachings of which are incorporated herein by reference, for description of use of dimethylformamide (DMF) and n-isobutyryl protecting groups.

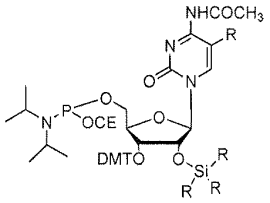
2. This synthesis of N^6 phenoxy acetyl deoxy adenosine derivatives as new reactive intermediates for preparation of linker containing oligonucleotide probes and modified LCAA (Long chain alkyl amino) – CPG (Controlled pore glass) supports was described in Edyta Krzymanska-Olejnik and Ryszard W. Adamiak,Nucleosides & Nucleotides, 10(1-3), 595-597 (1991), the entire teachings of which are incorporated herein by reference.

For the synthesis of propargyl modified oligonucleotides, 2'- propargyl -3'- DMT-5'- phosphoramidites synthons can be incorporated within sequence through the reverse synthesis process. Phosphoramidites are further postulated bearing 2'-hexyne terminal group to obtain precursor- oligonucleotides bearing free hexyl linker capable of reacting with reagents introducing various reporter probes, See U.S. Patent Number 5,744,595 Srivastava, *et al*, the entire teachings of which are incorporated herein by reference.



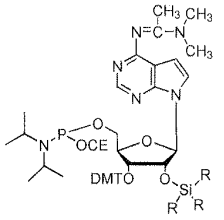
(r-A-N- DMF)

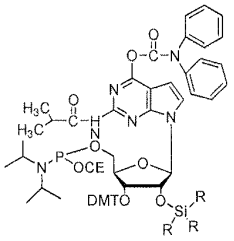


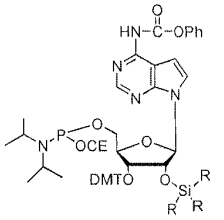


(r-C-N-isobutyryl)

r-C-N-acetyl and 5- modified –rC –n-ac)

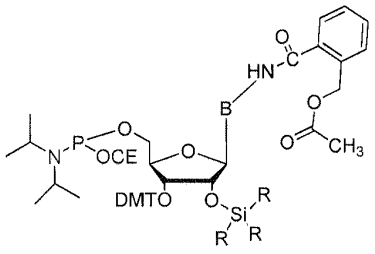






(rA-DMF-methyl amidine) (N^6 diphenylcarbamoyl-rG-n-ibu) (N^6 phenoxy carbonyl r-A)

3. The use of partially methylphosphonate-modified oligodeoxy-nucleotides were synthesized on solid-phase by employing the easily removable 2-(acetoxy-methyl)benzoyl (AMB) group as base-protecting group for the synthesis of partially methylphosphonate-modified oligodeoxy-nucleotides, synthesized on solid-phase is known in the art, see for example, W.H.A. Kuijpers, *et al., Nucleic Acids Research,* 1993, Vol. 21, No.15 3493-3500, the entire teachings of which are incorporated herein by reference. The AMB protecting group was accomplished in methanolic potassium carbonate. However, the lability of the methylphosphonate linkage towards potassium carbonate/methanol excluded the use of this deprotection reagent. Subsequently saturated ammonia solution in methanol was found to be an alternative reagent for AMB removal. It was demonstrated that the combination of the AMB protective group and ammonia/methanol as deprotection reagent significantly improves the synthesis of methylphosphonate-modified DNA fragments. A mild overnight treatment at room temperature is sufficient for complete removal of the AMB group, whereas deprotection of conventionally protected oligonucleotides requires much longer exposure to basic conditions at elevated temperatures.

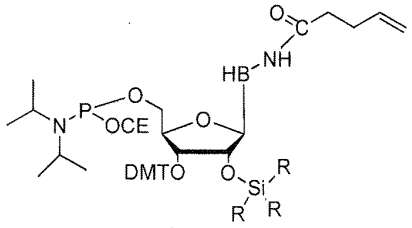


(AMB –protected nucleobase proposed for our reverse RNA synthons)

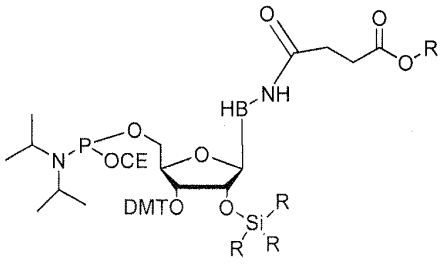
4. The following nucleobase protecting groups have been found to be very useful and are anticipated to be adopted in nucleobase protection of monomers of our invention *N-pent-4-enoyl (PNT) Group As a Universal Nucleobase Protector*, see, for example, "Applications in the Rapid and Facile Synthesis of Oligonucleotides, Analogs, and conjugates", Radhakrishan P. *et al., Tetrahedron,* Vol. 53, No. 8, pp. 2731-2750,

1997, the entire teachings of which are incorporated herein by reference. The synthesis of missed backbone oligonucleotides (MBOs) as antisense agents with the use of PNT nucleoside phosphoramidites in conjunction with PNT nucleoside H-phosphonates and PNT nucleoside phosphonamidites and the use of PNT group in preparation of bioreversible oligonucleotide conjugates is described therein.

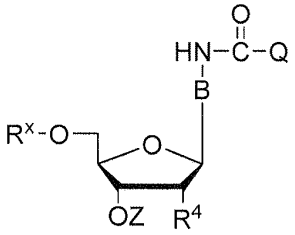
The Pent-4-enoyl Group: A Novel Amine-Protecting Group; see, for example, Robert Madsen, Carmichael Roberts and Bert Fraser-Reid, *J. Org.Chem., 60*, 7920-7926, (1995), the entire teachings of which are incorporated herein by reference. The protection of primary and secondary amines as N-pent-4-enoyl derivatives resulted in N-pent-4-enamides and were found to be highly crystalline. Deprotection was found to be rapidly and efficient under mild conditions by treatment with 3 equiv of iodine in aqueous THF solution. It shown that although an oxidizing medium is required during the deprotection , it does not effect oxidizable functionalities including p-methoxybenzyl ethers and alkyl sulfides. A representative compound of the invention including the Pent-4-enoyl group is shown below:



Succinyl group as exocyclic amine protecting group. Succinyl group on exocyclic amine can be utilized to further derivative/ attach various supports for solid phase oligonucleotide synthesis. A representative compound of the invention including the succinyl group is shown below:



Alternatively, the exocyclic amine of 3',5' protected nucleoside can be derivatized with a succinimidyl group which can be attached to a solid support, such as structure 3 below, for synthesis in the 5' → 3' direction.

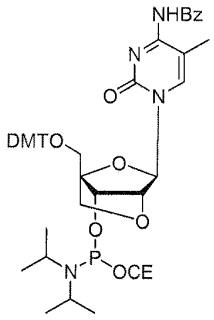


(structure 3)

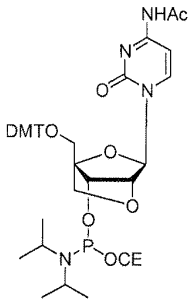
Incorporation of locked nucleic acid™*, also know as* 2'-O, 4'-C-methylene ribonucleosides and phosphoramidites (LNA) *via Reverse RNA synthesis process:* 2'-O, 4'-C-methylene ribonucleosides and phosphoramidites, a novel class of conformationally restricted oligonucleotide analogs (structure 1-6) have been shown to possess high binding ability to complementary DNA and RNA sequences. Various 2'-O, 4'-C-methylene ribonucleosides and phosphoramidites are being currently evaluated for evaluation of synthetic DNA, RNA and chimeras for various therapeutic and diagnostic applications[1-5]. The most common phosphoramidite synthons used for the synthesis of defined sequence oligonucleotide are LNA-C (n-bz) -5'- DMT-3'- cyanoethyl phosphoramidites (1), LNA-C (n-ac) -5'- DMT-3'- cyanoethyl phosphoramidites (2), LNA-thymidine -5'- DMT-3'- cyanoethyl phosphoramidites (3), LNA-A (n-bz) -5'- DMT-3'- cyanoethyl phosphoramidites (4), LNA-G (n-

dimethylformamidine) -5'- DMT-3'- cyanoethyl phosphoramidites (5;R; dimethylformamidine),

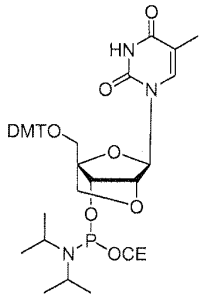
The 2'-O, 4'-C-methylene ribonucleosides and phosphoramidites oligos have been shown to help in design and efficacy of oligonucleotides for gene regulation, gene expression, antisense , si RNA, and in delivery of RNA in to cell. They have been shown to increase DNA and RNA stabilibity[1-5]. The 2'-O-4'-C-methylene ribonucleosides and phosphoramidites currently described in the art possess a 5'- DMT and 3' phosphoramidite function (6).



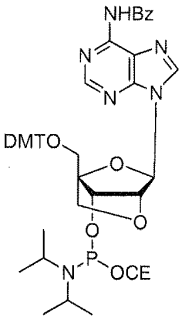
(1)



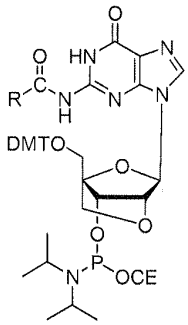
(2)



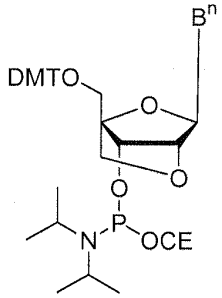
(3)



(4)



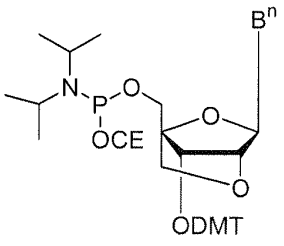
(5)



(6)

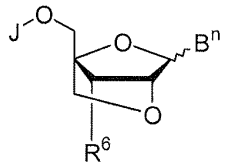
Incorporation of 2'-O-4'-C-methylene ribonucleosides proposed in our invention described in the art possess these units in oligonucleotides and the synthons to constitute a 3'- DMT and 5' phosphoramidite (structure 7), is amenable to reverse RNA synthesis according to the methods of our invention.

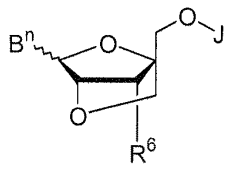
Shanghai Hongene Exhibit 1002



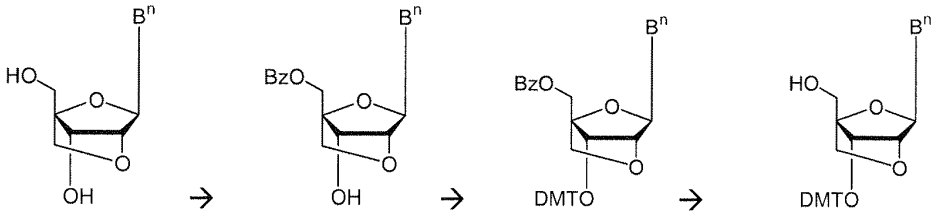
(7).

Compounds of the invention including 2'-O,4'-C-methylene ribonucleosides and phosphoramidites are shown below:





Scheme for synthesis of 2'-O-4'-C-methylene ribonucleoside- 3'- DMT nucleosides, 5'- phosphoramidites and 5'- supports



The teachings of the following references are incorporated herein by reference:

1. A.A.Koshlin, S.K. Singh, P.Nielsen, V.K.Rajwanshi, R.Kumar, M. Meldgaard, C.E. Olsen and J. Wengel, Tetrahedron, 1998m54,3607-3630.

Shanghai Hongene Exhibit 1002

2. S.K.Singh, P.Neilsen, A.A. Koshkin, and J. Wengel, Chem.Comm., 1998, (4), 455-456.

3. D.A.Braasch, D.R.Corey, Biochemistry, 2002,41,4503-4510.

4. J.S.Jespen, M.D.Sorensen, and J. Wengel, Oligonucleotide, 2004, 14,130-146.

5. B.Vester and J. Wengel, Biochemistry, 2004,43,13233-41.

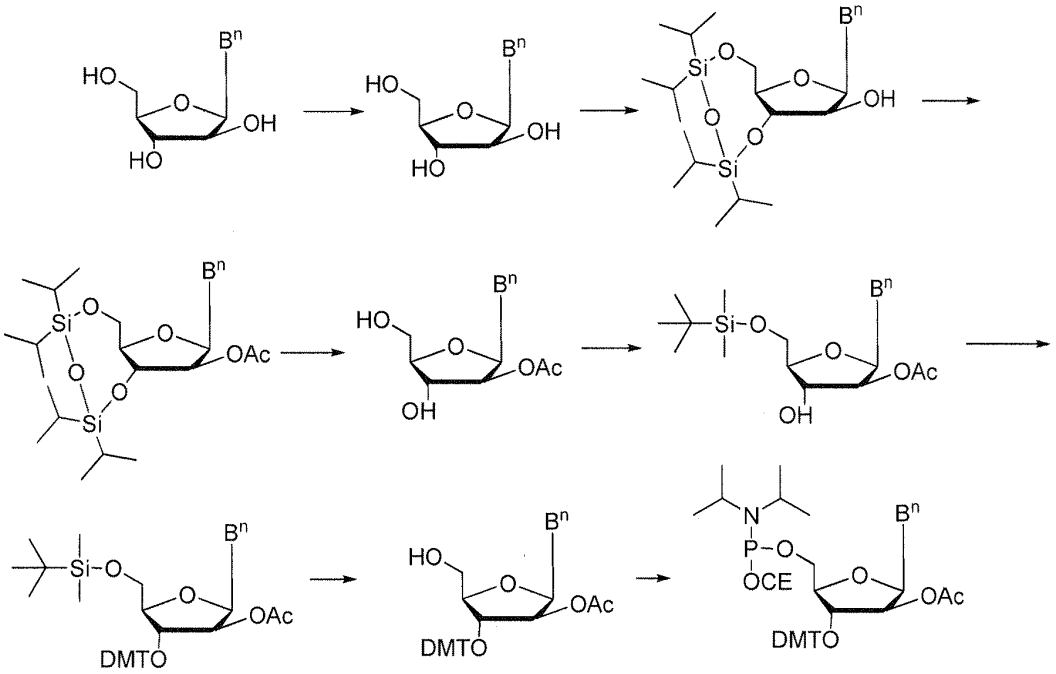
6. S.Obika, D.Nanbu, Y. Hari, J-i Andoh, K-i Morio, T. Doi, T. Imanashi, Tet. Lett., 39 (30),5401-4, 1998.

Introduction of Sugars into Oligonucleotides

Sugars

The compounds of the invention may include, for example, ribose or arabinose. Arabinose nucleosides can be prepared through a procedure similar to that described for Ribose nucleosides. An example synthesis is shown in the scheme below:

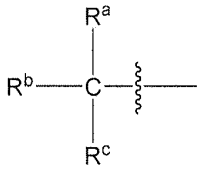
Scheme: **2' –Arabinose Reverse Amidite Synthesis:**

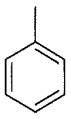


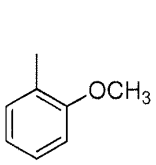
Protection of 3' Hydroxy group:

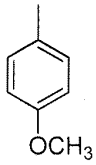
A series of triaryl methyl groups have previously been investigated as the 5'-hydroxy protecting group of deoxy nucleosides and evaluated for trityl removal during oligonucleotide synthesis. The different color cations obtained were very useful for colorimetric monitoring and differentiation between nucleosides used in oligo synthesis, see "Color coded triarylmethyl protecting groups useful for deoxypolynucleotide synthesis"; E.F. Fisher and M.H. Caruthers, Nucleic Acids Research, Vol. 11, 5, 1589-1599 (1983), the entire teachings of which are incorporated by reference. The triarylmethyl groups for use in the invention include di-p-anisylphenyl methyl, p-fluorophenyl-1- naphthylphenyl methyl, p-anisyl-1- naphthylphenyl methyl, di-o-anisyl-1- naphthyl methyl, di-o-anisylphenyl methyl, p-tolyldiphenylmethyl, di-p-anisylphenylmethyl, di-o-anisyl-1- naphthylmethyl, di-p-anisylphenyl methyl, di-o-anisyl phenyl methyl, di-p-anisylphenyl methyl, and p-tolyldiphenylmethyl.

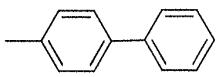
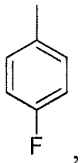
In addition, triarylmethyl 3' hydroxy protecting groups are represented by the formula:

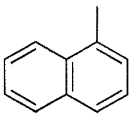
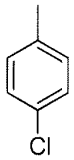


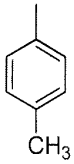
, wherein ≀ indicates attachment to the 3' oxygen atom and R^a, R^b, and R^c are independently selected from the following structural formulas:  ,

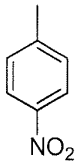


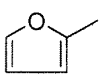
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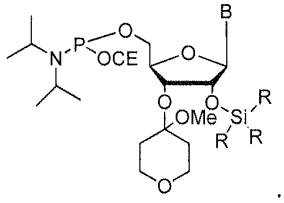
, 

, or 

.

Tetrahydropyranyl and methoxytetrahydropyranyl group as a 3' hydroxy protecting agent and removal under acidic conditions. See, for example, "Synthesis of

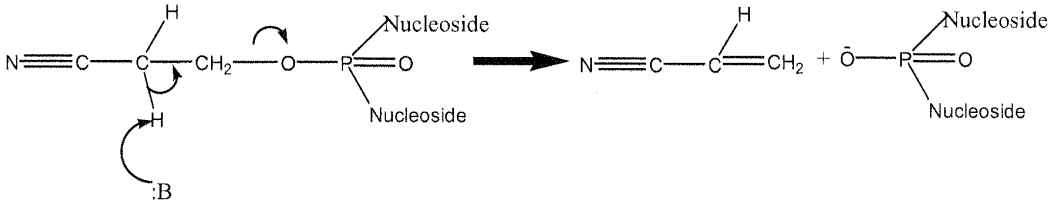
oligonucleotides with sequences identical with or analogous to the 3'- end of 16 S ribosomal RNA of E coli: preparation A-C-C-U-C-C via modified phosphotriester method"; J.H.van Boom, P.M. J. Boom, P.M.J. Burgers, G. van der Marel, C.H.M. Verdegaal and Mrs. G. Wille, the entire teachings of which are incorporated herein by reference. A representative 3' methoxytetrahydropyranyl group is shown below:



Phosphate protecting groups (represented by R^3)

As used herein, the term "phosphate protecting group" refers to a moiety that, when present in a molecule of the invention, is eliminated following the formation of oligonucleotide. For example, the phosphate moiety can be protected by a cyanoethyl protecting group. It is well known that the cyanoethyl protecting group for internucleotide phosphate formation is eliminated by β-elimination mechanism leading to acrylonitrile and phosphodiester oligonucleotides.(Scheme 3

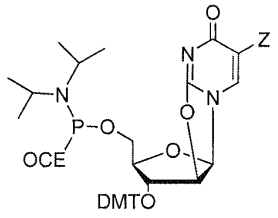
Scheme 3. Elimination of cyanoethyl phosphate group via base :B.



Phosphate protecting groups include $-CH_2CH_2CN$, $-CH_2CH_2-Si(CH3)_2C_6H_5$, $-CH_2CH_2-S(O)_2-CH_2CH_3$, $-CH_2CH_2-C_6H_4-NO_2$, $-CH_2CH_2-NH-C(O)-C_6H_5$, or $-CH_2CH_2-O-C_6H_4-C(O)CH_3$, and R^4 is $--O-Si(R^5)_3$. Other Phosphate protecting groups are known in the art and include (2-Acetoxyphenoxy)ethyl (APOE) (See Cheruvallath, Z.S., *et. al*; *Org. Process Res. Dev.*, 2006, 10 (2), pp 251-256, the entire teachings of which are incorporated herein by reference), and 2-

Benzamidoethyl group (See Guzaev AP, *J. Am. Chem. Soc.* 2001 Feb 7;123(5):783-93, the entire teachings of which are incorporated herein by reference).

A 2'-blocking group is a 2-O-anhydro nucleobase represented by the following structural formula:



3' Functional Groups

The present invention is directed to the synthesis of high purity RNAs, specifically to introduce selected groups at the 3'- end of oligonucleotides of synthetic RNAs. Such RNA molecules have applications in therapeutics, diagnostics, drug design and selective inhibition of an RNA sequence within cellular environment, blocking a function of different types of RNA present inside cell.

Oligonucleotides have been shown to be taken up by mammalian cells rather easily. Uptake has been shown to result in nuclear accumulation. Attachment of lipophilic molecules to oligonucleotides has been shown to increase their uptake properties considerably. Specifically, attachment of cholesterol and poly-L-lysine have been studied in detail.

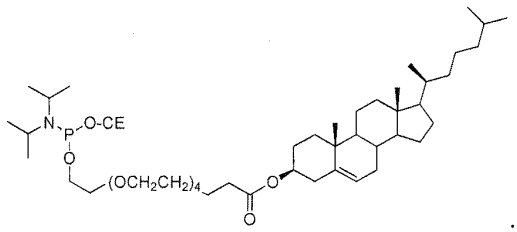
Other RNA conjugates include peptide-RNA conjugates. Peptide transfer RNA molecules are key molecules for the biosynthesis of proteins taking place in ribosomes, and in translation of genetic code to functional proteins. They generally play important role in anchoring RNA to compartmentalization and concentrate in liposomes (See Lazar, A. *et al.,* International Round Table on Nucleosides, Nucleotides and Nucleic Acids, IRT-XVII, Sep 3-7, 2006, page 47, Bern , Switzerland, the teachings of which are incorporated herein by reference.)

The peptide attachment of these functional groups generally takes place at the 3'- end, and are referred to as a "3' Functional Group".

As used herein, a "3' Functional Group" refers to moieties attached to the 3' end of the RNA molecule. The Reverse Synthesis Method described herein provides for attachment of a moiety at the end of the oligonucleotide chain. The 3' functional group may include lipids such as fatty acids and cholesterol, steroids, peptides, enzymes and labels, including moieties that are fluorescent, chemiluminescent, or radiolabelled.

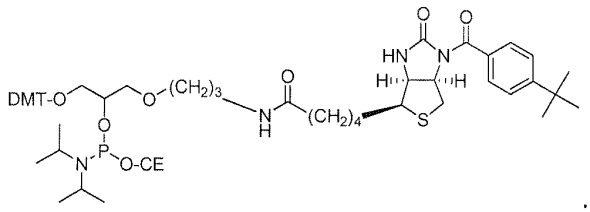
The 3' functional groups may be introduced through the reaction of a phosphoramidite linkers shown below:

1. The attachment of the 3' functional group to the RNA leads to amphiphilic 3'-peptidyl –RNA conjugates. Such molecules mimic natural peptide – transfer RNA. Synthesis of such RNA have been done on solid support by the above referenced authors. The RNA was joined to a peptide via an amide linkage to a variety of peptides. For example, the compound represented by the following structural formula can be attached at the 3' end using the Reverse Synthetic method disclosed herein:



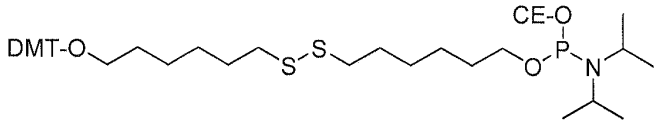
2. Biotin attachment at 3'- End of an RNA

3'- Biotin attachment via biotin amidite is possible in a single step and avoids the use of biotin CPG. Generally, a protected biotin amidite is used to attach biotin by solid phase oligonucleotide synthesis in order to get high purity oligonucleotides. A "protected biotin" is known in the art, see, for example, U. Pieles, B.S. Sproat and G. M. Lamm, *Nucleic Acids Research,* Vol. 18, No. 15, 4355 (1990), the entire teachings of which are incorporated herein by reference. A representative protected biotin that can be used in the invention is as follows:



3. Disulfide linker for 3' functional groups.

The oligonucleotides of our invention can be derivatized at the 3'- end by a disulfide linker, which can generate an -SH group. Subsequent coupling to an enzyme carrying a terminal SH function or an activated sulfide to lead to disulfide linked olgio- enzyme conjugate. A representative disulfide linker is as follows:



These disulfide linker phophoramidite can be conveniently attached to the 3'- terminal of an oligonucleotide. The attached disulfide attached via a phosphate at 3'- end can then be conjugated to various peptides, enzymes via sulfide coupling or exchange reaction known in the art.

For attachment of 3'- thiol modification, 3'- disulphides from readily available amidites, viz., C-3 disulfide, C-6 disulfide can be used. Oligonucleotides containing a free sulphhydryl group and subsequent attachment of thiol specific probes have been previously described and can be modified for attachment of the thio group at the 3' end. (See Connolly, B.A. *NAR*, 13, 12, 4485, 1985, the teachings of which are incorporated herein by reference). Oligonucleotide probes containing a free sulphydryl group at their 5'- terminal have been synthesized and further derivatized with thio specific probes. S-triphenyl- O- cyanoethyl phosphoramidite- 2- mercapto ethanol and other alkyl chains can be synthesized and incorporated in an oligonucleotide at the 3'- end.

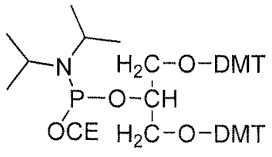
4. 3'- Branched linkers for multiple group attachment

The synthesis of branched oligonucleotides as signal amplification multimers in nucleic acid assay is described in T. Horn, *et al., Nucleotides and Nucleotides*, 895&6), 875-877 (1989), the entire teachings of which are incorporated herein by reference.

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Enzyme probes are described in "Highly sensitive detection of DNA using enzyme linked DNA- probes using colorimetric and fluorometric detection", Akira Murakai, *et al., Nucleic Acids Research*, Vol. 17, No.14, 5587 (1989), the entire teachings of which are incorporated herein by reference.

Branching phosphoramidite can be attach to oligonucleotide terminals. The branched phosphoramidite can be utilized to attach various reporter molecules, chromophores, enzymes, ligands, polyethylene glycols, peptides, or other 3' functional groups described herein. A branched oligonucleotide is prepared by reacting the 3'-hydroxy of the sugar with a compound of the following structural formula:



. The DMT protecting group can be replaced with other appropriate hydroxy protecting groups as described herein.

In addition, a vast number of applications are possible for attachment at the 3'-end of an oligonucleotide. Bulky molecules can be attached via direct coupling at the 3'- end of the RNA, such as cholesterol, long chain aliphatic chains such as C-18, triethylene glycols, hexaethylene glycols.

Polyethylene Glycols, such as PEG 2000 amide and PEG 4000 amidites at the 3'- end of an RNA have been achieved.

The modification of the overhang of the sense strand (3'- End) of SiRNA is not expected to affect targeted mRNA recognition, as the antisense SiRNA strand guides target recognition. Useful modification for improvement of delivery of SiRNA can be designed.

Non radioisotopic hybridization assay methods and diagnostic applications using fluorescent, chemiluminescent and enzyme labeled oligonucleotide probes are known in the art. (See Urdea, M. *et al., NAR,* 16, 11, 1988, the entire teachings of which are incorporated herein by reference). In addition, radiolabelled polynucleotide probes have been extensively applied for detection of complementary nucleic acids by specific hybridization. The reverse synthesis method disclosed herein can be used to label long

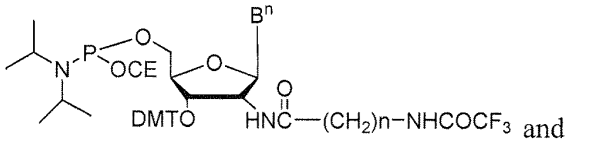
oligonucleotides (such as those including 100 bases). Examples of labels that can be attached via the reverse synthetic method disclosed herein include, for example, Fluoresceine; Texas red; rhodamine; chemiluminiscent molecules such as isoluminol; enzymes such as horseradish peroxidase; alkaline phosphatase labels; and enzymes.

2' substituents

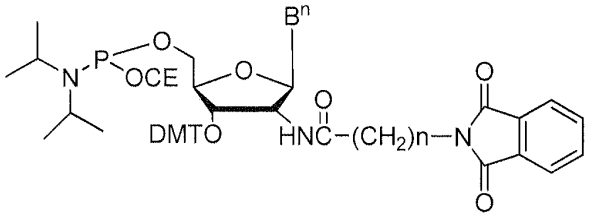
The 2'- silyl ethers have been developed extensively and they are known to have remarkable stability. Solvolysis of silyl ethers have been extensively studied and it is known that bulky alkyl silyl ethers have a high degree of stability; (See Bazani, B. and Chvalowski, V., Chemistry of Organosilicon Compounds, Vol. 1, Academic Press, New York, 1965, the entire teachings of which are incorporated herein by reference). Extensive research work was subsequently done by Ogilvie and coworkers as 2'-hydroxy protecting group for oligo ribonucleotide synthesis (See Ogilvie, K.K., *et al.*, *Tetrahedron Letters*, *15*: 2861-2864, 1974; and Ogilvie, K.K., et al. *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, the entire teachings of which are incorporated herein by reference).

The t-butyldimethyl silyl protecting group on 2'- hydroxyl of ribonucleosides has been the group of choice for making 3'- phosphoramidites and for utilizing them for oligonucleotide synthesis which have been shown to migrate to 3'- hydroxyl position rather easily. (See Ogilvie, K.K., and Entwistle, D.W. *Carbohydrate Res.*, *89*: 203-210, 1981; and Wu, T., and Ogilvie, K.K. *J. Org. Chem.*, *55*: 4717-4734, 1990, the entire teachings of which are incorporated herein by reference). Such migration complicates the synthesis of the desired phosphoramidites and requires an efficient method of purification that clearly resolves corresponding isomers and prevents any contamination of the final monomer. In contrast, the migration to the 3' hydroxyl is not a factor for during Reverse (5' → 3') Synthesis.

Representative 2' amino protecting groups include compounds represented by the following structural formulas:

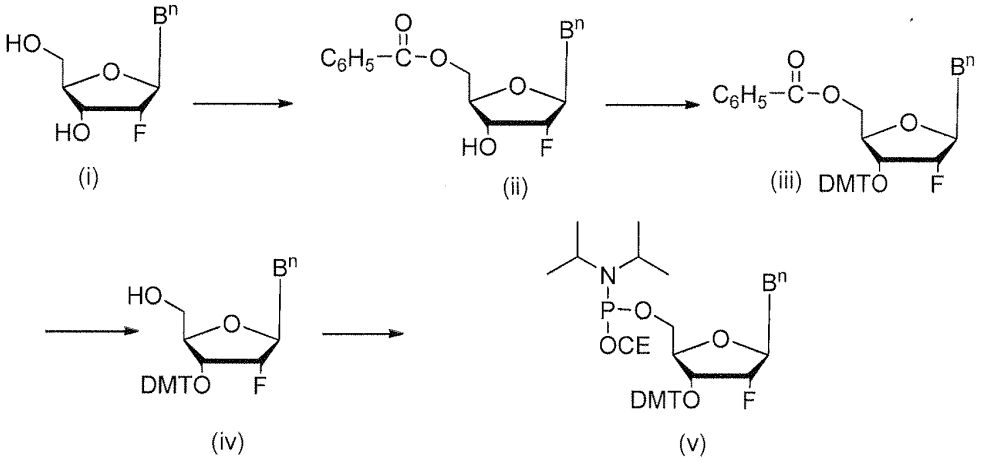


and



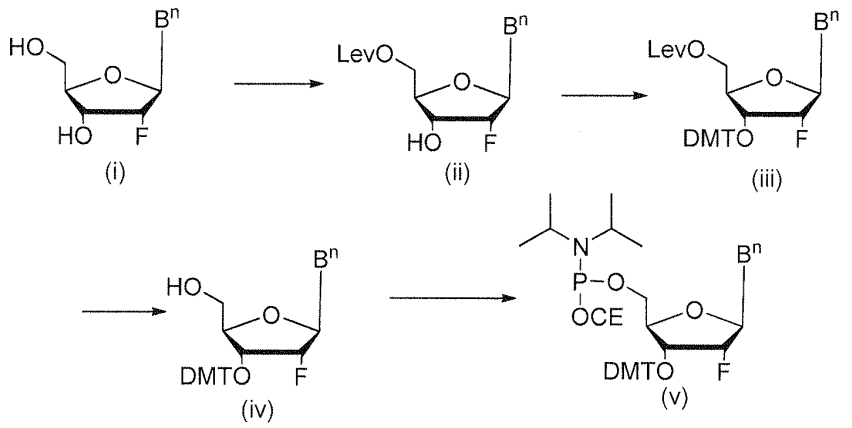
2'-Fluoro- 3'- DMT-nucleoside-5'- phosphoramidites.

The 2'-Fluoro substituent can be incorporated through the following proposed synthesis of 3'- DMT-2'- fluoro-N- protected-nucleoside-5'- phosphoramidites:



Alternatively, the 2'-Fluoro substituent can be incorporated through the following proposed synthesis of 2'-Fluoro -3'-DMT-N-protected (with fast deprotecting groups) nucleoside -5'- phosphoramidites:

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Selective 5'- levulinyl protection followed by crystallization to yield compound (ii); DMT-Cl reaction to yield compound (iii), followed by reaction with ammonia for 4-5 min to yield compound (iv) The 5'- phosphoramidites can then be synthesized by standard phosphitylation chemistry process to yield (v

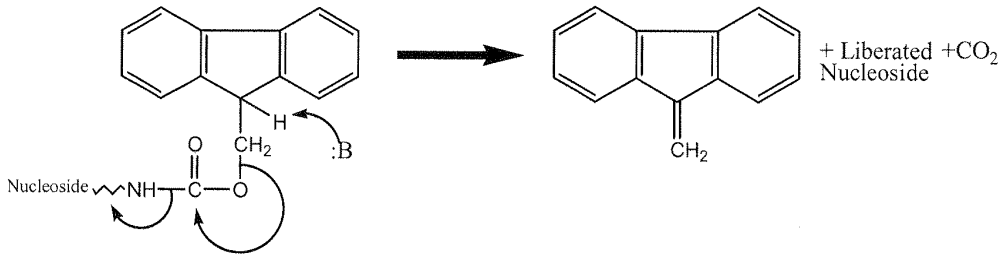
The standard Jones process can be utilized to prepare 2'- arabinose fluoro nucleosides (FANA) as well. The process includes: Conversion of (i) to (ii) steps; a; transient protection with TMS chloride; followed by reaction with phenoxyacetyl chloride/ pyridine; b; 2-4 minutes aq ammonia treatment to selectively remove TMS groups; c; crystallization of phenoxyacetyl protected -2'- fluoro nucleosides.

The 2'- fluoro modification of sugar portion of nucleosides, either 2'- ribo fluoro-2'- deoxy or 2'- arabino fluoro-2'- deoxy- nucleosides (FANA) have found significant application in design of various class of DNA and RNA such as antisense, microRNA, siRNA, aptamers. The selective introduction of such units into an oligonucleotides requires careful deprotection after solid phase oligonucleotide synthesis. It has been demonstrated that if harsh ammonia deprotection is carried out there is depyrimidation of oligonucleotides and loss of fluorine from sugar moiety. Thus, the development of optimized protecting group of the nucleoside exocyclic functional group is required in general is required to ensure all modified nucleosides units within an oligonucleotide will be compatible with mild base deprotection.

Several protecting groups such as FMOC, phenoxyacetyl, tertiary butyl phenoxyacetyl (t-BPAC), isopropyl phenoxy acetyl (isoPrPAC) and guanosine N-2 nitrogen protectected with acetyl (N- acetyl guanosine) are therefore being utilized to minimize either loss of fluorine from the fluoronucleoside units. The reverse RNA synthesis units therefore need to be protected with labile protecting group so they can be removed under mild deprotection conditions after oligonucleotide synthesis. Similarly mild phosphate deprotecting groups, such as cyanoethyl phosphoramidite chemistry are being currently used in present state of the art in this technology in DNA and RNA synthesis.

Deprotection of FMOC protecting group has been carried out under various very mild basic reaction conditions. (See Heikkila, J. and Chattopadhyaya, J., *Acta Chem. Scand. B* 37, No.3, 263-265, 1983, the entire teachings of which are incorporated herein by reference.) It is possible to utilize either aqueous 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 , as seen in the scheme below:

Scheme showing FMOC- β -Elimination



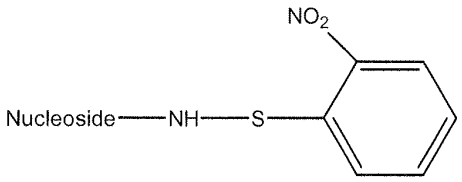
It is therefore possible to modulate the FMOC protecting group removal conditions from oligonucleotides, and the FMOC as base protecting group can be removed by the process of β-elimination, just like the β-elimination process to remove cyanoethyl group. Other protecting groups, for example, including phenoxyacetyl or alkylated phenoxyacetyl groups, can also be utilized in the reverse synthesis method described herein to generate highly pure deprotected oligonucleotides.

Shanghai Hongene Exhibit 1002

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

These base protecting groups in conjunction with cyanoethyl phosphate protecting group therefore provide the opportunity to remove both N- protecting groups and cyanoethyl groups from the synthesized deoxy and ribo oligonucleotides on the support cleanly, preferably with non aqueous bases, and on support for many diagnostics application.

The FMOC protecting group is very well established in peptide synthesis and one of the preferred reagent for amino group protection of alpha-amino group of amino acids for step wise peptide synthesis (See Carpino, L.A., and Han, G. Y., *J. Amer. Chem. Soc., 92*: 5748, 1970, the entire teachings of which are incorporated herein by reference). Another N- protecting group is 2- nitrophenyl sulfenyl (NPS) for the protection of amino function of cytidine, adenosine, guanosine and the corresponding 2'- deoxyribo nucleosides. (See J. Heikkila, J. *et al.*, *Acta Chem. Scand B 37*: 857-864, 1983, the entire teachings of which are incorporated herein by reference). The attachment of NPS to an exocyclic amine is represented by the following structural formula:



Phosphoramidite

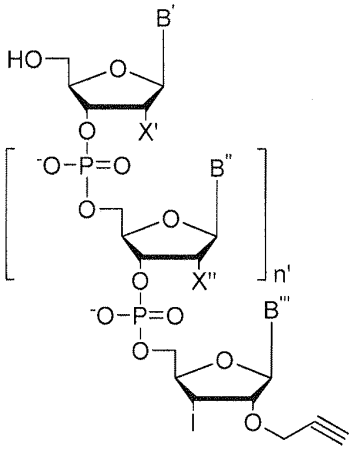
Studies on the formation of the internucleotode n bond in RNA Synthesi using dialkylamino phosphoramidites; G. Gasparutto, D. Molko & R. Teoule, Nucleosides & Nucleotides, 9(8), 1087-1098 (1990), the entire teachings of which are incorporated

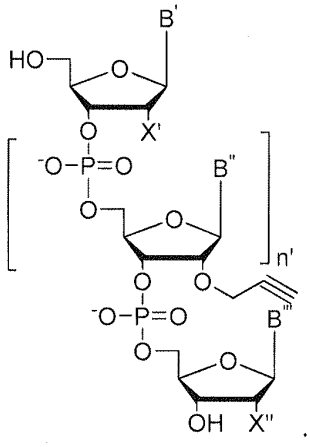
herein by reference. Among various 5'- DMT-2'- TBDMS- U- 3'- n, n-dialkyl amino cyanoethyl phosphoramidites tested during olignucleotide synthesis, it was found by the above authors that n,n-diethyl and n-ethyl,n- methylamino protection gave the best coupling result of average 97% after 4 minutes of coupling to form homopolyme of rU. For example, 5' diethylamino – cyanoethyl can be used in the invention disclosed herein.

Addition of 2' or 3' functional groups using Click chemistry via Reverse RNA synthesis process

Copper (I) catalyzed Huisgen 1,3- dipolar cycloaddition of azides with terminal alkynes is a well established example of a click reaction used in click chemistry (See Broggl, J., *et al.*, International Round Table Conference on Nucleosides, Nucleotides and Nucleicv acids, Sep 3-7, 2006, Bern , Switzerland, , p. 348, the entire teachings of which are herein incorporated by reference).

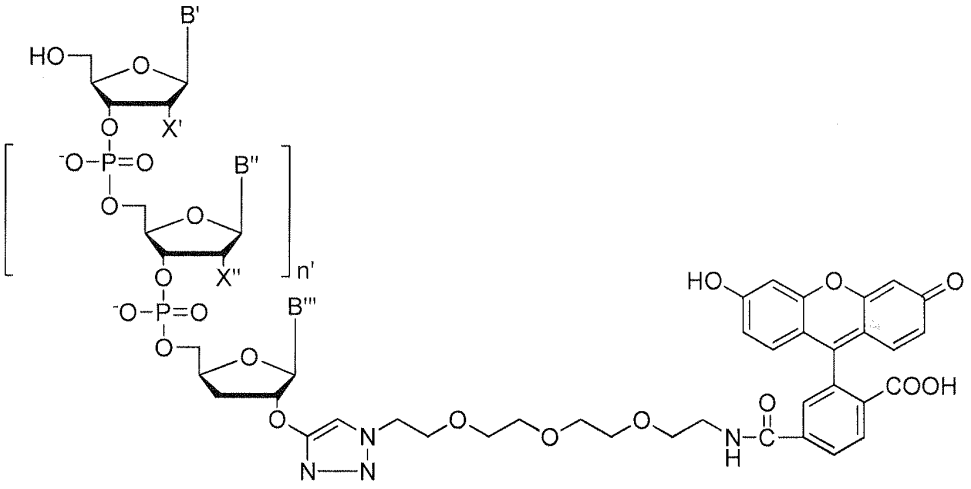
The 3'- DMT-2'- alkyne- 5'- phosphoramidite compounds of the invention would offer further advantage of modification and attachment of various macromolecules at 3'- terminal of an RNA . Reverse RNA synthesis process would allow introduction of various modifications at 3'- end of oligos , as well as internal positions during solid phase oligo nucleotide synthesis:



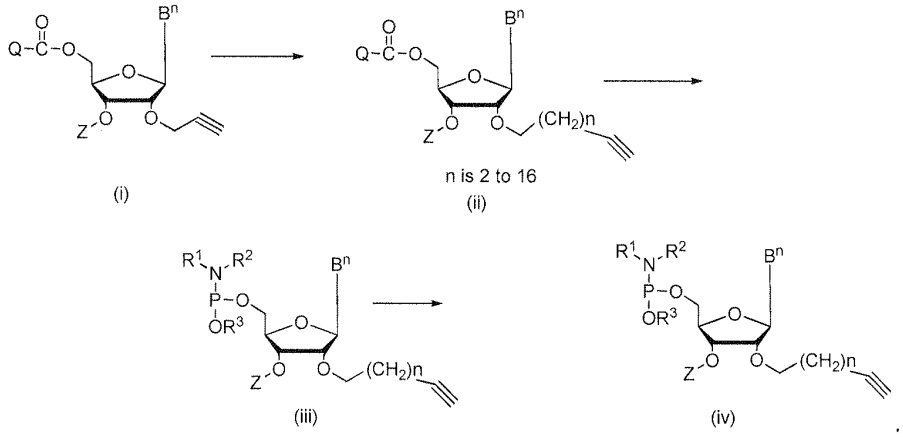


Shanghai Hongene Exhibit 1002

With 5'- solid support the reverse amidites, viz., 3'-DMT-2'- alkyne-5'-phosphoramidites would undergo oligo synthesis. Macromolecules such as, chromophores, ligands, biologically significant polypeptides, cholesterol and polyethyleneglycols can be regiospecifically attached via click chemistry:



The click chemistry process on solid phase support allows clean cycloaddition products in which all the reactants are washed out, followed by liberation of oligonucleotide. The modifications include highly efficient quencher dyes for use in molecular sensors and attached to oligonucleotides via "click chemistry". A proposed synthesis for compounds of the invention that can be used in click chemistry is depicted in the scheme below:



Shanghai Hongene Exhibit 1002

Building blocks for combinatorial "click chemistry" have been developed; multiple cycles of click reaction have been performed leading to oligonucleotides bearing single or multiple units of various chromophores and other macromolecules. We have improved the catalytical 1,3-cycloaddition efficiency for "click" reactions for synthesis of high purity DNA/RNA based probes on automated solid support based oligonucleotide synthesis. We have also developed novel highly efficient quencher dyes for use in molecular sensors and attached to oligonucleotides via click chemistry. The teachings of the following citations are incorporated herein by reference:

1. V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, Angew. Chem. Int. Ed., 2002, 41, 2596-2599.

2. A. V. Ustinov, *et al, Tetrahedron*, 2007, 64, 1467-1473.

3. Agnew, B. *et al.*, US Patent application 20080050731/A1.

4. X. Ming, P.Leonard, D. Heindle and F. Seela, Nucleic Acid Symposium Series No. 52, 471-472, 2008.

5. Srivastava, S. *et al.*, US Patent 5,744,595

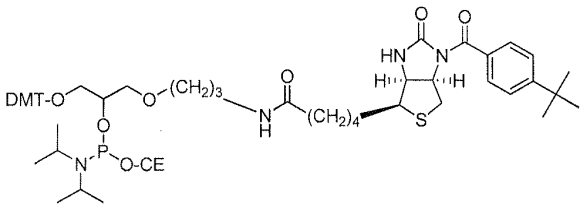
6. M. Manohoran, K. L. Tivel, and P. D. Cook, *Tetrahedron Lett.,* 1995, 36, 3651-3654.

7. G. S. Rule, J. Frim, J. E. Thompson, J. R. Lepock, and J. Kruuv, *Cryobiology*, 1978 15, 408-414.

8. C. J. Yu, Y. Wan, H. Yowanto, J. li, C. Tao, M. D. James, C.L. Tan, G. F. Blackburn, and T.J. Meade, *J. Am. Chem. Soc.*, 2001, 123, 11155-11161.

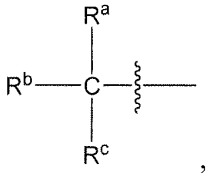
Biotin attachment at 3'- End of an RNA

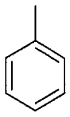
Generally, a protected biotin amidite is used to attach biotin by solid phase oligonucleotide synthesis in order to get high purity oligonucleotides. A "protected biotin" is known in the art, see, for example, U. Pieles, B.S. Sproat and G. M. Lamm, *Nucleic Acids Research*, Vol. 18, No. 15, 4355 (1990), the entire teachings of which are incorporated herein by reference.

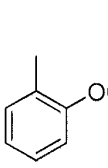


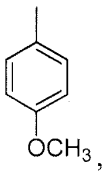
Protection of 3'- Hydroxy:

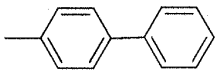
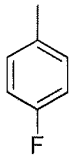
1. Additional triaryl methyl protecting groups: See for example, "Color coded triarylmethyl protecting groups useful for deoxypolynucleotide synthesis"; E.F. Fisher and M.H. Caruthers, *Nucleic Acids Research*, Vol. 11, 5, 1589-1599 (1983), the entire teachings of which are incorporated herein by reference. Triarylmethyl Groups reported include di-p-anisylphenyl methyl, p-fluorophenyl-1- naphthylphenyl methyl, p-anisyl-1-naphthylphenyl methyl, di-o-anisyl-1- naphthyl methyl, di-o-anisylphenyl methyl, p-tolyldiphenylmethyl, di-p-anisylphenylmethyl, di-o-anisyl-1- naphthylmethyl, di-p-anisylphenyl methyl, di-o-anisyl phenyl methyl, di-p-anisylphenyl methyl, p-tolyldiphenylmethyl. Additional triaryl methyl protecting groups are represented by the following structural formula:

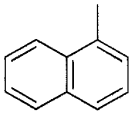
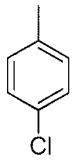


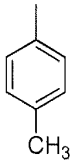
, wherein ≀ indicates attachment to the 3' oxygen atom and R^a, R^b, and R^c are independently selected from the following structural formulas:  ,

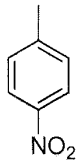


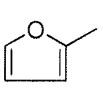
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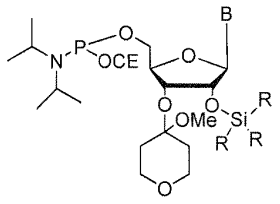
, 

, 

, or 

.

2. Use of tetrahydropyranyl and methoxytetrahydropyranyl group as protecting agent and removal under acidic conditions for the 3'- protecting group. This protecting group which can be removed under acidic conditions, see for example, "Synthesis of oligonucleotides with sequences identical with or analogous to the 3'- end of 16 S ribosomal RNA of E coli: preparation A-C-C-U-C-C via modified phosphotriester method"; J.H.van Boom, P.M. J. Boom, P.M.J. Burgers, G. van der Marel, C.H.M. Verdegaal and Mrs. G. Wille, the entire teachings of which are incorporated herein by reference. A representative compound of the invention including methoxytetrahydropyranyl is shown below:



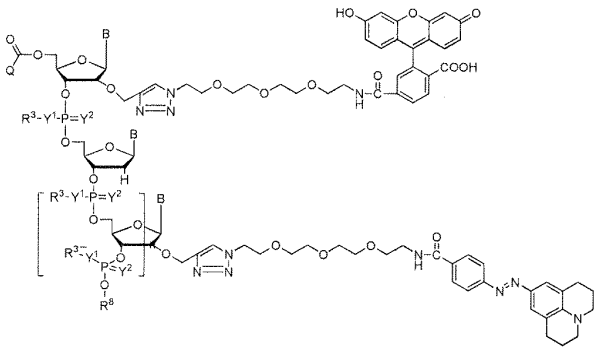
Advantages of Reverse RNA Method

We have synthesized full length oligos with a coupling time of 2 minutes using BTT as activator. The crude oligo purity obtained was 78.95% by HPLC. Using ETT as an activator, a 4.0 minute coupling time was possible, resulting in the crude oligo purity obtained to be 89.09%. The crude oligo purity by reverse process has been generally in the range of 90%. Using the reverse RNA method on a large scale synthesis (12 umol scale) we achieved similar results (crude oligo was approx. 92% and purified oligo was approx. 98%.), using a 6 minites coupling time. We were able to synthesize phosphorothioate oligonucleotides and mixed phosphorothioate/phosphate backbone without loss of coupling efficiency or oligonucleotide quality. In contrast, the convention (3'→5') direction synthesis resulted in crude oligo purity in the range of 80%, requiring several purifications to increase the purity to approx. 90%. The conventional RNA synthesis results in impurities on both the sides of desired band. While the reverse RNA synthesis , even with 2' coupling time does not give any N+1 impurities and HPLC trace shows right hand side of the peak is fairly straight.

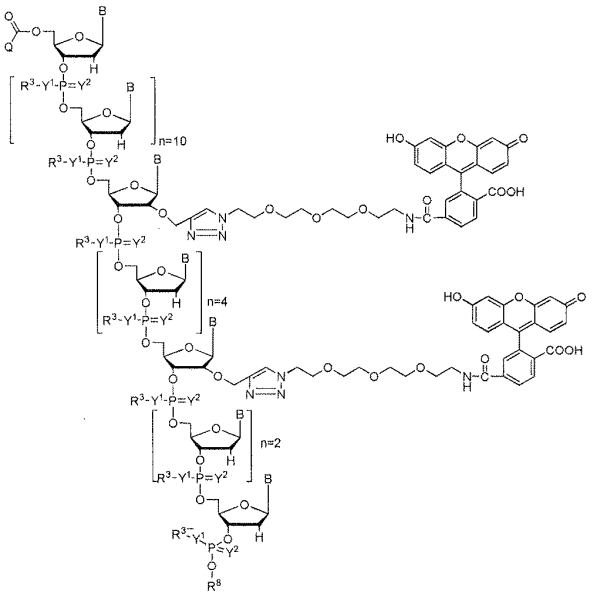
Previously, reverse RNA synthesis; 5'→3' showed that crude purity of oligonucleotides was approx. 80% by HPLC. Currently, reverse RNA synthesis; 5'→3' crude oligo purity to the extent of 90% due to perhaps to increased purity of the monomer synthons, and/or the reduced coupling time of 4 minutes of coupling time with ETT as activator, as compared to 10 minutes.

Representative Examples of chrompohores and Quencher Dye attachment to Oligo nucleotides using Reverse RNA synthesis Approach:

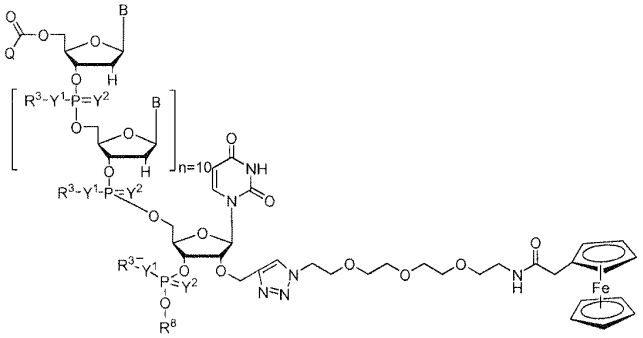
1. Reverse RNA synthesis utilizing 2'- Propargyl synthons and an azide linked quencher dye (ChemGene's proprietary quencher bis azo dye):



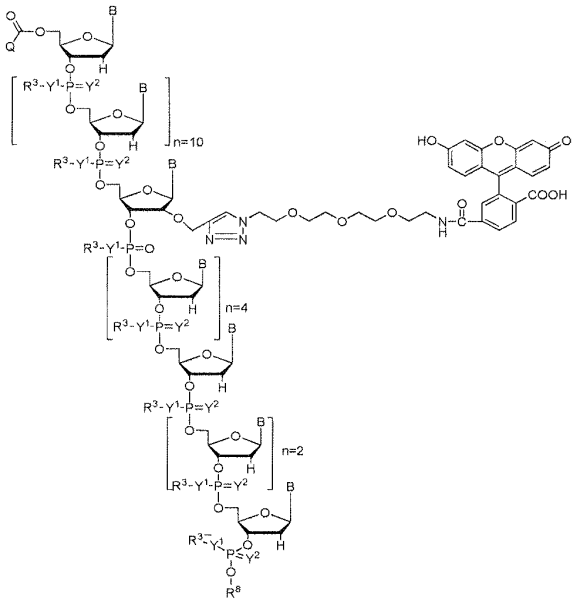
2. Reverse RNA synthesis utilizing 2'- Propargyl synthons and an azide linked chromophore(6- FAM) multiple internal incorporation:



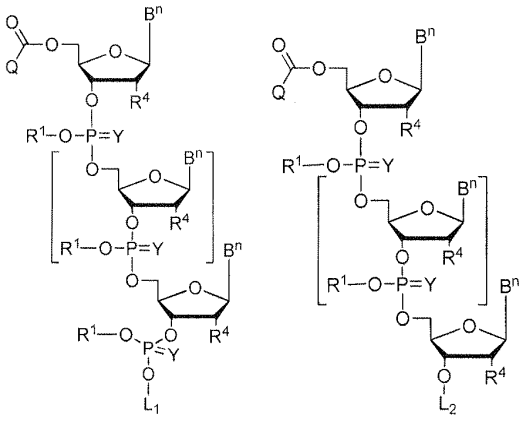
2. Reverse RNA synthesis utilizing 2'- Propargyl synthons and an azide linked chromophore, Ferrocine; 3'- End attachment



4. Reverse RNA synthesis utilizing 2'- Propargyl synthons and an azide linked chromophore(6- FAM) (single internal incorporation:



5. Linker (L) can be attached via two step process (a); The 3'- end base has a protecting group which can be conveniently removed to lead to free 3'- hydroxyl group, (b) activation of the free 3'- hydroxyl group via succinmidyl carbonate and subsequent reaction of the succinimidyl carbonate with an amine terminated linker) to lead to compound of structure 2. The structure 1 is derived by last coupling with a linker having a phosphoramidite function.



(structure 1) (structure 2)

List Of Linkers, chromophores (designated as L_1 and L_2)

The L's could be derived from a Linker , chromophores, fluorescent dyes, fluorescent nucleosides, fluorescent molecule attached to a nucleoside and can be coupled as a phosphoramidite or they could be derived from an active ester, such as NHS ester. The list include as follows:

Functional groups for further derivatization of an oligo at 3'- end or internal position;

amino modifier C-3, amino modifier(C-6), amino modifier C-12, amino modifier C-5-dU, amino modifier C-5- dU, 3'- thiol modifier (C-6 spacer), thiol modifier (C6-disulphide), carboxy modifier (with spacer), carboxy modifier (C-10 spacer), C-8 (amino modifier- C6-spacer)- r-adenosine, FMOC protected amino modifier –5-r cytidine (spacer), FMOC protected amino modifier-C-5 uridine (spacer), 3'- thiol modifier (C-3 spacer) disulphide,

3'- Chemical phosphorylation of an oligonucleotide

Phosphate- on – phosphorylating reagent (sulfonyl diethanol mono DMT, mono phosphoramidite), biscyanoethyl phosphorylating reagent

3'- aldehyde attachment to an oligonucleotide:

3'- Aldehyde modifier C-2 spacer, formyl indole,

Spacer attachment to oligonucleotides:

To generate space between the 3'- end of an oligonucleotide and subsequent attachm,ent of a molecule of interest such as peptides, amino acids, chromophores, polyethylene glycols, asymmetric doubler , symmetrical doubler , long trebler, trebler,

Chromophores, dyes attachment at 3' end on or within a sequence:
Chromophores, dye and spacer attachment in internal position or 3'- end of an oligonucleotide synthesized via our process can be conveniently achieved;

Dabcyl with a spacer, dabcyl –C-5 uridine or 2'- deoxy uridine, biotin with a spacer , biotin with tetraethylene glycol spacer, biotin –C-5 deoxy thymidine , biotin –C-5 uridine, biotin (tetraethylene glycol spacer), 5- (spacer) flurosceine, 6- (Spacer) fluoresceine (6- FAM) , 5-(spacer) hexachlorofluoresceine, 5- (spacer) tetrachlorofluoresceine, 6-(spacer) hexachlorofluoresceine, 6- (spacer) tetrachlorofluoresceine, fluoresceine-C-5 deoxy thymidine, fluoresceine –C-5-rU, tetramethyl rhodamine (TAMRA), Cy5™ , Cy 5.5 ™Cy 3™, Cy 3.5™ (cy dyes are trade mark of General Electric ; GE- Amersham), Epoch Richmond Red™, Epoch Kokimo Yellow ™, Epoch Gig Harbor Green™ , Epock Eclipse Quencher ™, (Eclipse dyes are trade mark of Epoch Biosciences Inc.), BHQ-0 ™, BHQ-1™, BHQ-2 ™, BHQ-3™ (BHQ dyes are trade mark of Biosearch Technologies, Inc.).

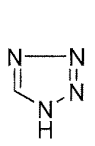
Various other dye attachment such as C-5 Pyrene-r-uridine, C-5 perylene-r-uridine, (5,6)-pyrrole-r-cytidine, Acridine dye attached to a spacer, dinitrophenyl amine attached to a spacer, cholesterol tetraethylene glycol attached to a spacer via 3- OH, psoralen attached to a spacer via furan ring, Ethylene diamine tetraacetic acid (EDTA) attached via spacer, puromycin.

Other linkers include: C-5 (rU and rC) acrylate Biotin, C-5 (rU and rC) fluoresceine , 6- FAM , 5- FAM , Tamra, rhodamine, acrylate.

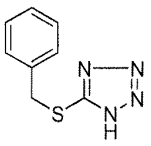
Use of an activator. An activator may be added during the coupling step in the method forming an oligonucleotide bond between the 5'- phosphoramidites of our invention and a hydroxyl group. The activator is chosen and is capable of activation and subsequent protonation of the amidite nitrogen. The activator could be selected from tetrazole,

Shanghai Hongene Exhibit 1002

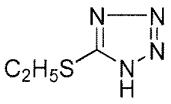
benzyl thio tetrazole , ethyl thio tetrazole, dicyanodiimidazole. The activators which lead to activation of the amidite bond for reaction coupling with an hydroxyl group top form phosphate.



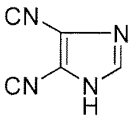
(Tetrazole)



(BTT)



(ETT)



(DCI)

Application of Reverse RNA synthesis in microRNA synthesis

microRNAs (miRNA) are generally non-coding RNAs highly conserved, having a length of 20 to 25 nucleotides in length that regulate expression of target genes through sequence specific hybridization to the 3' untranslated region (UTR) of messenger RNAs and either block translation or direct degradation of their target messenger RNAs and are present in plants and animal alike. This novel class of RNAs was first discovered in *C. elegans* in 1993 by the laboratory of Dr. Victor Ambrose, (Lee R.C., *et al.* (1993), 14. *Cell 75*: 843-854, the entire teachings of which are incorporated herein by reference). They have now been identified in almost every species including the discovery of microRNAs in humans (Lim L.P., *et al.* (2003), *Science 299*: 1540, the entire teachings of which are incorporated herein by reference). Each miRNA is thought to regulate multiple genes, and since hundreds of miRNA genes are predicted to be present in higher eukaryotes, the potential regulatory circuitry afforded by miRNA is enormous. Several research groups have provided evidence that miRNAs may act as key regulators of processes as diverse as early development (Reinhart 2000), cell proliferation and cell death (Brennecke 2003), apoptosis and fat metabolism (Xu 2003). microRNAs have been shown to play an integral role in numerous biological processes including the immune response, cell-cycle control, metabolism, viral replication, stem cell differentiation and human development. Many

microRNAs are conserved across multiple species indicating the evolutionary importance of these molecules as modulators of critical biological pathways. However microRNA expression or function is significantly altered in many disease states, including cancer, heart failure, and viral infections. Targeting pathways of human disease with miRNA-based drugs represents a potentially powerful new therapeutic approach.

The reverse RNA synthesis approach present an opportunity to synthesize such RNAs, to include modifications for stability of such RNA in intracellular environment and to incorporate ligands or delivery agents for uptake and therapeutic development.

Application of Reverse RNA synthesis in RNAi synthesis

Silencing gene expression with RNA interference (RNAi) has become a well studied approach offering potential for selective gene inhibition and application in the control and management of various biochemical and pharmacological processes. Early studies by, showed that RNA interference in *Caenorhabditis elegans* is mediated by 21 and 22 nucleotide RNA sequences. (See Fire *et al., Nature, 391*: 806-811, 1998, the entire teachings of which are incorporated herein by reference). This was further confirmed as a general phenomenon of specific inhibition of gene expression by small double stranded RNA's being mediated by 21 and 22 nucleotide RNAs, (See *Genes Dev., 15*: 188-200, 2001, the entire teachings of which are incorporated herein by reference). Subsequently a vast amount of research led to the confirmation of above studies and established RNAi as a powerful tool for selective, and very specific gene inhibition and regulation. (See Nishikura, K., *Cell, 107*, 415-418, 2001; and Nykanen, A., *et al., Cell, 107*: 309-321, 2001; and Tuschl, T., *Nat. Biotechnol., 20*: 446-448, 2002; and Mittal, V., *Nature Rev., 5,* 355-365, 2004; *Proc. Natl. Acad. Sci. USA, 99*, 6047-6052, 2002; and Donze, O. & Picard, D., *Nucl. Acids. Res., 30*, e46, 2002; and Sui, G.,*et al.., Proc. Natl. Acad. Sci. USA, 99*, 5515-5520, 2002; and Paddison, P.J. *et al., Genes Dev., 16*, 948-959, 2002, the entire teachings of which are incorporated herein by reference). Besides the natural

double stranded (ds) RNA sequences, chemically modified RNA have been shown to cause similar or enhanced RNA interference in mammalian cells using 2'-deoxy-2'-fluoro- β-D-arabinonucleic acid (FANA) into sequences for siRNA activities. (See Dowler, T., *et al., Nucl. Acids Res., 34*, 1669-1675, 2006, the entire teachings of which are incorporated herein by reference).

Various other modifications to improve siRNA properties have been pursued, which include alteration in backbone chemistry, 2'- sugar modifications, and nucleobase modifications, some of which have been recently reviewed. (See Nawrot, B, and Sipa, K., *Curr. Top. Med. Chem., 6*: 913-925, 2006; and Manoharan, M., *Curr. Opin. Chem. Biol., 8*, 570-579, 2004, the entire teachings of which have been incorporated herein by reference). The PS modifications of siRNA are well tolerated , although some reports indicate increased toxicity and somewhat reduced efficacy. (See Harborth, J, *Antisense Nucleic Acid Drug Dev., 13*, 83-105, 2003, the entire teachings of which are incorporated herein by reference). Among these is also the 2'- O- Methyl modification, although it maintains A form (RNA like) helix, and has been shown to be either retaining or reducing siRNA activity depending on the number of such modifications within a sequence. (See Chiu, Y.L., Rana, T.M., *RNA, 9*:1034-1048, 2003, the entire teachings of which have been incorperated herein by reference). It has also been shown that extensive 2'- O-Methyl modification of a sequence can be made in the sense strand without loss of siRNA activity. (See Kraynack,B.A., Baker, B.F., *RNA, 12*: 163-176, 200, the entire teachings of which are incorporated herein by reference).

*Support and Linking Grou*ps

The support material (represented in the structural formulas herein as "Q") is a non-swellable solid support. The support material could be solid, liquid, or in gel form. The "linking group" is a moiety such as a carbonyl that connects the nucleoside to the support and suitable linking groups are described in the following paragraphs. The support material Q is a) a support comprised of a linking group and a spacer , for example, succinyl , hydroquinolyl, oxalyl, that can be cleaved to form a

hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl. Alternatively, an irreversible linker can be used.

The "linking group and spacer" is a moiety such as a carbonyl that connects the nucleoside to the support and suitable linking groups are described in the following paragraphs.

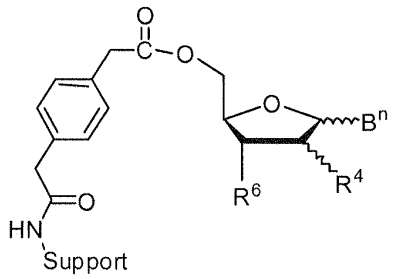
The two most often used solid-phase materials are Controlled Pore Glass (CPG) and macroporous polystyrene (MPPS). CPG is commonly defined by its pore size. In oligonucleotide chemistry, pore sizes of 500, 1000, 1500, 2000, and 3000 Å are used to allow the preparation of about 50, 80, 100, 150, and 200-mer oligonucleotides, respectively. To make native CPG suitable for further processing, the surface of the material can be treated with (3-aminopropyl)triethoxysilane to give Aminopropyl CPG. The aminopropyl arm may be further extended to result in Long Chain Aminoalkyl (LCAA) CPG. The amino group is then used as an anchoring point for linkers suitable for oligonucleotide synthesis. MPPS suitable for oligonucleotide synthesis is a low-swellable, highly cross-linked polystyrene obtained by polymerization of divinylbenzene (min 60%), styrene, and 4-chloromethylstyrene in the presence of a porogeneous agent. The macroporous chloromethyl MPPS obtained is converted to aminomethyl MPPS.

To make the support material suitable for oligonucleotide synthesis, non-nucleosidic linkers (universal supports) or nucleoside succinates are covalently attached to the reactive amino groups in the solid support material by routine methods. The remaining unreacted amino groups are capped with acetic anhydride. For example, the synthesis starts with the universal support where a non-nucleosidic linker is attached to the support material. A phosphoramidite respective to the 5'-terminal nucleoside residue is coupled to the universal support in the first synthetic cycle of oligonucleotide chain assembly using the standard protocols. The chain assembly is then continued until the completion, after which the support-bound oligonucleotide is deprotected. The characteristic feature of the universal solid

supports is that the release of the oligonucleotides occurs by the hydrolytic cleavage of a P-O bond that attaches the 5'-O of the 5'-terminal nucleotide residue to the universal linker. The critical advantage of this approach is that the same support is used irrespectively of the sequence of the oligonucleotide to be synthesized.

Alternatively, the 5'-hydroxy group of the 5'-terminal nucleoside residue is attached to the support via, most often, 5'-O-succinyl arm. The oligonucleotide chain assembly starts with the coupling of a phosphoramidite building block respective to the nucleotide residue second from the 5'-terminus. The 5'-terminal hydroxy group in oligonucleotides synthesized on nucleosidic supports is deprotected under the conditions somewhat milder than those applicable for universal supports.

Another linking group includes Q- support, which is a hydroquinone spacer, conveniently cleaved as compared to succinyl supports (See University Technologies International, LP(UTI) & Publication; R.T. Pon and S.Y. Yu, *Tetrahedron Lett.*, 1997, 38, 3327-3330, the teachings of which are incorporated herein by reference.) The structural formula is as follows: Support- NH- C(=O)- CH2-C6H4-CH2-C(=O)- O- 5'-nucleoside, and is represented by the following structural formula:



Solid Supports for Oligonucleotide Synthesis:

There are vast variety of supports currently available for oligonucleotide synthesis with choice to adopt to different types of oligonucleotides. Some of the key support technologies and descriptions are noted in the following paragraphs.

See Richard T. Pon; Current Protocols in Nucleic Acid Chemistry, Unit 31, Feb. 2000, the entire teachings of which are incorporated herein by reference. The physical

& chemical properties of supports are described in this manual and suitability for various chemistries of oligonucleotide synthesis.

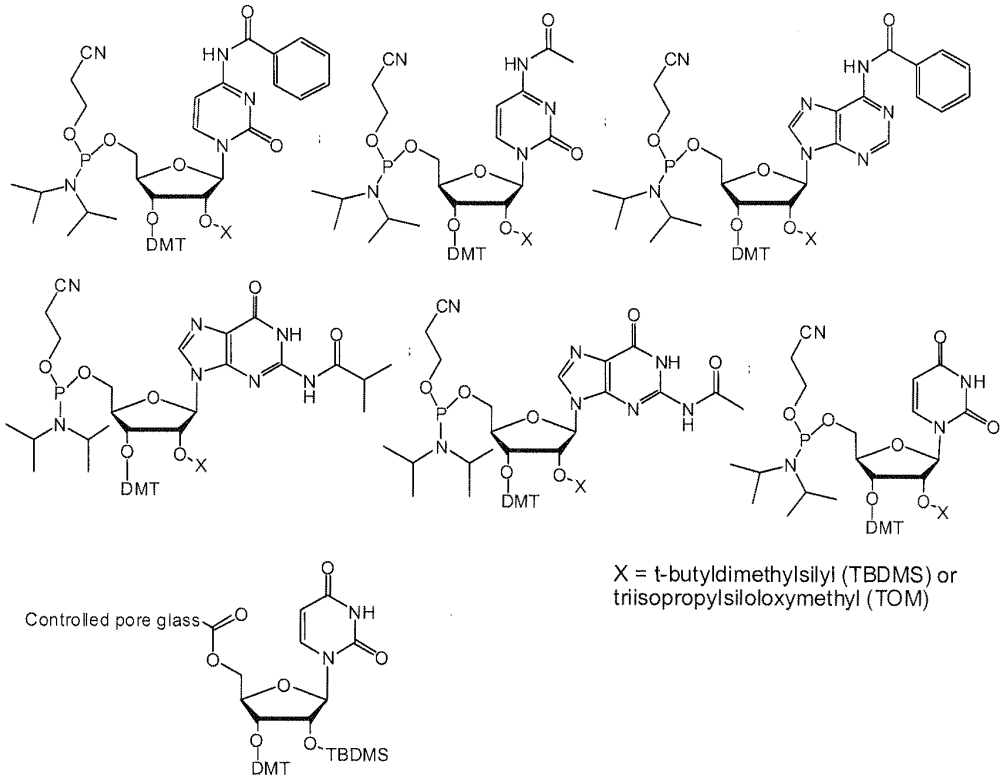
Universal support have found significant application in oligonuicleotides. UnyLinker technology as developed by Isis Pharmaceuticals, allows synthesis of oligonucleotides using single molecule as compared to derivatization of individual DNA or RNA bases. The cleavage of Unylinker molecules takes place smoothly to include a free 3'- end hydroxyl group on the 3'- end nucleoside. Our invention proposed to introduce such Unylinker molecule at the 5'- end of an oligonucleotide of our 5'-→3'- oligonucleotide synthesis process. After solid phase oligonucleotide synthesis the Universal support can be conveniently removed to generate free 5'- end hydroxy group. Isis Pharmaceutical technology has an intellectual property to covers this molecule for carrying out 3'-→5'- oligonucleotide synthesis and is covered by the following patents; the entire teachings of which are incorporated herein by reference: US patent application 60/520.179 (DVCM0009US.L), filed November 13, 2003 and entitled Supports for oligomer synthesis; US patent application 60/530.477 (DVCM0010US.L), filed December 16, 2003 and entitled Supports for oligomer synthesis. A subsequent publication by Isis Pharmaceutical scientists on this Universal support technology was reported.

A universal support has been described by AM Chemicals , LLC. The company described a convertible solid support which allows introduction of variety of ligands, functional groups at 3'- terminal. Our invention proposed to utilize this solid support for incorporated in our process for functionalization at 5'- position. A publication describing universal support described by AM Chemicals , LLC outlines application in detail of 3'- →5'- direction oligonucleotide synthesis; A conformationally Preorganized Universal Support for Efficient Oligonucleotide Synthesis, Andre P. Guzaev & Muthiah Manoharan, J. Am. Chem.Soc., 2003, 125, 2380-2381, the entire teachings of which are incorporated herein by reference.

Nitto Phase ^{R} (a trade mark of Nitto Denko Technical Corporation). Nitto phase^{R} support has been demonstrated to have potential for use in the synthesis of therapeutic grade DNA and RNA. Nitto Phase^{R} support, marketed through Kinovate Life Sciences , a wholly owned subsidiary of Nitto Denko Corp. This can be utilized as a support in our process and invention as a support for 5'- position attachment of nucleosides. With our superior process for RNA synthesis in reverse direction, and combination with this support we anticipate synthesis of high quality oligonucleotides. Prime Synthesis Inc., reports (see Website of Prime Synthesis Inc.) use of controlled pore glass (CPG) of various linker/ spacers for attachment to CPG bead surface.

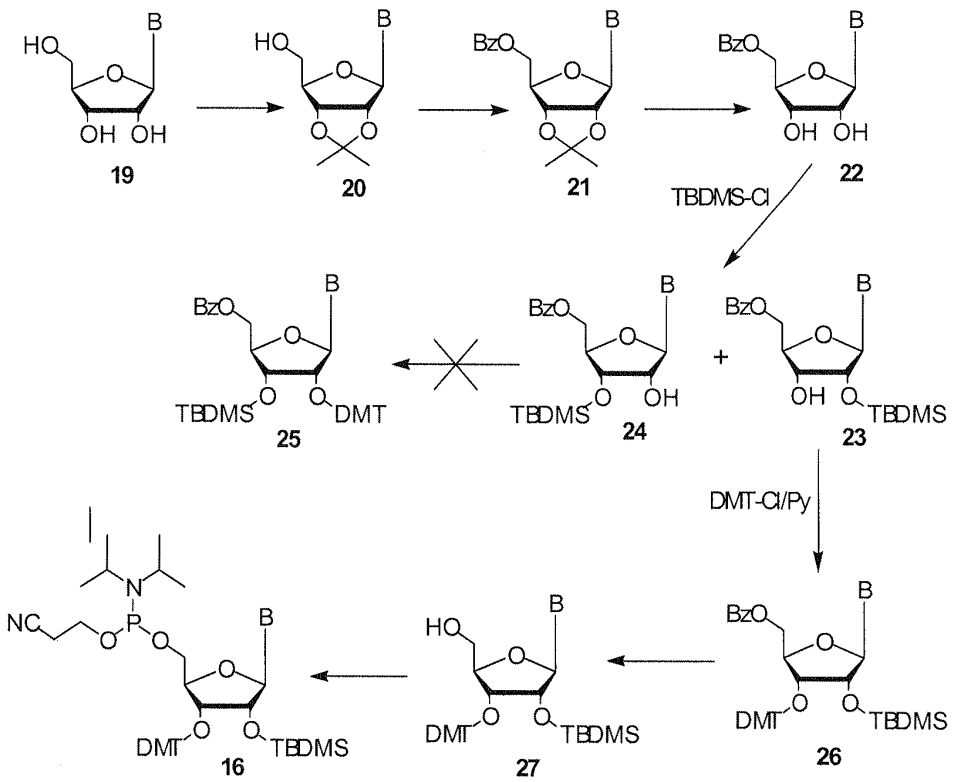
GE Health Care, a division of GE (General Electric) has described a custom support for oligonucleotide synthesis, known as Primer Support 200 (apczech.cz/pdf/df-primer support.pdf). The support has been shown by GE Health Care, suitable for DNA synthesis, RNA synthesis, custom base addition during oligonucleotide synthesis and growing oligonucleotide chain, labeling of various chromophores such as fluoresceine, dabsyl, phosphate –ON reagents etc. Primer support has been loaded to from 20-250 umole /g level. However no 5'-→3' direction RNA synthesis has been known or proposed to best of our knowledge.

The following compounds are not compounds of the present invention:



Exemplification

The details of synthesis scheme are outlined in the Scheme 1:



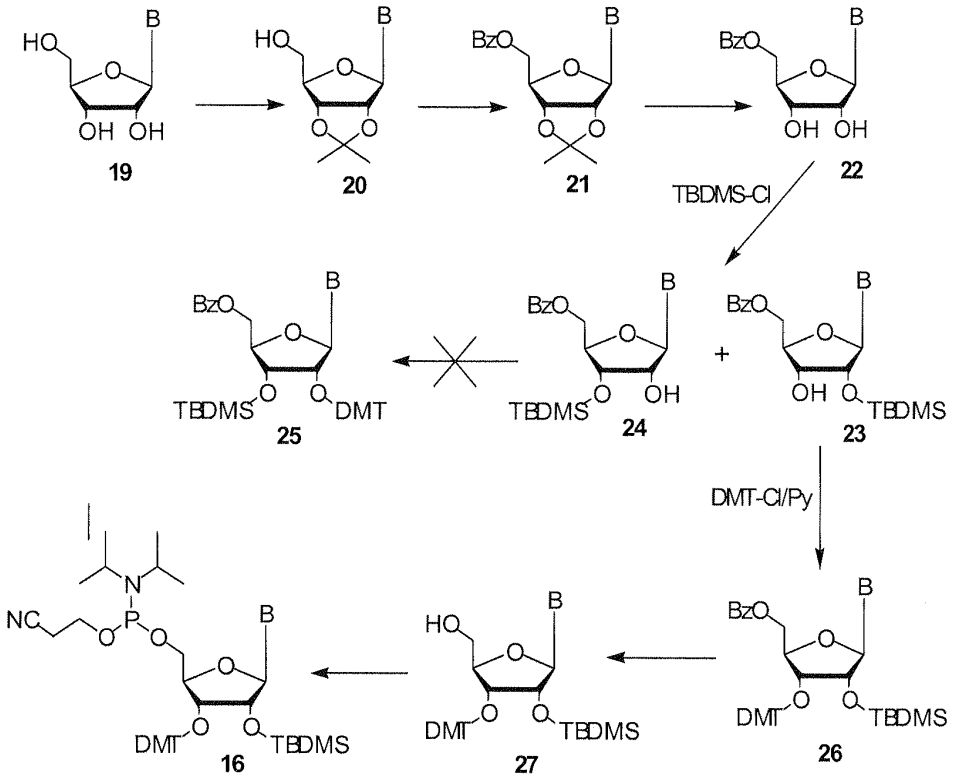
The 2',3'-Isopropylidene function is utilized to protect the 2', 3' hydroxyl groups of ribose of n- protected ribonucleosides. A number of preferred n- protecting groups are shown in the Scheme (1). The 5'- hydroxyl group is subsequently protected, preferably with benzoyl group to obtain compounds of general structure 21. The isopropylidene group is then selectively removed under mild acidic conditions well known in the art. This step leads to compounds of general formula 22. Subsequent reaction with TBDM Silyl chloride (tert-butyl dimethyl silyl chloride) leads to mono silyl compound of general formula 23. The present inventors have observed that 3'-TBDMS group, i.e., the formation of compound structure 24 is not preferred in this process. In most of the cases they observed a clean product whose structure was confirmed to be 23 by chemical and analytical methods.

Purification is carried out at each step either via crystallization or column chromatography at each of the steps of the process mentioned above. Subsequent reaction with dimethoxytrityl chloride (DMT-chloride) in pyridine leads to 3'-

DMT-2'- TBDMS-n-protected nucleosides of the general structure 26. Each of the compounds were fully purified by column chromatography.

Although they utilized TBDMS group to produce 2'- TBDMS ether, other silyl ethers can be utilized at this step. A careful aqueous/ methanolic NaOH hydrolysis resulted in compounds with free 5'- hydroxyl group, general structure 27. Selective 5'- benzoyl removal with aqueous or methanolic base is well known in the art. The compounds 3'- DMT-2'- TBDMS-n-protected nucleosides (structure 27) were purified by silica gel column chromatography. The purified compounds (structure 27) were subsequently phosphorylated with phosphorylating reagents, such as n,n-diisopropylamino cyanoethyl phosphonamidic chloride or 2- cyanoethyl,n,n,n,n-tetraisopropyl phosphane to yield the corresponding phosphoramidites (structures 16). Both the phosphorylating reagents, n,n-diisopropylamino cyanoethyl phosphonamidic chloride or 2- cyanoethyl, n,n,n,n-tetraisopropyl phosphane are readily available in the market Manufactured by ChemGenes Corp., and the methods of phosphorylation to produce corresponding phosphoramidites are well known in the art.

Large Scale synthesis of high purity 3'- DMT-2'-TBDMS-nucleoside -5'-phosphoramidites for Reverse RNA synthesis. Typical synthesis of 70-100 g quantity of the phosphoramidites is illustrated in the following examples. Each of the phosphoramidite synthesis process demonstrate purity of 100% by 31 P NMR and greater than 98% purity by high pressure liquid chromatography (HPLC) analysis. The quality control data are presented in separate table.



Where B = a) A (*N*-Bz), b) C (*N*-Bz), c) C (*N*-Ac), d) G (*N*-iBu)

e) A (*N*-tBPac), f) C (*N*-tBPac), g) G (*N*-tBPac),

h) A (*N*-Pac), i) C (*N*-Pac), j) G (*N*-Pac), k) U.

Synthesis of 3'-ODMT- 2' OTBDMS – 7-deaza rG (n- ibu)-5'- OP

Step (a): 5 'ODMT- 2' TBDMS – 7-deaza rG (n-ibu)

Step (b): 5'OH- 2'- TBDMS -7-deaza rG- (n-ibu)

Step (c): 5'-OBZ- 2'TBDMS -7-deaza rG-(n-ibu)

Step (d): 5'-OBZ- 3'-ODMT- 2'-TBDMS-7-deaza rG (n-ibu)

Step (e): 5'-;OH- 3'-ODMT- 2'- TBDM S- 7-deaza rG (n-ibu)

Step (f): 3'-ODMT-2'-TBDMS- 7-deaza rG(n-ibu)-5'-cyanoethyl phosphoramidite

Step (a): 5 'ODMT- 2' TBDMS – 7-deaza rG (n-ibu) was produced by known procedure as published in literature

Step (b): 5'OH- 2'- TBDMS -7-deaza rG- (n-ibu):

5'-O-DMT- 2'-TBDMS-7- deaza rG (n-ibu) ; 30 gm was taken in trichloroacetic acid in dichloromethane(3% solution,w/v; 2eq) for selective DMT group removal from 5'-position. The mixture was shaken vigoursly to get clear solution which get dark purple as the reaction proceeds. The solution was further stirred at room temperature for 10 minutes. The reaction mixture was then quenched with 10%aq sodium bicarbonate solution (precooled to 05 C) at zero degree to neutralized reaction to get pH between 7-8. The orgabnic layer was washed with saturated brine once , followed by passing through anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel (70-230 mesh; Merck grade) to get pure 5', 3'- dihydroxy -2'- TBDMS-7deaza rG (n-ibu); yield 15 gm (85%); tlc rf. 0.2 (Solvent system (5:3:2): Chl: Hex:Acetone .

Step (c): 5'-OBz- 2'TBDMS -7-deaza rG-(n-ibu):

5'OH- 2'- TBDMS -7-deaza rG- (n-ibu) was benzoylated at 5'- position selectively. 5'OH- 2'- TBDMS -7-deaza rG- (n-ibu) (15 gm) was taken in dry pyridine (10 fold w/v; 150 ml), brought to -10C to 0 under anhydrous conditions. Benzoyl chloride (1.1 eq ,4.10 ml) was added in one portion and the mixture stirred for 1.5 hours at the same temperature . The mixture was quenched with cold methanol, followed by removal of solvent in vacuo. The mixture was extracted in chloroform, washed with saturated aq

bicarbonate, followed by washing once with saturated brine solution. The organic layer passed through anhydrous sodium sulfate, followed by removal of solvent under low vacuum. The residue was purified by crystallization in ethyl ether and ethyl acetate mixture to get 17 gm pure compound . HPLC purity 99%. rf. 0.5 . (Solvent system (5:3:2): Chl: Hex:Acetone.

Step (d): 5'-OBz- 3'-ODMT- 2'-TBDMS-7-deaza rG (n-ibu)

The previouis step compound ; 5'-OBz- 2'TBDMS -7-deaza rG-(n-ibu (17 g) was dried with anhydrous pyridine twice , followed by taking in pyridine w/v; 1:10, 170 ml) and the solution was protected from moisture and brought to 0-5 C. DMT-chloride (25.2 g; 2.5 eq was added to the solution and the reaction mixture was stirred at room temperature for 24 hours, followed by quenching the reaction with chilled methanol. The solution was vacuum evaporated and worked up by extraction in ethyl acetate. The organic layer was washed with saturated sodium bicarnbonate , followed by saturated brine solution, followed by passing the organic layer over anhydrous sodium sulfate. The solution was concentrated and residue was purified by column chromatography (Silica gel 70-230 mesh E. Merck) , yield 9 gm pure, purity 98% by HPLC, and unreacted starting material (8gm) was also recovered.

Step (e): 5'-;OH- 3'-ODMT- 2'- TBDM S- 7-deaza rG (n-ibu):

The compound (6.0 g) obtained after preceding step was hydrolyzed selectively under control hydrolysis condition 2N NaOH in pyridine :MeoH 60 ml (80:20) for 30 minuts at 5-10 O c. followed by neutralization of reaction mixture with Dowex-pyridinium cation exchange resin, followed by filtration to remove Dowex resin to get crude product. The solvents were pumped and the residue was subsequently purified by column chromatography to get pure compound , yield 4.0 g. HPLC purity 98.5% . Mass and 1 H NMR

Step (f): 3'-ODMT-2'-TBDMS- 7-deaza rG(n-ibu)-5'-cyanoethyl phosphoramidite:

The compound obtained in the preceding step was thouroughly dried with anhydrous acetonitrile twice. The dried product was taken in dry distilled tetrahydrofuran. Diisopropyl ethyl amine (2.o eq) was subsequently added to reaction mixture while stirring under anhydrous conditions. To the reaction mixture was added diisoprpyl 2-cyano ethyl chloro reagent (1.1eq). The mixture was allowed to stir for 2.0 hours at room temperature. To crude reaction mixture was quenched with saturated sodium buicarbonate (chilled to zero C) , followed by dilution with excess ethyl acetate. The organic layer was washed once with saturated brine solution. The organic layer was passed through anhydrous sodium sulfate. The solvent removed under vacuo, and the crude reaction mixture was purified by column chromatography (Silicagel 230-400 mesh, E. Merck grade); solvent system for purification ; 45:45:10 :: Chloroform: ethylacetate: triethylamine) to get pure phosphoramidite. HPLC purity > 98%. 31p nmr , 1 H NMR, MASShnmr mass hplc .

Coupling efficiency test showed > 98% coupling

Synthesis of 3'-O- DMT- 2'- TBDMS- L-rU phosphoramidite.

Step (a) 1- O Ac-2,3,5- tri-O-bz- L- ribose (using silylated uracil)

Step (b) 2',3',5'- tri-O-bz- L- uridine

Step (c) L- uridine

Step (d) 2',3'-isopropylidine- L-rU

Step (e) 5'-O-Bz-2',3'-isopropylidine- L-rU

Shanghai Hongene Exhibit 1002

Step (f) 5'-O-Bz- L-rU

Step (g) 5'-O-Bz-2'- TBDMS- L-rU

Step (h) 5'-O-Bz-2'- TBDMS- 3'-O-DMT-L-rU

Step (i) 5'-OH-2'- TBDMS- 3'-O-DMT-L-rU

Step (j): 3'-O-DMT- 2'- TBDMS- L-rU- 5'-cyanoethyl phosphoramidite

Step (a):

1-O-Acetyl –tri-O-benzoyl- L- ribose (i) was synthesized similar to synthesis of 1-acetyl –tri- O-benzoyl-D- ribose which is well known in the art.

Step (b):

2',3',5'-Tri-O-benzoyl- L- uridine .

The silylated uracil was made by treatment with hexamethyl disilazane (Hexamethyldisilazane; HMDS; 20 eq). The silylated uracil was then fused with 1-O-Acetyl –tri-O-benzoyl- L- ribose in presence of tin (IV) chloride (SnCl4 as catalyst) . The crude product was worked up by neutralization by solidf sodium bicarbonate , followed by filteration with acetonitrile. The solid was discarded. The filtrate was pumped out under vacuum. This crude compound was purified by column chromatography on Silicagel column (E. Merck ; 70-230mesh) . The pure fractions were pumped and the product was characterized by HPLC , UV and ESI/MS.

Step (c):

2,3,5-Tri-hydroxy - L- uridine (L- uridine):

The pure fully protected intermediate compound obtained in step (b) was the hydrolyzed with aq ammonia(29%) in pyridine (50:50;v/w) for 36 hours at 37 degree C to yield crude product. The crude compound was washed with diethyl ether followed by washing with ethylacetate to remove solvent and benzoic acid .The compound is subsequently crystallized in ethanol. The pure dried product , yield 80%. The product was analyzed by HPLC , UV and ESI/MS.

Step (d):

2',3'-isopropylidine- L-rU

The dried compound was taken in take in distilled acetone (6 fold with respect to the weight of dried weight. Of the precursor), The mixture was stirred at room temperature after addition of catalytic amount of H2SO4, followed by addition of 2,2, di methoxy propane (4 eq. with respect L-rU), and further diluted with acetone & stirred for 1 hr. After this period sodium carbonate was added to the reaction mixture to bring pH to neutral. The mixture was filtered to remove solid, and the filtrate concentrated in vacuo. The crude (2',3' isopropylidene - LrU) was purified on by column chromatography (Silica gel 70-230 mesh size) , solvent system; CHCl3: MeoH (90:10), yielded pure compound, yield 85%. The product was characterized by UV, JPLC and ESI/MS. Tlc; CHCl3:MeOH (9:1); rf. 0.45); purity >98%.of the dried compound.

Step (e) 5'-O-Bz-2',3'-isopropylidine- L-rU:

The product obtained after step (d) was taken in dry pyridine (10 fold) and benzoyl Chloride (1.1 eq) was added at 0-5 degree C, and the reaction mixture was stirred at 0-5 C. for 1.5 hours. The crude reaction mixture was worked up after quenching the reaction mixture with cold methanol, followed by removal of solvent. The crude reaction product was subsequently purified by column chromatography in solvent

Shanghai Hongene Exhibit 1002

system (Chl: Hexane: acetone: 50:30:20). Pure dried product was characterized by UV, HPLC, ESI/MS. Yield; 80%.

Step (f) 5'-O-Bz- L-rU

The product obtained in the preceding step was taken in dioxane (5 fold with respect to the pure dried solid) and 2 N HCl (5 fold V;V) was added . The mixture was stirred overnight at room temperature. The mixture was quenched with solid sodium bicarbonate at 0 C till pH is neutral. The solvent was filtered and filtrate was pumped to dryness. The residue was crystallized in acetonitrile, pure product was dried and characterized by UV, HPLC, ESI/MS, yield 75%.

Step (g) 5'-O-Bz-2'- TBDMS- L-rU:

The preceeding product was taken in dry tetrahydrofuran (10 fold w/v) was added to silver nitrate/pyridine complex under stirring and under dry conditions, followed by addition of TBDMS-chloride (1.1 eq). The reaction mixture was stirred for 8 hours at room temperature.

The crude tlc indicated formation of two major spots. The reaction mixture was worked up by dilurtion with 100 fold excess ethylacetate. The organic layer was washed with saturated bicarbonate, followed by saturated brine solution. The organic layer was filtered through anhydrous sodium sulfate. The organic layer was then pumped to dryness and residue was purified by column chromatography. The pure band was characterized by UV, HPLC 1 H NMR and ESI/MS. Yield of desired 2'- isomer, approx. 55%.

Step (h) 5'-O-Bz-2'- TBDMS- 3'-O-DMT-L-rU

The preceding step well dried compound was taken in dry pyridine (10 fold; w/v) and

to the solution was added DMT-Chloride (DMT Chloride; 2.5 equivalent) . The reaction mixture was stirred for 24 hours to yield crude product. The reaction was quenched with chilled methanol (2 eq with respect to DMT- Chloride used in the reaction). The crude mixture was then concentrated in vacuum and the residue was purified by column chromatography (Silicagel; 230 400 mesh Merck grade). The pure fractions were pooled , concentrated and the product obtained was characterized by UV, HPLC, 1 H NMR and ESI/MS. Yield ; 85%.

Step (i) 5'-OH-2'- TBDMS- 3'-O-DMT-L-rU

The pure product obtained in the preceding step was taken in pyridine/ methanol (50:50 V;V) and treated with 2 N NaOH at 5 degree C for 30 minutes, while pH was maintained at 12.5-13. After 30 minutes the reaction mixture was neutralized by addition of Dowex- pyridinium cation exchange resin to yield crude product to yield. The crude compound was purified by silica gel column chromatography Silica gel 230-400 mesh E. Merck grade). The pure fractions were pooled and solvent removed . The dried product was analyzed and characterized by HPLC, UV, 1- H NMR, and ESI/MS. Yield; 90%.

Step (j): 3'-O-DMT- 2'- TBDMS- L-rU- 5'-cyanoethyl phosphoramidite

The pure dry product was phosphitylated with n, n- diisopropyl -2- cyanoethyl chloro reagent (1 .1 eq) in diisopropyl ethyl amine (2 eq,) in THF for 1.5 hours reaction at room temperature. The crude reaction was worked in usual way, followed by column chromatography to get pure product. The product was analyzed & characterized by UV, HPLC , 1 H NMR, ESI/MS and 31 P NMR.

Oligonucleotide 1 Synthesis: Oligonucleotide 1 was synthesized using 5'→3' directed REV- RNA phosphoramidite chemistry in 1 μmol scale. The synthesis were performed on Expedite 8900 synthesizer using standard RNA 1 μmol cycle and coupling time of the monomers with solid support 4.0 minute.

Amidites used (see table for activator used):

(1) N^6-Benzoyl-*2'*-*O*-TBDMS-3'-*O*-DMT-adenosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (A-N-Bz). LOT # AL300-2

(2) N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (C-N-Ac). LOT # NS143-19

(3) N^2-Isobutryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (G-N-Ibu). LOT # NS42-19

(4) *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite. LOT # NS147-19

Products Used:

(5) *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-5'-Succinyl CPG 1000A. Trityl Value; 28.4um/gm LOT # NS24-19

(6) DDTT ((Dimethylamino-methylidene)amino)-3H-1,2,4-dithiazoline -3- thione) , lot # AG015

(7) Ethyl thio tetrazole (ETT); (0.25M), lot # DP 152-4

General Procedure for 1.0 umol phosphodiester and phosphorothioate:

The aforementioned amidites (solid) were each individually taken in 20mL expedite bottle and dissolved in a quantity of dry acetonitrile to make the solution 0.075M. The bottles were flushed with Argon and shaken after sealing the screw cap promptly to dissolve solid completely. Due to the limited solubility of G-N-Ibu in dry acetonitrile, G-N-Ibu was dissolved in 50% anhydrous dichloromethane followed by addition of dry acetonitrile to make a 50:50 dichloromethane: acetonitrile solution. The monomer solution bottles were then screwed in to the synthesizer as follows: Amidite No.1 on port # 6; Amidite No.2 on port # 7; Amidite No.3 on port # 8; and Amidite No.4 on port # 9. In addition, 1.0 um expedite column with Product No.5 was prepared and attached to the synthesizer.

After completion of the synthesis per summary key features as listed in the table, the controlled pore glass (CPG) solid support was washed with 3.0 ml diethyl ether and transferred to a 2 ml microfuge tube. Oligonucleotide 1 were cleaved from the CPG

and deprotected by incubation for 30 min at 65°C in 1 ml of 40% methylamine solution in water. The supernatant was removed and the CPG was washed with 1 ml of water; supernatants were pooled and dried. The t-butyl-dimethylsilyl protecting group was removed from the RNA residue by treatment with 500 ul of fresh 12.0% solution of tetraethyl ammonium fluoride in DMSO, at 45C in ultrasonic bath for 1 hour. Oligonucleotide 1 was precipitated with 1.5 ml of n-butanol; the sample was cooled at –20°C for 1 hour then centrifuged at 10,000g for 10 minutes. The supernatant was decanted, the pellet was washed with n-butanol one more time and finally washed with 500ul ethanol and then again centrifuge at 10000 rpm for 5 minutes, the supernatant was decanted. The pellet was dissolved in 1000ul M.Q water and check the OD's (Crude desalt). Oligonucleotide 1 was then purified by Ion-Exchange HPLC using a linear gradient of in buffer A = (10.0%, 0.5M TRIS and 10.0% ACN) pH 7.5 and buffer B = 1.0 M Lithium Chloride in buffer A.

The entire sample was loaded on a Source15Q column (1.0 cm x 25 cm) and eluted with a linear 5% to 75% acetonitrile gradient over 40 minutes. Samples were monitored at 260 nm and peaks corresponding to the desired oligonucleotide species were collected, and precipitated by adding 5.0 volume of (2% $LiClO_4$, in acetone), followed by centrifuging at 10,000g for 10 minutes. The supernatant was decanted, and the pellet was washed with ethanol.

Oligonucleotide 2: Oligonucleotide 2 was synthesized using 5' → 3' directed REV- RNA phosphoramidite chemistry in 1 μmole scale. The synthesis was performed on Expedite 8900 synthesizer using standard RNA 1 μmole cycle and coupling time of the monomers with solid support 4.0 minute.

Amidites used (see table for activator used):

(1.) N^6-Benzoyl-*2'-O*-TBDMS-3'-*O*-DMT-adenosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (rA), LOT # AL300-2

(2.) N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (rC), LOT # NS143-19

(3.) N^2-Isobutryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite(rG), LOT # NS42-19

(4.) *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite(rU), LOT # NS147-19

(5.) N^6-Benzoyl-*2'*-*O*-Me-3'-*O*-DMT-adenosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite, LOT # 133-8SS

(6.) *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-5'-Succinyl CPG 1000A (rU), TV-8.4um/gm, LOT # NS24-19

(7.) Ethyl thio tetrazole (ETT); (0.25M), lot # DP 152-4

The aforementioned amidites (solid) were each individually taken in 20mL expedite bottle and dissolved in a quantity of dry acetonitrile to make the solution 0.075M. Due to the limited solubility of G-N-Ibu in dry acetonitrile, G-N-Ibu was dissolved in 50% anhydrous dichloromethane followed by addition of dry acetonitrile to make a 50:50 dichloromethane: acetonitrile solution. The monomer solution bottles are then screwed in to the synthesizer as follows: Amidite No.1 on port # 6; Amidite No.2 on port # 7; Amidite No.3, on port # 8 and Amidite No.4 on port # 9; and Amidite No.5 on port # 5. In addition, 1.0 um expedite column with Product No.6 was prepared and attached to the synthesizer. For oligonucleotide 2, the sulfurizing reagent Dimethylamino-methylidene)amino)-3H-1,2,4-dithiazoline-3-thione(DDTT) was dissolved in a pyridine:acetonitrile (90:10) to make 0.1M solution. This reagent was put on the auxillary port of the synthesizer.

Following synthesis, the controlled pore glass (CPG) solid support was washed with 3.0 mL diethyl ether and transferred to a 2 mL microfuge tube. Oligonucleotides were cleaved from the CPG and deprotected by incubation for 30 min at 65°C in 1 ml of 40% methylamine solution in water. The supernatant was removed and the CPG was washed with 1 ml of water; supernatants were pooled and dried. The t-butyl-dimethylsilyl protecting group was removed from the RNA residue by treatment with 500 uL of fresh 12.0% solution of tetraethyl ammonium fluoride in DMSO, at 45C in

ultrasonic bath for 1 hours. The oligonucleotide was precipitated by 1.5 mL of n-butanol; the sample was cooled at –20°C for 1 hour then centrifuged at 10,000g for 10 minutes. The supernatant was decanted, the pellet was washed with n-butanol one more time and washed with 500ul ethanol and centrifuged at 10000 rpm for 5 minutes. Following centrifugation, the supernatant was decanted. The pellet was dissolve in 1000ul M.Q water and the OD's was checked (Crude desalt).

The oligonucleotides were then purified by Ion-Exchange HPLC using a linear gradient of A = (10.0%, 0.5M TRIS and 10.0% ACN) pH 7.5. Buffer B = 1.0M Lithium Chloride in buffer A. The entire sample was loaded on a Source15Q column (1.0 cm x 25 cm) and eluted with a linear 15% to 95% gradient over 40 minutes. Samples were monitored at 260 nm and peaks corresponding to the desired oligonucleotide species were collected, and precipitated by adding 5.0 volume of (2% $LiClO_4$, in acetone), followed by centrifuging at 10,000g for 10 minutes. The supernatant was decanted, and the pellet was washed with ethanol.

Oligonucleotide sequences synthesized by Reverse Synthesis method.

Oligonucleotide 1 Phosphodiester Oligonucleotide	rCrArCrArGrCrArUrArCrArUrCrUrCrGrArCrCrArU (SEQ ID NO: 2) rA is N^6-Benzoyl-*2'*-*O*-TBDMS-3'-*O*-DMT-adenosine-OP rC is N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-OP rG is N^2-Isobutryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-OP rU is *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-OP
Oligonucleotide 2 Phosphorothioate oligonucleotide sequence with 2'- O-methyl bases on terminal	mA(ps)-rArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO: 4) Phosphorothioate rA is N^6-Benzoyl-*2'*-*O*-TBDMS-3'-*O*-DMT-adenosine-OP; rC is N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-OP; rG is N^2-Isobutryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-OP rU is *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-OP; mA is N^6-Benzoyl-*2'*-*O*-Me-3'-*O*-DMT-adenosine-OP; DDTT

Large Scale Oligonucleotide Synthesis:

12 umol scale phosphorothioate oligonucleotide synthesis bearing terminal 2'-O-methyl bases (seq #2) was carried out . The following data are included;

(a)Trityl Histogram; (b) CE (capillary Gel electrophoresis) of crude oligo synthesized; (c) CE & HPLC of purified oligonucleotide (d) ESI-MS analysis for molecular weight determination.

General Procedure

12 .0 umol phosphorothioate oligonucleotide:

The amidites and products were prepared and the synthesis was performed on Expedite 8900 synthesizer as described above for Oligonucleotides 1 and 2. The Scale, Monomers Coupling Time, Activator, and DDTT/Iodine reagent were as described in the table below.

Table of oligo synthesis conditions for 4min and 6min coupling time.

Monomers in dry ACN (0.075M)	**Scale**	**Monomers Coupling Time**	**Activator**	**DDTT/Iodine reagent/ Time**	**OD'S Crude (desalt)**	**CE Analysis Crude (desalted)**
Rev-RNA amidites (21 MER)	1.0 umol	4.0 min	0.25 M (ETT)	Iodine Oxidizer, 0.02M	82.0 OD'S (21-mer)	95.29%
Rev-RNA with 2'-OMe (21 MER)	1.0 umol	4.0 min	0.25 M (ETT)	Iodine Oxidizer, 0.02 M	90.0 OD'S (21-mer)	89.03%
Rev-RNA with 2'-OMe-Phosphorothioate	1.0 umol	4.0 min	0.25 M (ETT)	DDTT,(2.0min) 0.1M in Py:ACN (90:10)	93.0 OD'S (21-mer)	89.09%
Rev-RNA amidite (21 MER)	1.0 umol	6.0 min	0.25 M (ETT)	Iodine Oxidizer, 0.02M	79.0 OD'S	93.69%
Rev-RNA amidite(76 Mer)	1.0 umol	6.0 min	0.25 M (ETT)	Iodine Oxidizer, 0.02M	190.0 OD'S	GEL Traces

Rev- RNA-2'-OMe-phosphorothioate	12.0 umol	6.0 min	0.25 M (ETT)	DDTT (2.0 min; 0.1 M in Pyr:ACN	1427 OD's	92.63%

After completion of the synthesis per summary key features as listed in the table, the controlled pore glass (CPG) solid support was washed with 15 mL diethyl ether and transferred to a 8X2 ml microfuge tube. Oligonucleotides were cleaved from the CPG and deprotected by incubation for 30 min at 65°C in 1 mL of 40% methylamine solution in water. The supernatant was removed and the CPG was washed with 1 ml of water; supernatants were pooled and dried. The t-butyl-dimethylsilyl protecting group was removed from the RNA residue by treatment with 500 ul of fresh 12.0% solution of tetraethyl ammonium fluoride in DMSO, at 45C in ultrasonic bath for 1 hour. The oligonucleotide was precipitated with 1.5 ml of n-butanol; the sample was cooled at –20°C for 1 hour then centrifuged at 10,000g for 10 minutes. The supernatant was decanted, the pellet was washed with n-butanol one more time and finally washed with 500ul ethanol and then again centrifuge at 10000 rpm for 5 minutes, the supernatant was decanted. The pellet was dissolve in 1000ul M.Q water and check the OD's (Crude desalt).

Crude RNA purity is obtained above is in the range of 90-92% by HPLC or CE analysis. Subsequent purification is done by either ion-exchange or reverse phase HPLC. The purification results in purified RNA ranging in 92% to 98% purity.

Details of Purification:

The oligonucleotide was then purified by Ion-Exchange HPLC using a linear gradient of in buffer A = (10.0%, 0.5M TRIS and 10.0% ACN) pH 7.5.
Buffer B = 1.0M Lithium Chloride in buffer A.

The entire sample was loaded on a Source15Q column (1.0 cm x 25 cm) and eluted with a linear 60% to 100% buffer B gradient over 40 minutes. Samples were monitored at 260 nm and peaks corresponding to the desired oligonucleotide peak was

collected, and precipitated by adding 5.0 volume of (2% $LiClO_4$, in acetone), followed by centrifuging at 10,000g for 10 minutes. The supernatant was decanted, the pellet was washed with ethanol, yield; 343.0 OD (260 nm); purity (analyzed by CE) ; 98.01%.

Abbreviations:
mA; (2'-Omethyl-r-adenosine);
rC; (r-cytidine);
rG(r-guanosine);
rU (r-uridine)

Sequence listings:

REV-RNA-Me – SEQ (With Methoxy)
SEQ: rUmrArCrCrArGrCrUrCrUrArCrArUrArCrGrArCrAmrA (SEQ ID NO 1)

REV-RNA-Me-THIO-4Min Coupling Time
SEQ: rU-p(s)mrA-p(s)rC-p(s)rC-p(s)rA-p(s)rG-p(s)rC-p(s)rU-p(s)rC-p(s)rU-p(s)rA-p(s)rC-p(s)rA-p(s)rU-p(s)rA-p(s)rC-p(s)rG-p(s)rA-p(s)rC-p(s)rA-p(s)mrA-p(s)
(SEQ ID NO 2)

REV-RNA- 4Min Coupling Time (Without Methoxy)
SEQ: rUrArCrCrArGrCrUrCrUrArCrArUrArCrGrArCrArC
(SEQ ID NO 3)

76 MER

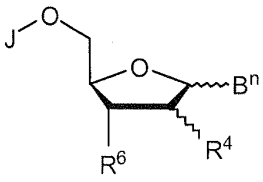
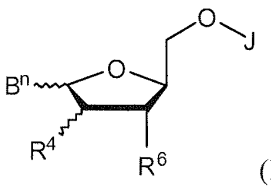
SEQ: rGrCrC rCrGrG rArUrA rGrCrU rCrArG rUrCrG rGrUrA rGrArG rCrArUrCrArG rArCrU rUrUrU rUrArU rCrUrG rArGrG rGrUrC rCrArG rGrGrUrUrCrA rArGrU rCrCrC rUrGrU rUrCrG rGrGrC rGrCrC rA
(SEQ ID NO 4)

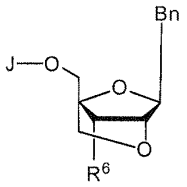
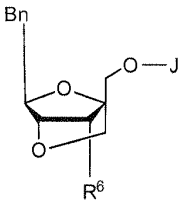
While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

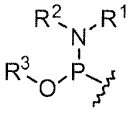
CLAIMS

What is claimed is:

1. A compound of Formula Ia, Ib, Ic, or Id:


(Ia) or

(Ib);


(Ic) or

(Id), wherein

J is H,  , or  , wherein ⌇ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl;

R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

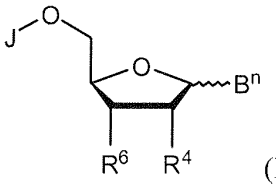
R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the

alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

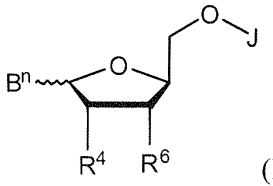
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

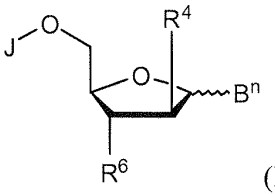
R^4 is a --halo, $--R^5$, $--NR^7R^8$, $-OR^9$, $--SR^{10}$, or 2'-blocking group,; or when Structural Formula Ia or Ib is:



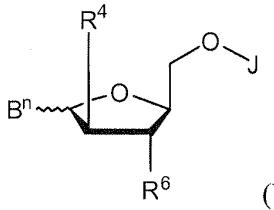
(II), or



(III); wherein R^4 is further selected from $O\text{-}Si(R^{11})_3$ or $O\text{-}CH_2\text{-}Si(R^{11})_3$; or when Structural Formula Ia or Ib is:



(IV), or



(V); R^4 is further selected from $-OC(=O)R^{12}$;

each R^5 is independently a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with $-NR^7R^8$, $(C_1\text{-}C_4)$alkylamino, di$(C_1\text{-}C_4)$alkylamino, $-OR^9$, $(C_1\text{-}C_6)$alkoxy, benzyl or substituted benzyl, $-SR^{10}$; or $-S\text{-}(C_1\text{-}C_6)$alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1-16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

Shanghai Hongene Exhibit 1002

N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C$(CH_2)_{1-8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

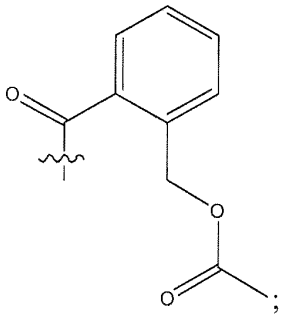
wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with

fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; -C(=O)$CH_2CH_2CH=CH_2$l; -C(=O)(C_1-C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; =CR^8N(C_1-C_6)alkyl)$_2$; -C(=O)-NR^8-$(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$;

-C(=O)-$(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$;

-C(=O)-$NR^8(CH_2)_{1\text{-}16}NR^8$C(=O)-phthalimide;

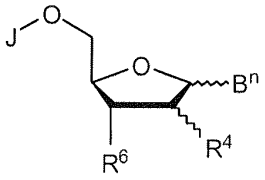
-C(=O)-$(CH_2)_{1\text{-}16}$-phthalimide; and



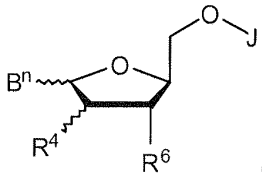
;

wherein any substitutable oxygen atom within the nucleobase is optionally substituted with –C(=O)N(C_1-C_6alkyl)$_2$ – C(=O)N(phenyl)$_2$.

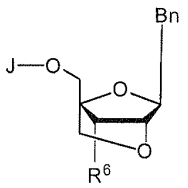
2. A compound of Formula Ia, Ib, Ic, or Id:



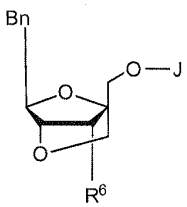
(Ia) or



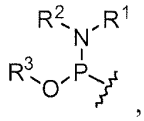
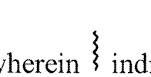
(Ib);



(Ic) or



(Id), wherein

J is H,  , or  , wherein ≀ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

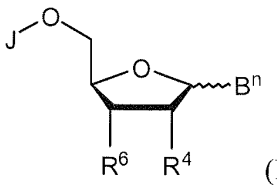
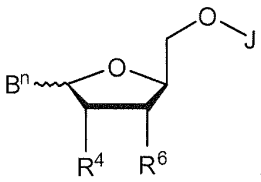
R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

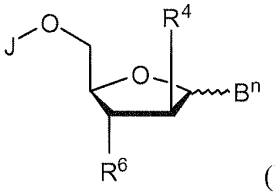
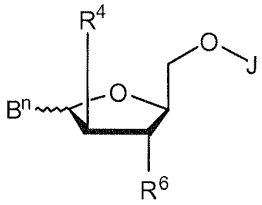
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

R^4 is a --halo, --R^5, --NR^7R^8, -OR^9, --SR^{10}, or 2'-blocking group,; or when Structural Formula Ia or Ib is:

(II), or (III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:

(IV), or (V); R^4 is further selected from -OC(=O)R^{12};

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with –NR^7R^8, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, -OR^9, (C_1-C_6)alkoxy, benzyl or substituted benzyl, -SR^{10}; or -S-(C_1-C_6)alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; -C(=O)-$(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1\text{-}16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1\text{-}16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1\text{-}16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

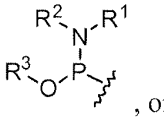
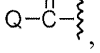
each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1\text{-}16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group; provided that if R^4 is –O-Si(R^{11})$_3$, and two R^{11} groups are both methyl, the other is not t-butyl or if R^4 is -O-CH_2-Si(R^{11})$_3$, then the three R^{11} groups cannot all be isopropyl;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

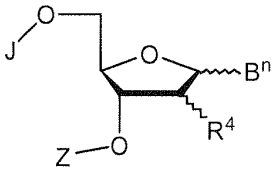
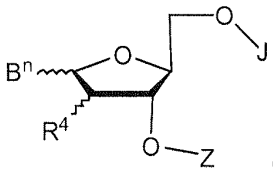
Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group.

3. The compound of Claim 1, wherein J is  , or  , wherein ≀ indicates where J is attached to the O atom.

Shanghai Hongene Exhibit 1002

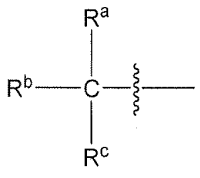
4. The compound of Claim 1, wherein the compound is represented by Formula Ia or Ib:


(Ia);

(Ib) or a salt thereof.

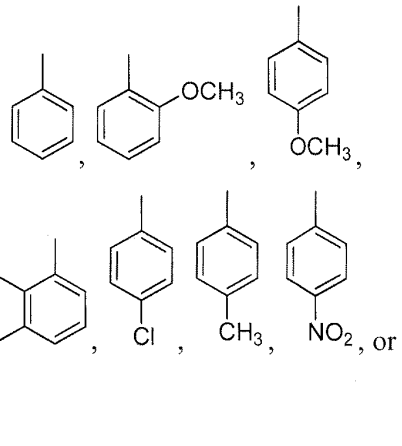
5. The compound of Claim 1, wherein Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl.

6. The compound of Claim 5, wherein Z is di-p-anisylphenyl methyl, p-fluorophenyl-1- naphthylphenyl methyl, p-anisyl-1- naphthylphenyl methyl, di-o-anisyl-1- naphthyl methyl, di-o-anisylphenyl methyl, p-tolyldiphenylmethyl, di-p-anisylphenylmethyl, di-o-anisyl-1-naphthylmethyl, di-p-anisylphenyl methyl, di-o-anisyl phenyl methyl, di-p-anisylphenyl methyl, or p-tolyldiphenylmethyl.

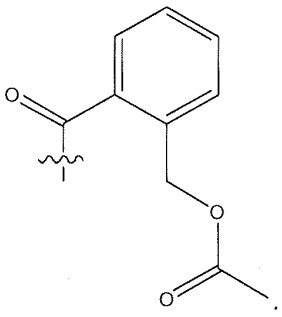
7. The compound of Claim 5, wherein Z is represented by the following structural formula:


, wherein ≀ indicates attachment to the 3' oxygen atom and R^a, R^b, and R^c are independently selected from the

Shanghai Hongene Exhibit 1002

following structural formulas: 

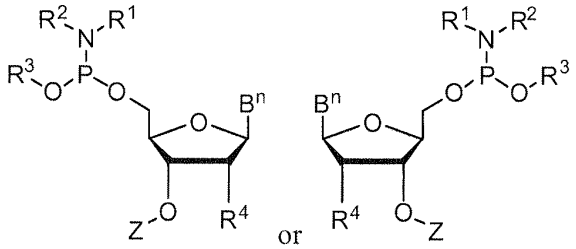
8. The compound of Claim 5, wherein Z is 4-methoxytrityl, 4, 4'-dimethoxytrityl, or 4, 4', 4"-trimethoxytrityl.

9. The compound of Claim 1, wherein the substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with $=CHN(CH_3)_2$; $C(=O)CH(CH_3)_2$; $-C(=O)CH_3$, $=C(CH_3)N(CH_3)_2$; $-C(=O)OPh$; $-C(=O)CH_2CH_2CH=CH_2$; $-C(=O)CH_2CH_2-C(=O)O(C_1-C_6)alkyl$; $-C(=O)-NR^8-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-NR^8(CH_2)_{1-16}NR^8C(=O)$-phthalimide;  $-C(=O)-(CH_2)_{1-16}$-phthalimide and .

10. The compound of Claim 4, wherein R^3 is $-CH_2CH_2CN$, $-CH_2CH_2-Si(CH3)_2C_6H_5$, $-CH_2CH_2-S(O)_2-CH_2CH_3$, $-CH_2CH_2-C_6H_4-NO_2$, $-CH_2CH_2-NH-C(O)-C_6H_5$, or $-CH_2CH_2-O-C_6H_4-C(O)CH_3$, and R^4 is $--O-Si(R^{11})_3$.

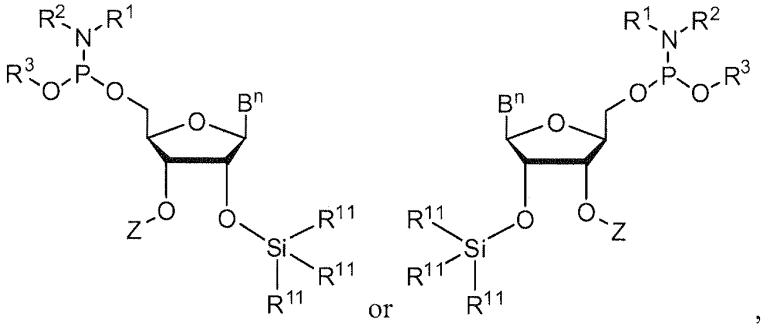
11. The compound of Claim 10, wherein R^4 is $-O-Si(CH_3)_2(C(CH3)_3)$ or $-O-CH_2-Si(CH(CH_3)_2)_3$).

12. The compound of Claim 1, wherein the compound is represented by one of the following structural formulas :



or a salt thereof.

13. The compound of Claim 12, wherein the compound is represented by one of the following structural formulas:

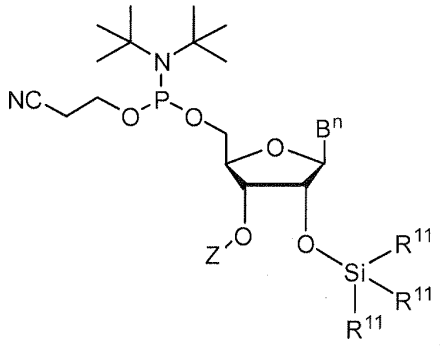


, or a salt thereof.

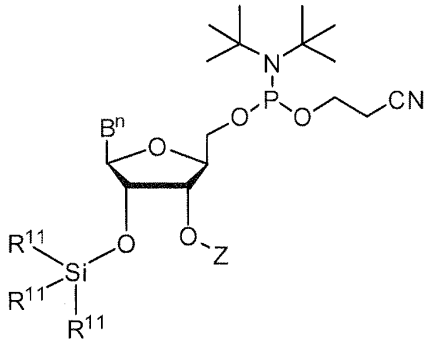
14. The compound of Claim 13, wherein R^3 is $-CH_2CH_2CN$.

Shanghai Hongene Exhibit 1002

15. The compound of Claim 14, wherein the compound is represented by one of the following structural formulas:

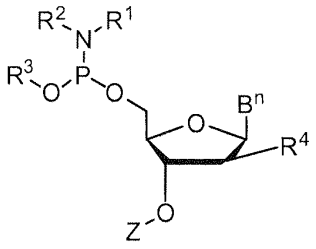


, or

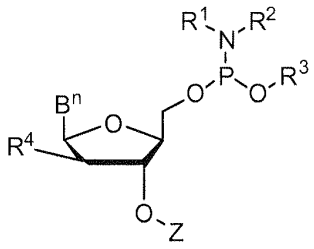


or a salt thereof.

16. The compound of Claim 1, wherein the compound is represented by one of the following structural formulas:

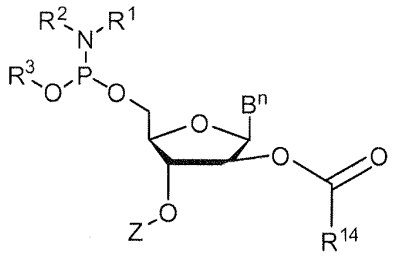
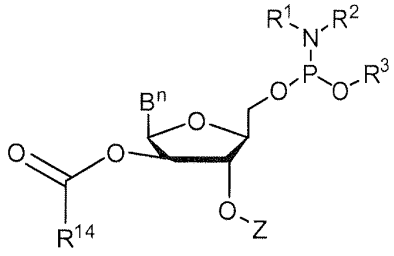


or



, or a salt thereof.

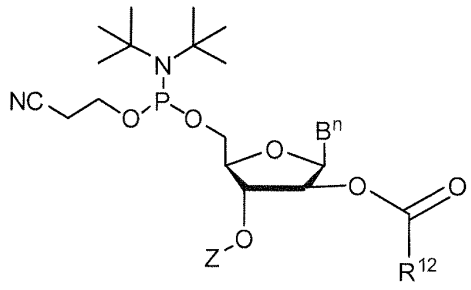
17. The compound of Claim 16, wherein the compound is represented by one of the following structural formula:

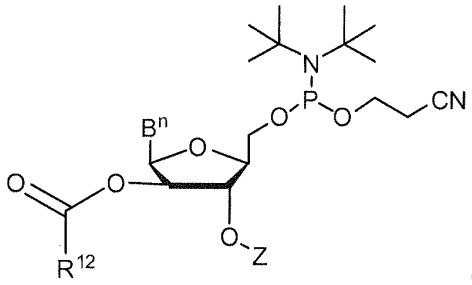
, or or a salt thereof.

18. The compound of Claim 17, wherein R^3 is CH_2CH_2CN.

19. The compound of Claim 18, wherein the compound is represented by one of the following structural formulas:

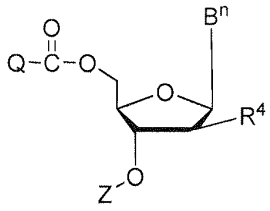
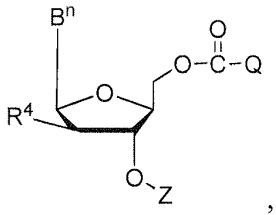


, or



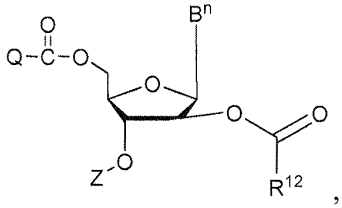
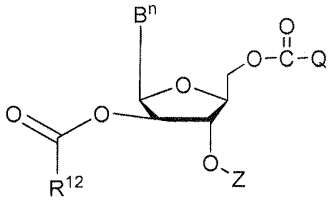
or a salt thereof.

20. The compound of Claim 1, wherein the compound is represented by one of the following structural formulas :

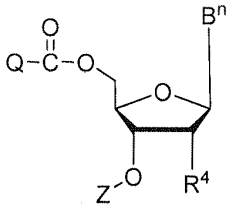
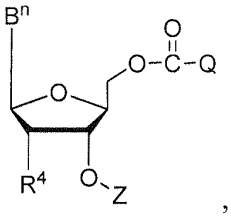
or , or a salt thereof.

21. The compound of Claim 20, wherein the compound is represented by one of the following structural formulas:

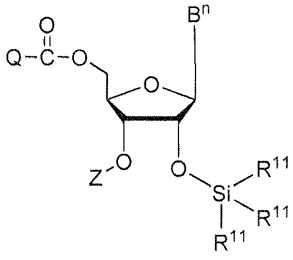
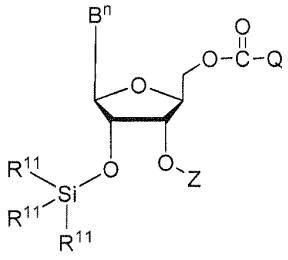
, or or a salt thereof.

22. The compound of Claim 1, wherein the compound is represented by one of the following structural formulas:

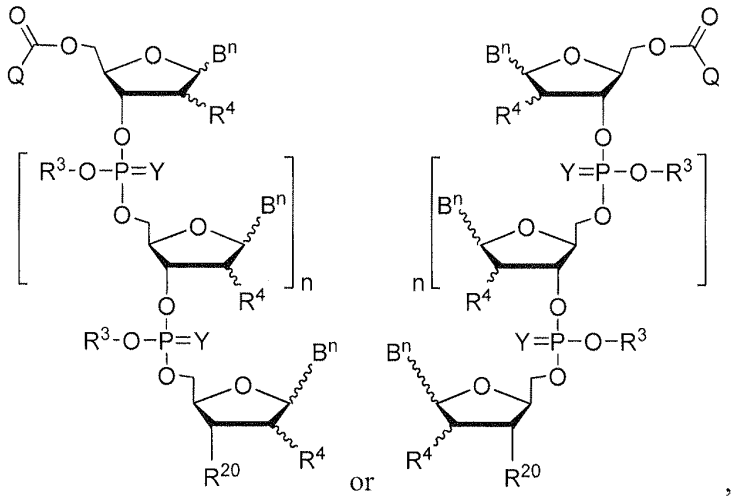
or , or a salt thereof.

23. The compound of Claim 22, wherein the compound is represented by one of the following structural formulas:

or , or a salt thereof.

24. A compound represented by one of the following structural formulas:



or

, wherein

each Y is independently oxygen or sulfur;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein

the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

R^4 is a --halo, $--R^5$, $--NR^7R^8$, $-OR^9$, $--SR^{10}$, or 2'-blocking group; or when R^4 is in the ribose conformation , R^4 is further selected from $O\text{-}Si(R^{11})_3$ or $O\text{-}CH_2\text{-}Si(R^{11})_3$; or R^4 is in the arabinose conformation, R^4 is further selected from $-OC(=O)R^{12}$;

each R^5 is independently a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with $-NR^7R^8$, $(C_1\text{-}C_4)$alkylamino, di$(C_1\text{-}C_4)$alkylamino, $-OR^9$, $(C_1\text{-}C_6)$alkoxy, benzyl or substituted benzyl, $-SR^{10}$; or $-S\text{-}(C_1\text{-}C_6)$alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; $-C(=O)\text{-}(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$; $-C(=O)\text{-}(CH_2)_{1\text{-}16}NR^8C(=O)$-phthalimide; $-C(=O)\text{-}(CH_2)_{1\text{-}16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group;

each R^8 is H or a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, or a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

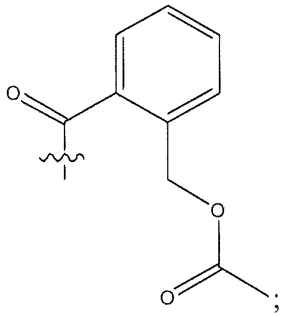
Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C$(CH_2)_{1-8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-

C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; -C(=O)$CH_2CH_2CH=CH_2$l; -C(=O)(C_1-C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; =CR^8N(C_1-C_6)alkyl)$_2$; -C(=O)-NR^8-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$NR^8(CH_2)_{1-16}NR^8$C(=O)-phthalimide; -C(=O)-$(CH_2)_{1-16}$-phthalimide; and



wherein any substitutable oxygen atom within the nucleobase is optionally substituted with $-C(=O)N(C_1\text{-}C_6alkyl)_2$ – $C(=O)N(phenyl)_2$;

R^{20} is H, –O-Z, or R^{21};

R^{21} is 3' functional group;

Z is an acid labile protecting group;and

n is 0 to 150;

or a salt thereof.

25. The compound of Claim 24, wherein R^{21} is

a) cyanoethyl phosphate-polyethylene glycols^{v}, where v is 2-100 and is number of glycol units;

b) cyanoethyl phosphate –linker attached with cholesterol, biotin, fluoresceins, cyanine dyes, psoralen, tetramethylrhodamine dye, dabcyl dye, C-3 disulfide, C-6 disulfide, symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}), symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}) with a terminal amino group protected with CF3C(=O) or phthalamido or FMOC, (C_1-C_{16})alkylene-amine protected with a amine protecting group, (C_1-C_5)alkylene- amine protected with an azide group; (C_1-C_5)alkylene-amine protected amine protected with an acetylene (C triple bond CH) group

c) cyanoethyl phosphate –ethane-2-ol- protected with DMT group or other acid labile groups, cyanoethyl phosphate –propane -3-ol- protected with DMT group or other acid labile groups,

d) (C_1-C_{50})alkylene with a terminal hydroxy;

e)lipids , carboxyl groups, or peptide; or

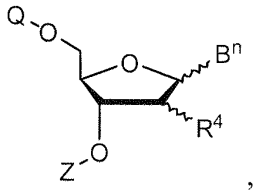
f) a branched phosphoramidite.

26. The compound of Claim 24, wherein n is 5-75.

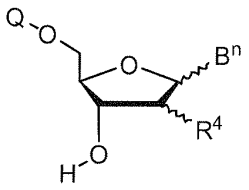
27. A synthetic RNA molecule with purity exceeding 97 % and synthesized from a 5'phosphoramidite nucleoside.

28. A method of preparing an oligonucleotide by bond formations in the 5'- to 3'- direction for the synthesis of RNA oligomers and enantiomers thereof, said method comprises the following steps

a) cleavage of the Z protecting group from a compound attached to the support represented by the following structural formula:

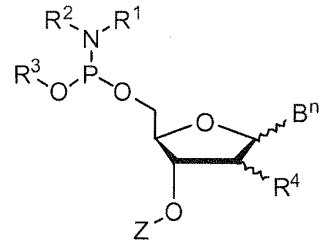


, thereby forming a compound represented by structural formula (XX):

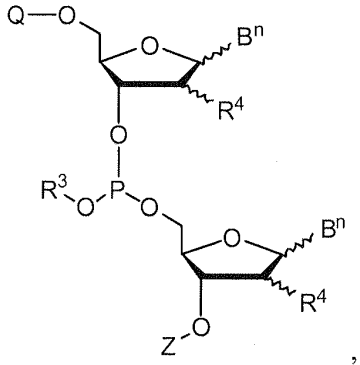


(XX);

b) reacting the compound represented by structural formula XX with a compound of structural formula XXI:



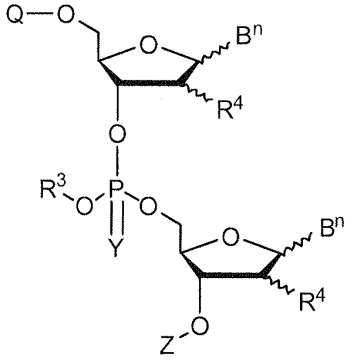
(XXI), thereby forming 2-mer compound represented by the following structural formula:



,

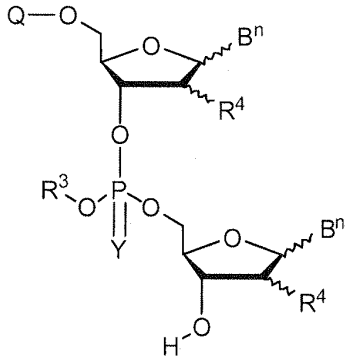
c) reacting the 2-mer with a capping agent;

d) oxidizing or sulfurization of the trivalent phosphorous group of the 2-mer compound to form a compound of structural formula XXII:



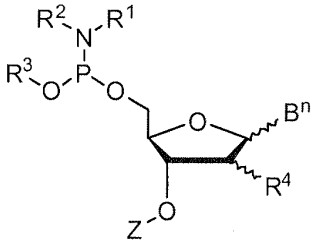
(XXII);

e) cleavage of the Z protecting group from a compound represented by the structural formula XXII, thereby forming a compound of structural formula XXIII:

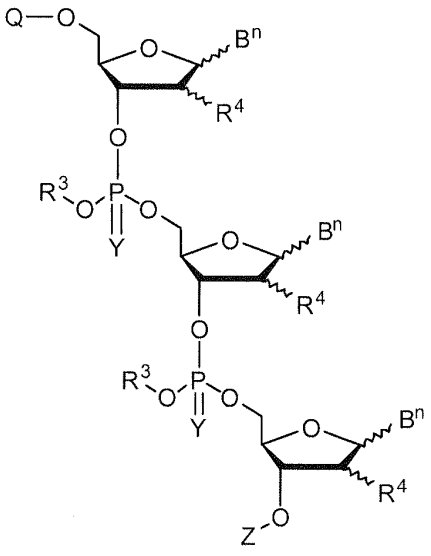


(XXIII);

f) reacting the compound represented by structural formula XXIII with a compound represented by the following structural formula:



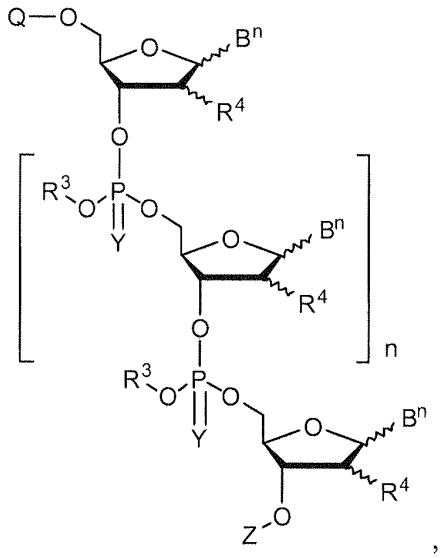
, thereby forming a 3-mer represented by the following structural formula XXIV:



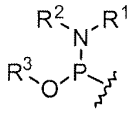
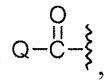
XXIV;

e) cleavage of the Z protecting group from a compound represented by structural formula XXIV;

g) repeating steps a) through e) n times, thereby forming a oligonucleotide represented by the following structural formula:



, or a salt thereof, wherein

J is  , or  , wherein ≀ indicates where J is attached to the O atom;

Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy , or levulinyl;

R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

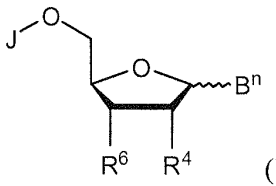
R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the

alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

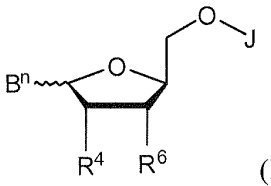
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

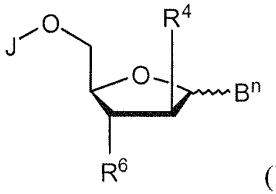
R^4 is a --halo, $--R^5$, $--NR^7R^8$, $-OR^9$, $--SR^{10}$, or 2'-blocking group,; or when Structural Formula Ia or Ib is:



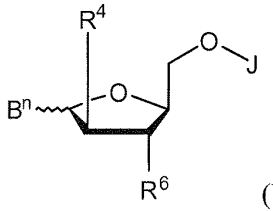
(II), or



(III); wherein R^4 is further selected from $O\text{-}Si(R^{11})_3$ or $O\text{-}CH_2\text{-}Si(R^{11})_3$; or when Structural Formula Ia or Ib is:



(IV), or



(V); R^4 is further selected from $-OC(=O)R^{12}$;

each R^5 is independently a substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group, a substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with $-NR^7R^8$, $(C_1\text{-}C_4)$alkylamino, di$(C_1\text{-}C_4)$alkylamino, $-OR^9$, $(C_1\text{-}C_6)$alkoxy, benzyl or substituted benzyl, $-SR^{10}$; or $-S\text{-}(C_1\text{-}C_6)$alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1-16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

Z is an acid labile protecting group;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6, N6-dimethyl adenine, N6-benzoyladenine, N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7- deaza-7-iodo adenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with -C≡C$(CH_2)_{1-8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6- methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, 4-thiouracil, N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoro methyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

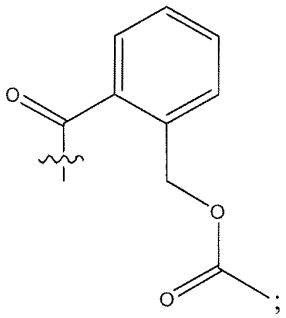
wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with

fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; -C(=O)$CH_2CH_2CH=CH_2$l; -C(=O)(C_1-C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; =CR^8N(C_1-C_6)alkyl)$_2$; -C(=O)-NR^8-$(CH_2)_{1-16}NR^8C(=O)CF_3$;

-C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$;

-C(=O)-$NR^8(CH_2)_{1-16}NR^8$C(=O)-phthalimide;

-C(=O)-$(CH_2)_{1-16}$-phthalimide; and



;

wherein any substitutable oxygen atom within the nucleobase is optionally substituted with –C(=O)N(C_1-C_6alkyl)$_2$ – C(=O)N(phenyl)$_2$; an

n is 1 to 150;

or a salt thereof.

29. The method of Claim 28, wherein each Y group is independently introduced via sulfurization to form a phosphorothioate linkage or via oxidation to form a phosphate linkage.

30. The method of Claim 29, wherein the R^3 group is eliminated after oxidation to form a phosphate linkage.

31. The method of Claim 29, wherein the R^3 group is eliminated after sulfurazation to form a phosphorothioate linkage.

32. The method of Claim 31, wherein the nucleobase protecting groups are deprotected with a base.

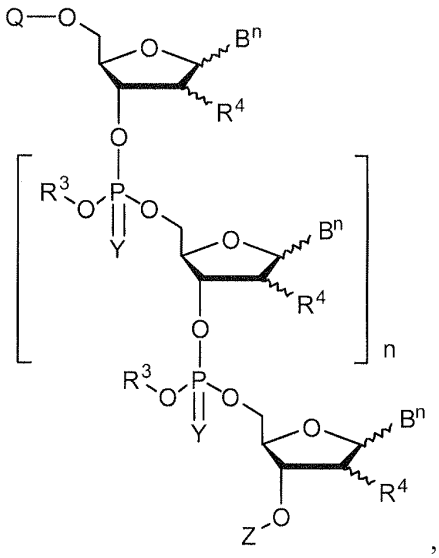
33. The method of Claim 32, wherein the base is selected from aq ammonia, methanolic ammonia, or ethanolic ammonia.

34. The method of Claim 32, wherein R^4 is $-OSi(R^{11})_3$.

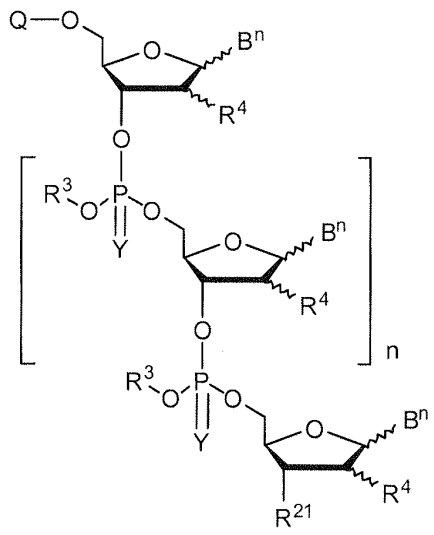
35. The method of Claim 34, wherein the method further comprises the step of cleaving $-OSi(R^{11})_3$ with a fluoride salt.

36. The method of Claim 35, wherein the fluoride salt is tetraethylammonium fluoride.

37. The method of Claim 28, further comprising the step of reacting the compound represented by the following structural formula:



, with a 3' functional group, thereby forming a compound of represented by the following structural formula;



, wherein R^{21} is the 3'functional group or a salt thereof.

38. The compound of Claim 37, wherein R^{21} is

a) cyanoethyl phosphate-polyethylene glycols^{v}, where v is 2-100 and is number of glycol units;

b) cyanoethyl phosphate –linker attached with cholesterol, biotin, fluoresceins, cyanine dyes, psoralen, tetramethylrhodamine dye, dabcyl dye, C-3 disulfide, C-6 disulfide, symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}), symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}) with a terminal amino group protected with CF3C(=O) or phthalamido or FMOC, (C_1-C_{16})alkylene-amine protected with a amine protecting group, (C_1-C_5)alkylene- amine protected with an azide group; (C_1-C_5)alkylene-amine protected amine protected with an acetylene (C triple bond CH) group

c) cyanoethyl phosphate –ethane-2-ol- protected with DMT group or other acid labile groups, cyanoethyl phosphate –propane -3-ol- protected with DMT group or other acid labile groups,

d) (C_1-C_{50})alkylene with a terminal hydroxy;

e) lipids, carboxyl groups, or peptide; or

f) a branched phosphoramidite.

39. A RNA molecule made by the method of Claim 28 having a purity of 97% or greater following purification of the synthesized RNA molecule by HPLC, ion exchange, or reverse phase chromatography.

ABSTRACT OF THE DISCLOSURE

The present invention provides building blocks and methods for synthesizing very pure RNA in a form that can efficiently be modified at the 3' end. Reverse RNA monomer phosphoramidites have been developed for RNA synthesis in 5'→ 3' direction, leading to very clean oligo synthesis that allows for the introduction of various modifications at the 3'-end cleanly and efficiently. Higher coupling efficiency per step have been observed during automated oligo synthesis with the reverse RNA amidites disclosed herein, resulting in a greater ability to achieve higher purity and produce very long oligonucleotides. The use of the reverse RNA phosphoramidites in the synthetic process of this invention leads to oligonucleotides free of N+1 species.

Shanghai Hongene Exhibit 1002

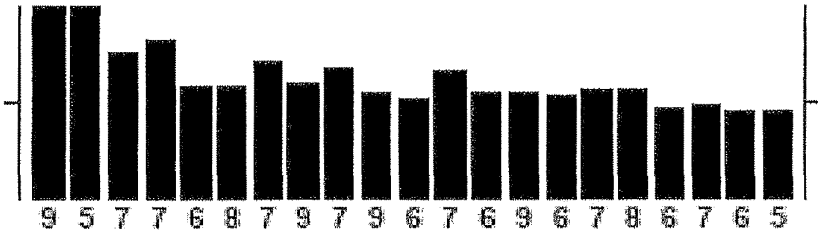


FIG. 1A

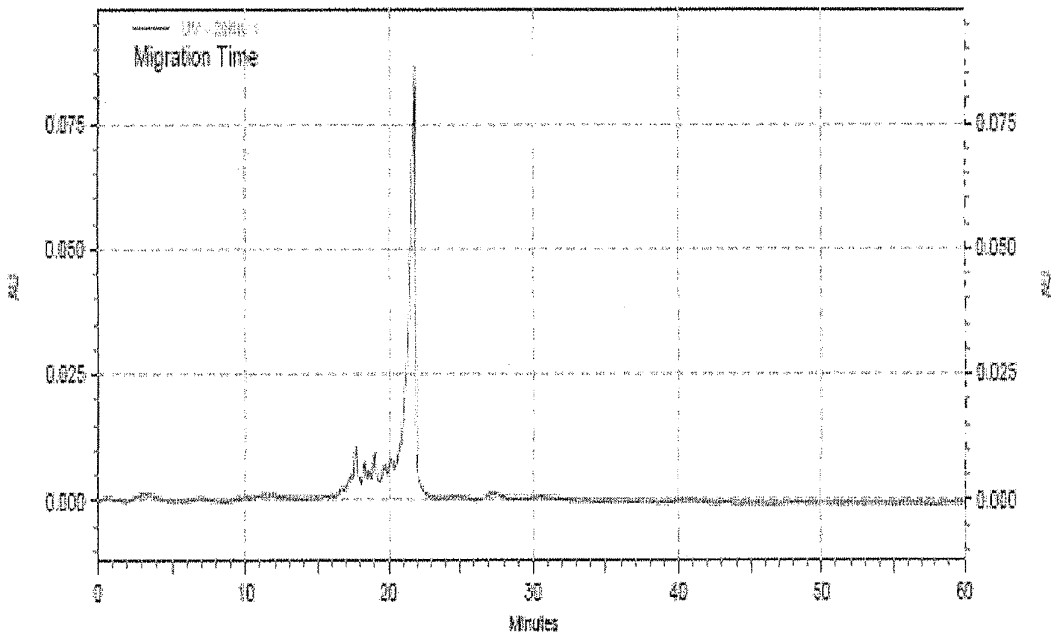


FIG. 1B

Shanghai Hongene Exhibit 1002

UV - 200nm
Results

Time	Height	Area	Area %
17.367	2830	16392	0.45
17.663	7726	56557	1.57
17.729	8696	59447	1.65
17.788	6589	13327	0.37
17.883	2591	11215	0.31
18.288	5460	36314	1.01
18.333	5684	17932	0.50
18.358	5244	9679	0.27
18.392	4241	13766	0.38
18.542	3130	10727	0.30
18.613	3767	29016	0.80
18.692	3198	15183	0.42
19.033	7751	138415	3.84
19.712	5169	129375	3.59
20.171	6366	164372	4.56
20.550	5723	37498	1.04
21.837	85024	2847215	78.95
Totals	169189	3606430	100.00

FIG. 1C

Shanghai Hongene Exhibit 1002

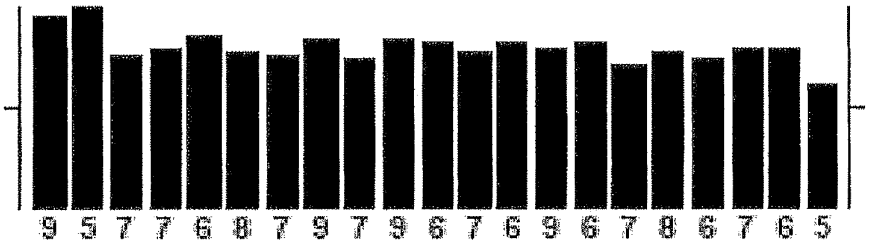

9 5 7 7 6 8 7 9 7 9 6 7 6 9 6 7 8 6 7 6 5

FIG. 2A

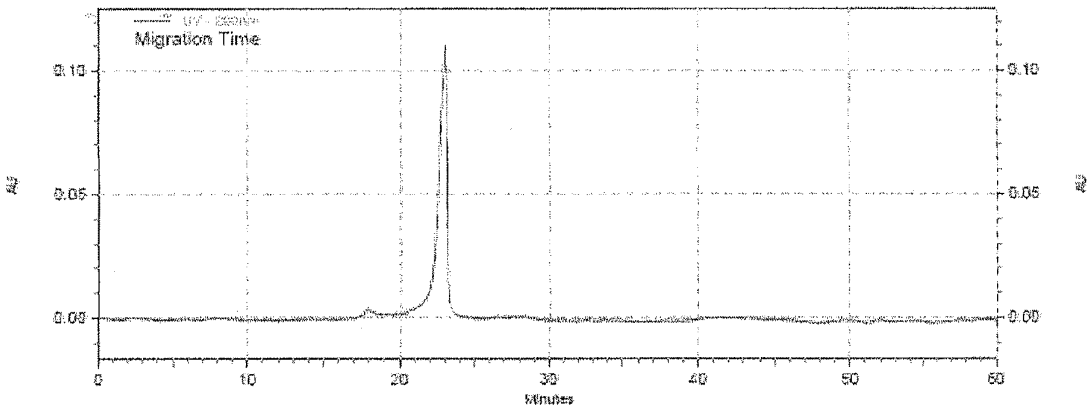

Migration Time
0.10
0.05
0.00
0
10
20
30
40
50
60
Minutes

FIG. 2B

UV - 200nm
Results

Time	Height	Area	Area %
17.550	617	14699	0.30
17.892	3270	84889	1.71
18.896	884	42940	0.87
19.079	1609	30490	0.62
19.804	1764	59025	1.19
21.058	3925	112388	2.27
21.550	6191	142628	2.88
23.046	110750	4414791	89.09
24.904	198	53425	1.08
Totals	129208	4955275	100.00

FIG. 2C

Shanghai Hongene Exhibit 1002

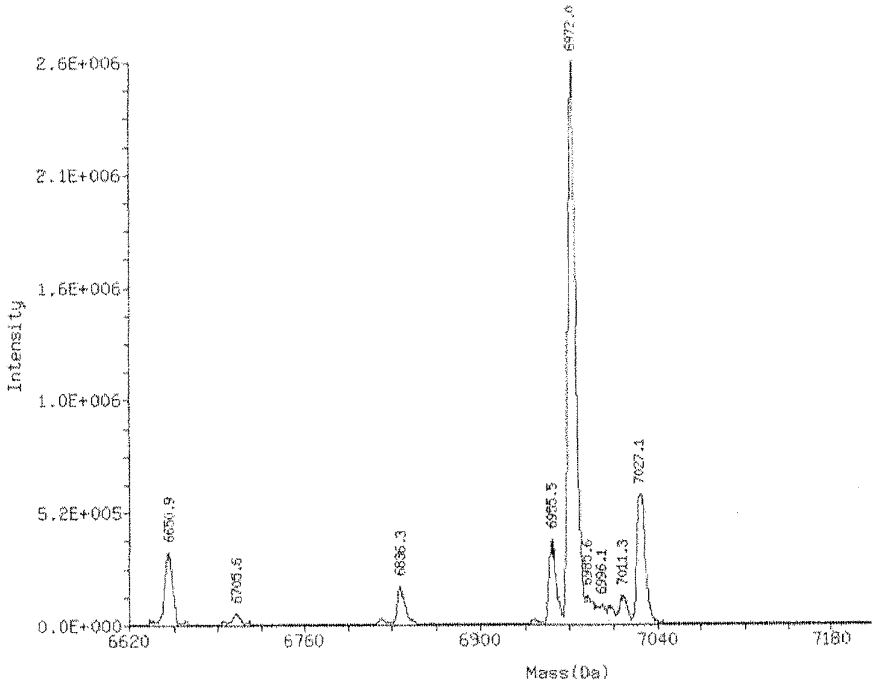


FIG. 2D

Shanghai Hongene Exhibit 1002

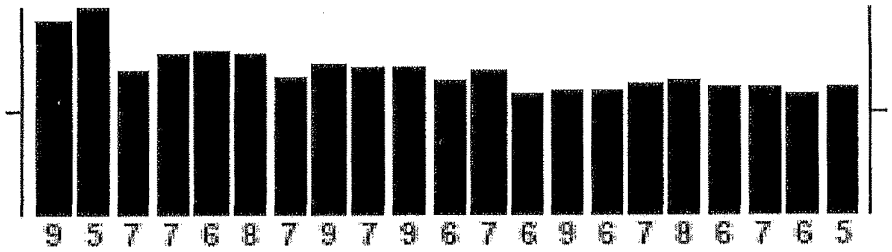


FIG. 3A

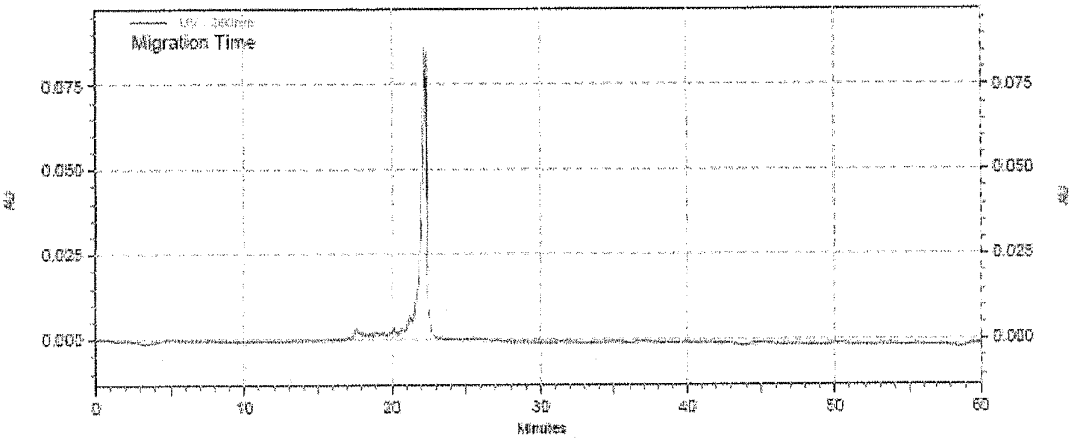


FIG. 3B

Shanghai Hongene Exhibit 1002

UV - 200nm
Results

Time	Height	Area	Area %
17.654	3340	12127	0.47
17.688	3452	9191	0.35
19.188	1584	9953	0.38
19.908	2163	9338	0.36
20.192	3111	11230	0.43
20.217	3348	9631	0.37
20.333	2004	14702	0.56
20.683	3015	28095	1.08
20.750	3029	26439	1.01
21.313	6686	155191	5.95
22.396	85829	2320510	89.03

Totals	117561	2606407	100.00

FIG. 3C

Shanghai Hongene Exhibit 1002



FIG. 4A

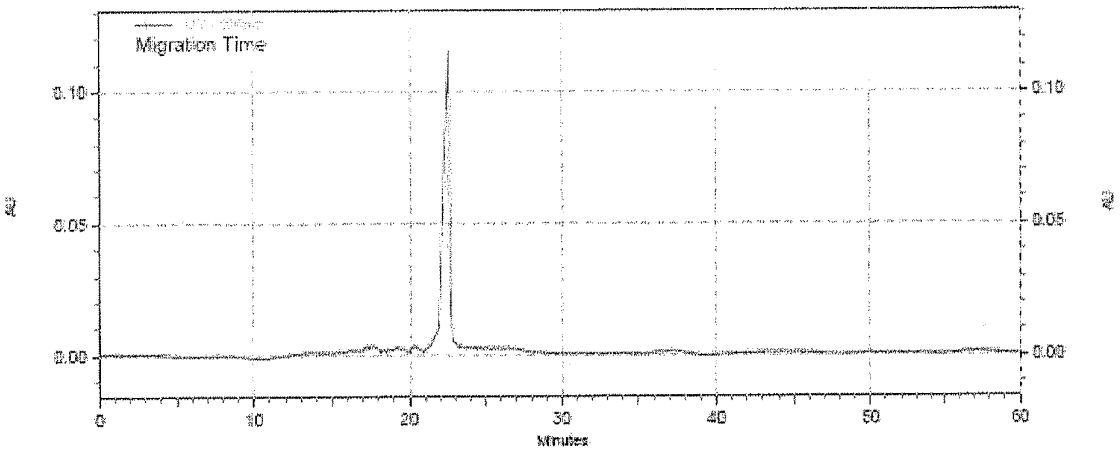


FIG. 4B

Shanghai Hongene Exhibit 1002

UV - 200nm
Results

Time	Height	Area	Area %
17.304	1410	20826	0.60
17.663	1508	12887	0.37
17.762	1385	16366	0.47
19.208	1113	16037	0.46
19.929	1225	16374	0.47
20.383	1568	19428	0.56
20.967	908	10362	0.30
21.329	1635	17295	0.50
22.613	113518	3311035	95.29
23.383	1236	9540	0.27
23.879	1061	11808	0.34
24.271	820	12711	0.37
Totals	127387	3474669	100.00

FIG. 4C

Shanghai Hongene Exhibit 1002

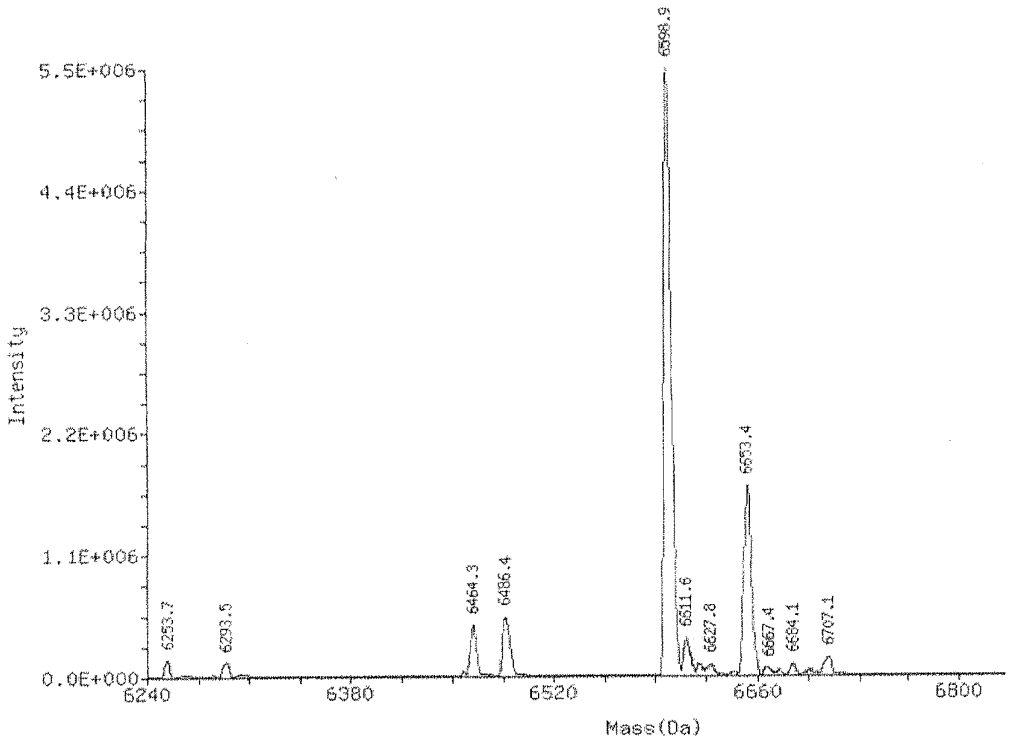


FIG. 4D

Shanghai Hongene Exhibit 1002

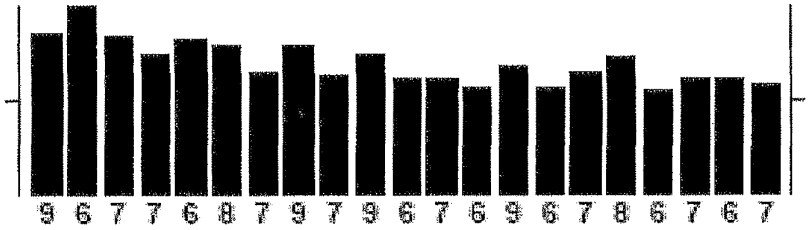

9 6 7 7 6 8 7 9 7 9 6 7 6 9 6 7 8 6 7 6 7

FIG. 5A

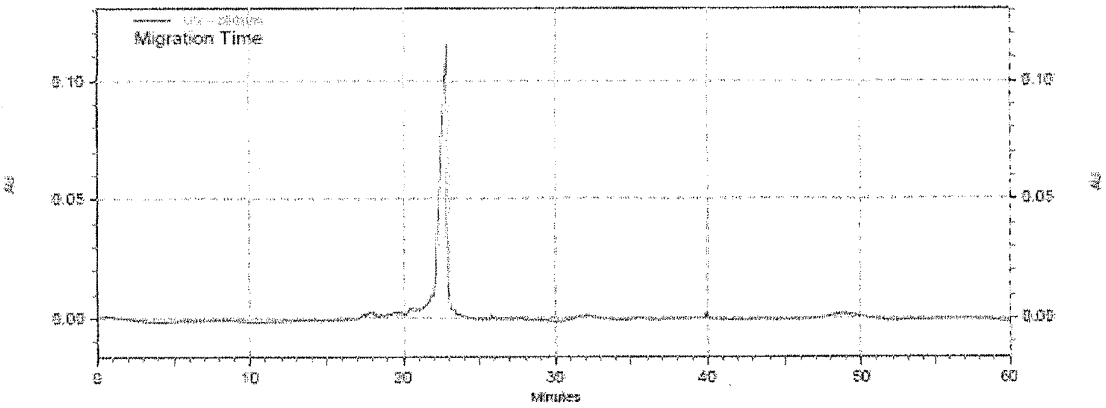

Migration Time
0.10
0.05
0.00
0
10
30
40
50
60
Minutes

FIG. 5B

UV - 200nm
Results

Time	Height	Area	Area %
17.867	2612	124390	3.14
19.767	2308	125679	3.17
22.879	114213	3710219	93.69
Totals	119133	3960288	100.00

FIG. 5C



FIG. 6A

Shanghai Hongene Exhibit 1002

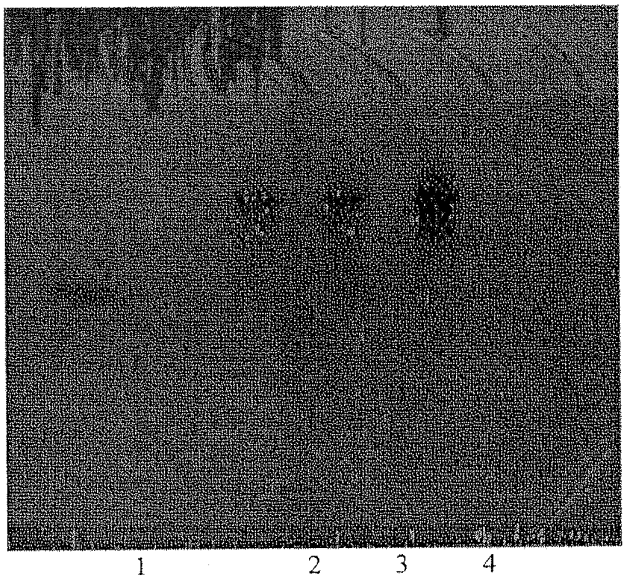


FIG. 6B

Shanghai Hongene Exhibit 1002

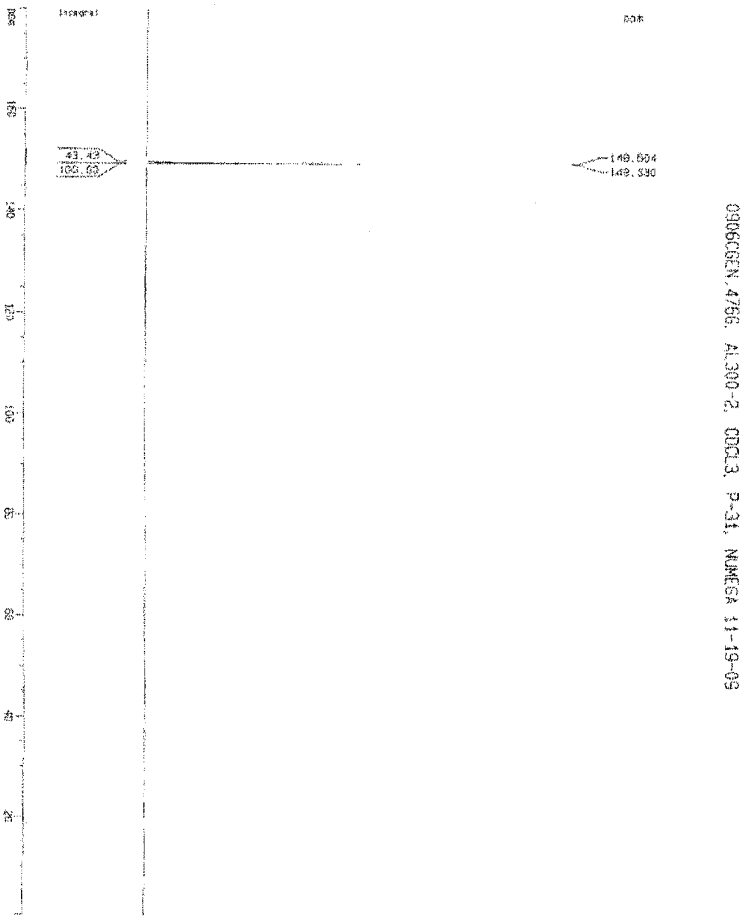

Integral
43.42
100.00
149.604
149.330
0906CSEN,4756, AL300-2, CDCL3, P-31, NUMESA 11-19-09

FIG. 7

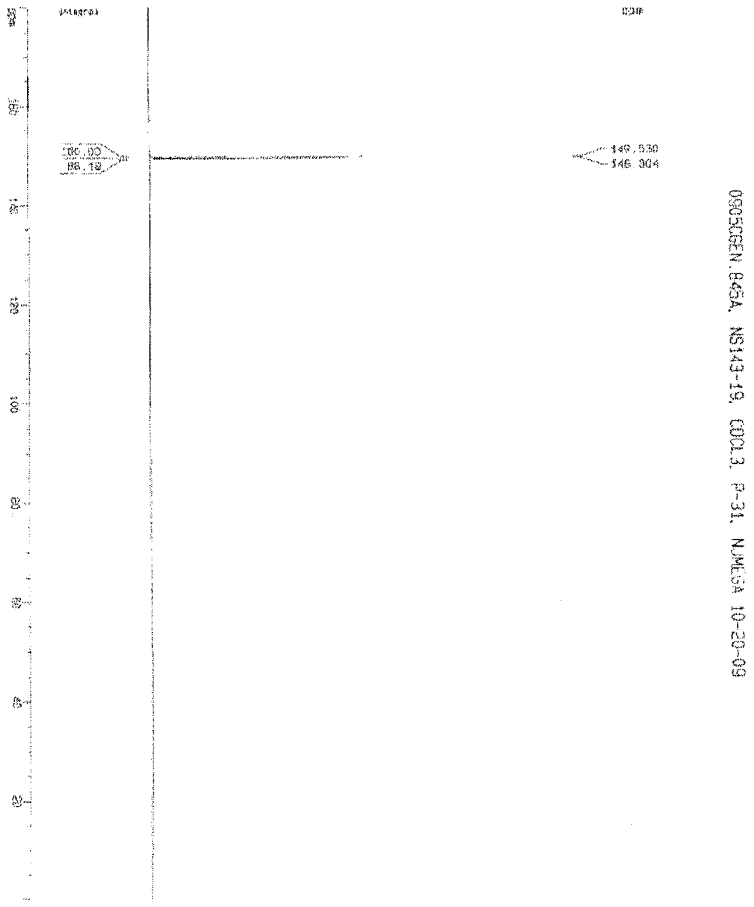


FIG. 8

Shanghai Hongene Exhibit 1002

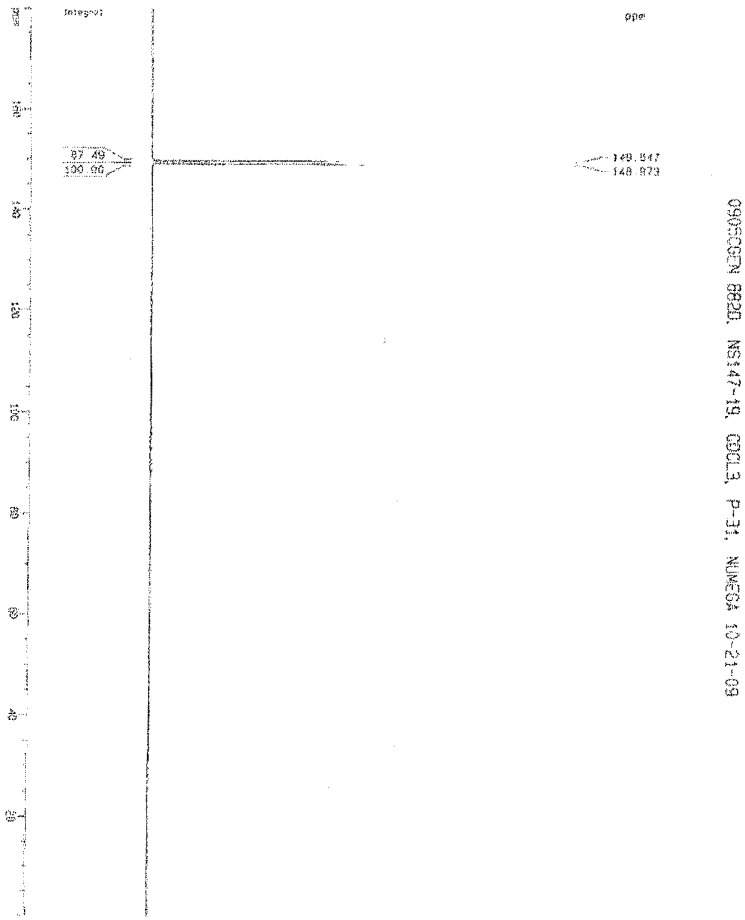


FIG. 9

Shanghai Hongene Exhibit 1002

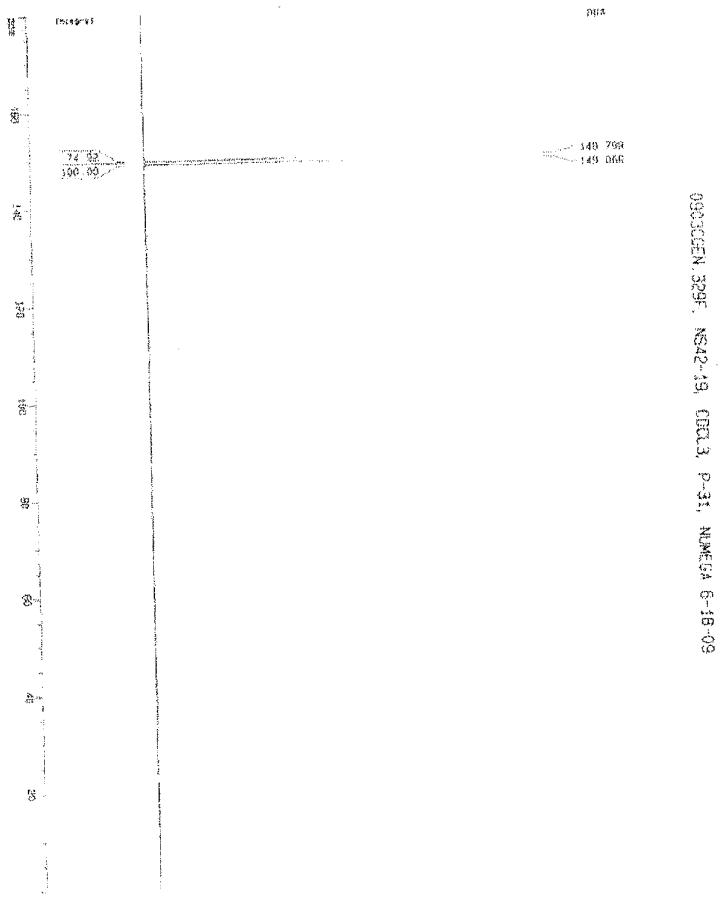


FIG. 10

HPLC Analysis
QCF-001
ChemGenes Corporation, 33 Industrial Way, Wilmington, MA 01887

Sample ID:	AL300-2	Injection Notes	3'-DMT-2'-TBDMS Adenosine (n-bz) amidite
Operator (Inj):	Dhaval Patel		
Data File:	c:\star\data\al300-2.run		
Injection Date:	11/19/2009 12:29:54 PM	Sample Prep Info	
Injection Method:	c:\star\methods_1\95-100_25.mth	Vial: 39	Injection Number: 1 Injection Volume: 5 ul
Instrument (Inj):	Varian Star # 1		

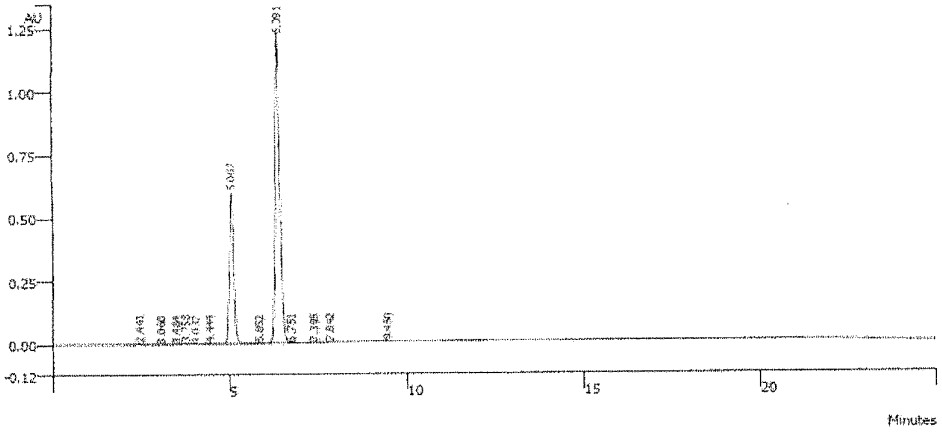


FIG. 11A

Shanghai Hongene Exhibit 1002

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		2.441	316307	0.19
2		3.060	76365	0.04
3		3.484	113880	0.07
4		3.758	241658	0.14
5		4.032	74999	0.04
6		4.444	228289	0.13
7	5'-DMT-2'-Si-Adenosine (n-bz) OP	5.067	50914964	29.99
8		5.852	154261	0.09
9	3'-DMT-2'-Si-Adenosine (n-bz) OP	6.391	116966520	68.90
10		6.751	375067	0.22
11		7.395	213522	0.13
12		7.842	49721	0.03
13		9.450	46789	0.03
	Totals		169772352	100.00

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep
Guard Column OmniSolver 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 95% ACN in 0.1M TEAA [pH 7.5]
Eluent B- ACN
Gradient: Increse B (0-50%) in 25 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

Sample Amount (mg): _____
Solvent Amount (ml): _____
Solvent:
Lot Number: _____
Exp. Date: _____

Analyst Initials: _____
PASS / FAIL

FIG. 11B

HPLC CHROMATOGRAM

Sample ID: N542-19
Operator (Inj): Dhawal Patel
Data File: c:\star\data\n542-19.run
Injection Date: 06/16/2009 06:30:48 PM
Injection Method: c:\star\methods_1\90-95_25.mth
Instrument (Inj): Varian Star # 1

Injection Notes: 3'-DMT-2'-TBDMS Guanosine (n-ibu) amidite

Sample Prep Info
Vial: 56 Injection Number: 1 Injection Volume: 5 ul

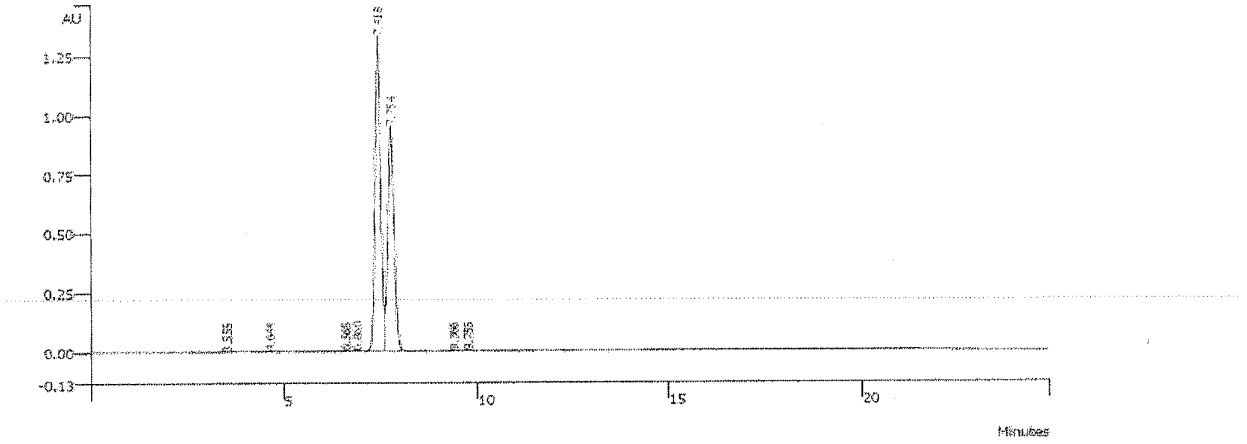


FIG. 12A

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		3.555	58277	0.02
2		4.644	162348	0.07
3		6.565	159521	0.07
4		6.860	314210	0.13
5	*3'-DMT-2'-TBDMS ibuG OP	7.418	136478720	56.37
6	*3'-DMT-2'-TBDMS ibuG OP	7.754	104749944	43.27
7		9.366	76431	0.03
8		9.755	99522	0.04
	Totals		242098960	100.00

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSpher 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 90% ACN in 0.1M TEAA [pH 7.5]
Eluent B- 95% ACN in 0.1M TEAA
Gradient: Increse B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

FIG. 12B

HPLC Analysis
QCF-001
ChemGenes Corporation, 33 Industrial Way, Wilmington, MA 01887

Sample ID: NS143-19
Operator (Inj): Dhaval Patel
Data File: c:\star\data\ns143-19.run
Injection Date: 10/20/2009 01:29:03 PM
Injection Method: c:\star\methods_1\95-100.mth
Instrument (Inj): Varian Star # 1

Injection Notes: 3'-DMT-2'-TBDMS Cytidine (n-acetyl) amidite

Sample Prep Info
Vial: 23 Injection Number: 1 Injection Volume: 5 ul

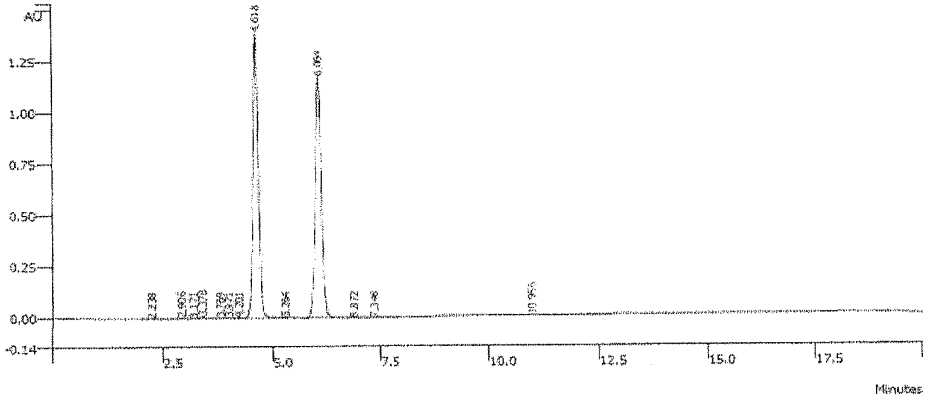


FIG. 13A

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		2.238	51545	0.02
2		2.906	257959	0.11
3		3.171	73365	0.03
4		3.378	761764	0.32
5		3.769	328242	0.14
6		3.971	178872	0.08
7		4.201	291630	0.12
8	*3'-DMT-2'-TBDMS Cytidine (n-ac) OP	4.618	118156432	49.60
9		5.264	101551	0.04
10	*3'-DMT-2'-TBDMS Cytidine (n-ac) OP	6.064	117767928	49.44
11		6.872	112231	0.05
12		7.346	67182	0.03
13		10.956	51009	0.02
	Totals		238199696	100.00

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSpher 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 95% ACN in 0.1M TEAA (pH 7.5)
Eluent B- ACN
Gradient: Increse B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

Sample Amount (mg): _____
Solvent Amount (ml): _____
Solvent:
Lot Number: _____
Exp. Date: _____

Analyst Initials: _____
PASS / FAIL

FIG. 13B

HPLC Analysis
QCF-001
ChemGenes Corporation, 33 Industrial Way, Wilmington, MA 01887

Sample ID:	NS147-19
Operator (Inj):	Dhaval Patel
Data File:	c:\star\data\ns147-19.run
Injection Date:	10/21/2009 02:19:42 PM
Injection Method:	c:\star\methods_1\95-100.mth
Instrument (Inj):	Varian Star # 1

Injection Notes: 3'-DMT-2'-TBDMS Uridine amidite

Sample Prep Info
Vial: 30 Injection Number: 1 Injection Volume: 5 ul

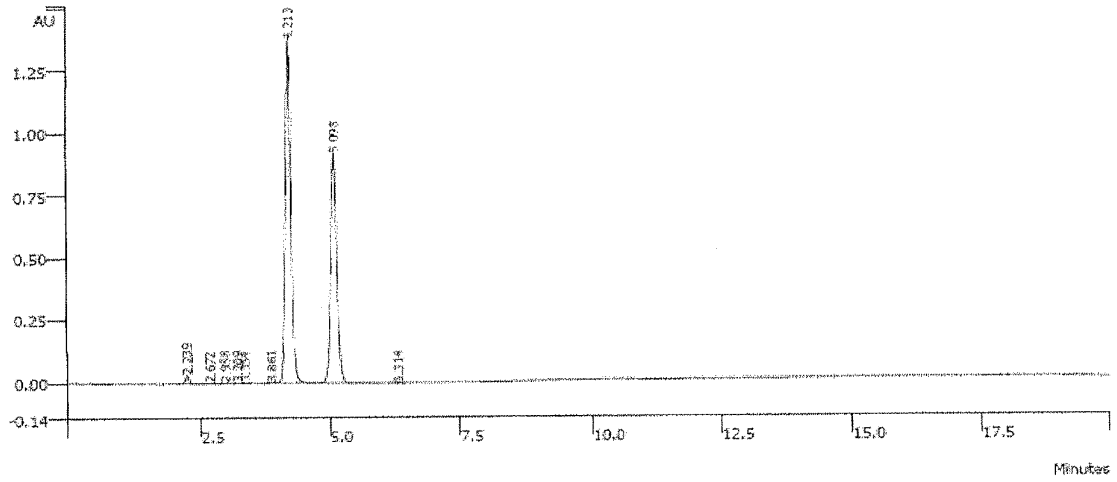


FIG. 14A

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		2.239	1713140	0.91
2		2.672	42783	0.02
3		2.958	157395	0.08
4		3.209	130255	0.07
5		3.354	127776	0.07
6		3.861	317837	0.17
7	*3'-DMT-2'-TBDMS Uridine OP	4.213	103188256	55.05
8	*3'-DMT-2'-TBDMS Uridine OP	5.098	81737304	43.61
9		6.314	31376	0.02
	Totals		187446128	100.00

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSpher 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 95% ACN in 0.1M TEAA (pH 7.5)
Eluent B- ACN
Gradient: Increse B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

Sample Amount (mg): _____
Solvent Amount (ml): _____
Solvent:
Lot Number: _____
Exp. Date: _____

Analyst Initials: _____
PASS / FAIL

FIG. 14B

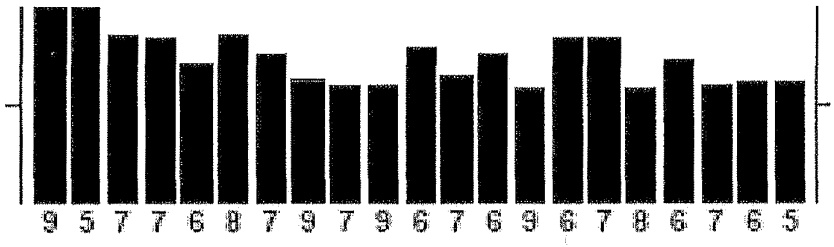


FIG. 15A

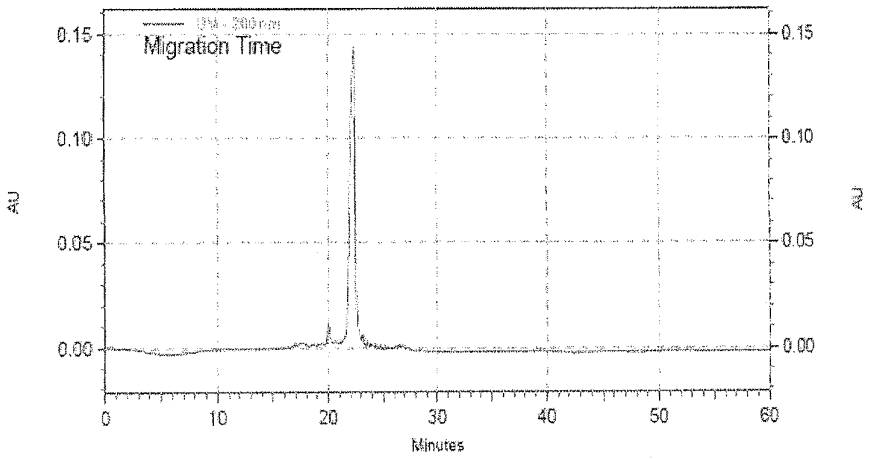


FIG. 15B

UV - 200nm
Results

Time	Height	Area	Area %
18.929	453	2418	0.05
19.004	550	2554	0.05
19.692	868	2721	0.06
20.042	8898	143692	2.92
22.408	140089	4552901	92.63
22.933	659	139402	2.84
23.087	3128	21046	0.43
23.142	3459	13274	0.27
23.329	1344	2550	0.05
23.354	1197	3151	0.06
23.517	834	3423	0.07
23.692	919	2454	0.05
23.729	1006	3436	0.07
23.900	828	3525	0.07
24.288	829	2412	0.05
24.333	1100	3250	0.07
24.717	1151	2318	0.05
24.771	1473	7753	0.16
24.821	861	2754	0.06
Totals	169646	4915034	100.00

FIG. 15C

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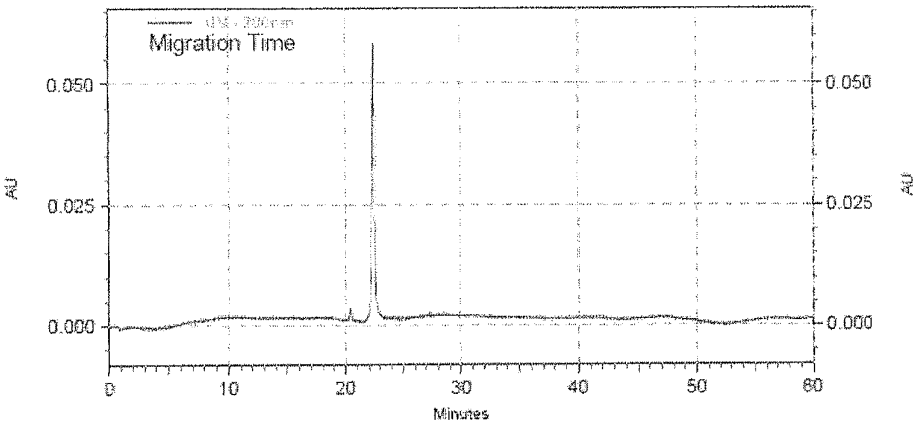


FIG. 15D

UV - 200nm
Results

Time	Height	Area	Area %
21.879	1374	5992	0.97
21.925	1346	3836	0.62
21.958	870	2521	0.41
24.087	34498	607012	98.01
Totals	38088	619361	100.00

FIG. 15E

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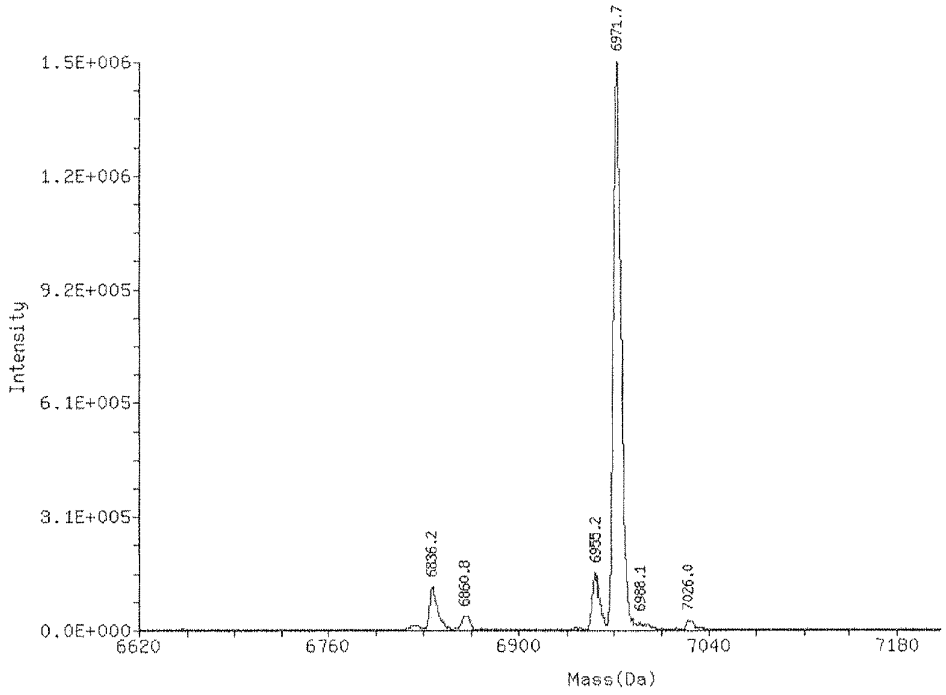

6971.7
1.5E+006
1.2E+006
9.2E+005
6.1E+005
3.1E+005
0.0E+000
Intensity
6836.2
6860.8
6955.2
6988.1
7026.0
6620
6760
6900
7040
7180
Mass(Da)

FIG. 15F

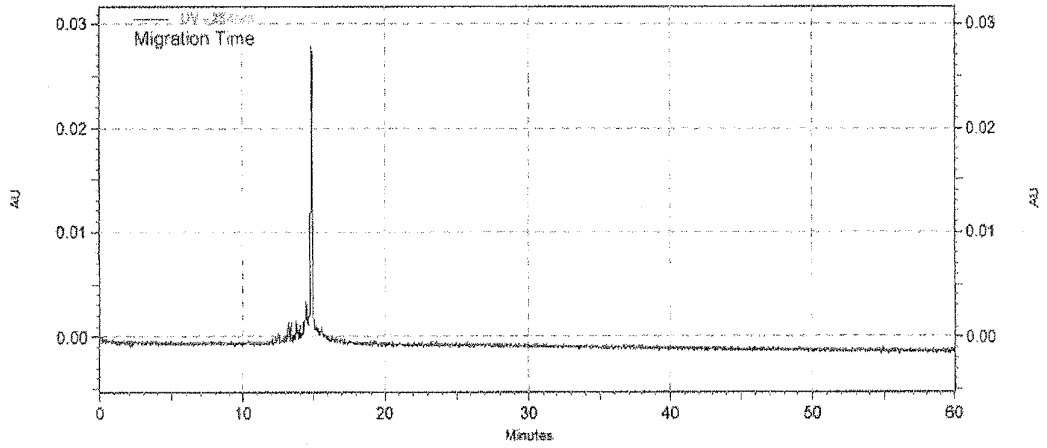


FIG. 16A

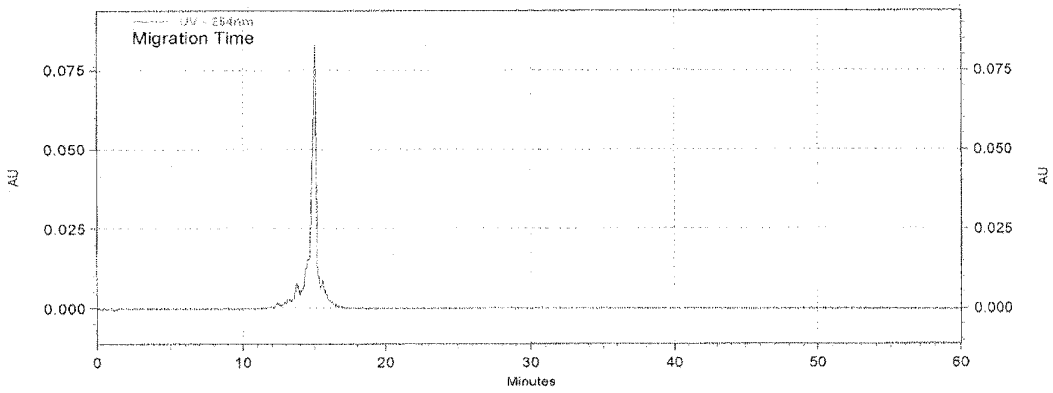


FIG. 16B

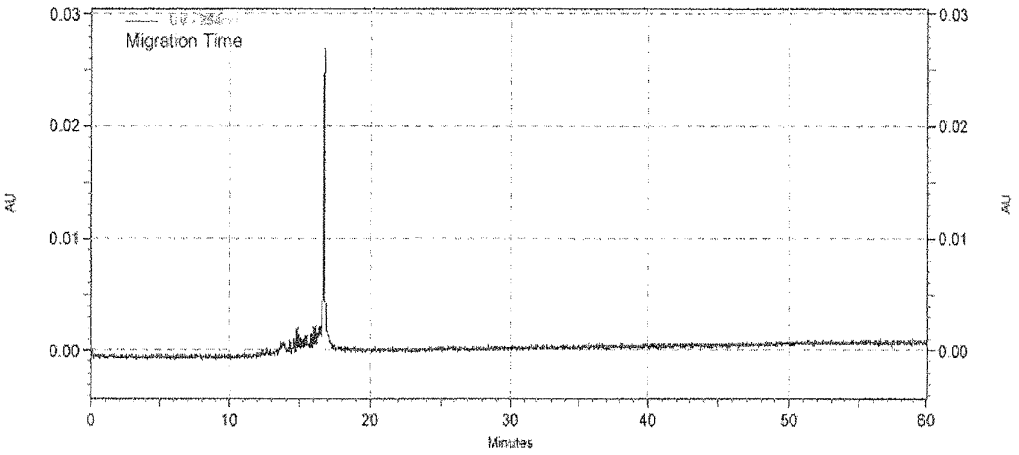

Migration Time
AU
Minutes
0.03
0.02
0.01
0.00
0
10
20
30
40
50
60

FIG. 17

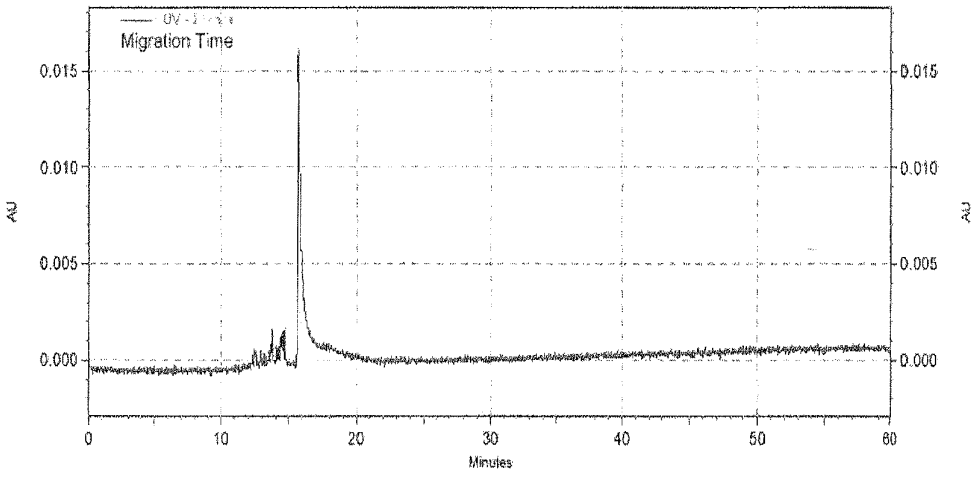

Migration Time
AU
Minutes
0.015
0.010
0.005
0.000
0
10
20
30
40
50
60

FIG. 18

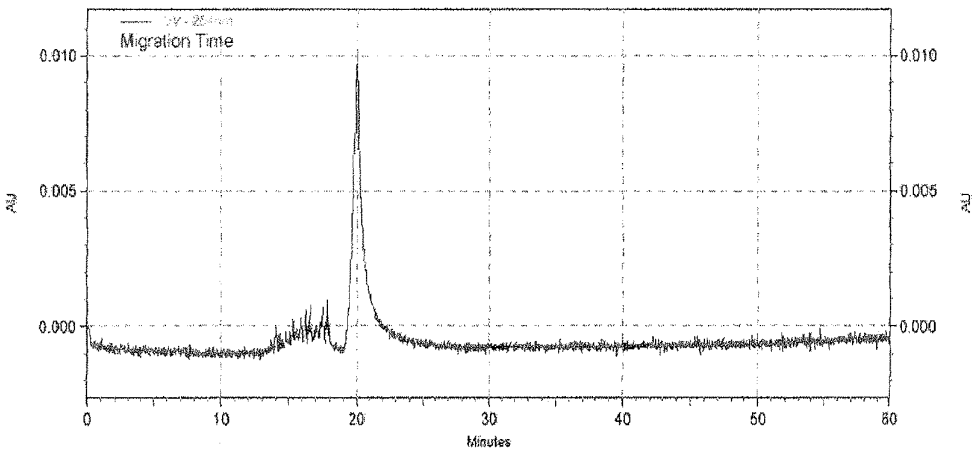


FIG. 19

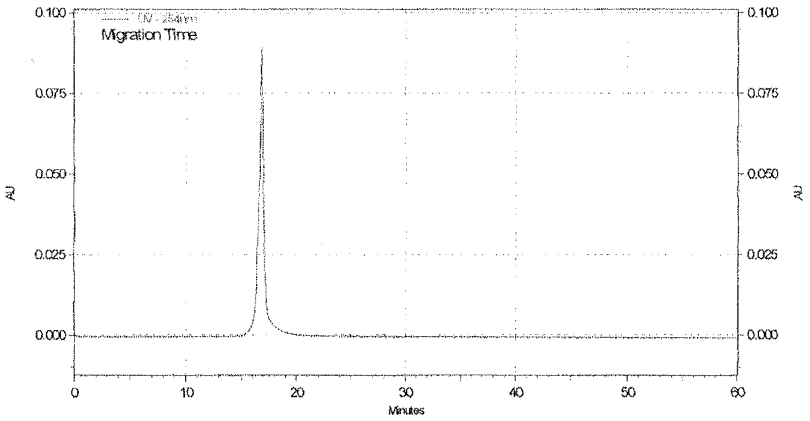


FIG. 20

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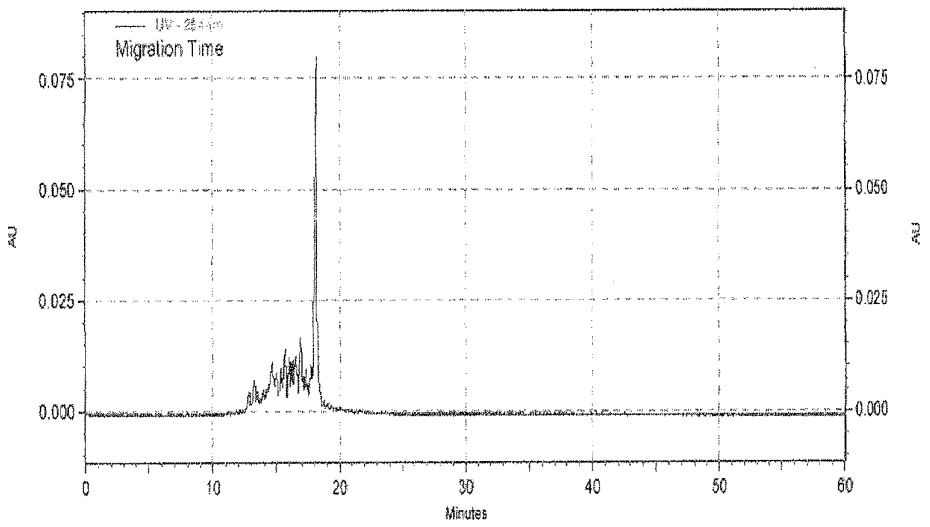


FIG. 21A

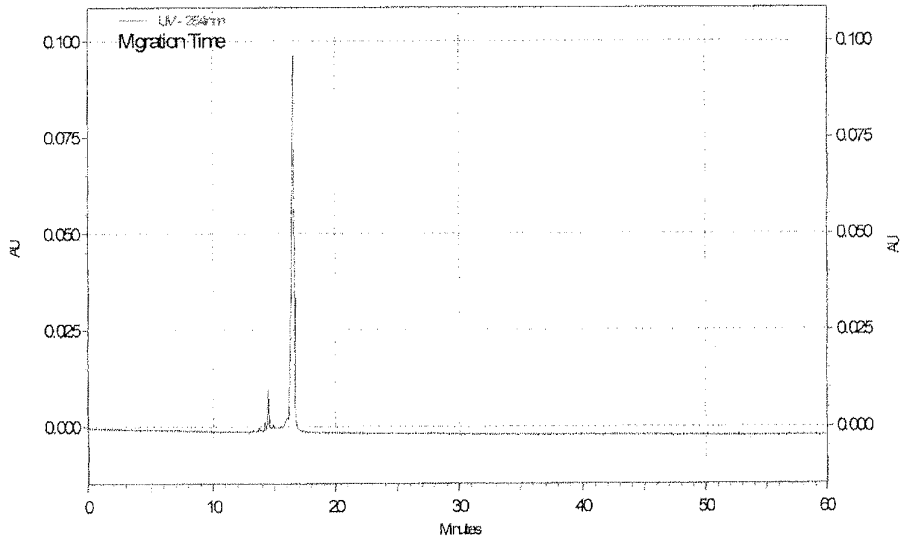


FIG. 21B

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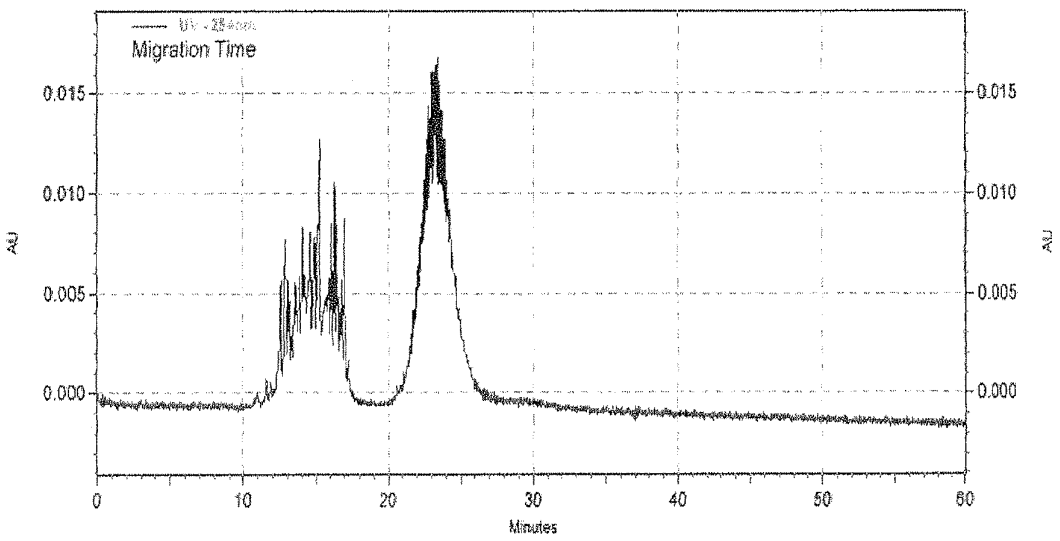


FIG. 22

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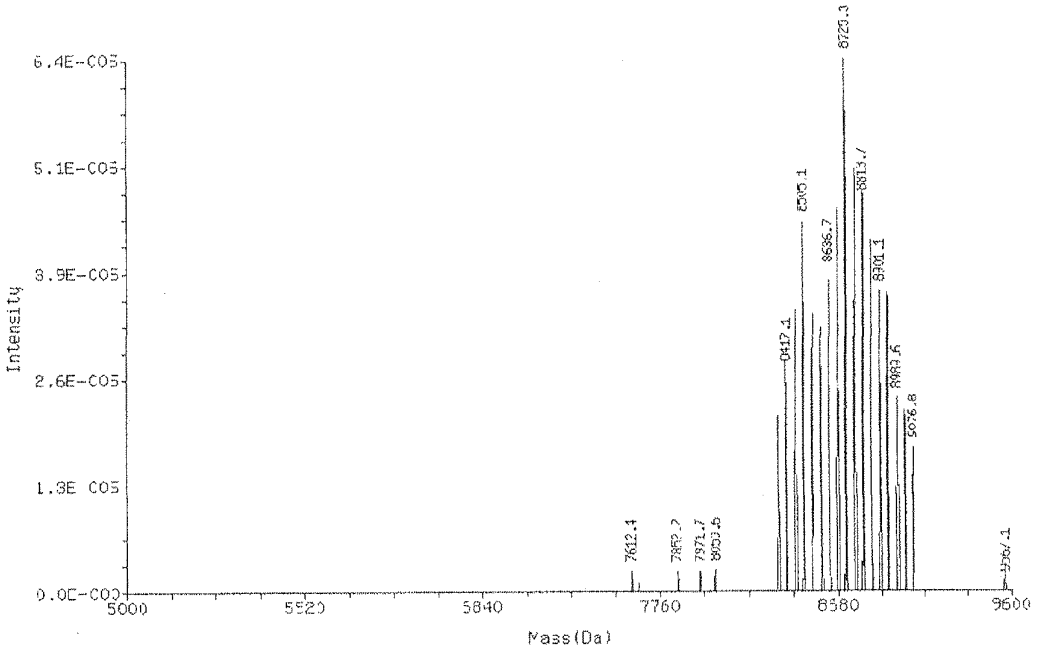


FIG. 23

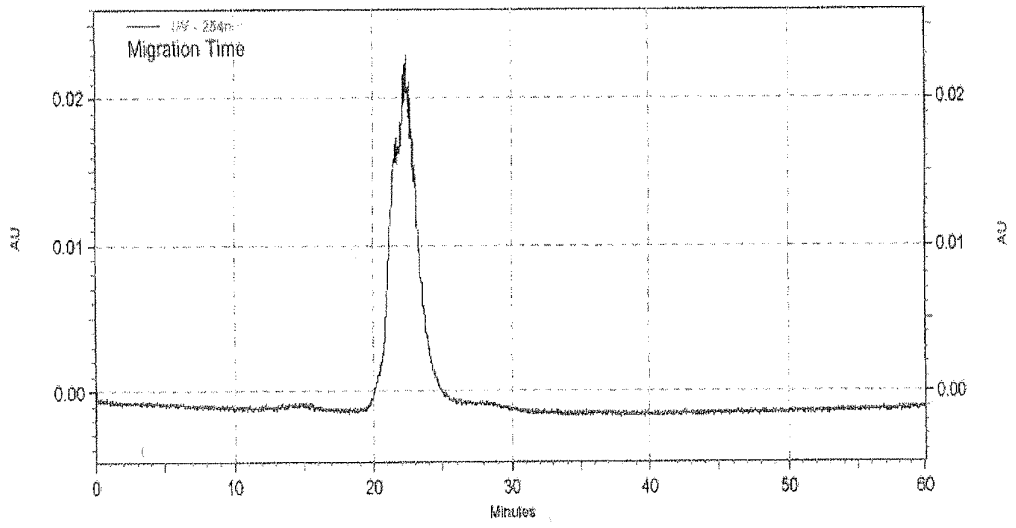


FIG. 24

Shanghai Hongene Exhibit 1002

Electronic Acknowledgement Receipt

EFS ID:	7045573
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3 (PRIME)-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Pamela A. Torpey/Kellie Varno
Filer Authorized By:	Pamela A. Torpey
Attorney Docket Number:	4441.1001-002
Receipt Date:	19-FEB-2010
Filing Date:	
Time Stamp:	14:27:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	44411001002CIPTransmittal.pdf	133538 fe6a8831b481edae61fb9dad22b74385b2fde978	no	1

Warnings:	
Information:	

2		44411001002Application.pdf	6393700 179bed0dfd7691e974d104a11038cd29f0363dba	yes	148

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	117
	Claims	118	147
	Abstract	148	148

Warnings:

Information:

3	Drawings-only black and white line drawings	44411001002Drawings.pdf	978876 eed4b6dde6c6e5a2daab8fad79c4b61702331261	no	32

Warnings:

Information:

Total Files Size (in bytes):	7506114

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

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

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

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

PTO/SB/06 (12-04)

Date: **02/19/2010**

Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
1E+07 lays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number **12/708,827**

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	LARGE ENTITY RATE ($)	LARGE ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	**330**
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	**540**
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	**220**
TOTAL CLAIMS (37 CFR 1.16(i))	**39** minus 20 =	**19**	X$ 26		OR	2X$52	**988**
INDEPENDENT CLAIMS (37 CFR 1.16(h))	**5** minus 3 =	**2**	X$110			1X$220	**440**
APPLICATION SIZE FEE (37 CFR 1.16(s))				**0**			**270**
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195	**0**		390	**0**
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	**2788**

APPLICATION AS AMENDED – PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDI-TIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDI-TIONAL FEE ($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDI-TIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDI-TIONAL FEE ($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T 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. Paten 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.

Shanghai Hongene Exhibit 1002

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/708,827	02/19/2010	1614	0.00	4441.1001-002	39	5

CONFIRMATION NO. 5297

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

FILING RECEIPT

OC000000040512869

Date Mailed: 03/10/2010

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, Residence Not Provided;

Assignment For Published Patent Application

ChemGenes Corporation, Wilmington, MA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CIP of PCT/US2009/005063 09/08/2009
which claims benefit of 61/191,065 09/06/2008

Foreign Applications

If Required, Foreign Filing License Granted: 03/03/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/708,827**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

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

NOT GRANTED

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002

CONFIRMATION NO. 5297

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

FORMALITIES LETTER

OC000000040512870

Date Mailed: 03/10/2010

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**330** to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

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

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings must be reasonably free from erasures and must be free from alterations, overwriting, interlineations, folds, and copy marks. See Figure(s) 12A.
  - Numbers, letters, and reference characters on the drawings must measure at least 0.32 cm (1/8 inch) in height. See Figure(s) 7-11A, and 12A-14A.
  - The drawings submitted to the Office are not electronically reproducible because portions of figures all are missing and/or blurry.
  - The drawings are not in compliance with 37 CFR 1.84 because figures 7-10 contain figure or view numbers that have incorrect orientation. Reference characters, sheet numbers, and view numbers must be oriented in the same direction as the view. See 37 CFR 1.84(p)(1).

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

To Download Patentin Software, visit http://www.uspto.gov/web/patents/software.htm
For questions regarding compliance to these requirements, please contact:
- **For Rules Interpretation, call (571) 272-0951**
- **For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.**
- **Send e-mail correspondence for Patentin Software Program Help to ebc@uspto.gov**

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

The applicant needs to satisfy supplemental fees problems indicated below.

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

- Additional claim fees of $**1428** as a non-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.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**2918** for a non-small entity
- $**330** Statutory basic filing fee.
- $**130** Surcharge.
- The application search fee has not been paid. Applicant must submit $**540** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $**220** to complete the examination fee for a non-small entity.
- The specification and drawings submitted electronically contain the equivalent of more than 100 pages. Applicant owes $**270** for **35** pages in excess of **100** pages for a non-small entity.
- Total additional claim fee(s) for this application is $**1428**
  - $**440** for **2** independent claims over 3.
  - $**988** for **19** total claims over 20.

Replies should be mailed to:

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

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
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If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/tle/

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

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 12708827 Document Date: 07/12/2010

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Sequence Listing

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 12708827 Document Date: 07/12/2010

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Design Drawing

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not Assigned
Confirmation No:	5297		
For:	Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

_____ _____

Date Signature

_____

Typed or printed name of person signing certificate

TRANSMITTAL OF SEQUENCE LISTING AND PRELIMINARY AMENDMENT

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

Sir:

In accordance with procedures regarding electronically filed applications containing a sequence listing in text format, Applicants state that the sequences contained in the sequence listing do not go beyond the sequences disclosed in the specification of the application being filed concurrently herewith. Additionally, it is understood that since the sequence listing is being submitted electronically, the requirement for submission of a computer readable form under 37 CFR 1.821(e) has been met. Please insert the attached Sequence Listing into the application.

Please amend the application as follows:

Shanghai Hongene Exhibit 1002

Amendments to the Specification

Please replace the paragraph at page 11, lines 9 through 15 with the following amended paragraph:

FIGS. 2A-2D are graphs and tables demonstrating the purity of REV-2'-OMe-phosphorothioate- Oligo mArArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO: [[1]]2) synthesized with a coupling time of 4 minutes with the activator (0.25M) ETT (ethyl thio tetrazole). FIG. 2A is a graph of the trityl histogram; FIG. 2B is a graph of the CE analysis of the crude RNA (desalted); FIG. 2C is a table containing the CE analysis report of crude RNA; and FIG. 2D is a graph of ESI/MS (crude) Actual MW: 6971.1; Found Value: 6972.0.

Please replace the paragraph at page 11, lines 16 through 20 with the following amended paragraph:

FIGS. 3A-3C are graphs and tables demonstrating the purity of REV-2'-OMe-phosphodiester – Oligo mArArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO: [[1]]3) synthesized with a coupling time of 4 minutes. FIG. 3A is a graph of the trityl histogram; FIG. 3B is a graph of the CE analysis of the crude oligo (desalted); and FIG. 3C is a table containing the CE analysis report of the crude RNA.

Please replace the paragraph at page 11, lines 21 through 26 with the following amended paragraph:

FIGS. 4A-4D are graphs and tables demonstrating the purity of REV-phosphodiester – Oligo rCrArCrArGrCrArUrArCrArUrCrUrCrGrArCrCrArU (SEQ ID NO: [[2]]4) synthesized with a coupling time of 4 minutes; FIG. 4A is a graph of the trityl histogram; FIG. 4B is a graph of the CE analysis crude (desalted); FIG. 4C is a table containing CE analysis report of the crude RNA; and FIG. 4D is a graph of ESI/MS Crude RNA (desalted); Calc.: MW: 6598.9.

Please replace the paragraph at page 11, lines 27 through page 12, line 2 with the following amended paragraph:

FIGS. 5A-5C are graphs and tables demonstrating the purity of REV-phosphodiester – Oligo CrArCrArGrCrArUrArCrArUrCrUrCrGrArCrCrArU (SEQ ID NO: [[2]]4) (crude desalted) using a coupling time of 6 minutes; FIG. 5A is a graph of the trityl histogram; FIG. 5B is a table of CE analysis crude (desalted); and FIG. 5C is a table of the CE analysis report crude RNA (desalted).

Please replace the paragraph at page 12, lines 3 through 14 with the following amended paragraph:

FIGS. 6A-6B is a graph and a picture of a gel demonstrating the purity of REV-phosphodiester – OLIGO-76 mer rArCrGrCrGrGrGrCrUrUrGrUrCrCrCrUrGrArArCrUrUrGrGrGrArCrCrUrGrGr GrArGrUrCrUrArUrUrUrUrUrCrArGrArCrUrArCrGrArGrArUrGrGrCrUrGrArCrUrCrGrArUr ArGrGrCrCrCrG (SEQ ID NO:[[3]]5) synthesized with a coupling time of 6 minutes. FIG. 6A is a graph of the trityl histogram; and FIG. 6B is a picture of a gel of the page analysis of 76 mer phosphodiester; band #1; Bromo phenol blue; band #2; 76 mer with regular RNA; band #3; 76mer with reverse RNA; band #4; 76mer with reverse TOM RNA. TOM RNA reverse phosphoramidites: 2'-TOM-3'-O-DMT-adenosine(n-acetyl)5'-cyanoethylphosphoramidite; 2'-TOM-3'-O-DMT-cytidine(n-acetyl)5'-cyanoethylphosphoramidite; 2'-TOM-3'-O-DMT-guanosine(n-acetyl)5'-cyanoethylphosphoramidite; 2'-TOM-3'-O-DMT-uridine-5'-cyanoethylphosphoramidite.

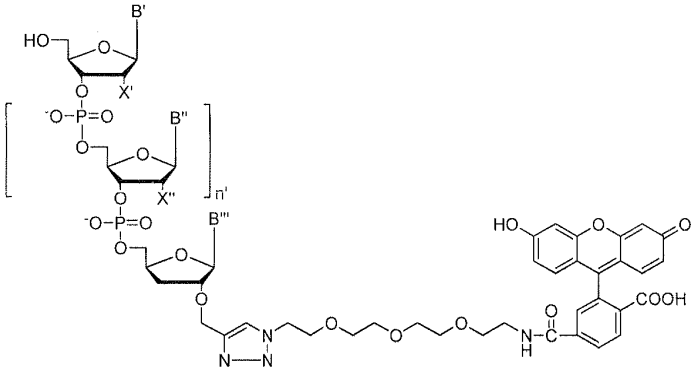
Please replace the paragraph at page 13, lines 7 through 12 with the following amended paragraph:

FIGS. 15A – 15F are graphs and tables demonstrating the purity of REV-RNA-Me-THIO- mArArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO:[[1]]6) synthesized with a coupling time of 6 minutes. FIG. 15A is a graph of the trityl histogram; FIG. 15B is a

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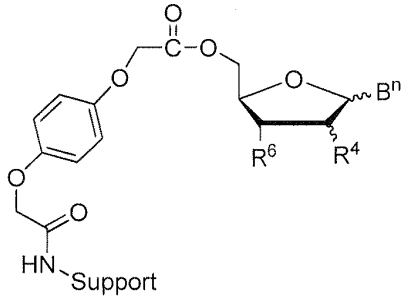
graph of the CE crude; FIG. 15C is table of the CE analysis; FIG. 15D is a graph showing the migration time; FIG. 15E is table of the CE report; and FIG. 15F is a graph of Mass Spectrum; Actual Value: 6971.1; Found Value: 6971.7.

Please replace the paragraph at page 84, lines 4 through 5 with the following amended paragraph:



Please replace the paragraph at page 97, lines 11 through 18 with the following amended paragraph:

Another linking group includes Q-support, which is a hydroquinone spacer, conveniently cleaved as compared to succinyl supports (See University Technologies International, LP(UTI) & Publication; R.T. Pon and S.Y. Yu, *Tetrahedron Lett.*, 1997, 38, 3327-3330, the teachings of which are incorporated herein by reference.). The structural formula is as follows: Support-NH- C(=O)-CH2-O-C6H4-O-CH2-C(=O)-O-5'-nucleoside, and is represented by the following structural formula:



Please replace the paragraph at page 114, lines 16 through 31 with the following amended paragraph:

Oligonucleotide sequences synthesized by Reverse Synthesis method.

Oligonucleotide 1 Phosphodiester Oligonucleotide	rCrArCrArGrCrArUrArCrArUrCrUrCrGrArCrCrArU (SEQ ID NO:[[2]]4) rA is N^6-Benzoyl-*2'*-*O*-TBDMS-3'-*O*-DMT-adenosine-OP rC is N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-OP rG is N^2-Isobutryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-OP rU is *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-OP
Oligonucleotide 2 Phosphorothioate oligonucleotide sequence with 2'- O-methyl bases on terminal	mA(ps)-rArCrArGrCrArUrArCrArUrCrUrCrGrArCrCmArU (SEQ ID NO:[[4]]7) Phosphorothioate rA is N^6-Benzoyl-*2'*-*O*-TBDMS-3'-*O*-DMT-adenosine-OP; rC is N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-OP; rG is N^2-Isobutryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-OP rU is *2'*-*O*-TBDMS-3'-*O*-DMT-Uridine-OP; mA is N^6-Benzoyl-*2'*-*O*-Me-3'-*O*-DMT-adenosine-OP; DDTT

Please replace the paragraph at page 117, lines 12 through 32 with the following amended paragraph:

Sequence listings:

REV-RNA-Me – SEQ (With Methoxy)
SEQ: rUmrArCrCrArGrCrUrCrUrArCrArUrArCrGrArCrAmrA (SEQ ID NO:[[1]]8)

REV-RNA-Me-THIO-4Min Coupling Time
SEQ: rU-p(s)mrA-p(s)rC-p(s)rC-p(s)rA-p(s)rG-p(s)rC-p(s)rU-p(s)rC-p(s)rU-p(s)rA-p(s)rC-p(s)rA-p(s)rU-p(s)rA-p(s)rC-p(s)rG-p(s)rA-p(s)rC-p(s)rA-p(s)mrA-p(s)
(SEQ ID NO:[[2]]9)

REV-RNA- 4Min Coupling Time (Without Methoxy)
SEQ: rUrArCrCrArGrCrUrCrUrArCrArUrArCrGrArCrArC
(SEQ ID NO:[[3]]10)

Shanghai Hongene Exhibit 1002

76 MER

SEQ: rGrCrC rCrGrG rArUrA rGrCrU rCrArG rUrCrG rGrUrA rGrArG rCrArUrCrArG rArCrU rUrUrU rUrArU rCrUrG rArGrG rGrUrC rCrArG rGrGrUrUrCrA rArGrU rCrCrC rUrGrU rUrCrG rGrGrC rGrCrC rA
(SEQ ID NO:[[4]]11)

Amendments to the Drawings

The original drawings have been objected to as being blurry and failing to meet the requirements under 37 C.F.R. §§ 1.84 and 1.121(d). A set of Substitute Drawings with higher legibility are submitted herewith to fulfill the requirements under 37 C.F.R. §§ 1.84 and 1.121(d).

Attachment: Replacement Sheets

REMARKS

Amendments to the Specification

In accordance with the Sequencing Listing submitted concurrently herewith, the Specification has been amended to correct the sequence identifiers associated with the synthetic RNA sequences disclosed in the Specification.

The Specification has been amended to correct the chemical structures. A -CH_2- has been inadvertently omitted from the 2' -O-CH_2- group synthesized via click chemistry at page 84, lines 4-5. The correct synthesis scheme for compounds of the invention that can be created from this click chemistry is depicted at page 84, lines 11-12, where the CH_2 is clearly shown. Further, the structure of Q-linker described at page 97, lines 15-18 has been amended to add two O groups linked to the phenyl group (*i.e.*, "-O-Ph-O-"). This is an obvious, inadvertent error because the structure of Q-linker was well known at the time of the invention (*see* R.T. Pon and S.Y. Yu, U.S. Patent No. 6,043,353, Figure 2 (Reference A1); R.T. Pon and S.Y. Yu, *Tetrahedron Lett.*, 1997, 38, 3327-3330 whose teachings are incorporated by reference) to contain the two -O- groups linking the phenyl group (*i.e.*, hydroquinone-O,O'-diacetic acid linker).

Amendments to the Drawings

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CONCLUSION

In view of the above amendments and remarks, it is believed that the application is ready for examination. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date: July 12, 2010

Amendments to the Drawings

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Shanghai Hongene Exhibit 1002

CONCLUSION

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Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date: July 12, 2010

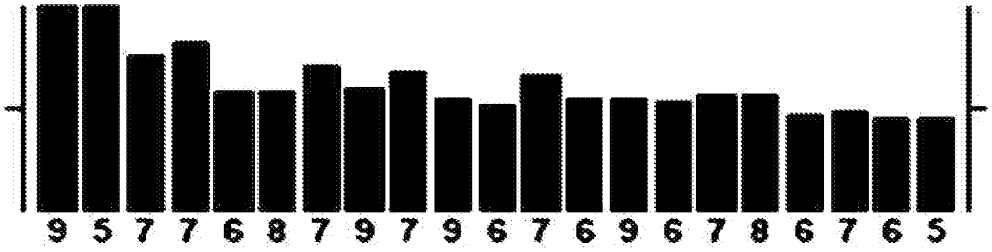


FIG. 1A

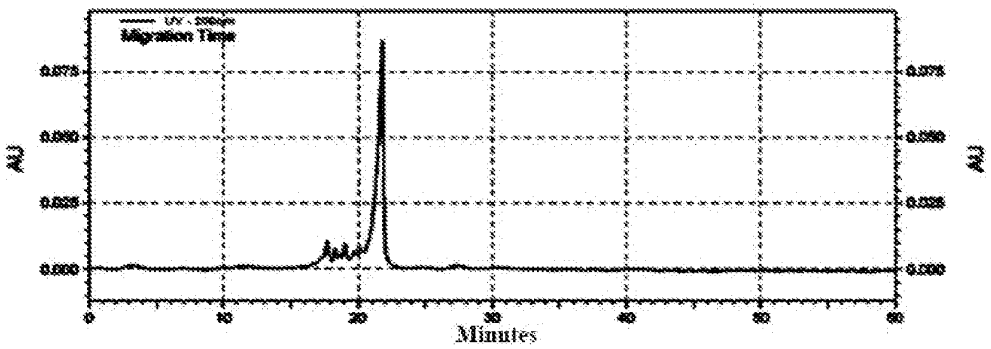


FIG. 1B

Shanghai Hongene Exhibit 1002

UV -200nm Results Time	Height	Area	Area%
17.367	2830	16392	0.45
17.663	7726	56557	1.57
17.729	8696	59447	1.65
17.788	6589	13327	0.37
17.883	2591	11215	0.31
18.288	5460	36314	1.01
18.333	5684	17932	0.50
18.358	5244	9679	0.27
18.392	4241	13766	0.38
18.542	3130	10727	0.30
18.613	3767	29016	0.80
18.692	3198	15183	0.42
19.033	7751	138415	3.84
19.712	5169	129375	3.59
20.171	6366	164372	4.56
20.550	5723	37498	1.04
21.837	85024	2847215	78.95
Totals	**169189**	**3606430**	**100.00**

FIG. 1C

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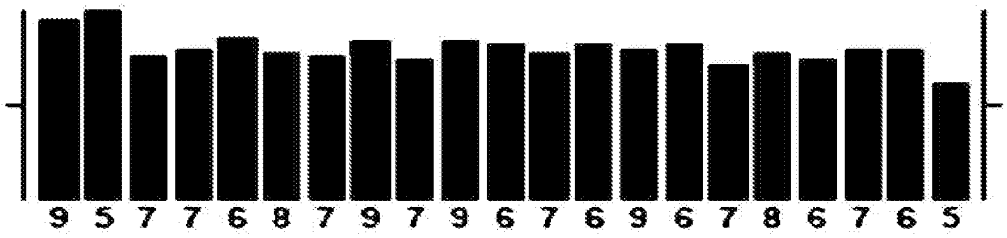


FIG. 2A

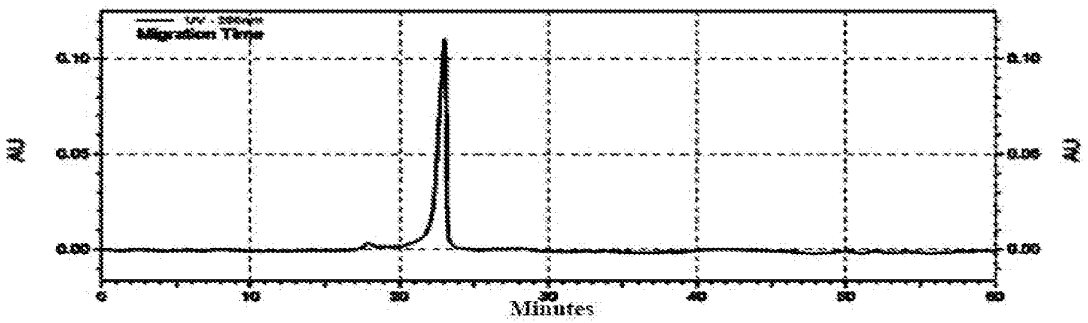


FIG. 2B

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UV -200nm Results

Time	Height	Area	Area%
17.550	617	14699	0.30
17.892	3270	84889	1.71
18.896	884	42940	0.87
19.079	1609	30490	0.62
19.804	1764	59025	1.19
21.058	3925	112388	2.27
21.550	6191	142628	2.88
23.046	110750	4414791	89.09
24.904	198	53425	1.08
Totals	**129208**	**4955275**	**100.00**

FIG. 2C

Shanghai Hongene Exhibit 1002

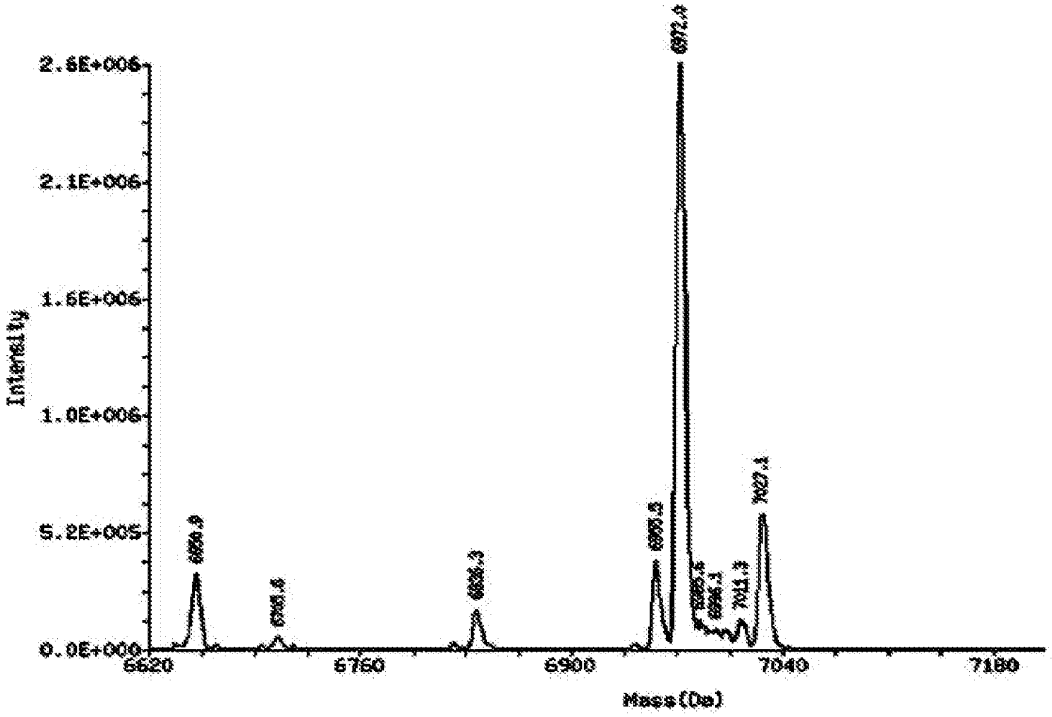

2.6E+006
2.1E+006
1.6E+006
1.0E+006
5.2E+005
0.0E+000
Intensity
6620
6760
6900
7040
7180
Mass(Da)
6956.9
6968.6
6988.3
6997.5
7027.1
7041.3

FIG. 2D

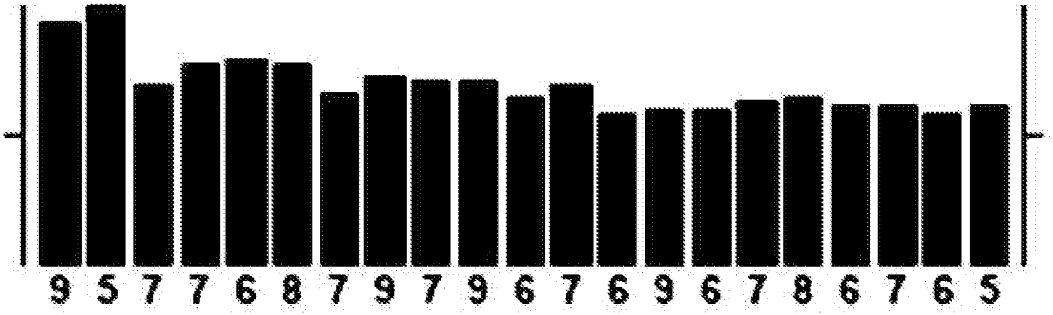


FIG. 3A

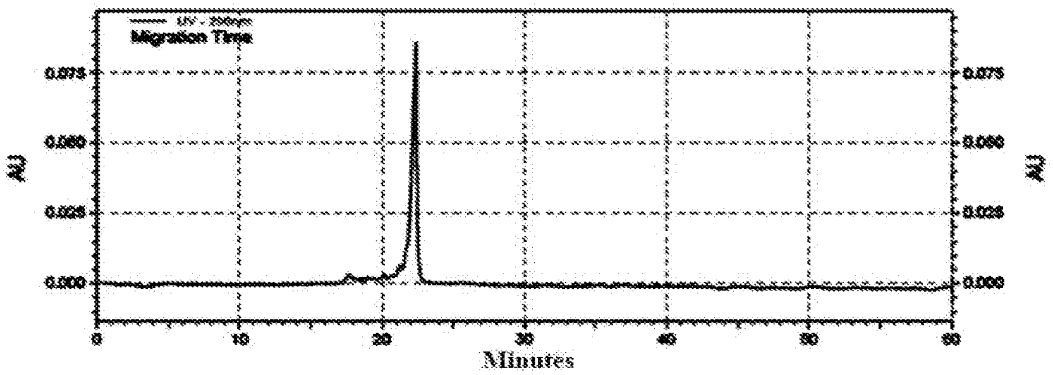


FIG. 3B

UV -200nm Results

Time	Height	Area	Area%
17.654	3340	12127	0.47
17.688	3452	9191	0.35
19.188	1584	9953	0.38
19.908	2163	9338	0.36
20.192	3111	11230	0.43
20.217	3348	9631	0.37
20.333	2004	14702	0.56
20.683	3015	28095	1.08
20.750	3029	26439	1.01
21.313	6686	155191	5.95
22.396	85829	2320510	89.03
Totals	**117561**	**2606407**	**100.00**

FIG. 3C

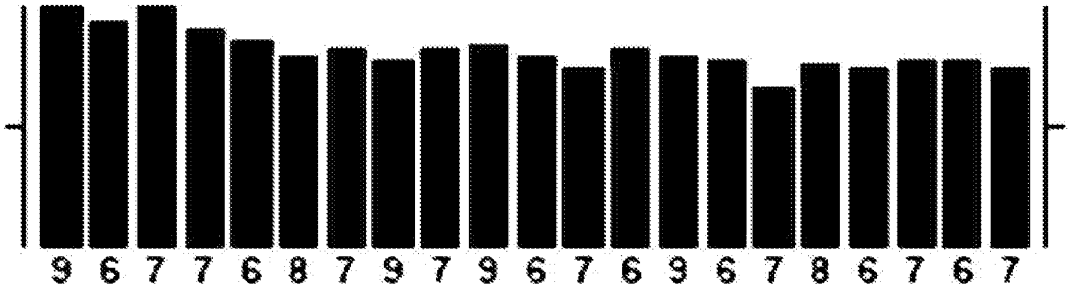


FIG. 4A

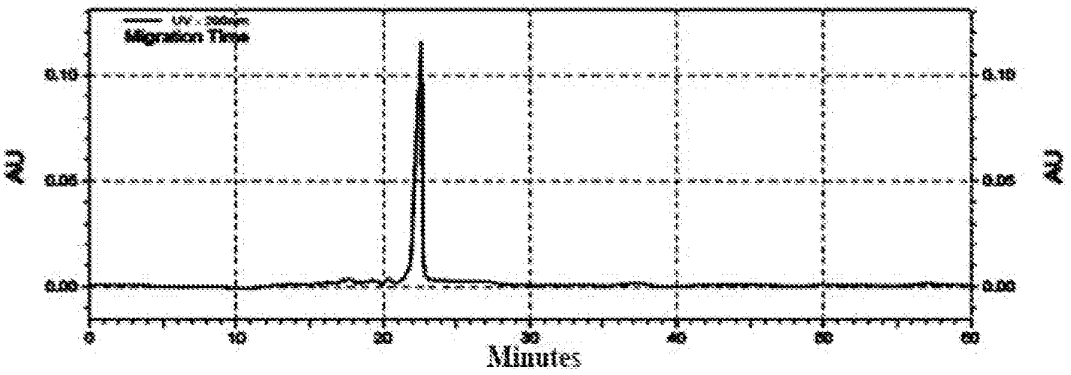


FIG. 4B

UV -200nm Results Time	Height	Area	Area%
17.304	1410	20826	0.60
17.663	1508	12887	0.37
17.762	1385	16366	0.47
19.208	1113	16037	0.46
19.929	1225	16374	0.47
20.383	1568	19428	0.56
20.967	908	10362	0.30
21.329	1635	17295	0.50
22.613	113518	3311035	95.29
23.383	1236	9540	0.27
23.879	1061	11808	0.34
24.271	820	12711	0.37
Totals	**127387**	**3474669**	**100.00**

FIG. 4C

Shanghai Hongene Exhibit 1002

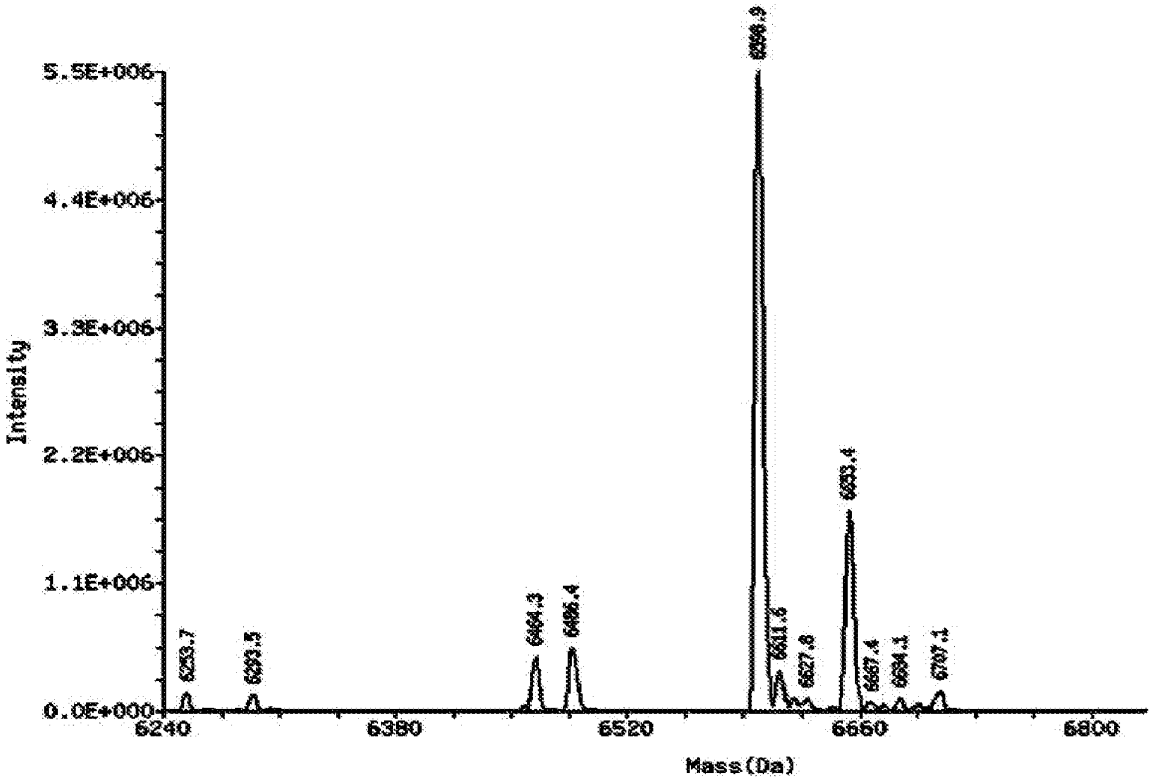

5.5E+006
4.4E+006
3.3E+006
2.2E+006
1.1E+006
0.0E+000
Intensity
6240
6380
6520
6660
6800
Mass(Da)
6253.7
6293.5
6464.3
6496.4
6611.6
6627.8
6633.4
6667.4
6694.1
6707.1
6656.9

FIG. 4D

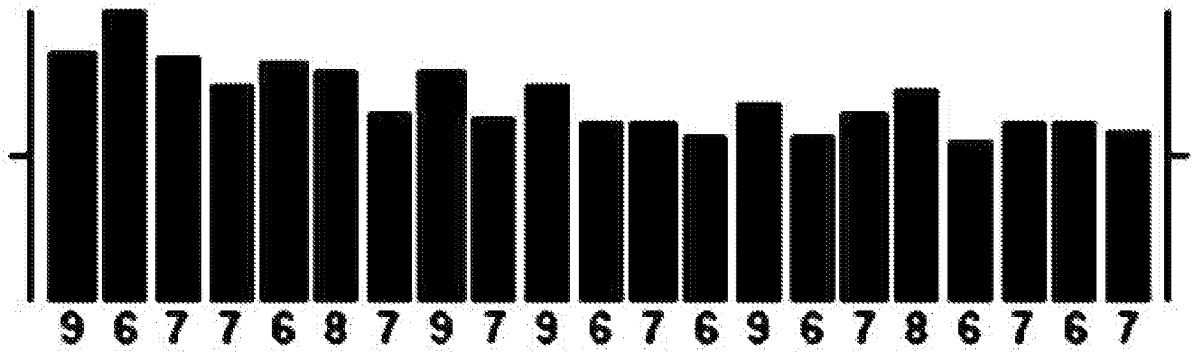

9 6 7 7 6 8 7 9 7 9 6 7 6 9 6 7 8 6 7 6 7

FIG. 5A

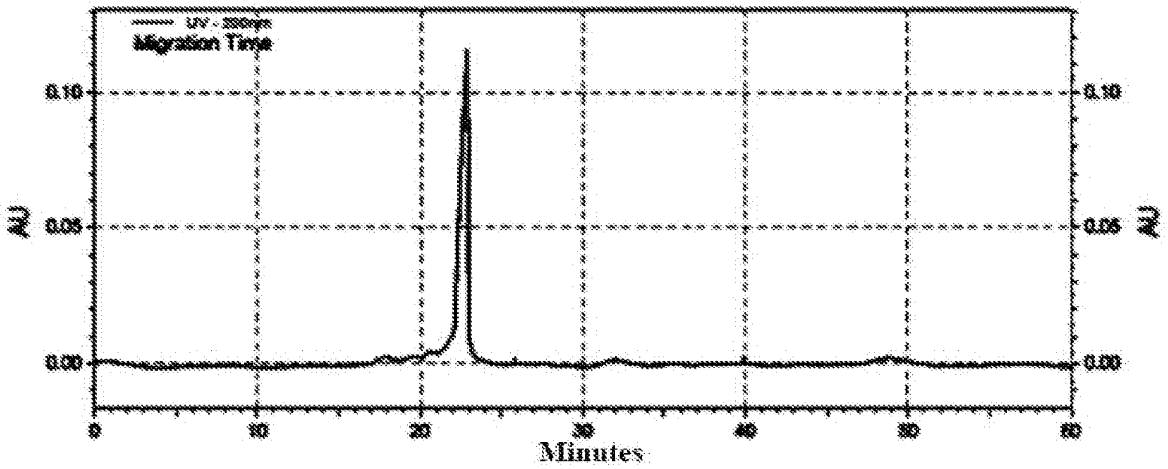

Migration Time
0.10
0.05
0.00
AU
Minutes

FIG. 5B

UV - 200nm
Results

Time	Height	Area	Area %
17.867	2612	124390	3.14
19.767	2308	125679	3.17
22.879	114213	3710219	93.69
Totals	119133	3960288	100.00

FIG. 5C



FIG. 6A

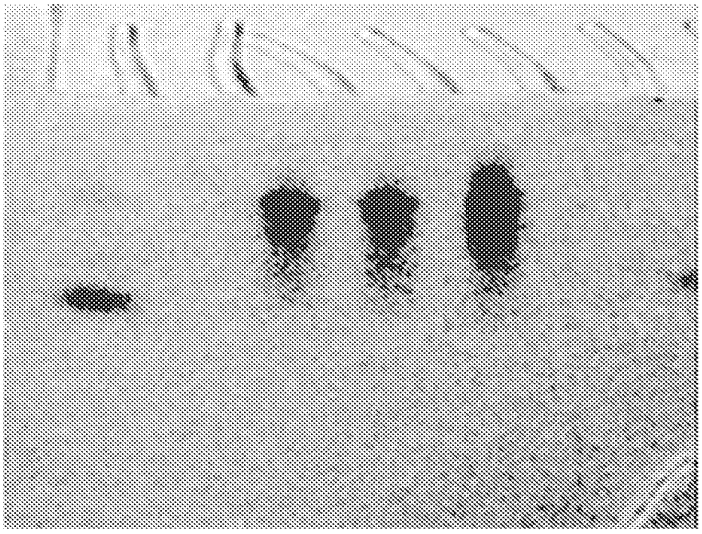


FIG. 6B

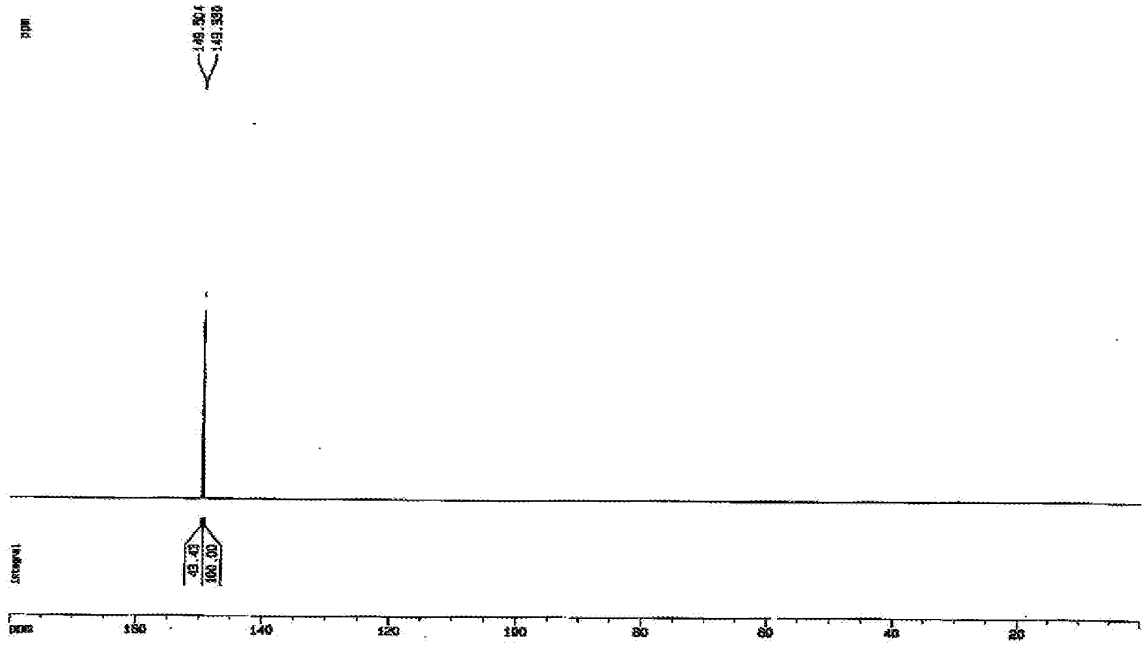


FIG. 7

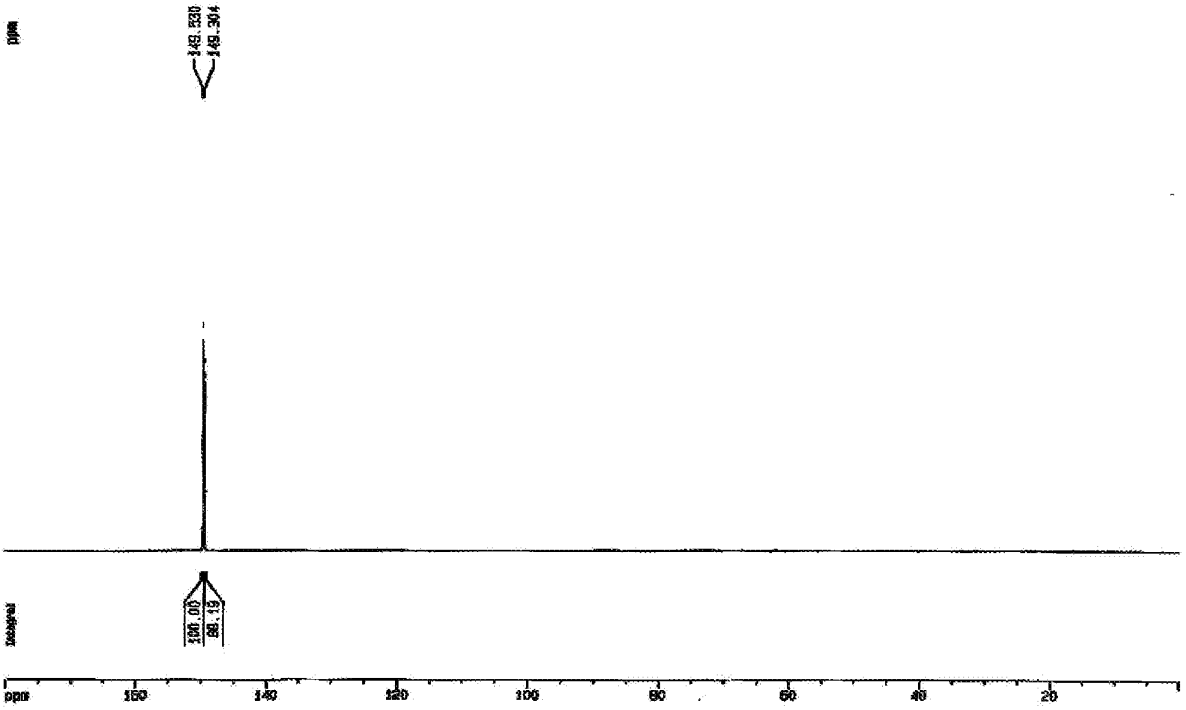


FIG. 8

Shanghai Hongene Exhibit 1002

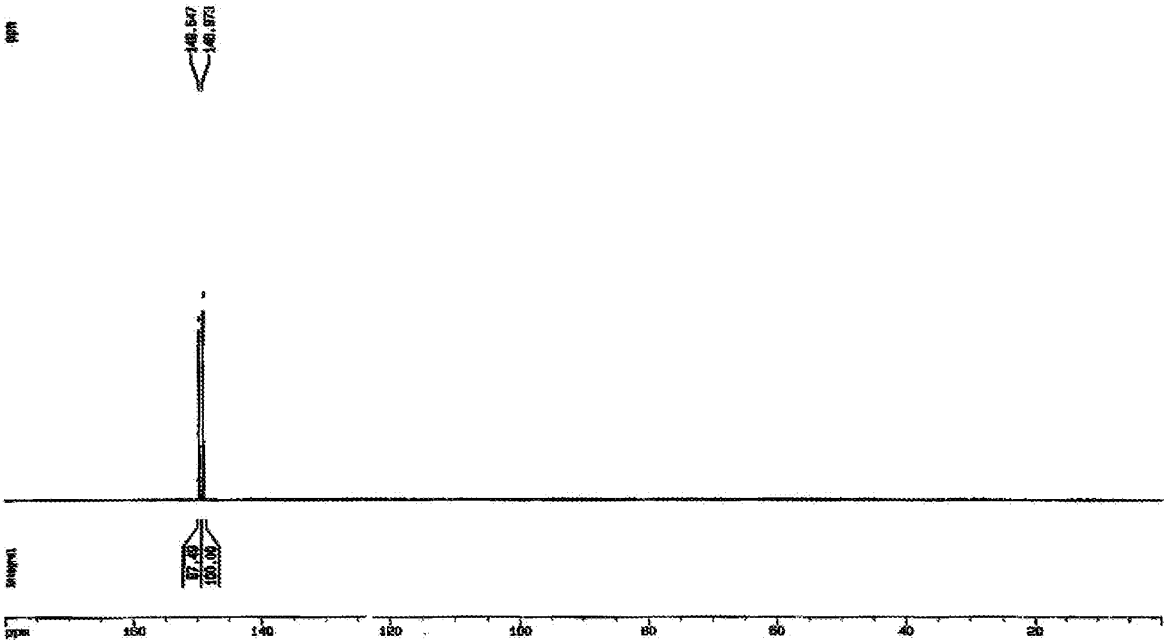


FIG. 9

Shanghai Hongene Exhibit 1002

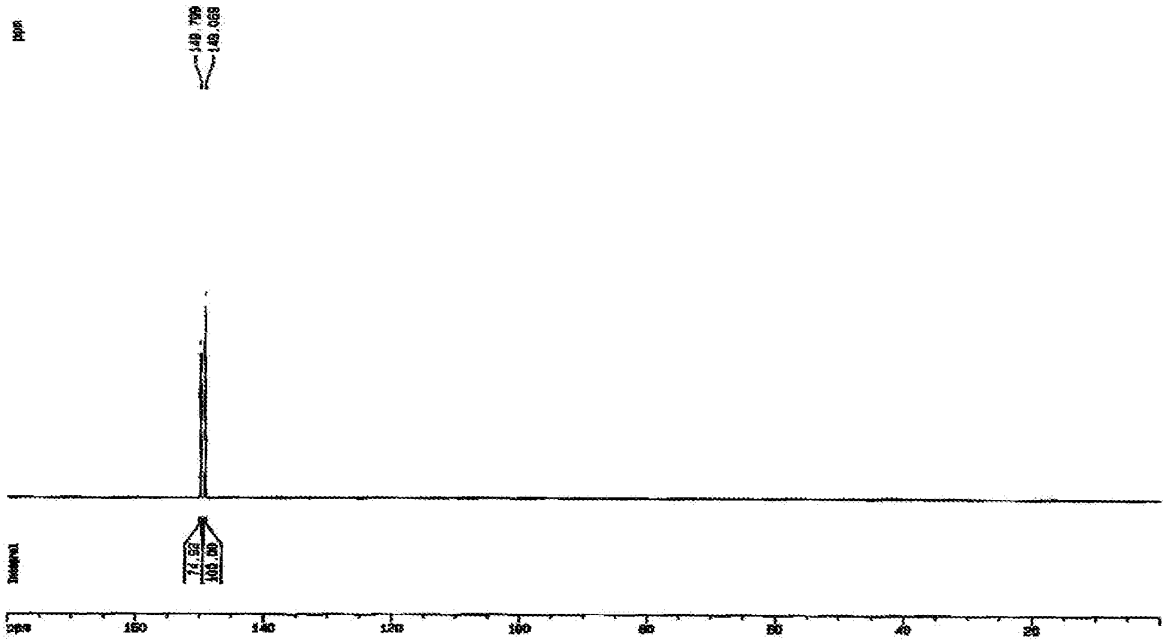


FIG-10

Shanghai Hongene Exhibit 1002

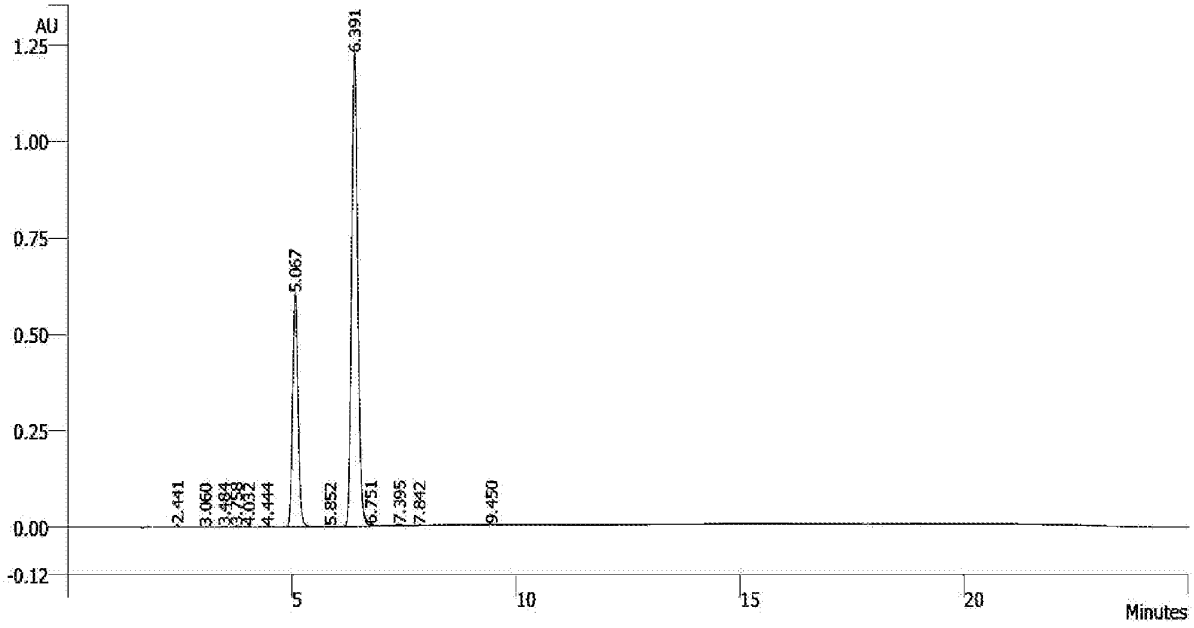

AU
1.25
1.00
0.75
0.50
0.25
0.00
-0.12
2.441
3.060
3.484
3.758
4.032
4.444
5.067
5.852
6.391
6.751
7.395
7.842
9.450
5
10
15
20
Minutes

FIG. 11A

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		2.441	316307	0.19
2		3.060	76365	0.04
3		3.484	113880	0.07
4		3.758	241658	0.14
5		4.032	74999	0.04
6		4.444	228289	0.13
7	*3'-DMT-2'-Si-Adenosine (n-bz) OP	5.067	50914964	29.99
8		5.852	154261	0.09
9	*3'-DMT-2'-Si-Adenosine (n-bz) OP	6.391	116966520	68.90
10		6.751	375067	0.22
11		7.395	213522	0.13
12		7.842	49721	0.03
13		9.450	46789	0.03
	Totals		**169772352**	**100.00**

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSpher 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 95% ACN in 0.1M TEAA [pH 7.5]
Eluent B- ACN
Gradient: Increse B (0-50%) in 25 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

Sample Amount (mg): _____
Solvent Amount (ml): _____
Solvent: _____
Lot Number: _____
Exp. Date: _____

Analyst Initials: _____
PASS / FAIL

FIG. 11B

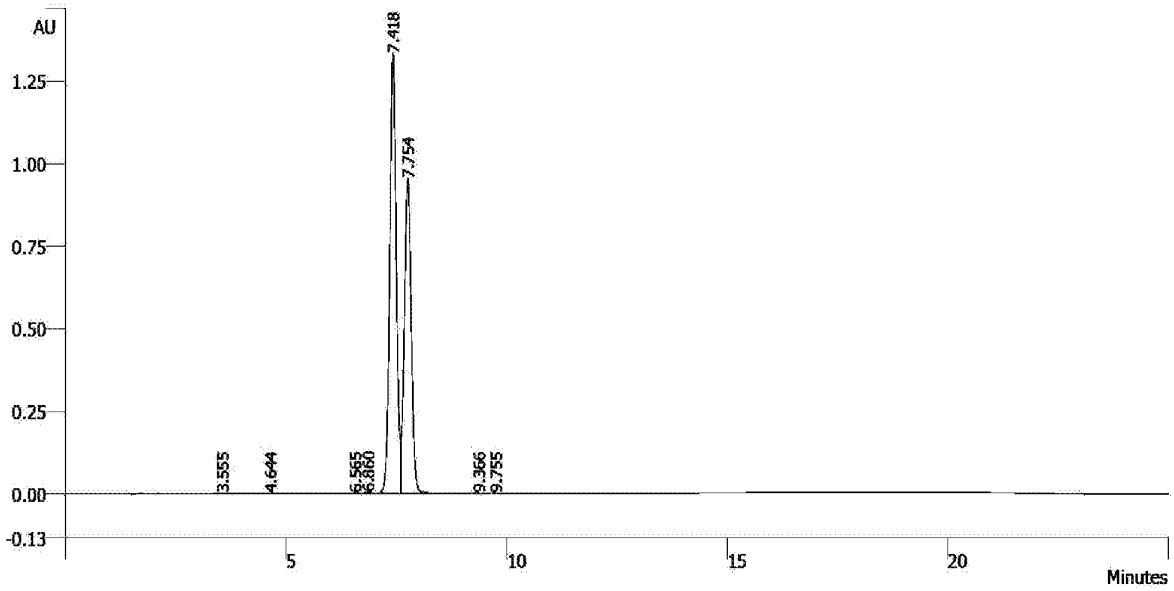


FIG. 12A

Shanghai Hongene Exhibit 1002

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		3.555	58277	0.02
2		4.644	162346	0.07
3		6.565	159521	0.07
4		6.860	314210	0.13
5	*3'-DMT-2'-TBDMS ibuG OP	7.418	136478720	56.37
6	*3'-DMT-2'-TBDMS ibuG OP	7.754	104749944	43.27
7		9.366	76431	0.03
8		9.755	99522	0.04
	Totals		**242098960**	**100.00**

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSpher 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 90% ACN in 0.1M TEAA [pH 7.5]
Eluent B- 95% ACN in 0.1M TEAA
Gradient: Increse B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

FIG. 12B

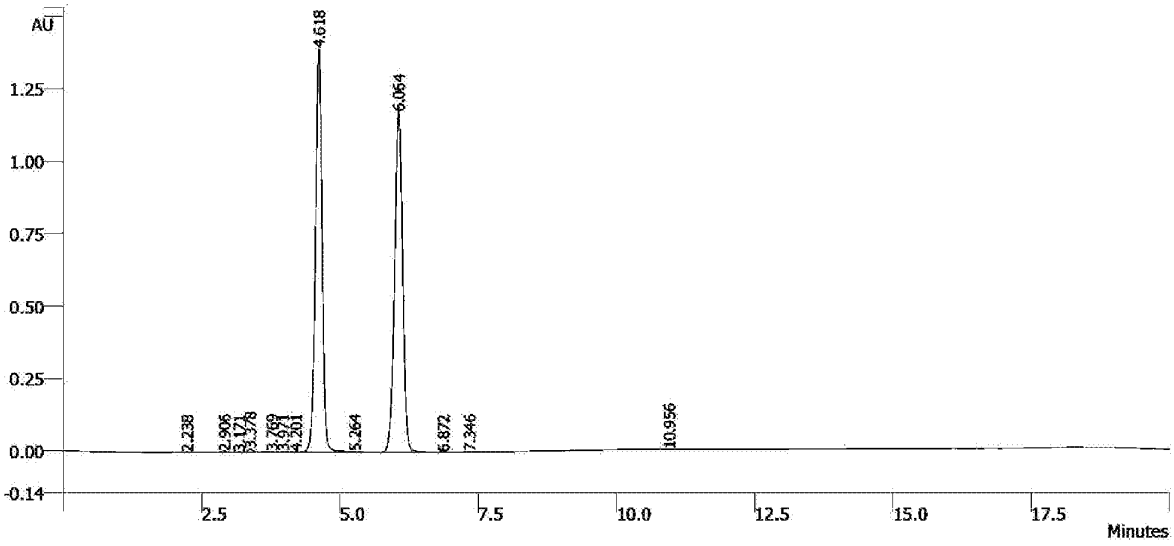

AU
1.25
1.00
0.75
0.50
0.25
0.00
-0.14
4.618
6.064
2.238
2.906
3.178
3.378
3.769
3.971
4.201
5.264
6.872
7.346
10.956
2.5
5.0
7.5
10.0
12.5
15.0
17.5
Minutes

FIG .13A

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		2.238	51545	0.02
2		2.906	257959	0.11
3		3.171	73365	0.03
4		3.378	761764	0.32
5		3.769	328242	0.14
6		3.971	178872	0.08
7		4.201	291630	0.12
8	*3'-DMT-2'-TBDMS Cytidine (n-ac) OP	4.618	118156432	49.60
9		5.264	101551	0.04
10	*3'-DMT-2'-TBDMS Cytidine (n-ac) OP	6.064	117767928	49.44
11		6.872	112221	0.05
12		7.346	67182	0.03
13		10.956	51009	0.02
	Totals		**238199696**	**100.00**

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSpher 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 95% ACN in 0.1M TEAA [pH 7.5]
Eluent B- ACN
Gradient: Increse B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

Sample Amount (mg): _____
Solvent Amount (ml): _____
Solvent: _____
Lot Number: _____
Exp. Date: _____

Analyst Initials: _____
PASS / FAIL

FIG. 13B

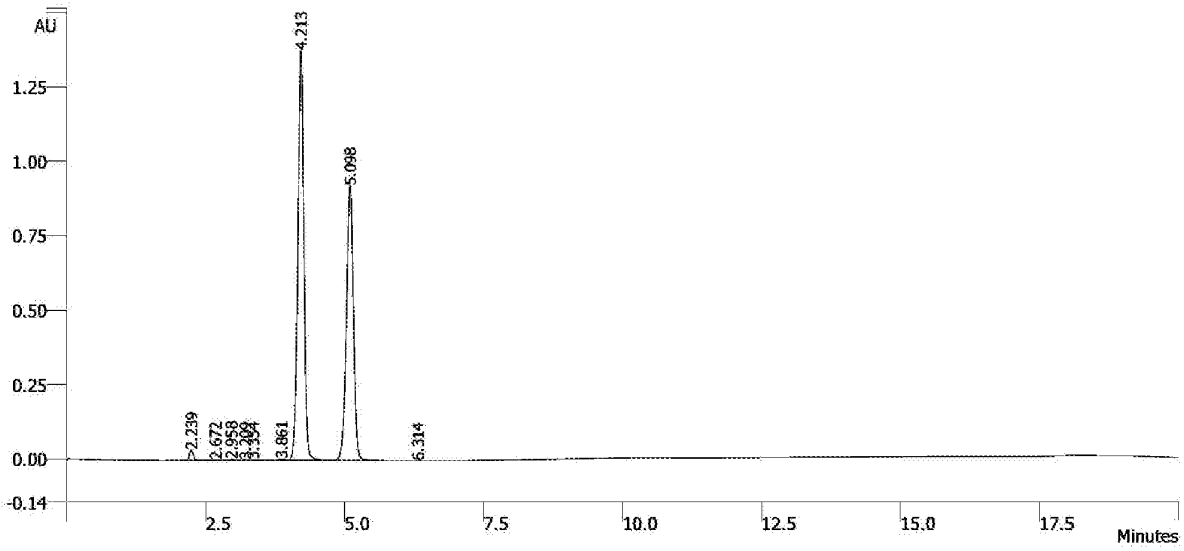


FIG. 14A

Shanghai Hongene Exhibit 1002

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		2.239	1713140	0.91
2		2.672	42783	0.02
3		2.958	157395	0.08
4		3.209	130255	0.07
5		3.354	127776	0.07
6		3.861	317837	0.17
7	*3'-DMT-2'-TBDMS Uridine OP	4.213	103188256	55.05
8	*3'-DMT-2'-TBDMS Uridine OP	5.098	81737304	43.61
9		6.314	31376	0.02
	Totals		**187446128**	**100.00**

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSpher 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 95% ACN in 0.1M TEAA [pH 7.5]
Eluent B- ACN
Gradient: Increse B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

Sample Amount (mg): _____
Solvent Amount (ml): _____
Solvent: _____
Lot Number: _____
Exp. Date: _____

Analyst Initials: _____
PASS / FAIL

FIG. 14B

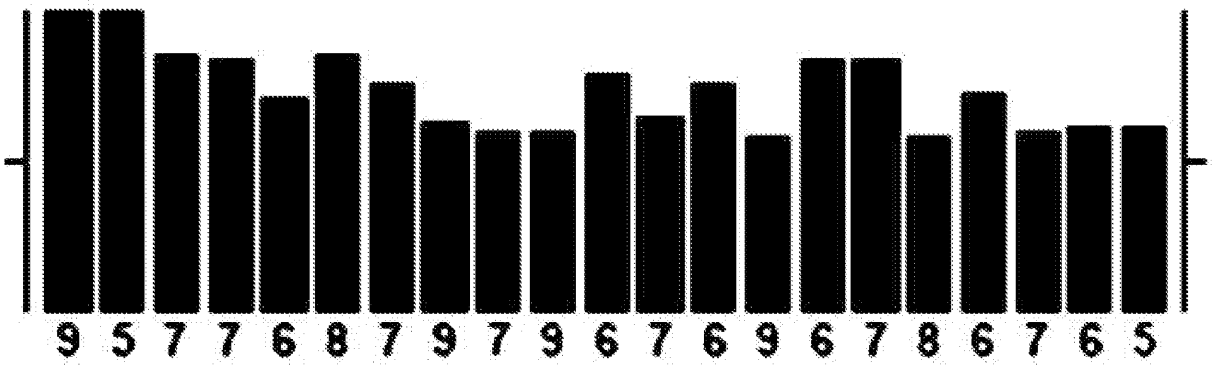


FIG. 15A

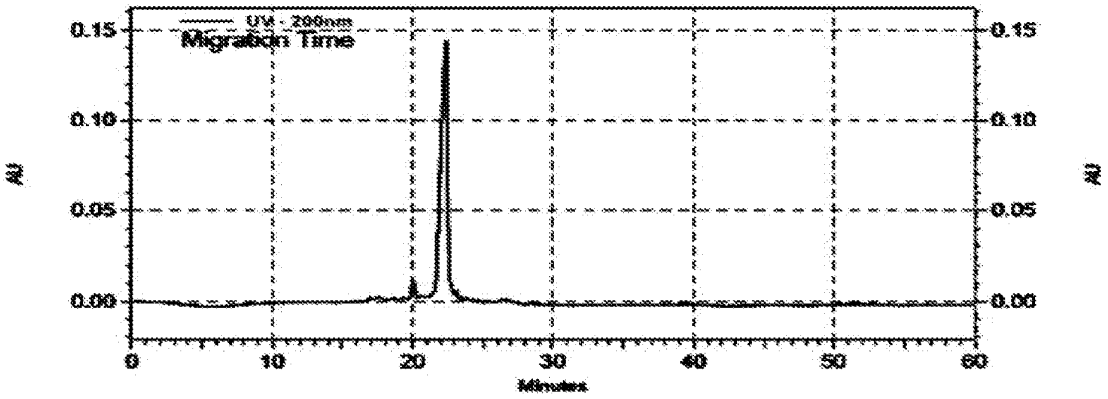

UV - 260nm
Migration Time
AU
0.15
0.10
0.05
0.00
0
10
20
30
40
50
60
Minutes

FIG. 15B

UV - 200nm Results

Time	Height	Area	Area %
18.929	453	2418	0.05
19.004	550	2554	0.05
19.692	868	2721	0.06
20.042	8898	143692	2.92
22.408	140089	4552901	92.63
22.933	659	139402	2.84
23.087	3128	21046	0.43
23.142	3459	13274	0.27
23.329	1344	2550	0.05
23.354	1197	3151	0.06
23.517	834	3423	0.07
23.692	919	2454	0.05
23.729	1006	3436	0.07
23.900	828	3525	0.07
24.288	829	2412	0.05
24.333	1100	3250	0.07
24.717	1151	2318	0.05
24.771	1473	7753	0.16
24.821	861	2754	0.06
Totals	169646	4915034	100.00

FIG. 15C

Shanghai Hongene Exhibit 1002

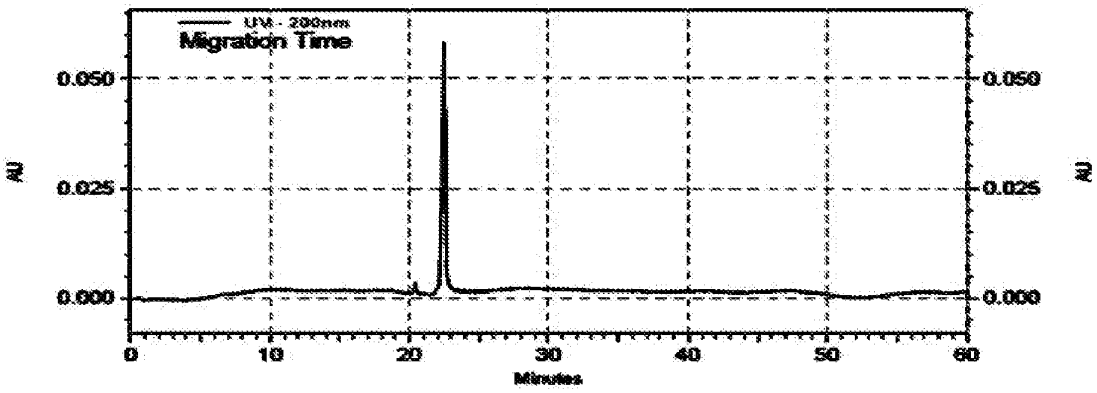

UV - 260nm
Migration Time
0.050
0.025
0.000
AU
0
10
20
30
40
50
60
Minutes

FIG. 15D

UV - 200nm Results

Time	Height	Area	Area %
21.879	1374	5992	0.97
21.925	1346	3836	0.62
21.958	870	2521	0.41
24.087	34498	607012	98.01
Totals	38088	619361	100.00

FIG. 15E

Shanghai Hongene Exhibit 1002

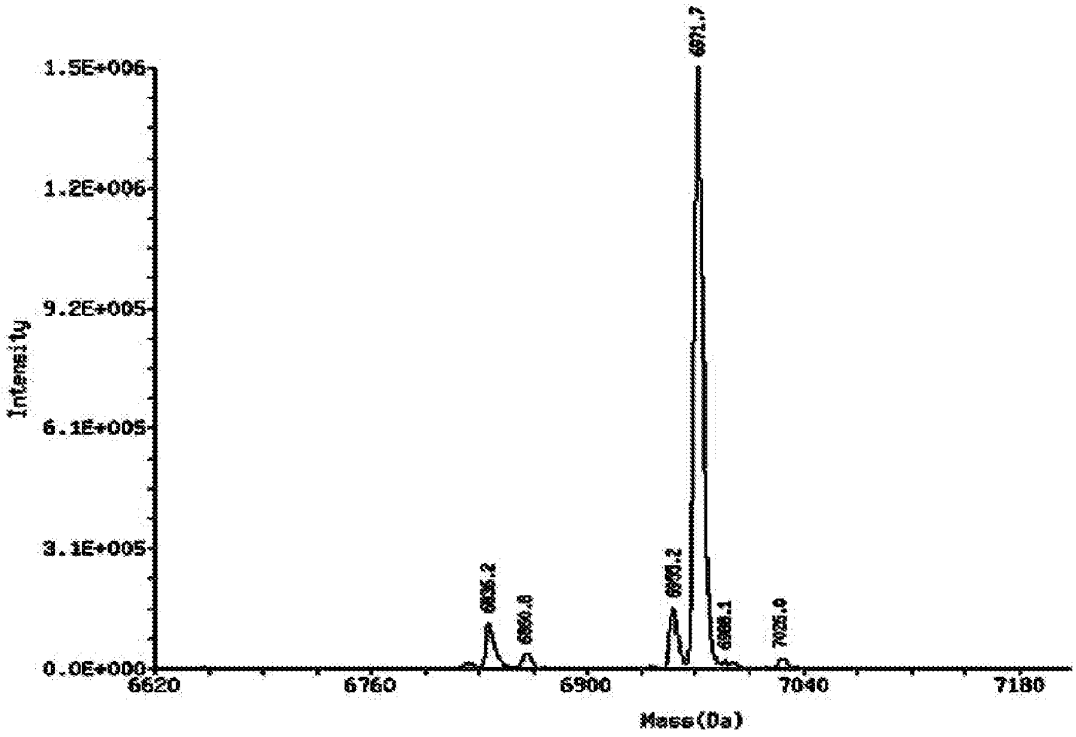

1.5E+006
1.2E+006
9.2E+005
6.1E+005
3.1E+005
0.0E+000
Intensity
6620
6760
6900
7040
7180
Mass(Da)
6835.2
6866.8
6950.2
6971.7
6988.1
7025.0

FIG. 15F

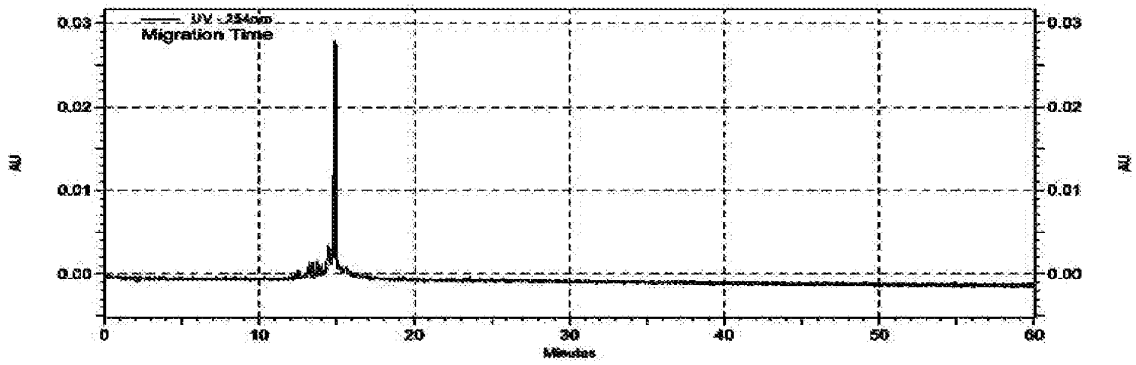


FIG. 16A

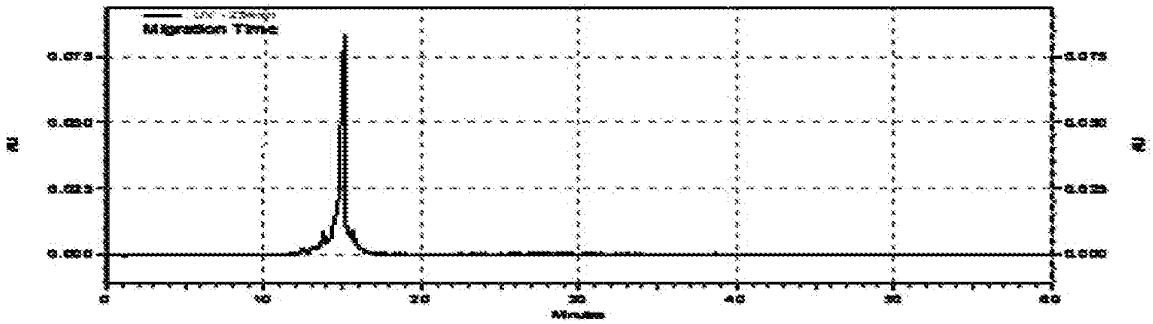


FIG. 16B

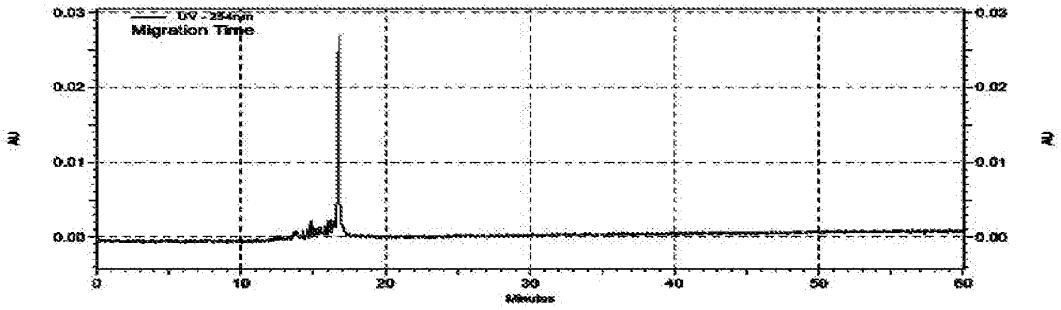

Migration Time
AU
Minutes
0.03
0.02
0.01
0.00
0
10
20
30
40
50
60

FIG. 17

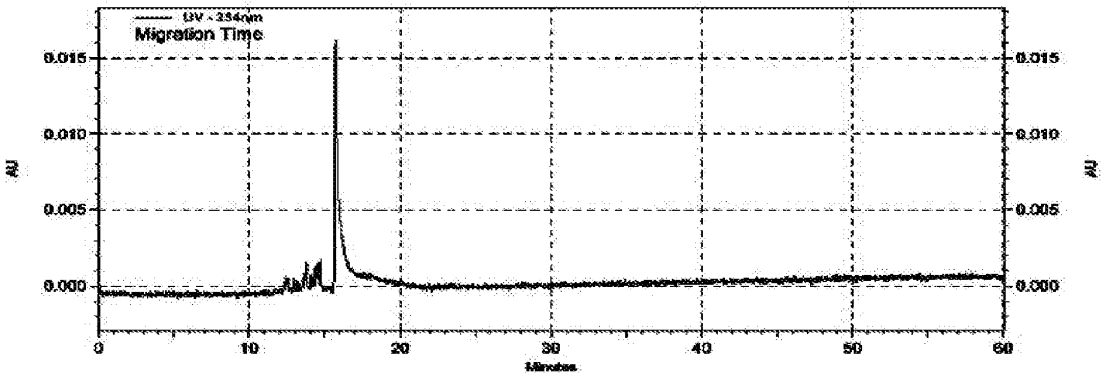

Migration Time
AU
Minutes
0.015
0.010
0.005
0.000
0
10
20
30
40
50
60

FIG. 18

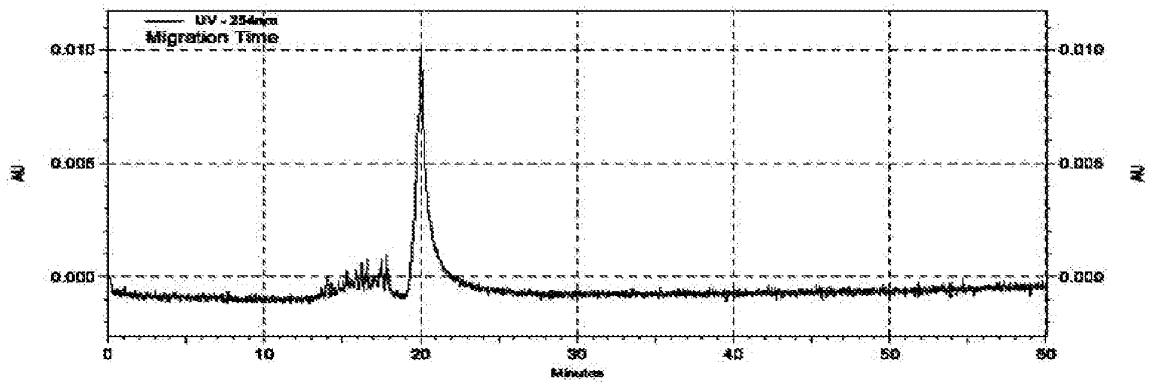

UV - 254nm
Migration Time
0.010
0.005
0.000
AU
0
10
20
30
40
50
60
Minutes

FIG. 19

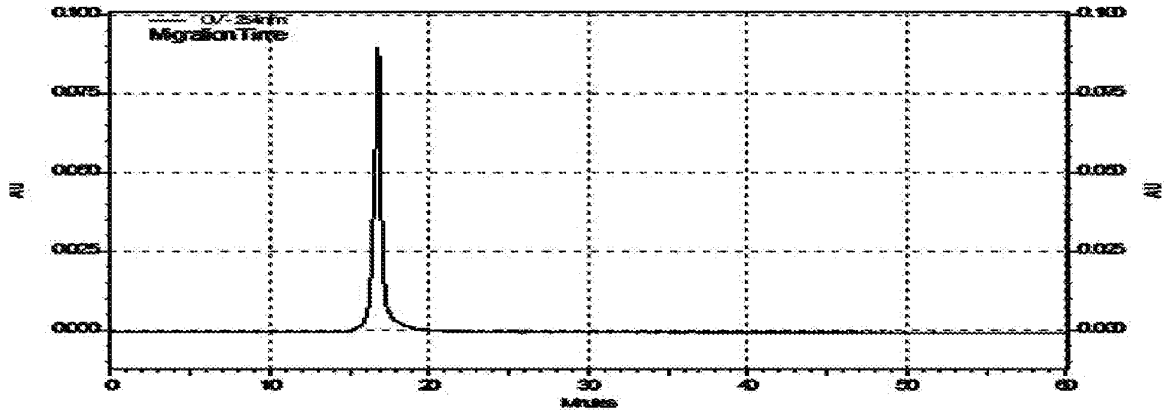

UV - 254nm
Migration Time
0.010
0.005
0.000
AU
0
10
20
30
40
50
60
Minutes

FIG. 20

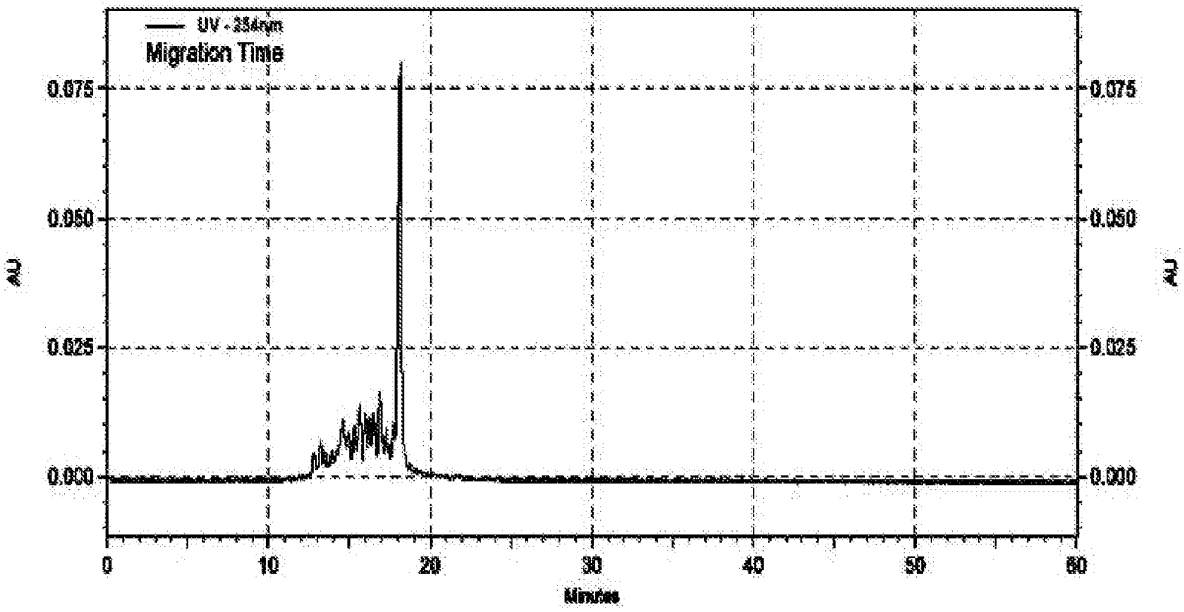

UV - 254nm
Migration Time
0.075
0.050
0.025
0.000
AU
0
10
20
30
40
50
60
Minutes

FIG. 21A

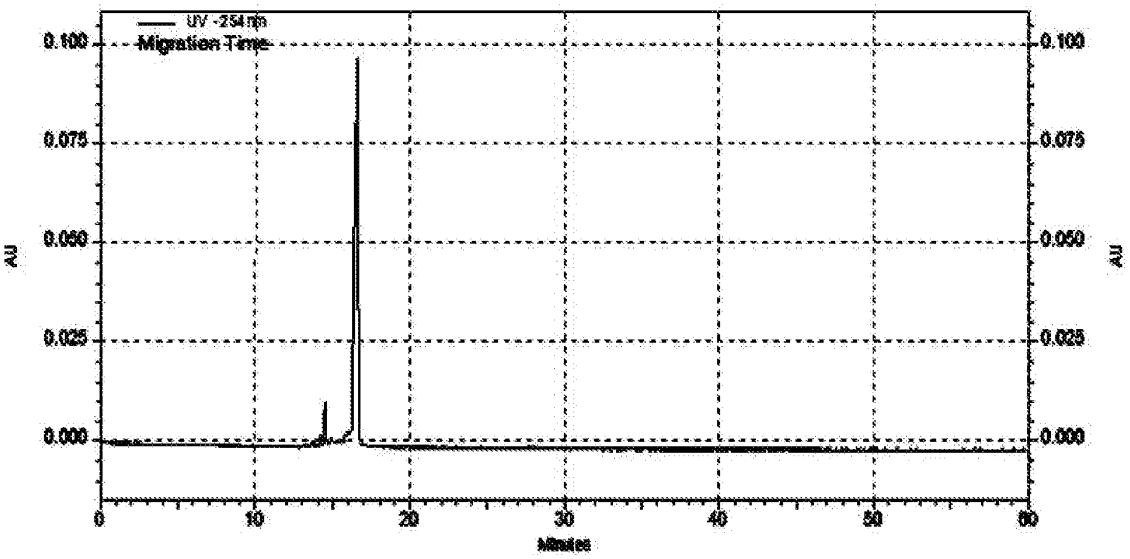


FIG. 21B

Shanghai Hongene Exhibit 1002

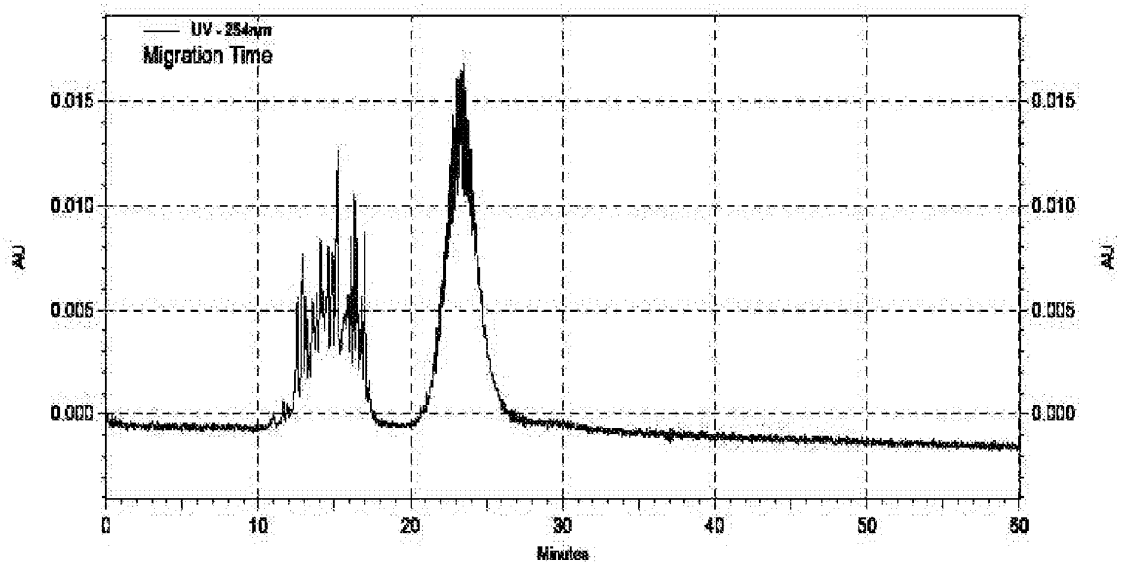


FIG. 22

Shanghai Hongene Exhibit 1002

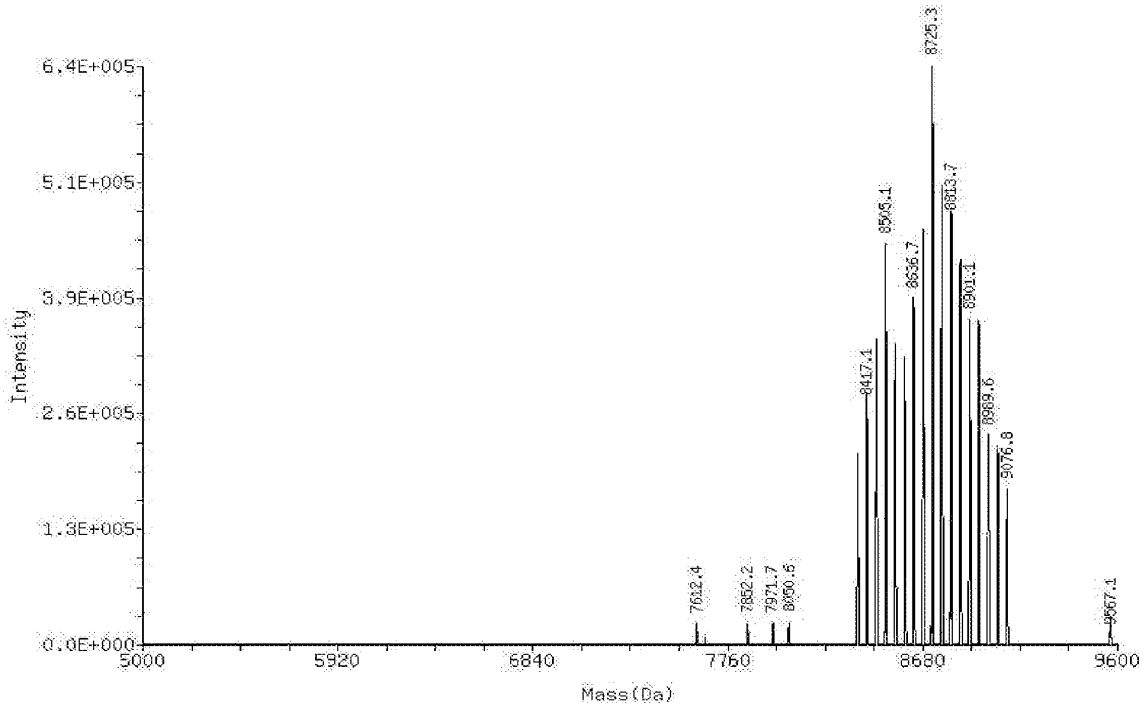

6.4E+005
5.1E+005
3.9E+005
2.6E+005
1.3E+005
0.0E+000
Intensity
5000
5920
6840
7760
8680
9600
Mass(Da)
7612.4
7852.2
7971.7
8050.6
8417.1
8505.1
8636.7
8725.3
8813.7
8901.1
8989.6
9076.8
9567.1

FIG. 23

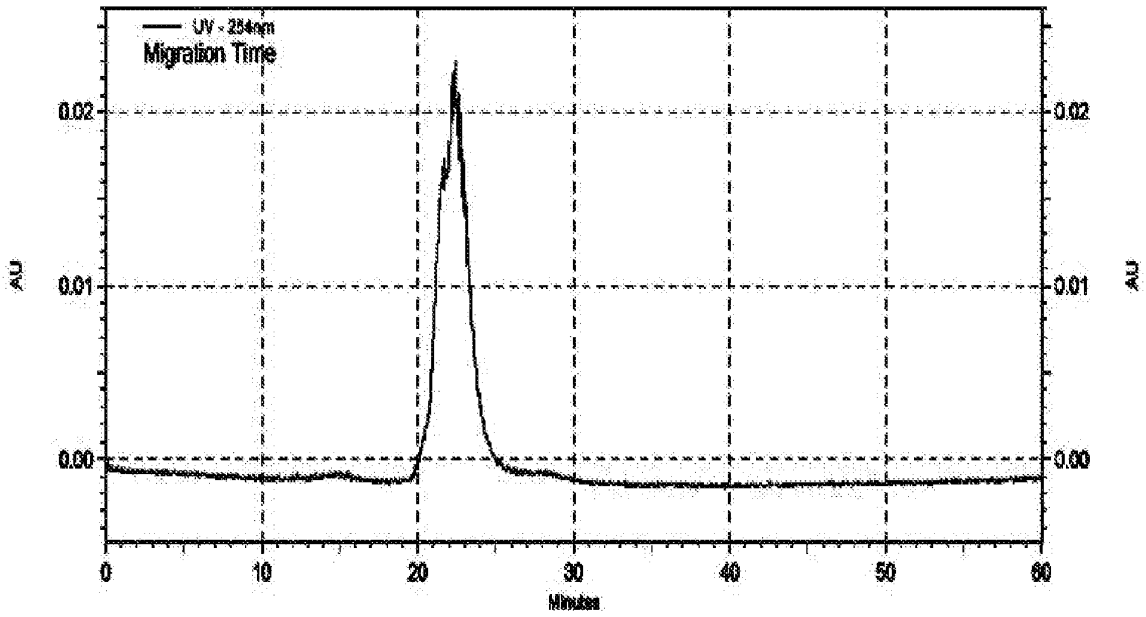


FIG. 24

Shanghai Hongene Exhibit 1002

Substitute for form 1449B/PTO **INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **July 12, 2010** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not assigned	CONFIRMATION NO. 5297	GROUP 1614

U.S. PATENT DOCUMENTS

Examiner's Initials	Ref. No.	DOCUMENT NUMBER Number-Kind Code (if known)	ISSUE DATE / PUBLICATION DATE MM-DD-YYYY	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	A1	6,043,353	03-28-2000	Pon *et al.*
	A2			
	A3			

FOREIGN PATENT DOCUMENTS

Examiner's Initials	Ref. No.	DOCUMENT NUMBER Country Code-Number-Kind Code (if known)	DATE MM-DD-YYYY	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	B1	WO 2010/027512 A2	03-11-2010	Chemgenes Corporation
	B2			
	B3			

We are not listing separately any prior U.S. Patent Office communications regarding the cited application(s) because the Examiner has access to any such actions through PAIR.

EXAMINER	DATE CONSIDERED

993039_1

Shanghai Hongene Exhibit 1002

Substitute for form 1449B/PTO **INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **July 12, 2010** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not assigned	CONFIRMATION NO. 5297	GROUP 1614

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C1	Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, PCT/US2009/005063, mailed 04-20-10
	C2	Wagner, T. and W. Pfleiderer, "Nucleotides, Part LXV, Synthesis of 2'-Deoxyribonucleoside 5'-Phosphoramidites: New Building Blocks for the Inverse (5'-3')-Oligonucleotide Approach," *Helvetica Chimica ACTA,* 83(8):2023-2035 (Aug. 2000)
	C3	Matysiak, S., *et al.*, "Acetal Oligonucleotide Conjugates in Antisense Strategy," *Nucleotides & Nucleotides*, 16(5&6):855-861 (Jan. 1997)
	C4	Schwartz, M.E., *et al.*, "A Universal Adapter for Chemical Synthesis of DNA or RNA on Any Single Type of Solid Support," *Tetrahedron Letters*, 36(1):27-30 (Jan. 1995)
	C5	Ravikumar, V.T. and R.K. Kumar, "Stereoselective Synthesis of Alkylphosphonates: A Facile Rearrangement of Cyanoethyl-Protected Nucleoside Phosphoramidites," *Organic Process Research & Development*, 8(4):603-608 (May 2004)
	C6	Srivastava, S.C., *et al.*, "RNA Synthesis: Phosphoramidites for RNA Synthesis in the Reverse Direction. Highly Efficient Synthesis and Application to Convenient Introduction of Ligands, Chromophores and Modifications of Synthetic RNA at the 3'-End," *Nucleic Acids Symposium Series*, 52(1):103-104 (Sep. 2008)
	C7	
	C8	
	C9	
	C10	
	C11	
	C12	
	C13	
	C14	
	C15	

EXAMINER	DATE CONSIDERED

993039_1

Shanghai Hongene Exhibit 1002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not Assigned
Confirmation No.:	5297		
For:	Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

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Date Signature

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Typed or printed name of person signing certificate

REPLY TO NOTICE TO FILE MISSING PARTS OF APPLICATION

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

Sir:

In reply to the Notice to File Missing Parts dated March 10, 2010, the following documents and fees are being submitted for filing in the captioned application.

☒ **COPY OF EXECUTED DECLARATION FOR PATENT APPLICATION**
(Separate transmittal letter and postcard not required)

☒ **POWER OF ATTORNEY DOCUMENT**
- ☐ Granted by Inventor(s)
- ☒ Granted by Assignee, including Statement under 37 CFR § 3.73(b)

(Separate transmittal letter and postcard not required)

☐ **PRELIMINARY AMENDMENT**
(Separate transmittal letter and postcard not required)

☒ **FILING FEE - with Fee Transmittal for Patent Applications**
Fee calculations based on:
- ☒ Claims as originally filed
  - ☐ The Notice to File Missing Parts states an erroneous number of claims.
- ☐ Claims upon entry of the Preliminary Amendment filed **[OPTION** [herewith][with the application]

(Separate transmittal letter and postcard not required)

☒ **SURCHARGE - surcharge fee of $130**
(Separate transmittal letter and postcard not required)

Shanghai Hongene Exhibit 1002

☒ **SEQUENCE LISTING - Filed concurrently and is attached**

☒ Preliminary Amendment included in Sequence Listing Transmittal
(Separate transmittal letter and postcard required)

☒ **REPLACEMENT DRAWINGS - 38 sheets of replacement drawings consisting of Figs. 1A - 24 are enclosed** ***(Separate transmittal letter and postcard not required)***

☐ A Petition to Accept Color Drawings/Photographs (Fig(s). [ ]) is attached as required.
(Separate check for fees and postcard required)

☒ **PETITION FOR EXTENSION OF TIME**

☒ Applicant hereby petitions to extend the time to respond to the Notice to File Missing Parts dated March 10, 2010 for two month(s) from May 10, 2010 to July 10, 2010. The appropriate fee of $490 is included as indicated in the Method of Payment section below.

☐ A [ ] month extension of time to respond to the Notice to File Missing Parts dated [ ] was filed on [ ] with payment of a $[ ] fee

☐ Applicant hereby petitions for an additional [ ] month extension of time to respond to the Notice to File Missing Parts. The appropriate fee of $[ ] is included as indicated in the Method of Payment section below.
(Separate Petition for Extension of Time and postcard not required)

☐ **REQUEST FOR CORRECTED FILING RECEIPT - Filed concurrently and is attached**
(Separate transmittal letter and postcard required)

☐ **STATEMENT CLAIMING SMALL ENTITY STATUS**

☐ Was filed on [ ]

☐ Is enclosed herewith
(Separate transmittal letter and postcard not required)

☐ In view of the small entity status of the captioned application, we hereby request a reimbursement of 50% of the filing fees in the amount of $[ ] which were paid on [ ] to be deposited in Deposit Account No. 08-0380

☒ **OTHER** Transmittal of Information Disclosure Statement, Listing of References and Foreign and Nonpatent References

☒ **METHOD OF PAYMENT**

☐ The fees required for filing the indicated documents are enclosed in the form of a check in the total amount of $[ ].

☒ Please charge Deposit Account 08-0380 in the amount of $3408 for the fees required for filing the indicated documents.

☒ Please charge any deficiency in fees and credit any overpayment to Deposit Account 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Alice O. Carroll
Registration No.: 33,542
Tel.: (978) 341-0036
Fax: (978) 341-0136

Concord, Massachusetts 01742-9133

Date: July 12, 2010

Shanghai Hongene Exhibit 1002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not Assigned
Confirmation No:	5297		

For: Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

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Date Signature

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Typed or printed name of person signing certificate

TRANSMITTAL LETTER FOR INFORMATION DISCLOSURE STATEMENT

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

Sir:

This Information Disclosure Statement is submitted:

☒ under 37 CFR 1.97(b), or
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application; or before the mailing date of a first office action on the merits; or before the mailing of a first office action after the filing of a Request for Continued Examination).

☐ under 37 CFR 1.97(c) together with either:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, or
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(After the 37 CFR 1.97(b) time period, but before any of a final action, notice of allowance, or an action that closes prosecution, whichever occurs first)

☐ under 37 CFR 1.97(d) together with:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, and
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(Filed after final action, notice of allowance, whichever occurs first, or if prosecution otherwise closes, but on or before payment of the issue fee)

993037_1

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☐ under 37 CFR 1.97(i):
Applicant requests that the IDS and cited reference(s) be placed in the application file.
(Filed after payment of issue fee)

Statement Under 37 CFR 1.97(e)

☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)
Applies to original applications (other than design) filed on or after May 29, 2000

☐ Each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the Information Disclosure Statement.

☒ Enclosed herewith is a Listing of References:

- ☒ Copies of the cited references are enclosed except as indicated below.
- ☒ Copies of issued U.S. patents and published U.S. applications are not required and are not being provided.
- ☐ Copies of the cited references submitted with an Information Disclosure Statement in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed, are not required under 37 CFR 1.98(d)(1) and (2) and are thus not provided.
- ☐ Pending non-published applications are not being provided, since the applications are available to the examiner.

☒ The listed references were cited in the enclosed Search Report in counterpart foreign application PCT/US2009/005063, which is listed in the attached Listing of References.

☐ The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

- ☐ the explanation provided on the attached sheet.
- ☐ the explanation provided in the Specification.
- ☐ submission of the enclosed International Search Report.
- ☐ submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.
- ☐ the enclosed English language abstract.

Method of payment:

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☐ Please charge Deposit Account 08-0380 in the amount of $[ ].

☐ A check for the fee noted above is enclosed, or the fee has been included in the check with the accompanying Reply.

☒ Please charge any deficiency in fees and credit any overpayment to Deposit Account 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: July 12, 2010

Electronic Patent Application Fee Transmittal

Application Number:	12708827
Filing Date:	19-Feb-2010
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Filer:	Alice O. Carroll/Beverly Weinberger
Attorney Docket Number:	4441.1001-002

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Utility Appl Size fee per 50 sheets >100	1081	1	270	270
Claims:				
Claims in excess of 20	1202	19	52	988
Independent claims in excess of 3	1201	2	220	440

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	490	490
Miscellaneous:				
		Total in USD ($)		**3408**

Electronic Acknowledgement Receipt	
EFS ID:	7988480
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Beverly Weinberger
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	12-JUL-2010
Filing Date:	19-FEB-2010
Time Stamp:	16:45:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$3408
RAM confirmation Number	3391
Deposit Account	080380
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	44411001002RefB1.pdf	3454060 d2f6e4cb12ac7d78801176b5204a8ebeb9a9db24	no	71
Warnings:					
Information:					
2	NPL Documents	44411001002RefC1.pdf	1316968 0db62f920060074c2b43526b50cd6207b7cceef7	no	20
Warnings:					
Information:					
3	NPL Documents	44411001002RefC2.pdf	882950 fa7db99482a468ce642ff74007231175a1158aec	no	13
Warnings:					
Information:					
4	NPL Documents	44411001002RefC3.pdf	337435 552b594385c767a6696368e3b5304721879b77cb	no	7
Warnings:					
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5	NPL Documents	44411001002RefC4.pdf	248654 f74cff3a19edd5e721935510f32981d5be016068	no	4
Warnings:					
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6	NPL Documents	44411001002RefC5.pdf	466857 64caeb5f75654614fd3e34f0c9531597ed32fab5	no	6
Warnings:					
Information:					
7	NPL Documents	44411001002RefC6.pdf	180314 123b7dc9dfa9cb07d4b931f25b4054af2ac90c82	no	2
Warnings:					
Information:					
8	Oath or Declaration filed	44411001002Declaration.pdf	128675 68d9560e61d47a388c9e6cf1d05dd963d6ac6089	no	2
Warnings:					
Information:					

9	Power of Attorney	44411001002PowerOfAtty.pdf	84694 f81fdd100d490d8e1aa876ba9da4ebeaf17bcbf3	no	1
Warnings:					
Information:					
10	Assignee showing of ownership per 37 CFR 3.73(b).	44411001002Statement373b.pdf	303566 b83a7adeaf6ab1c41ae308dfc0444136fb172c4b	no	4
Warnings:					
Information:					
11	Fee Worksheet (PTO-875)	44411001002FeeTransmittal.pdf	243196 cf3c059631f8e7c4b4044f4818edcb601ab21159	no	1
Warnings:					
Information:					
12		44411001002TransmittalOfSeqListAndPrelimAmend.pdf	338022 d7a82568bd91793cf2ae849708bce8bbd35f88a2	yes	9

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	6
Drawings-only black and white line drawings	7	7
Applicant Arguments/Remarks Made in an Amendment	8	9

Warnings:					
Information:					
13	Drawings-only black and white line drawings	44411001002ReplacementDrawings.pdf	1193017 0ae4eb467755a79d412be596061423b0bd48e3e5	no	38
Warnings:					
Information:					
14	Sequence Listing (Text File)	44411001002SequenceListing.txt	9979	no	0
Warnings:					
Information:					
15	Information Disclosure Statement (IDS) Filed (SB/08)	44411001002ListOfReferences.pdf	150334 7ad590d4be944659a417edc4f0e64a0970ff4ee6	no	2
Warnings:					

Information:					
This is not an USPTO supplied IDS fillable form					
16	Applicant Response to Pre-Exam Formalities Notice	44411001002ReplyToNTFMP.pdf	142509 c02e5f10732522e2e890dd498a7c12612595d870	no	2
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Information:					
17	Transmittal Letter	44411001002IDSTransmittal.pdf	165874 0753b6bcfb20af4991bd7d7cd39dcb0351523f8e	no	3
Warnings:					
Information:					
18	Fee Worksheet (PTO-875)	fee-info.pdf	43853 d4b5b960d0fcf0ebf97297cc6f48460739680975	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	9690957		

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

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

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

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

(19) World Intellectual Property Organization
International Bureau

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11 March 2010 (11.03.2010)

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8 September 2009 (08.09.2009)

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(26) Publication Language: English

(30) Priority Data:
61/191,065 6 September 2008 (06.09.2008) US

(71) Applicant *(for all designated States except US)*: **CHEMGENES CORPORATION** [US/US]; 33 Industrial Way, Wilmington, MA 01887 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SRIVASTAVA, Suresh, C.** [US/US]; 7 Donald Road, Burlington, MA 01803 (US). **PANDEY, Divya** [IN/IN]; 7 Alfa Farm, Chini Godam Road, Barabirwa, Kanpur Road, Lucknow, UP 226012 (IN). **SRIVASTAVA, Naveen, P.** [US/US]; 4 Baron Park Lane, Apartment 10, Burlington, MA 01803 (US). **BAJPAI, Satya, P.** [IN/IN]; D-14 Sarojini Nagar, Kanpur Road, Industrial Area, Lucknow, UP 226008 (IN).

(74) Agents: **CARROLL, Alice, O.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2010/027512 A2

(54) Title: 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

(57) Abstract: The present invention relates to novel phosphoramidites, A-n-bz, C-n-bz, C-n-ac, G-n-ac and U are produced with an HPLC purity of greater than 98% and ^{31}P NMR purity greater than 99%. A novel process of reverse 5'→ 3' directed synthesis of RNA oligomers has been developed and disclosed. Using that method demonstrated high quality RNA synthesis with coupling efficiency approaching 99%.

B1

Shanghai Hongene Exhibit 1002

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

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/191,065, filed on September 6, 2008. The entire teachings of the above application are incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to the synthesis of novel RNA monomer phosphoramidites, and corresponding solid supports that are suitable for a novel method of RNA oligonucleotide synthesis in reverse 5' → 3' direction. This approach leads to very clean oligonucleotide synthesis allowing for introduction of various modifications at the 3'-end cleanly and efficiently in order to produce high purity and therapeutic grade RNA oligonucleotides.

BACKGROUND OF THE INVENTION

Defined sequence RNA synthesis in the 3' → 5' direction is now well established and currently in use for synthesis and development of a vast variety of therapeutic grade RNA aptamers, tRNAs, siRNA and biologically active RNA molecules.
This approach utilizes a ribonucleoside with suitable N- protecting group: generally 5'-Protecting group, the most popular being dimethoxytriphenyl, i.e. the DMT group; 2'-protecting group, out of which most popular is t-Butyldimethylsilyl ether; and, a 3'-phosphoramidite, the most popular of which 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 (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 leading to dimers and oligoribonucleotides, followed by oxidation (3'→5' direction synthesis), also leads to a protected dinucleotide having a 3'-5'- internucleotide linkage, Ogilvie, K.K., Can. J. Chem., 58, 2686, 1980 (scheme 1).

However, the synthesis of RNA in the reverse direction (5'- 3' direction) has not been achieved so far to the best of our knowledge.

Shanghai Hongene Exhibit 1002

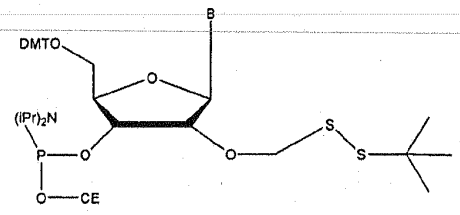
The 2'- silyl ethers of component 1 have been developed extensively and they are known to have remarkable stability. Solvolysis of silyl ethers have been extensively studied and it is known that bulky alkyl silyl ethers have a high degree of stability; Bazani, B and Chvalowski, V Chemistry of Organosilicon compounds, Vol. 1, Academic Press, New York, 1965. Extensive research work was subsequently done 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., Nicoghosian, K, and Cedergren, R.J. *Proc. Natl. Acad. Sci. USA*, 85, 5764-5768, 1988 ; Bratty, J., Wu, T., Nicoghosian, 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 processes is amenable to carry out the synthesis of RNA in reverse direction (5'→3'direction); hence they lack the capability of the convenient and efficient introduction of many ligands and

Shanghai Hongene Exhibit 1002

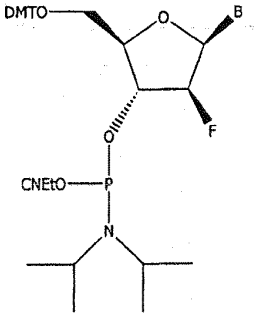
chromophores at the 3'-end of RNA molecules, achievable through reverse direction synthesis.

Chemically modified RNA have been synthesized having modified arabino sugars, 2'-deoxy-2'- fluoro- beta-D_arabinonucleic acid (FANA; structure 2)) and 2'-deoxy-4'- thio-2'- fluoro- beta-D_arabinonucleic acid (4'-Thio-FANA; structure 3) 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 the several new 2' –protecting groups the chemistry for which have been developed , the 2'-protecting 2-cyanoethoxymethyl (CEM) (structure 4) has been shown for producing very long RNA, however, which also carries out RNA synthesis in the conventional, i.e., the 3'→5'direction. Furthermore, the quality of RNA produced by these processes remains in question.



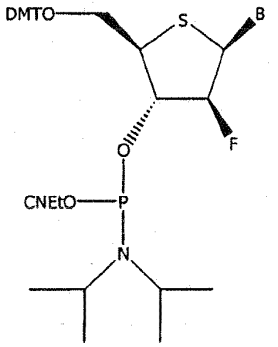
(2'- DTM – RNA amidites)

Structure (1)



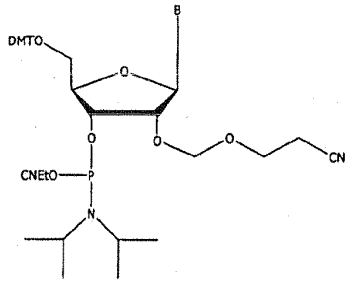
Structure (2)

2'- F-ANA modified phosphoramidites



Structure (3)

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



Structure (4)

2'- CEM Protected RNA Intermediates

The 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 has 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., Nicoghosian, K., Cedrgren, R.J., Proc. Natl. Acad. Sci., USA, 85:5764-5768, 1988; Bratty, J., Wu, T., Nicoghosian, 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. None of the techniques mentioned in this paragraph, however contemplate the synthesis of RNA in reverse direction (5'→3'direction), and hence the practical and convenient introduction of a number of groups required for selective introduction at 3'-end remains elusive.

The present inventors have observed higher coupling efficiency per step during automated oligo synthesis with our reverse RNA amidites, resulting in a greater ability to achieve higher purity and produce very long oligos. They also demonstrate that the process of this invention leads to oligonucleotides free of M+1 species, which species

lead to closer impurities as shoulder of desired peak during HPLC analysis or purification or Gel purification.

The t-butyldimethyl silyl protecting group on 2'- hydroxyl of ribonucleosides has been the group of choice for making 3'- phosphoramidites and for utilizing them for oligonucleotide synthesis which have been shown to migrate to 3'- hydroxyl position rather easily. This has been documented amply and in detail (Ogilvie, K.K., and Entwistle, D.W. *Carbohydrate Res.*, 89, 203-210, 1981; Wu, T., and Ogilvie, K.K. *J. Org. Chem.*, 55, 4717-4734, 1990). Such migration complicates the synthesis of the desired phosphoramidites and requires an efficient method of purification that clearly resolves corresponding isomers and prevents any contamination of the final monomer.

The present invention is directed towards the synthesis of high purity RNAs, specifically to introduce selected groups at 3'- end of oligonucleotides of synthetic RNAs. Such RNA's have vast application in therapeutics, diagnostics, drug design and selective inhibition of an RNA sequence within cellular environment, 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 shows great promise for application in the control and management of various biochemical and pharmacological processes. Early studies by Fire etal., 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 a 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 the confirmation of above studies and established RNAi as a powerful tool for selective, 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,

Shanghai Hongene Exhibit 1002

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.

Besides the natural double stranded (ds) RNA sequences, chemically modified RNA have been shown to cause similar or enhanced RNA interference in mammalian cells using 2'-deoxy-2'- fluoro- beta-D-arabinonucleic acid (FANA) 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.

Various other modifications to improve siRNA properties have been pursued, which include alteration in backbone chemistry, 2'- sugar modifications, and nucleobase modifications, some of which have been recently reviewed; Nawrot, B, and Sipa, K., Curr. Top. Med. Chem., 6,913-925, 2006; Manoharan, M. Curr. Opin. Chem. Biol., 8, 570-579, 2004. The PS modifications of siRNA are well tolerated , although some reports indicate increased toxicity and somewhat reduced efficacy; Harborth, J., Elbasir, S.M., Vandenburgh, K., Manninga, H., Scaringe, S.A., Weber, K., Tuschl, T., Antisense Nucleic Acid Drug Dev., 13, 83-105, 2003. Among these is also the 2'- Omethyl modification , although it maintains A form (RNA like) helix, and has been shown to be either retaining or reducing siRNA activity depending on the number of such modifications within a sequence, Chiu, Y.L., Rana, T.M., RNA, 9, 1034-1048, 2003. It has also been shown that extensive 2'- O-Methyl modification of a sequence can be made in the sense strand without loss of siRNA activity, Kraynack,B.A., Baker, B.F., RNA, 12, 163-176, 2006.

Bicyclic locked nucleic acids (LNA's) that confer high binding affinity have also been introduced in siRNA sequences, especially when the central region of siRNA sequence is avoided, Braash, D.A., Jensen, S., Liu, Y., Kaur, K., Arar, K., White, M.A., and Corey , D.R., Biochemistry, 42, 7967-7995, 2003. Similarly altritol sugar modified oligonucleotides (ANA) have recently been reported. Altrilol sugar offers a rigid conformation and is shown to form very stable duplexes with RNA in a sequence sprecific manner, and further shown to stay in A (RNA type) conformation. It was shown that ANA modified siRNAs targeting MDR1 gene exhibited improved efficacy as compared to unmodified controls, specifically effective when this modification was near the 3'- end of sense or antisense strand; Fisher, M., Abramov, M., Aerschot, A.V., Xu, D., Juliano, R.L., Herdewijn, P., Nucl. Acids Res.,35, 1064-1074, 2007.

Shanghai Hongene Exhibit 1002

Among the various requirements for effective RNA interference (RNAi) to take place, a number of observations and facts have been established. Thus the RNA has to be double stranded (ds) in the region of identity to the target. For the chemical requirement, besides the capability of 5'- end to be converted to triphosphates, modifications of A, C, G were found to be fully compatible with interference activity. Backbone modification of RNA, such as 2'- fluoro, 2'- amino uracil, 2'- deoxy thymidine, and 2'- deoxycytidine appear to stabilize the modified RNA in the resulting double strand. Amongst the nucleoside base modification 5- bromouracil, 4- thiouracil, 5-iodouracil, 5-(3-aminoallyl)- uracil, inosine are readily incorporated in the RNA interference complex (RNAi & RISC complex). Similarly inosine may be substituted for guanosine.
It has been shown that cholesterol – conjugated siRNA can achieve delivery into cells and silence gene expression. Further, it has been shown that lipid conjugated siRNA, bile acids, and long chain fatty acids can mediate siRNA uptake into cells and silence gene expression *in vivo.* Efficient and selective uptake of siRNA conjugates in tissues is dependent on the maximum association with lipoprotein particles, lipoprotein / receptor interactions and transmembrane protein mediated uptake. It has been shown that high density lipoproteins direct the delivery of siRNA into liver, gut , kidney and steroidal containing organs. It has been further shown that LDL directs siRNA primarily to the liver and that LDL receptor is involved in the delivery of siRNA. These results show great promise for siRNA uptake by an appropriate delivery system which can be exploited in development of therapeutics. (Article by Marcus Stoffel, OTS, 2007, p.64.)

It has been proposed that siRNA can be designed with chemical modifications to protect against nuclease degradation, abrogate inflammation, reduce off target gene silencing , and thereby improve effectiveness for target genes. Delivery vehicles or conjugates of lipids and other lipophilic molecules which allow enhanced cellular uptake are essential for therapeutic developments. Such siRNA's are presently being developed for human target validation, interfering with diseases pathways and developing new frontier for drug development. Alan Sachs, Merck, Oligonucleotide Therapeutics Conference (OTS), page 80, 2007.

The 3'- end of sense strand of siRNA can be modified and has been shown to tolerate modification, and that attachment of ligands is most suited at this end (FIGs. 1 & 2), as detailed in a number of key publications; siRNA function in RNAi: a chemical modification, Ya-Lin Chiu and Tariq Rana, RNA, 9, 1034-1048, 2003; M. Manoharan,

Shanghai Hongene Exhibit 1002

Curr. Opin. Chem.Biol, 6, 570-579,2004; Nawrot, B. and Sipa, K., Curr.Top.Med. Chem., 6, 913-925, 2006; Scaringe, S., Marshall, W.S., Khvorova, A., Naty. Biotechnol., 22, 326-30, 2004.

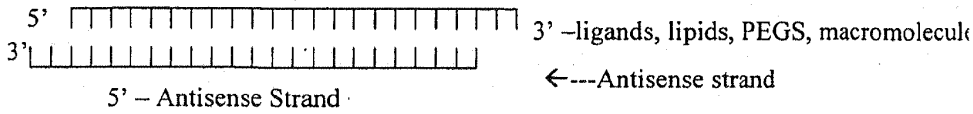


Diagram (1). (siRNA duplex)

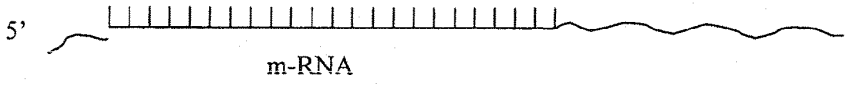


Diagram (2). (m-RNA Complementary to antisense strand)

The introduction of lipophilic or hydrophobic groups and enhancing of siRNA delivery and optimization of targets has been addressed and achieved through bio-conjugation (Diagram 1). Generally the attachment is done, preferably at the 3'- end of senses strand, and occasionally on the 3'- end of the antisense strand. The design of nuclease resistant siRNA has been the subject of intense research and development recently in order to develop effective therapeutics. Thus base modifications such as, 2-thiouridine, pseudouridine, dihydrouridine have revealed the effect on conformations of RNA molecules and the associated biological activity; Sipa, K., Sochacka, E., Kazmierczak-Baranska, J., Maszewska, M., Janicka, M., Nowak, G., Nawrot, B., RNA, 13, 1301-1316, 2007. It was shown that 2'- modified RNA's especially 2'- Fluoro have great resistance towards nuclease and are biological active *in- vivo*, Layzer, J.M., McCaffrey, A.P., Tanner, A.K., Huang, Z., Kay, M.A., and Sullenger, B.A., RNA, 10, 766-771, 2004. 2'- O-Alkyl-modification , such as 2'- Omethyl's and 2'- O-MOE, Prakash, S., Allerson, CV.R., Dande,P., Vickers, T.A., Siofi, T.A., Jarres, R., Baker, B.F., Swayze, E.E., Griffey, R.H., and Bhat, B., J.Med. Chem., 48, 4247, 4253, 2005. The same authors used 4'-thio modified sugar nucleosides in combination of 2'- O alkyl modification for improving siRNA propertie s and RNAi enhancement, Dande, P., Prakas, T.P., Sioufi, N., Gaus, H., Jarres, R., Berdeja, A., Swayne, E.E., Griffey, R.H., Bhat, B.K, J. Med. Chem., 49, 1624-1634, 2006. The Replacement of internucleotide

Shanghai Hongene Exhibit 1002

phosphate with phosphorothioate and boranophosphates of siRNAs show promise *in-vivo*, Li, Z.Y., Mao, H., Kallick, D.A., and Gorenstein, D.G., Biochem. Biophys. Res. Comm., 329, 1026-1030, 2005; Hall, A.H.S., Wan, J., Shaughnessy, E.E., Ramsay Shaw, B., Alexander, K.A., Nucl. Acids Res., 32, 5991-6000, 2004.

Bioconjugation of siRNA molecules, biologically RNA molecules, aptamers and synthetic DMNA molecules require, in addition to in vivo stability and appropriate modification of nucleosides, a key feature for cell membrane permeability,: Insufficient cross- membrane cellular uptake limits the utility of siRNA's, other single stranded RNA's or even various DNA molecules. Thus cholesterol attached at 3'- end of siRNA has been shown to improve *in-vivo* cell trafficking and therapeutic silencing of gene, Soutschek, J., Akine, A., Bramlage, B., Charisse, K., Constein, R., Donoghue, M., Elbasir, S., Geickk, A., Hadwiger,P., Harborth, J., Nature, 432, 173-0178, 2004.

Among the various conjugations, besides cholesterol, which have been developed are:

(a) Natural and synthetic protein transduction domains (PTDs), also called cell permeating peptides (CPPs) or membrane permeant peptides (MPPs) which are short amino acid sequences that are able to interact with the plasma membrane. The uptake of MPP-siRNA conjugates takes place rapidly. Such peptides can be conjugated preferably to the 3'- of stand strand.

(b) Other polycationic molecules can be conjugated at the 3'- end of either sense or antisense strand of RNA.

(c) PEG (polyethylene glycols-oligonucleotide conjuagates) have been used in various complex possess significant gene silencing effect after uptake in target cells, Oishi, M., Nagasaki, Y., Itaka, K., Nishiyama, N., and Kataoka, K., J. Am. Chem. Soc., 127, 1624-1625, 2005.

(d) Aptamers have been used for site specific delivery of siRNA's. Since Aptamers have high affinity for their targets, the conjugates with siRNA act as excellent delivery system, which result in efficient inhibition of the target gene expression, Chu, T.C., Twu, K.Y., Ellington, A.D. and Levy, M., Nucl. Acids Res., 34(10), e73, 2006. These molecules can once again be conjugated at the 3'- end of siRNA or other biologically active oligonucleotides.

Shanghai Hongene Exhibit 1002

(e) Various lipid conjugations at the 3'- end can be achieved through the present invention and can be utilized for efficient internalization of oligonucleotides. The lipophilic moiety can consist of a hydroxyl function to synthesize a phopsphoramidite. Similarly the lipophilic moiety can have carboxylic function at the terminus. The later can be coupled to a 3'-amino group having a spacer, synthesized by last addition of amino linkers such as C-6 amino linker amidite, of the reverse synthesized oligonucleotide, to the carboxylic moiety using DCC (dicyclohexyl cabodiimide) or similar coupling reagent.

This research has been reviewed elegantly by Paula, De. D., Bentley, M.V.L.B., Mahao, R.L., RNA, 13, 431-456,2007.

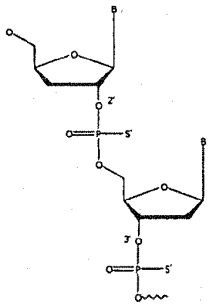
Another class of RNA, closely related to siRNA are microRNA, commonly referred as miRNA.These are a large class of non coding RNA's which have a big role in gene regulation, Bartel, D.P. Cell, 116,281-297, 2004; He, L., Hannon, G.J. Nat. Rev. Genet, 5:522-531, 2004; Lagos-Quintana, M., Rauhut, R., Lendeckel, W., Tuschl, T., Science, 204:853-858,2001. In human genome there are at least 1000 miRNA scattered across the entire genome. A number of these micro RNA's down regulate large number of target mRNAs, Lim, L.P., Lau, N.C., Garrett- Engele, P., Grimson, A., Schelter, J.M., Castle, J., Bartel, D.P., Linsey, P.S., Johnson, J.M., Nature, 433:769-773, 2005. Different combination of miRNAs are possibly involved in the regulation of target gene in mammalian cell. It has also been shown that siRNA can function as miRNAs; Krek, A., Grun, D., Poy, M.N., Wolf, R., Rosenberg, L., Epstein, E.J., MacMenamin, P., da Piedade, I., Gunsalus, K.C., Stoffel, M., Nat. Genet., 37: 495-500, 2005; Doench, J.G., Petersen, C.P., Sharp, P.A., Genes Dev., 17:438-442, 2003. The miRNA have great potential in therapeutics and in gene regulation, Hammond, S.M., Trends Mol. Med. 12:99-101, 2006. A vast amount of effort is being currently devoted towards understanding miRNA pathways, their role in development and disease, focusing specially on cancer. The miRNA targets are being developed for therapeutic and diagnostics development. A great number of miRNA are being identified and their role is being determined through microarrays, PCR and informatics. Syntheses of RNA designed to target miRNA also require RNA synthesis and other modification as required for siRNA's, for the stability of RNA and the bioconjugation for better cellular

Shanghai Hongene Exhibit 1002

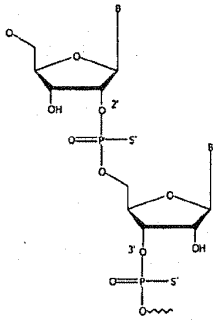
uptakes. The reverse synthesis envisioned by the present invention can greatly accelerate the pace of this research and development.

Synthesis of vast variety of therapeutic grade RNA and siRNA requires a modification or labeling of 3'- end of an oligonucleotide. In the case of siRNA, generally it is the 3'- end of sense strand. The synthesis of 3'- end modified RNA requiring lipophilic, long chain ligands or chromophores, using 3' → 5' synthesis methodology is challenging, requires corresponding solid support and generally results in low coupling efficiency and lower purity of the final oligonucleotide, in general, because of the large amount of truncated sequences containing desired hydrophobic modification.

The present inventors have approached this problem by developing reverse RNA monomer phosphoramidites for RNA synthesis in 5'→ 3'- direction. This arrangement leads to very clean oligonucleotide synthesis allowing for introduction of various modifications at the 3'- end cleanly and efficiently. In order to enhance stability and eliciting of additional favorable biochemical properties, this technique can utilize 2'-5'-linked DNA (Structure 5) and RNA (Structure 6) which have been developed in the past.



Structure (5). (2'-5'- linked DNA unit)

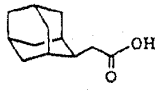


Structure (6). (2'-5'- linked RNA unit)

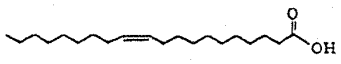
For the efficient delivery of RNA and to increase cellular concentration of oligonucleotides, lipids containing oligonucleotides are generally synthesized, since lipids containing synthetic nucleosides enhance uptake of many synthetic nucleoside drugs, like AZT. Lipipoid nucleic acids are expected to reduce the hydrophilicity of oligonucleotides. Similarly hydrophobic molecules such as cholesterol can bind to LDL particles and lipoproteins, and activate a delivery process involving these proteins to transport oligonucleotides. It has also been shown that lipidoic nucleic acids improve

Shanghai Hongene Exhibit 1002

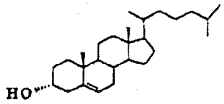
the efficacy of oligonucleotides. Shea, R.G., Marsters, J.C., Bischofberger, N., Nucleic Acids Res., 18, 3777, 1990; Letsinger, R.L., Zhang, G., Sun, D.K., Ikeuchi, T., Sarin, P.S., Proc. Natl. Acad. Sci. USA 86, 6553, 1989; Oberhauser, B., and Wagner, E., Nucleic Acids Res., 20, 533, 1992; Saison,-Behmoaras, T., Tocque, B., Rey, I., Chassignol, M., Thuong, N.T., Helene, C. The EMBO Journal , 10, 1111, 1991; Reed, M.W., Adams, A.D., Nelson, J.S., MeyeR.B., Jr., Bioconjugate Chem., 2, 217, 1991; Polushin,N.N., Cohen, J., J. Nucleic Acids Res., 22, 5492, 1994; Vu, H., Murphy, M., Riegel, Joyce, M., Jayaraman, K., Nucleosides & Nucleotides , 12, 853, 1993; Marasco, Jr., Angelino, N.J., Paul, B., Dolnick, B.J., Tetrahedron Lett., 35, 3029, 1994. In the studies, the Tm of a series of hydrophobic groups, such as adamantane (structure 7) , eicosenoic acid (structure 8), and cholesterol were attached to oligodeoxy nucleotide sequences at the 3'- end and were hybridized to complementary RNA sequences; the Tm was found to be unaffected, which indicates that such groups do not interfere with oligo hybridization properties; Manoharan, M., Tivel, K.L., Andrade, L.K., Cook, P.D., Tetrahedron Lett., 36, 1995; Manoharan, M., Tivel, K.L., Cook, P.D., Tetrahedron Lett., 36, 3651-3654, 1995; Gerlt, J.A. Nucleases, 2 nd Edition, Linn, S.M., Lloyd, R.S., Roberts, R.J., Eds. Cold Spring Harbor Laboratory Press, p-10, 1993.



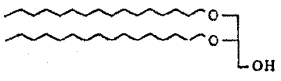
Structure 7. Adamantane acetic acid



Structure 8.Cis-11-eicosenoic acid



Structure 9. Cholesterol hexadexyl-rac-



Structure 10. 2,3- Di glycerol

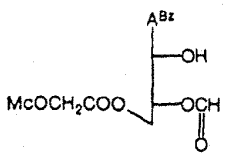
Besides the preceding lipidoic molecules other class of molecules, which have shown high promise are short and long chain polyethylene glycols (PEG), Bonora, G.M.,

Shanghai Hongene Exhibit 1002

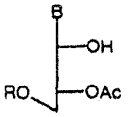
Burcovich, B., Veronese, F.M., Plyasunova, O., Pokrovsky, A. and Zarytova, V., XII International Round Table Conference, Nucleosides, Nucleotides and their Biological Applications, La Jolla, CA, Sept., 15-19, PPI 89, 1996. For efficient delivery of synthetic RNA, and DNA molecules PEG attachment to various oligonucleotides have shown to very favorable properties. PEG – oligomers have shown nice enzymatic stability by preventing fast digestion. The thermal melting behavior was not affected, thereby still retaining properties of double strand formation.

The approach of the present inventors to produce reversed RNA phosphoramidites required selective introduction of 5'- esters, such as 5'- benzoyl, acetyl, levulinyl or substituted- 5'- benzoyl –n-protected ribonucleoside. Subsequent introduction of an appropriate protecting group at 2'- position, such as 2'- tBDsilyl or 2'- TOM (triisopropyl silyl methoxy; TOM) was required. In their scheme they show synthesis of selected molecules to achieve this purpose.

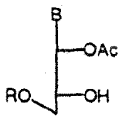
In order to produce target compounds, structures (16a-e), the key intermediate required was 2'- silylether-5'- O acylated-N-protected ribonucleoside, compounds (23a-e). The first intermediate required for this was 5'- acylated-N-protected ribonucleoside compound (22a-e). To the best of our knowledge, the compounds (21a-e) have not been reported. The compounds, which are reported for RNA synthesis in the past utilized intermediates, structure 11, 12 and 13. Various 2' and 3' acetates with 5'- acetate; viz., 5'- benzoyl protected nucleosides; Reese, B.E., Jarman, M., Reese, C.B., Tetrahedron, 24, 639, 1968; Neilson, T., Werstiuk, E.S., Can. J. Chem. 49, 493, 1971; Neilon, T., Wastrodowski, E.V., Werstiuk, E.S., Can. J. Chem., 51, 1068, 1973; Eckstein, F., Cramer, F., Chem.Ber., 98, 995, 1965; Zemlicka, J., Chladek, S., Tet. Lett., 3057, 1965, Amarnath,V. & Broom, A.D., Chemical Reviews, 77, 183-219,1977. The present invention, however, required free 2' and 3' hydroxyl groups, such as in structures (22a-e).



Structure 11.



Structure 12



Structure 13

In the present invention, comparative synthesis and purification of RNA's were carried out, both by conventional method (3'→5') and reverse Direction (5'→3'). Observed were: High Purity of RNAs, Smooth 3'- Conjugation- Cholesterol, HEG and PEG (Polyethylene glycols) & Demonstration of Absence of M+1 in Reverse RNA Synthesis

The details of synthesis scheme are outlined in the Scheme (2). The 2',3'-Isopropylidene function is utilized to protect the 2', 3' hydroxyl groups of ribose of n-protected ribonucleosides. A number of preferred n- protecting groups are shown in the Scheme (2). The 5'- hydroxyl group is subsequently protected, preferably with benzoyl group to obtain compounds of general structure 21. The isopropylidene group is then selectively removed under mild acidic conditions well known in the art. This step leads to compounds of general formula 22. Subsequent reaction with TBDM Silyl chloride (tert-butyl dimethyl silyl chloride) leads to mono silyl compound of general formula 23. The present inventors have observed that 3'- TBDMS group, i.e., the formation of compound structure 24 is not preferred in this process. In most of the cases they observed a clean product whose structure was confirmed to be 23 by chemical and analytical methods.

Purification is carried out at each step either via crystallization or column chromatography at each of the steps of the process mentioned above. Subsequent reaction with dimethoxytrityl chloride (DMT-chloride) in pyridine leads to 3'- DMT-2'-TBDMS-n-protected nucleosides of the general structure 26. Each of the compounds were fully purified by column chromatography.

Although they utilized TBDMS group to produce 2'- TBDMS ether, other silyl ethers can be utilized at this step. A careful aqueous/ methanolic NaOH hydrolysis resulted in compounds with free 5'- hydroxyl group, general structure 27.

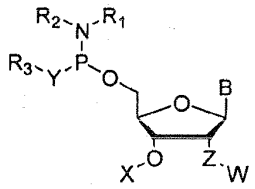
Selective 5'- benzoyl removal with aqueous or methanolic base is well known in the art. The compounds 3'- DMT-2'- TBDMS-n-protected nucleosides (structure 27) were purified by silica gel column chromatography. The purified compounds (structure 27) were subsequently phosphorylated with phosphorylating reagents, such as n,n-diisopropylamino cyanoethyl phosphonamidic chloride or 2- cyanoethyl,n,n,n,n-tetraisopropyl phosphane to yield the corresponding phosphramidites (structures 16). Both the phosphorylating reagents, n,n-diisopropylamino cyanoethyl phosphonamidic chloride or 2- cyanoethyl, n,n,n,n-tetraisopropyl phosphane are readily available in the

Shanghai Hongene Exhibit 1002

market[1], and the methods of phosphorylation to produce corresponding phosphoramidites are well known in the art.

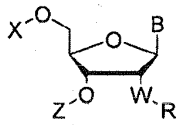
SUMMARY OF THE INVENTION

The present invention provides novel RNA monomer phosphoramidites shown below in Structure (14). The synthetic route that has been developed allows obtaining desired phosphoramidites without contamination from unwanted isomers.



Structure (14)

The RNA phosphoramidite monomers in this invention contain 3'- DMT group in ribonucleosides, carrying 5'-cyanoethylphosphoramidite (CED) and various methyloxy or silyl protecting groups at 2'- position of the ribose moiety (Structure 14). The solid support has protected RNA nucleosides containing 3'- DMT group and 5' terminus is attached to solid support (Structure 15).



Structure (15)

The RNA phosphoramidites can be used in the reverse, 5'→ 3'- directed oligonucleotide synthesis. A large number of RNA synthesis, Conventional (3'→5') and Reverse Direction (5'→3') were performed as part of the experimentation.

The modification or labeling at 3'-terminus of RNA oligomer can be attached by using corresponding phosphoramidite or active ester at the end of the synthesis and do

[1] Manufactured by ChemGenes Corp.

not require special solid support. Moreover, the approach of this invention leads to a very clean 3'- labeled oligonucleotide and expensive methods of purification are not required.

High Purity levels of RNAs were consistently obtained in the RNA synthesis by Reverse Direction (5'→3'), resulting in Smooth 3'- Conjugation of molecules such as Cholesterol, HEG (hexaethyloxyglycol) and PEG (Polyethylene glycols). It was also further demonstrated that in the RNA synthesis in the reverse Direction (5'→3'), there is absence of M+1 oligonucleotide impurities.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing will be apparent from the following more particular description of example embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating embodiments of the present invention.

FIG. 1. HPLC- Chromatogram of *N*⁴-Benzoyl-*2'O*-TBDMS-3'-*O*-DMT-adenosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16a), 98.6% purity.

FIG. 2. NMR ^{31}P Spectrum of *N*⁴-Benzoyl-*2'O*-TBDMS-3'-*O*-DMT-adenosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16a), sharp doublet at 149.465ppm & 149.307 ppm; delta;0.158, 98.6% purity.

FIG. 3. HPLC- Chromatogram of N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-5'-cyanoethyl-N,N-diisopropyl-phosphoramidite (16c), 96.9% purity.

FIG. 4. NMR 31P Spectrum of N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-5'-cyanoethyl-N,N-diisopropyl-phosphoramidite (16c), sharp doublet at 149.447 ppm & 149.197 ppp; delta;0.250,100% purity.

FIG. 5. HPLC- Chromatogram of N2-Isobutyryl-2'-O-TBDMS-3'-O-DMT-guanosine-5'-cyanoethyl-N,N-diisopropyl-phosphoramidite (16d), 98.3% purity.

Shanghai Hongene Exhibit 1002

FIG. 6. NMR 31P Spectrum of N2-Isobutyryl-2'-O-TBDMS-3'-O-DMT-guanosine-5'-cyanoethyl-N,N-diisopropyl-phosphoramidite (16d), sharp doublet at 149.731 ppm & 149.048ppm, delta;0.683, 100% purity.

FIG. 6a. Mass Spectrum of the compound (16 d); N2-Isobutyryl-2'-O-TBDMS-3'-O-DMT guanosine-5'-cyanoethyl-N,N-diisopropyl-phosphoramidite, Negative ion mass; observed at 969.4; calculated ; 970.18.

FIG. 6b. Mass Spectrum of the compound (16 d); N^2-Isobutyryl-2'-*O*-TBDMS-3'-*O*-DMT- guanosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite, Positive ion mass; observed at 993.0; calculated ; 993.18 (+Na).

FIG. 7. Diagrammatic representation of 5'→3' RNA synthesis and application to 3'- modifications.

FIG. 8. Coupling Efficiency Trityl Histogram Notes (21 mer RNA synthesis): Coupling Efficiency (step wise yield by base leveling) : 99.6%; Final Yield (by rolling average): 100% ; Stepwise Yield for monomer G: 100% ; Stepwise Yield for monomer A: 99.2% ; Stepwise Yield for monomer C: 99.6% ; Stepwise Yield for monomer C: 99.6% ; Stepwise Yield for monomer U :100.0%

FIG. 9. Electropherogram of the crude oligonucleotide SEQ ID No: 1 made by conventional method (3'→5' direction).

FIG. 9a. Electropherogram of the purified oligonucleotide SEQ ID No: 1 made by the conventional method (3'→5' direction). Expedite Model 8909-1 umole scale. Crude purity;90.78%.

FIG. 10. Electropherogram of the crude 21-mer RNA made by Reverse RNA synthesis (5'→3' direction). Expedite Model 8909-1 umole scale. Crude purity;78.55. Note: M+1 seems to be non- existent in the reverse synthesis.

FIG. 11. Electropherogram of the crude oligonucleotide SEQ ID No: 2 made by conventional method. Crude 21- mer RNA with 3'- cholesterol CPG, made by conventional method (3'→5' direction). Expedite Model 8909-1 umole scale. Crude purity; 82.83%. Note: The humps present at right side, most likely due to M+1 species.

Shanghai Hongene Exhibit 1002

FIG. 12. Electropherogram of the crude oligonucleotide SEQ ID No: 2 made by Reverse RNA synthesis (5'→3' direction). Expedite Model 8909-1 umole scale. Crude purity; 85.76%. Note: M+1 seems to be non-existent in the reverse synthesis.

FIG. 13. 21-Mer RNA with 3'- Cholesterol-TEG linker. Reverse direction (5'→3') synthesis and HPLC purification. 1 umole scale. Purity; 99.9%.

FIG. 14. Electropherogram of the crude oligonucleotide SEQ ID No: 4 made by reverse RNA synthesis. Crude purity; 56.60%.

FIG. 15. 21-Mer RNA synthesized by reverse direction (5'→3'), followed by HEG (Hexa-ethyloxyglycol) attachment. After HPLC purification, Purity; 94.39%.

FIG. 16. Electropherogram of the crude oligonucleotide SEQ ID No: 3 made by reverse synthesis. 21- mer RNA synthesis with 3'-PEG (Polyethyleneglycol; MW; 2000) . Expedite model 8909-1 umole scale synthesis. Crude purity; 91.87%. Cleanly separated broad peak present.

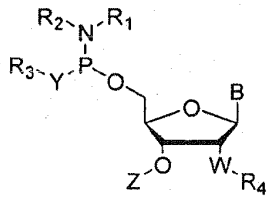
FIG. 17. Electropherogram of the oligonucleotide SEQ ID No: 4 made by reverse synthesis. 21- mer RNA synthesis with 3'-PEG (Polyethyleneglycol; MW; 2000) . Expedite model 8909-1 umole scale synthesis. Reverse phase HPLC Purified ; Purity; 100%.

FIG. 18. ESI Mass Spectral analysis of 21- mer RNA with 3'- PEG -2000 attachment, purified RNA as shown in Fig. 17. The synthesis was carried out in reverse direction (5' → 3' direction) . The PEG-2000 was attached as last step via the corresponding phosphoramidite, ChemGenes catalog ;CLP-3119 Calculated Molecular Weight: 8684.1 Observed Molecular Weight: 8681.1 Note: There is a distribution of at least 14 PEG species of the RNA on both sides of the Calculated molecular weight with PEG-2000. Thus species from 8417.1 to 8945.3 are present with a molecular weight difference of a glycol unit (+/- 44).

DETAILED DESCRIPTION OF THE INVENTION

In an embodiment, the invention pertains to novel phosphoramidites of Formula (1),

Shanghai Hongene Exhibit 1002



Formula (1)

wherein,

Y is oxygen or sulfur;

W is oxygen, nitrogen and fluorine;

R_4 is a member of the group consisting of tert butyl dimethyl silyl (TBDMS), triisopropylsilyl oxymethylene, fluorenylmethyloxycarbonyl (Fmoc), alkyl, aryl, and acetyl;

Z is a protecting group consisting of dimethoxy triphenyl (DMT), monomethoxy triphenyl (MMT) and trimethoxy triphenyl (TMT);

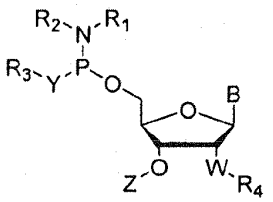
R_1 is an alkyl or aryl group;

R_2 is an alkyl or aryl group;

R_3 is cyanoethyl, alkyl or aryl; and

B is hydrogen or a nucleobase which is optionally functionalized at each primary amine with an amine protecting group.

In another embodiment, the invention pertains to phosphoramidites of Formula (1):



Formula (1)

wherein,

Y is oxygen or sulfur;

W is sulphur;

R_4 is benzoyl, acetyl or disulfide;

Z is a protecting group consisting of dimethoxy triphenyl (DMT), monomethoxy triphenyl (MMT) and trimethoxy triphenyl (TMT);

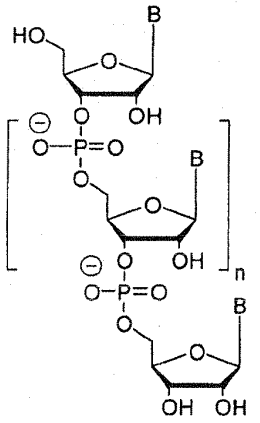
R_1 is an alkyl or aryl group;

R_2 is an alkyl or aryl group;

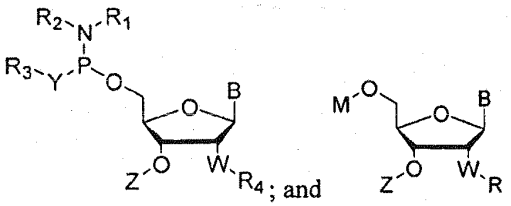
R_3 is cyanoethyl, alkyl or aryl; and

B is hydrogen or a nucleobase which is optionally functionalized at each primary amine with an amine protecting group.

The invention also pertains to methods of preparing an oligonucleotide by bond formations in the 5'- to 3'- direction for the synthesis of RNA oligomers represented by a structural formula selected from:



said method comprises the step of reacting a compound



wherein;

B is hydrogen or a nucleobase which is optionally functionalized at each primary amine with an amine protecting group;

n is 0 through 98

Y is oxygen or sulfur;

W is oxygen, nitrogen, sulfur or fluorine;

R_4 is silyl ether such as TBDMS, triisopropylsilyl oxymethylene, Fmoc, alkyl, aryl, or acetyl, when W is not sulphur; but in case when W is sulfur R_4 is benzoyl, acetyl or disulfide;

Z is DMT, MMT, TMT protecting group;

R_1 and R_2 are independently selected from an alkyl or aryl group;

R_3 is cyanoethyl, alkyl or aryl; and

M is a hydrogen radical or Y-CO-; wherein Y is a linker suitable for attaching to a solid support.

The term "alkyl", used alone or as part of a larger moiety such as "arylalkyl" or "cycloalkylalkyl" means a straight or branched hydrocarbon radical having 1-10 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl and the like.

The term "cycloalkyl" means a monocyclic, bicyclic or tricyclic, saturated hydrocarbon ring having 3-12 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, spiro [4.4]nonane, adamantyl and the like.

"Aryl", used alone or as part of a larger moiety as in "arylalkyl", means a 6-10 membered carbocyclic aromatic monocyclic or polycyclic ring system. Examples include phenyl and naphthyl. The term "aryl" also includes phenyl rings fused to non-aromatic carbocyclic ring or to a heterocyclyl group. The term "aryl" may be used interchangeably

with the terms "aromatic group", "aryl ring" "aromatic ring", "aryl group" and "aromatic group".

"Hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O. A hetero ring may have 1, 2, 3, or 4 carbon atom members replaced by a heteroatom.

"Heterocyclyl" refers to a saturated or unsaturated, non-aromatic, monocyclic or polycyclic ring system of 3 to 20 atoms, 3 to 12 atoms, or 3 to 8 atoms, containing one to four ring heteroatoms chosen from O, N and S. Exemplary heterocyclyls include pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-2-one, piperidine, piperidin-2-one, 2-pyridone, 4-pyridone, piperazine, 1-(2,2,2-trifluoroethyl)piperazine, piperazin-2-one, 5,6-dihydropyrimidin-4-one, pyrimidin-4-one, tetrahydrofuran, tetrahydropyran, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, oxazolidin-2-one, imidazolidin-2-one, imidazolidine-2,4-dione, tetrahydropyrimidin-2(1H)-one, morpholine, N-methylmorpholine, morpholin-3-one, 1,3-oxazinan-2-one, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-1,2,5-thiaoxazole 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide and isothiazolidine 1,1-dioxide.

"Heterocyclyl" also includes heteroaryl groups. The term "heteroaryl" means a 5-10 membered monovalent heteroaromatic monocyclic and polycylic ring radical containing 1 to 4 heteroatoms independently selected from N, O, and S. The term "heteroaryl" also includes monocyclic heteroaryl ring fused to non-aromatic carbocyclic ring or to a heterocyclyl group. Heteroaryl groups include furyl, thienyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridinyl-N-oxide, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzo[b]furyl, benzo[b]thienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzodioxolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, cinnolinyl, phthalzinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,5-thiadiazolyl-1-oxide, 1,2,5-thiadiazolyl-1,1-dioxide, 1,3,4-thiadiazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, tetrazolyl, and pteridinyl. The terms "heteroaryl", "heteroaryl ring", and "heteroaryl group" are used interchangeably herein.

Shanghai Hongene Exhibit 1002

B is hydrogen, a natural or unnatural nucleobase, protected nucleobase, protected natural or unnatural nucleobase, heterocycle or a protected heterocycle. For example, a nucleobase can be optionally functionalized at each primary amine with an amine protecting group, including but not limited to those illustrated in the examples and A(N-Bz), A(N-Ac), A(N-tBPac), A(N-Pac), C(N-Bz), C(N-Ac), C(N-tBPac), C(N-Pac), G(N-iBu), G(N-Ac), G(N-tBPac), G(N-Pac), I, or U.

Any solid support suitable for solid phase synthesis known to those skilled in the art can be used in the invention. Examples of suitable solid supports include controlled pore glass, polystyrene, microporous polyamide, such as poly(dimethylacrylamide), and polystryrene coated with polyethylene. Also contemplated herein is the use of linkers that are suitable for attaching the compounds of the invention to solid supports. Linkers are well known to those skilled in the art.

Amine, hydroxy and thiol protecting groups are known to those skilled in the art. For examples of amine protecting groups see Greene, et al., Protective Groups in Organic Synthesis (1991), John Wiley & Sons, Inc., pages 309-405, the teachings of which are incorporated herein by reference in their entirety. Preferably, amines are protected as amides or carbamates. For examples of hydroxy protecting groups see Id., pages 10-142, the teachings of which are incorporated herein by reference in their entirety. A preferred hydroxy protecting group is t-butyldimethylsilyl group. For examples of thiol protecting groups see Id., pages 277-308, the teachings of which are incorporated herein by reference in their entirety. An acid labile protecting group is a protecting group which can be removed by contacting the group with a Bronsted or a Lewis acid. Acid labile protecting groups are known to those skilled in the art. Examples of common acid labile protecting groups include substituted or unsubstituted trityl groups (Id., pages 60-62), substituted or unsubstituted tetrahydropyranyl groups (Id., pages 31-34), substituted or unsubstituted tetrahydrofuranyl groups (Id., pages 36-37) or pixyl groups (Id., page 65). A preferred acid labile protecting group is a substituted or unsubstituted trityl, for example 4,4'-dimethoxytrityl (hereinafter "DMT"). Trityl groups are preferably substituted by electron donating substituents such as alkoxy groups. Nucleoside bases include naturally occurring bases, such as adenine, guanine, cytosine, thymine, and uricil and modified bases such as 7-deazaguanine, 7-deaza-8-azaguanine, 5-propynylcytosine, 5-propynyluricil, 7-deazaadenine, 7-deaza-8-azaadenine, 7-deaza-6-oxopurine, 6-oxopurine, 3-deazaadenosine, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-

Shanghai Hongene Exhibit 1002

methylpyrimidine, 4-oxo-5-methylpyrimidine, 2-amino-purine, 5-fluorouricil, 2,6-diaminopurine, 8-aminopurine, 4-triazolo-5-methylthymine, and 4-triazolo-5-methyluricil. A protected nucleoside base is a nucleoside base in which reactive functional groups of the base are protected. Similarly, a protected heterocycle is a heterocycle in which reactive substitutents of the heterocycle are protected. Typically, nucleoside bases or heterocycles have amine groups which can be protected with an amine protecting group, such as an amide or a carbamate. For example, the amine groups of adenine and cytosine are typically protected with benzoyl protecting groups, and the amine groups of guanine is typically protected with an isobutyryl group, an acetyl group or t-butylphenoxyacetyl group. However, other protection schemes may be used. For example, for fast deprotection, the amine groups of adenine and guanine are protected with phenoxyacetyl groups and the amine group of cytosine is protected with an isobutyryl group or an acetyl group. Conditions for removal of the nucleobase or heterocycle protecting group will depend on the protecting group used. When an amide protecting group is used, it can be removed by treating the oligonucleotide with a base solution, such as a concentrated ammonium hydroxide solution, n-methylamine solution or a solution of t-butylamine in ammonium hydroxide.

Salient Features of the processes of the present invention, from the discussion, experimental data and the drawing figures 9-18, described herebelow, include the following observations:

I. The crude RNA's have much closer impurities (N-1) in the conventional method (3'-5'-direction), as compared to reverse RNA synthesis (5'- 3' direction). Therefore after purification RNA synthesized by reverse RNA synthesis are purer.

II The feature mentioned above is much more visible in the synthesis of cholesterol attached to 3'- end of RNA (see FIG. 11 vs. FIG. 12). Therefore it is easier to purify RNA with cholesterol at 3'- end synthesized by reverse RNA synthesis (see FIG. 12).

III. M+1 impurities are essentially absent in the RNA's synthesized by reverse RNA synthesis method.

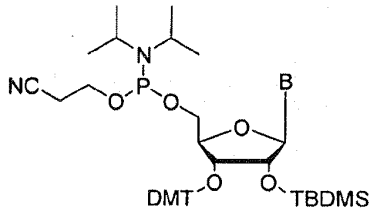
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It is postulated that in the molecule, ribonucleoside- 3'- DMT-2'- tBDsilyl-5'- phosphoramidites, the 3'- DMT is not cleaved by 5-ethylthiotetrazole or similar activators during oligonucleotide coupling step and within the coupling time of oligonucleotide chain extension.

IV. RNA containing macromolecules at the 3'- end which are generally inaccessible by conventional methods (3'→5') are easily synthesized by reverse RNA synthesis (5'→3' direction). These RNA's can be produced in high purity.

V. 3'- PEG RNA (21- mer) was synthesized, and after purification was essentially 100% pure (see FIGS. 16, 17 and 18).

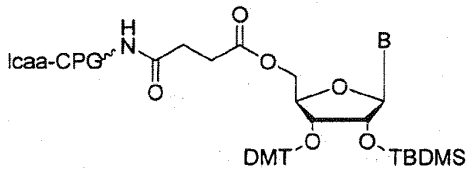
The reverse RNA monomer phosphoramidites in the present invention carry a 3'- DMT group in ribonucleosides, carrying 2'-tBDsilyl (tBDSi) -5'-cyanoethylphosphoramidite (CED) (Structure 16), 3'-DMT-2'-tBDsilyl-5'-succinyl-Icaa CPG-n-protected nucleosides (Structure 17) or 3'- DMT-2'-triisopropylsiloloxymethyl (TOM)- 5'- CED phosphoramidite group (Structure 18).



Where B = A (*N*-Bz), C (*N*-Bz), C (*N*-Ac), G (*N*-iBu),
A (*N*-*t*BPac), C (*N*-*t*BPac), C (*N*-tBPac), G (*N*-tBPac),
A (*N*-Pac), C (*N*-Pac), C (*N*-Pac), G (*N*-Pac), U.

Structure (16). 3'-DMT-2'-tBDSilyl-5'-Amidites
(Reverse RNA-tBDsilyl- amidites)

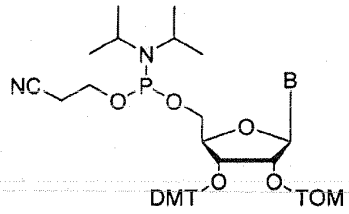
Shanghai Hongene Exhibit 1002



Where B = A (*N*-Bz), C (*N*-Bz), C (*N*-Ac), G (*N*-iBu),
A (*N*-*t*BPac), C (*N*-*t*BPac), C (*N*-tBPac), G (*N*-tBPac),
A (*N*-Pac), C (*N*-Pac), C (*N*-Pac), G (*N*-Pac), U.

Structure (17). 3'-DMT-2'-tBDSilyl-5'-CPG

(Reverse RNA-tBDsilyl- 5'-Icaa CPG)



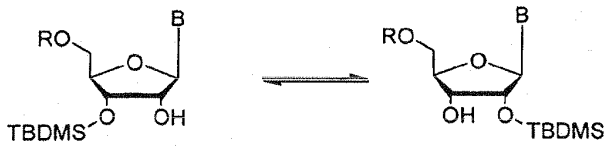
Where B = A (*N*-Ac), C (*N*-Ac), G (*N*-Ac), U.

Structure (18). 3'-DMT-2'-TOM (triisopropylsilyl oxymethylene) -5'-amidites

(Reverse RNA- TOM -5'-amidites)

The invention also teaches the method for preparing the disclosed compositions. The starting base protected nucleoside **19** affording isopropyliden protected nucleoside **20**. Benzoylation followed by isopropyliden group removal yields 5'-benzolylated nucleoside **22**. Consecutive silylation reaction with TBDMS chloride in pyridine provides mixture of 2'- and 3'- TBDMS protected nucleosides (**23** and **24**) in the ratio of 3:2 respectively. After column chromatography isomers have been resolved and isolated in % yield. Further reaction of the isomer **23** afforded 3'-DMT-2'-TBDMS protected nucleoside **26**.

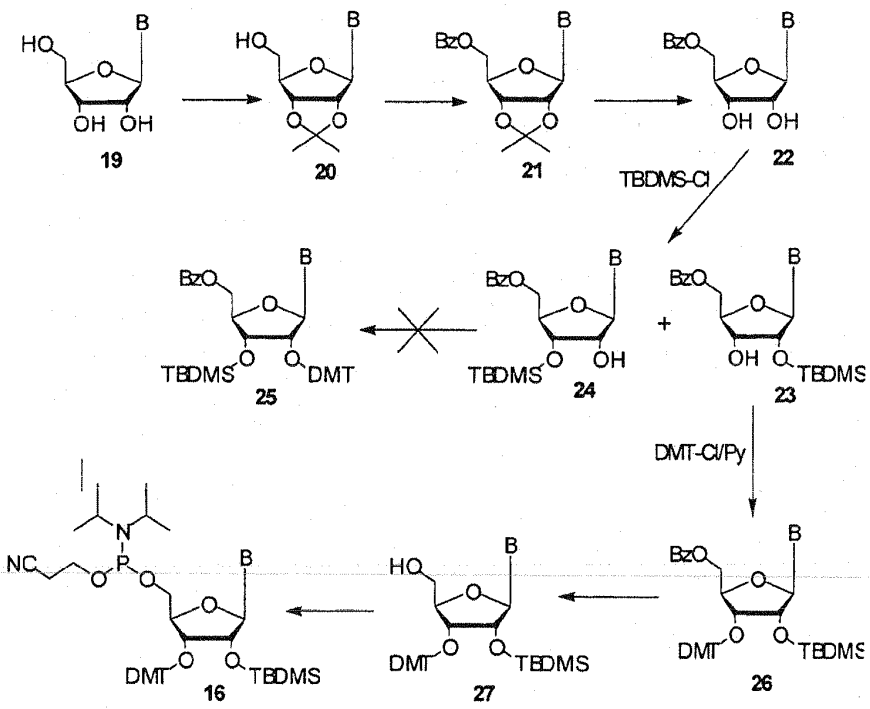
It is therefore conceivable that during subsequent functionalization of 3'– hydroxyl group, there will be significant migration of 2'– tBdsilyl group.



Scheme (1)

During the functionalization of 3'– hydroxyl group with DMT- (4,4-dimethoxytrityl), no significant migration was observed to occur. Moreover, the 3'-TBDMS protected isomer **24** also was involved in the same tritylation reaction as isomer **23** with DMT chloride in pyridine, however nucleoside **25** was not observed in that reaction. Therefore, in case of contamination of the 2'-TBDMS protected nucleoside **23** with its isomer **24**, unwanted isomer **25** cannot be formed in the tritylation conditions and desired nucleoside **26** can be isolated in high purity. The 3'-TBDMS protected nucleoside **24** can be utilized in the synthesis of the desired product and converted into **23** due to isomerization process outlined in the scheme 1.

Removal of 5'-benzoyl group with sodium hydroxide in methanol followed by phosphitilation reaction using CEDP and DIPA tetrazolate affords the final reverse phosphoramidite **16**.



Where B = a) A (*N*-Bz), b) C (*N*-Bz), c) C (*N*-Ac), d) G (*N*-iBu)
e) A (*N*-tBPac), f) C (*N*-tBPac), g) G (*N*-tBPac),
h) A (*N*-Pac), i) C (*N*-Pac), j) G (*N*-Pac), k) U.

Scheme (2)

Oligonucleotide synthesis using reverse phosphoramidites was performed in the direction from 5'→ 3'.

The examples provided below further illustrate the invention; these are illustrative only and should not be construed as in any way limiting the scope of the invention. In particular the following examples demonstrate synthetic methods for obtaining the compounds of the invention. Starting materials useful for preparing the compounds of the invention and intermediates thereof, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents. All oligonucleotide sequences are written from the 5'-terminus on the left to

the 3'-terminus on the right. The coupling efficiency of the 3'- DMT -5'- CED phosphoramidites indicated per step coupling surpassing 99%, leading to high purity RNA. A large number of homopolymers and 20-21 mers oligonucleotides have been synthesized using these monomer phosphoramidfites. The typical data is presented in the Figure (8).

Our data show that there is no difference in coupling efficiency during oligo synthesis using the reverse RNA monomers (for 5'→3'- direction) as compared to standard 3'- CED phosphoramidites in synthesis in 3'→5' direction (see figures 9 and 10).

In another embodiment the invention provides method for synthesis of ribonucleic acid oligomers with modification or labeling of 3'- end of an oligonucleotide. The synthesis of 3'- end modified RNA requiring lipophilic, long chain ligands or chromophores fluorophores and quenchers can be performed using corresponding phosphoramidites. Our data, as captured in FIGS. 11 and 12, show that 5'→3'- direction synthesis has very distinct advantage compared to conventional method.

In addition, the 3'-modifications that not available on solid support such as HEG or PEG-2000 can be easily introduced by using 5'→3'- direction synthesis and purified by reverse-phase HPLC. The oligonucleotide SEQ ID No 4 has been purified by RP HPLC affording 95-98 % pure products (see FIG. 15).

EXAMPLE 1

Synthesis of **N^2-Isobutyryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-5'-cyanoethyl-*N*,*N*-diisopropyl-phosphoramidite (16d)** as shown in the scheme 2.

N^2-Isobutyryl-2'-*O*-TBDMS-3'-*O*-DMT-5'- *O*-benzoyl-guanosine (26d): To the solution of 4 g (7.0 mmol) of the compound **23d** in 60 mL of pyridine were added 9.5 g (28.0 mmol) of DMT chloride in one portion at room temperature for 48 hrs. Reaction mixture was quenched with 2mL of cold methanol then half of the solvent was removed under diminished pressure, mixed with 20 mL of chloroform, washed with 50 mL of saturate sodium bicarbonate and 50 mL of brine. Organic layer was separated and dryed over anhydrous Na_2SO_4. Flash chromatography with 5:2:3 chloroform/hexanes/acetone

Shanghai Hongene Exhibit 1002

provided 1.7 g (27.8%) of the compound **26d**. TLC system: 5:2:3 chloroform/hexanes/acetone, Rf = 0.42. ESMS 896.1 [$C_{48}H_{55}N_5O_9Si$ $(M+Na)^+$ requires 896.1].

***N*^{2}-Isobutyryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine (27d)**: To the solution of 14 g (16.0 mmol) of the compound **26d** in 196 mL of pyridine and 21 mL of methanol mixture were added 16 mL of 2 M aqueous solution of sodium hydroxide (32.0 mmol) dropwise with stirring at 0-5 °C during the course of 25 min. The reaction mixture was neutralized with 15 mL of 2 M HCl. The solvent was removed under diminished pressure and residue was extracted with two portions of 25 mL of chloroform. Organic layer was combined, washed with 50 mL of brine and dried over anhydrous Na_2SO_4. Flash chromatography with 5:2:3 chloroform/hexanes/acetone provided 10.4 g (84.3%) of the compound **27d**. ^{1}H NMR ($CDCl_3/D_2O$) δ -0.54 (s, 3H), 0.01 (s, 3H), 088 (s, 9H), 1.21 (d, 3H, J=7.0 Hz), 1.23 (d, 3H, J=7.0), 2.66 (qq, 1H, J=7.0), 2.89 (d, 1H, J=12 Hz), 3.28 (s, 1H), 3.37 (dd, 1H, $J_{5a,5b}$=15 Hz, $J_{5,4}$=2.5Hz) 3.80 (s, 6H), 4.24 (d, 1H, J=5 Hz), 4.83 (dd, 1H, $J_{2,1}$=8 Hz, $J_{2,3}$=5 Hz), 5.97 (d, 1H, J=8 Hz), 6.84 (dd, 4H, J=9 Hz, J=2 Hz), 7.23 (t, 1H, J=7.5 Hz), 7.30 (t, 2H, J=7 Hz), 7.45 (m, 4H), 7.59 (d, 2H, J=7.5 Hz), 7.77 (s, 1H). ESMS 792.8 [$C_{41}H_{51}N_5O_8Si$ $(M+Na)^+$ requires 792.9].

***N*^{2}-Isobutyryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16d)**: To the solution of 10.4 g (13.5 mmol) of the compound **27**, 3.4 g (26.12 mmol) of ethylthiotetrazole, 4.7 mL (27 mmol) of DIPEA and 1.08 mL (13.5 mmol) of *N*-methylimidazole in 104 mL of acetonitrile were added 8.4 mL (26.12 mmol) of 2-cyanoethyl-*N,N,N,N*-tetraisopropylphosphane dropwise with stirring under Ar at room temperature. After 3 hrs the reaction mixture was diluted with 100 mL of ethylacetate and washed with 200 mL of saturated sodium bicarbonate and 200 mL of brine. The organic layer was separated and dried over 2 g of anhydrous Na_2SO_4. Flash chromatography with 7:2:1 chloroform/hexanes/triethylamine provided 12 g (92.1%) of the compound **16d**. ^{31}P NMR ($CDCl_3$) δ 149.05 and 149.73. ESMS 993.3 [$C_{50}H_{68}N_7O_9PSi$ $(M+Na)^+$ requires 993.2].

Shanghai Hongene Exhibit 1002

EXAMPLE 2

Synthesis of **N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16c)**.

N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine (27c): To the solution of 5 g (6.2 mmol) of the compound **26c** in 54 mL of pyridine and 6 mL of methanol mixture were added 6.2 mL of 2 M aqueous solution of sodium hydroxide (12.4 mmol) dropwise with stirring at 0-5 °C during the course of 25 min. The reaction mixture was neutralized with 6 mL of 2 M HCl. The solvent was removed under diminished pressure and residue was extracted with two portions of 15 mL of chloroform. Organic layer was combined, washed with 50 mL of brine and dried over anhydrous Na_2SO_4. Flash chromatography with 5:2:3 chloroform/hexanes/acetone provided 4 g (91.9%) of the compound **27c**. ^{1}H NMR ($CDCl_3/D_2O$) δ 0.07 (s, 3H), 0.16 (s, 3H), 0.97 (s, 9H), 2.24 (s, 3H), 3.16 (br.d, 1H, $J_{5a,5b}$=12 Hz), 3.55 (br.d, 1H, $J_{5a,5b}$=12 Hz) 3.79 (s, 6H), 4.08 (t, 1H, J=4.5 Hz), 4.44 (br.s., 1H), 4.78 (br.s., 1H), 5.61 (d, 1H, J= 4.1), 6.80 (dd, 4H, J=7 Hz, J=3 Hz), 7.22 (t, 1H, J=7.5 Hz), 7.27 (t, 2H, J=7 Hz), 7.38 (m, 4H), 7.52 (d, 2H, J=7.3 Hz), 8.08 (br.s, 1H). ESMS 724.8 [$C_{38}H_{47}N_3O_8Si$ $(M+Na)^+$ requires 724.3].

N^4-Acetyl-2'-*O*-TBDMS-3'-*O*-DMT-cytidine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16c): Was prepared analogously to N^2-Isobutyryl-2'-*O*-TBDMS-3'-*O*-DMT-guanosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16d). Yield is 62.6 %. ^{31}P NMR ($CDCl_3$) δ 149.1 and 149.5. ESMS 925.0 [$C_{47}H_{64}N_5O_9PSi$ $(M+Na)^+$ requires 924.4].

EXAMPLE 3

Synthesis of **2'-*O*-TBDMS-3'-*O*-DMT-Uridine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16k)**.

2'-*O*-TBDMS-3'-*O*-DMT-Uridine (27k): To the solution of 30 g (39.3 mmol) of the compound **26k** in 450 mL of pyridine and 45 mL of methanol mixture were added 40 mL of 2 M aqueous solution of sodium hydroxide (80.0 mmol) dropwise with stirring at 0-5 °C during the course of 25 min. The reaction mixture was neutralized with 40 mL of 2 M HCl. The solvent was removed under diminished pressure and residue was extracted with two portions of 50 mL of chloroform. Organic layer was combined,

Shanghai Hongene Exhibit 1002

washed with 50 mL of brine and dried over anhydrous Na_2SO_4. Flash chromatography with 6.5:2:1.5 chloroform/hexanes/acetone provided 24 g (92.5%) of the compound **9k**. ^1H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.14 (s, 3H), 0.97 (s, 9H), 2.12 (br.d, 1H, J=4 Hz), 3.16 (br.dd, 1H, $J_{5a,5b}$=12.7 Hz, J_{5a4}=7.6 Hz), 3.55 (br.d, 1H, $J_{5a,5b}$=12.7 Hz J_{5b4}=4.3 Hz) 3.65-3-64 (m, 1H) 3.79 (s, 6H), 4.07 (t, 1H, J=4.3 Hz), 4.28 (t, 1H, J=4.3 Hz), 5.66 (d, 1H, J=4.9 Hz), 5.69 (d, 1H, J= 8.1 Hz), 6.82 (dd, 4H, J=7 Hz, J=3 Hz), 7.22 (t, 1H, J=7.5 Hz), 7.28 (t, 2H, J=7 Hz), 7.38 (d, 4H, J=8.9 Hz), 7.54 (d, 2H, J=8.8 Hz), 7.68 (d, 1H, J=8.2), 8.74 (br.s, 1H). ESMS [$C_{36}H_{44}N_2O_8Si$ $(M+Na)^+$ requires 683.3].

***2'-O*-TBDMS-3'-*O*-DMT-Uridine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16k)**: To the solution of 24.0 g (36.4 mmol) of the compound **27k**, 24 mL (182 mmol) of collidine, 2.88 mL of *N*-methylimidazole in 190 mL of THF were added 16.22 mL (72.8 mmol) of 2-cyanoethyl-*N,N*, diisopropylphosphonamidic chloride dropwise with stirring under Ar at room temperature. After 1.25 hrs the reaction mixture was diluted with 100 mL of ethylacetate and washed with 200 mL of saturated sodium bicarbonate and 200 mL of brine. The organic layer was separated and dried over 20 g of anhydrous Na_2SO_4. Flash chromatography with 5:4:1 ethylacetate/hexanes/triethylamine provided 18 g (80.0%) of the compound **16k**. ^{31}P NMR ($CDCl_3$) δ 148.9 and 149.6. ESMS 884.1 [$C_{45}H_{61}N_4O_9PSi$ $(M+Na)^+$ requires 884.0].

EXAMPLE 4

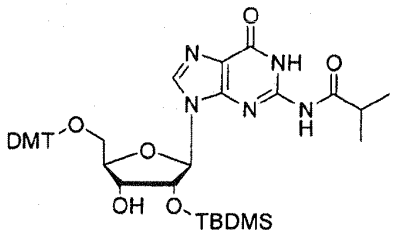
Synthesis of ***N*⁶-Benzoyl-*2'O*-TBDMS-3'-*O*-DMT-adenosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16a)**.

***N*⁶-Benzoyl-2'-*O*-TBDMS-3'-*O*-DMT-adenosine (27a)**: To the solution of 14 g (15.7 mmol) of the compound **26a** in 189 mL of pyridine and 21 mL of methanol mixture were added 15.7 mL of 2 M aqueous solution of sodium hydroxide (31.4 mmol) dropwise with stirring at 0-5 °C during the course of 25 min. The reaction mixture was neutralized with 12 mL of 2 M HCl. The solvent was removed under diminished pressure and residue was extracted with two portions of 25 mL of chloroform. Organic layer was combined, washed with 50 mL of brine and dried over anhydrous Na_2SO_4. Flash chromatography with 6.5:2:1.5 chloroform/hexanes/acetone provided 11.0 g (88.9%) of the compound **27a**. Yield is %. ^1H NMR ($CDCl_3/H_2O$) δ –0.75 (s, 3H), -0.01 (s, 3H),

0.86 (s, 9H), 3.03 (t, 1H, $J_{5a,5b}$=12.8 Hz), 3.29 (s, 1H), 3.47 (br.d, 1H, $J_{5a,5b}$=12.8 Hz) 3.80 (s, 6H), 4.35 (d, 1H, J=4.9 Hz), 5.17 (dd, 1H, J=8 Hz, J=5 Hz), 5.93 (dd, 1H, J= 12 Hz, J=2 Hz), 6.15 (d, 1H, J=8 Hz), 6.85 (dd, 4H, J=7 Hz, J=3 Hz), 7.23 (t, 1H, J=7.5 Hz), 7.30 (t, 2H, J=7 Hz), 7.48 (m, 4H), 7.52 (t, 2H, J=7.3 Hz), 7.62 (d, 3H, J=7.5 Hz), 8.03 (d, 2H, J=7.5 Hz), 8.14 (s, 1H), 8.77 (s, 1H), 9.07 (s, 1H). ESMS [$C_{44}H_{49}N_5O_7Si$ $(M+Na)^+$ requires 787.3].

***N*⁴-Benzoyl-*2'*-*O*-TBDMS-3'-*O*-DMT-adenosine-5'-cyanoethyl-*N,N*-diisopropyl-phosphoramidite (16a)**: To the solution of 11.0 g (12.0 mmol) of the compound **27a**, 9.2 mL (60.0 mmol) of collidine, 1.1 mL of *N*-methylimidazole in 88 mL of distilled THF were added 6.23 mL (24.0 mmol) of 2-cyanoethyl-*N,N*, diisopropyl-phosphonamidic chloride dropwise with stirring under Ar at room temperature. After 1.25 hrs the reaction mixture was diluted with 50 mL of ethylacetate and washed with 100 mL of saturated sodium bicarbonate and 100 mL of brine. The organic layer was separated and dried over 10 g of anhydrous Na_2SO_4. Flash chromatography with 5:4:1 ethylacetate/hexanes/triethylamine provided 9.0 g 77.7%) of the compound **16a**. ^{31}P NMR ($CDCl_3$) δ 143.97 and 144.14. ESMS 987.2 [$C_{53}H_{66}N_7O_8PSi$ $(M+Na)^+$ requires 987.45].

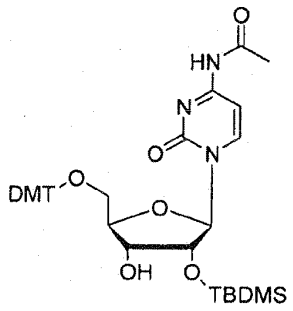
Comparative ^1H NMR data of structures 3'-*O*-DMT-2'-*O*-TBDMS nucleosides 27a, 27c, 27d, 27k, 16a, 16c, 16d, 16k and 5'-*O*-DMT-2'-*O*-TBDMS nucleosides 28-31.



Structure (28)

Table 1. Comparative ^{1}H NMR data of structures **27d**, **16d** and structure 28.

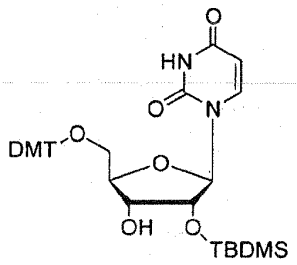
Structure	H-1'	H-2'	H-3'	H-4'	H-5'ab	H-8	CH	CH_3
27d	5.97, d. J=8.0	4.83, dd J=8.12	4.24, d. J=5	3.28, br.s.	3.37, dd. J=15.0, 2.5 2.98, d. J=15.0	7.76, s.	2.66, qq. J=7	1.31, d., J=7 1.27, d., J=7
28	5.78, d. J=7 and 5.72, d. J=6.7	5.13, dd. J=7, 5 and 4.87, dd. J=7, 5.5	4.8, br.s.	4.356-4.353, m. and 4.242-4.223, m.	3.89, dd. J=10, 2.5 3.54, dd. J=10, 2.5 3.11 J=10, 2.5	7.84, s.	2.78, qq. J=7	1.192, d. J=7 1.179, d. J=7
16d	6.22, d., J=7,5 and 5.96, d., J=5					8.21, s. and 8.08, s.		



Structure (29)

Table 2. Comparative ^{1}H NMR data of structures **27c**, **16c** and structure 29.

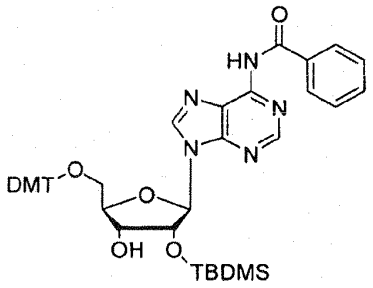
Structure	H-1'	H-2'	H-3'	H-4'	H-5'ab	H-5	H-6	-$COCH_3$
27c	5.61, d. J=4.1	4.78, br.s.	4.43, br.s.	4.08, t., J=4.6	3.55, br.d. J=12.5 3.16, br.d. J=11.5	6.81, d. J=7	7.21, d. J=7	2.24, s.
29	5.90, s. and 5.62, d. J=5	4.34-436, m.	4.20-428, m.	4.10, br.d. J=5	3.58, d.d. J=11.5, 2 3.52, dd. J=11.5, 2	7.12, d. J=7	7.16, d. J=7	2.25, s.
16c	5.83, d., J=2 6.32, d., J=5							



Structure (30)

Table 3. Comparative ^{1}H NMR data of structures **27k**, **16k** and structure **30**.

Structure	H-1'	H-2'	H-3'	H-4'	H-5'ab	H-5	H-6
27k	5.66, d. J=4.9	4.28, t. J=4.7	4.07, t., J=4.3	3.64-3.65, br.m.	3.53, br.dd. J=13.7, 4.4 3.19, br.dd. J=13.7, 7.6	5.68, d. J=8.1	7.68, d. J=8.1
30	5.95, d. J=2.8 and 5.69, d. J=4.6	4.49, t. J=5 and 4.19, t. J=5	4.05-4.08, m.	4.10-4.11, br.s.	3.49-3.51, m. 3.90-3.93, m.	5.30, d. J=8.2 5.73, d. J=8.1	7.95, d. J=8.2 7.75, d, J=7.2
16k	6.00, d., J=4.5 and 6.38, d., J=7.1					7.75, d. J=8.2 7.92, d. J=8.2	



Structure (31).

Table 4. Comparative ^{1}H NMR data of structures **27a, 16a** and structure **31**.

Structure	H-1'	H-2'	H-3'	H-4'	H-5'ab	H-2	H-8
27a	6.15, d. J=8	5.17, dd. J=8, 4.8	4.35, d. J=4.8	3.29, br.s.	3.47, br.dd. J=11.5, 2 3.04, t. J=12.3	8.14, s.	8.76, s.
31	5.82, d. J=7	5.00, t. J=5.5	4.37-4.35, m.	4.27, dd. J=7, 3.4	3.54, dd. J=10.7, 3 3.40, dd. J=10.7, 3.8	8.21, s.	8.71, s.
16a	6.53, d., J=7 and 6,24, d., J=4.5					8.54, s. and 8.48, s.	8.87, s. and 8.79, s.

EXAMPLE 5

Synthesis of **2'-*O*-TBDMS-3'-*O*-DMT-uridine-5'-succinyl-CPG.**

2'-*O*-TBDMS-3'-*O*-DMT-Uridine-5'-succinate: To the solution of 2.0 g (3.03 mmol) of the compound **27k** and 0.11 g (0.91 mmol) of DMAP in 20 mL of pyridine were added 0.9 g (9.1 mmol) of succinic anhydride with stirring at 37 °C. After 12 hrs the reaction mixture was diluted with 30 mL of chloroform and washed with 50 mL of brine. The organic layer was separated and dried over anhydrous Na_2SO_4. Flash chromatography with 5:3:2:0.01:0.05 chloroform/hexanes/acetone/pyridine/methanol provided 1.8 g (75.9 %) of 2'-*O*-TBDMS-3'-*O*-DMT-uridine-5'-succinate. ^{1}H NMR ($CDCl_3/D_2O$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.96 (s, 9H), 2.21 (dt, 1H, J=17 Hz, J=6 Hz), 2.40-2.46 (m, 1H), 2.51 (dt, 1H, J=17 Hz, J=6 Hz), 2.60-2.66 (m, 1H), 3.42 (t, 1H, J=3.3

Hz), 3.77 (s, 6H), 3.95-3.98 (m, 2 H), 4.11 (br.d, 1H, J=12.8 Hz), 4.16 (m, 1H), 5.72 (d, 1H, J=2.8 Hz), 5.74 (d, 1H, J= 8.1 Hz), 6.79 (dd, 4H, J=9 Hz, J=1.9 Hz), 7.21 (t, 1H, J=7 Hz), 7.25 (t, 2H, J=7 Hz), 7.38 (d, 4H, J=8.9 Hz), 7.48 (d, 2H, J=7.2 Hz), 7.61 (d, 1H, J=8.2 Hz), 7.72 (t, 1H, J=5.9 Hz), 8.61 (br.d, 1H, J=4.4 Hz). ESMS 784.2 [$C_{40}H_{48}N_2O_{11}Si$ $(M+Na)^+$ requires 783.9].

2'-*O*-TBDMS-3'-*O*-DMT-uridine-5'-succinyl-CPG: To the suspension of 18 g of amino-lcca-CPG and 3.6 mL of triethylamine in 60 mL of DMF was added the solution of 1.8 g (2.3 mmol) of *O*-TBDMS-3'-*O*-DMT-uridine-5'-succinate, 0.408 g (3.55 mmol) *N*-hydroxysuccinimide and 0.586 g (2.76 mmol) of DCC in 4 mL of DMF. The reaction mixture was warmed to 37 °C. After 16 hrs CPG was filtered, washed with 3x20 mL portions of acetonitrile, capped with acetic anhydride in pyridine/*N*-methylimidazole mixture and washed 3x20 mL portions of acetonitrile. The solid support was dried under diminished pressure and nucleoside loading was measured by DMT removal procedure yielding 18 g of final product with 44.2 μmol/g loading.

EXAMPLE 6

Oligonucleotide Synthesis: The following oligonucleotides (Table 5) were synthesized using 3' → 5' directed standard RNA phosphoramidite chemistry in 1 μmole scale. The syntheses were performed on Expedite 8900 synthesizer using standard RNA 1 μmole cycle.

Following synthesis, the controlled pore glass (CPG) solid support was transferred to a 2 ml microfuge tube. Oligonucleotides were cleaved from the CPG and deprotected by incubation for 30 min at 65°C in 1 ml of 40% methylamine solution in water. The supernatant was removed and the CPG was washed with 1 ml of water; supernatants were pooled and dried. The t-butyl-dimethylsilyl protecting group was removed from the RNA residue by treatment with 250 ul of fresh anhydrous triethylammonium-trihydrogen fluoride at room temperature in ultrasonic bath for 2 hours. The oligonucleotide was precipitated by 1.5 ml of n-butanol; the sample was cooled at –70°C for 1 hour then centrifuged at 10,000g for 10 minutes. The supernatant was decanted, the pellet was washed with n-butanol one more time.

The oligonucleotides were then purified by reverse-phase HPLC using a linear gradient of acetonitrile in 0.1 M triethyl-ammonium acetate (TEAA) pH 7.2. The entire sample was loaded on a Hamilton PRP-1 column (1.0 cm x 25 cm) and eluted with a linear 5% to 50% acetonitrile gradient over 40 minutes. Samples were monitored at 260 nm and peaks corresponding to the desired oligonucleotide species were collected, pooled, and lyophilized.

The oligonucleotide samples were dissolved in 200 ul of sterile water and precipitated by adding 1 ml of 2% $LiClO_4$, followed by centrifuging at 10,000g for 10 minutes. The supernatant was decanted, the pellet was washed with 10% aqueous acetone.

The standard dT and cholesterol corresponding solid supports suitable for oligonucleotide synthesis have been used.

Table 5. Oligonucleotide sequences synthesized by conventional method.

SEQ ID No: 1	rCrArGrGrUrGrCrArGrArGrCrCrUrUrGrCrCrCTT
SEQ ID No: 2	rCrArGrGrUrGrCrArGrArGrCrCrUrUrGrCrCrCTT-Cholesterol

The following oligonucleotides (Table 6) were synthesized using 5' → 3' directed reverse phosphoramidite chemistry in 1 mmole scale. The same synthesis cycle and ancillary reagents as in standard process have been used for reverse synthesis. The reverse rC-lcaa-CPG was used in all oligonucleotide syntheses. The 3'-modifications of the oligonucleotides SEQ ID No. 2-4 have been introduced by using cholesterol, PEG-2000 or HEG phosphoramidites respectively.

Table 6. Oligonucleotide sequences synthesized by reverse method.

SEQ ID No: 1	rCrArGrGrUrGrCrArGrArGrCrCrUrUrGrCrCrCTT
SEQ ID No: 2	rCrArGrGrUrGrCrArGrArGrCrCrUrUrGrCrCrCTT-Cholesterol
SEQ ID No: 3	rCrArGrGrUrGrCrArGrArGrCrCrUrUrGrCrCrCTT-PEG/2000
SEQ ID No: 4	rCrArGrGrUrGrCrArGrArGrCrCrUrUrGrCrCrCTT-HEG

Crude oligonucleotides were analyzed by CE and ESI mass-spectrometry.

Shanghai Hongene Exhibit 1002

A vast number of applications are possible for easy attachment at 3'- End of an oligonucleotide. Some of the examples are outlined in figure 7:

1. For attachment of bulky molecules at the 3'- end of the RNA, such as cholesterol, long chain aliphatic chains such as C-18, triethylene glycols, hexaethylene glycols. Direct coupling with these amidites can be achieved easily.

2. Attachment of Polyethylene Glycols such as PEG 2000 amidite and PEG 4000 amidites at the 3'- end of the RNA molecule.

3. For Easy attachment of 3'- thiol modification. 3'-Disulfides from readily available amidites, viz., C-3 disulfide, C-6 disulfide.

4. 3'- Biotin attachment *via* biotin amidite in a single step and avoiding biotin CPG for this purpose.

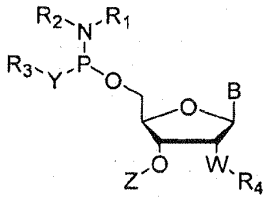
5. Modification of 3'- End of the Sense Strand of siRNA. The modification of the overhang of the sense strand (3'- End) of siRNA is not expected to affect targeted mRNA recognition , as the antisense siRNA strand guides target recognition. Useful modification for improvement of delivery of siRNA can be easily designed.

Table 3. Comparative ^{1}H NMR data of structures **27k, 28k** and formula 8.

Structure	H-1'	H-2'	H-3'	H-4'	H-5'ab	H-5	H-6
27k	5.66, d. J=4.9	4.28, t. J=4.7	4.07, t., J=4.3	3.64-3.65, br.m.	3.53, br.dd. J=13.7, 4.4 3.19, br.dd. J=13.7, 7.6	5.68, d. J=8.1	7.68, d. J=8.1
Formula 8	5.95, d. J=2.8 and 5.69, d. J=4.6	4.49, t. J=5 and 4.19, t. J=5	4.05-4.08, m.	4.10-4.11, br.s.	3.49-3.51, m. 3.90-3.93, m.	5.30, d. J=8.2 5.73, d. J=8.1	7.95, d. J=8.2 7.75, d, J=7.2
28k	6.00, d., J=4.5 and 6.38, d., J=7.1					7.75, d. J=8.2 7.92, d. J=8.2	

We summarize in the notes below the various innovations, advantages and possibilities, and some product and process details of the present invention. This list is meant to serve as a convenient and illustrative summary, and is not complete, exhaustive or limiting.

- Derivatized nucleoside and phosphoramidites of general formula 1:



wherein

Y is oxygen or sulfur;

W is oxygen, nitrogen, sulfur or fluorine;

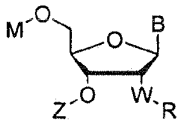
R_4 is silyl ether such as TBDMS, triisopropylsilyl oxymethylene, Fmoc, alkyl, aryl, or acetyl, when W is not sulphur; but in case when W is sulfur R_4 is benzoyl, acetyl or disulfide;

Z is DMT, MMT, TMT protecting group;

R_1 and R_2 are independently selected from an alkyl or aryl group;

R_3 is cyanoethyl, alkyl or aryl.

- Derivatized nucleoside attached to solid support of general formula 2:



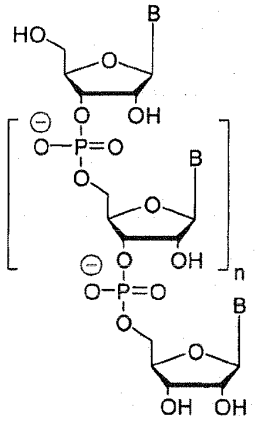
wherein

M is a hydrogen radical or Y-CO-;

Y is a chain of atoms from 2 to 20 in length, consisting essentially of a hydrocarbon chain optionally substituted by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur,

or any linker that is suitable for linking a solid support thereto, such as CPG, polystyrene or any other solid support suitable for oligonucleotide synthesis;
W is oxygen, nitrogen, sulfur or fluorine;
R is silyl ether such as TBDMS, triisopropylsilyl oxymethylene, Fmoc, alkyl, aryl, amino or acetyl, when W is not sulphur; but in the case when W is sulfur R is benzoyl, acetyl or disulfide;
Z is DMT, MMT, TMT protecting group.

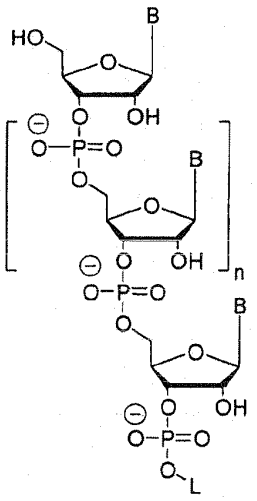
- A method for reverse, *via* 5' to 3' direction of oligonucleotide bond formations shown in formula 10 in synthetic RNA oligomers. The RNA could consist of natural or modified nucleo bases, gapmers, phosphodiesters, phosphorothiates, phosphoselenates. The synthesis may be performed on automated, semi automated DNA/RNA or other synthesizers or manually. The synthesis can be performed at various scales from microgram to kilogram scales.



Formula (10).

- A method of attachment of modifications to 3'-terminus of RNA molecules using corresponding phosphoramidites (Formula 11),

wherein L is a modification such as biotin or cholesterol, or selected from the group consisting of fluorophore, quencher dyes, polyethylene glycols, and peptides.



Formula (11).

- Synthesis of automated high purity RNA using Reverse Direction (5'→3') RNA synthesis resulting in high purity RNA.
- 3'- Conjugation of RNA with macromolecules such as Cholesterol, hexaethyloxyglycols (HEG) and Polyethylene glycols (PEG).
- Application of the automated RNA synthesis in the reverse Direction (5'→3'), resulting in the absence of M+1 oligonucleotide impurities.
- The modified nucleosides incorporated by this method mentioned above 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.

- Labelling of internal positions of an RNA synthesized by this method is achievable with chromophores such as , but not limited to Fluoroscein-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).

- 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 the method of this invention.

- 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.

- 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.

- The sugar modification of modified nucleosides could consist of 2'-deoxy-2'-terminal amino ribo nucleosides (2'-terminal NH2), attached via

Shanghai Hongene Exhibit 1002

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.

- 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.

- 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.

- 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.

- 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.

- The RNA may be carried out with one or more 2'-5'- linkage within the sequence , at the 3'- end of the sequence or at the 5'- end of the sequence.

- The RNA having a 3'- end, may be synthesized by the method of this invention containing reverse attached deoxy nucleosides such as dT, dC, dG , thymidine, attached via their 3'- hydroxyl function.

Shanghai Hongene Exhibit 1002

- The RNA having a 3'- end may be 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.

- The reverse RNA synthesis may be achieved comprising 2'- triisopropylsilyloxy methyl (TOM) protecting group.

- The reverse RNA synthesis may be achieved comprising 2'- t-butyldithiomethyl (DTM) protecting group.

- The reverse RNA synthesis may be achieved comprising the modified base comprising 2'- deoxy-2'- fluoro- beta-D-arabinonucleic acid (FANA).

- The reverse RNA synthesis may be achieved comprising the modified base comprising 4'-thio- 2'- deoxy-2'- fluoro- beta-D-arabinonucleic acid (4'-Thio- FANA).

- The reverse RNA synthesis may be achieved comprising the modified sugar using 2'- OMethyl modification.

- The reverse RNA synthesis may be achieved by using Bicyclic locked nucleic acids (LNA's).

- The reverse RNA synthesis may use the modified sugar comprising altritol sugar modified oligonucleotides (ANA).

- The reverse RNA synthesis may comprise the step of conjugation of lipophilic or hydrophobic groups at the 3'- end of the RNA either through a amidite function on the hydrophobic moiety or through an amino linker at the 3'- end of reverese synthesized oligonucleotide having a terminal amino group. The later synthesis involving a coupling step between amino at the 3'- terminal of oligonucleotide and carboxylic function on the lipophilic moiety. The lipophilic moieties consist of various glycol,

such as triethylene glycol, hexaethylene glycol, polyethylene glycols, various lipids.

- The reverse RNA synthesis may comprise 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 a 3'- end of the reverse synthesized RNA.

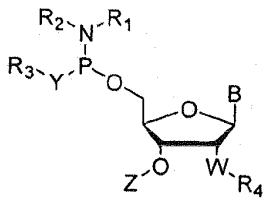
- The reverse RNA synthesis comprise the 2'-5'- linked DNA units or 2'-5'- RNA units within the sequence, at the 3'- end of the sequence or at the 5'- end of the sequence.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims. Any combination of the embodiments disclosed in the dependent claims are also contemplated to be within the scope of the invention.

CLAIMS

What is claimed is:

1. A phosphoramidite of Formula (1),



Formula (1)

wherein,

Y is oxygen or sulfur;

W is oxygen, nitrogen and fluorine;

R_4 is a member of the group consisting of tert butyl dimethyl silyl (TBDMS), triisopropylsilyl oxymethylene, fluorenylmethyloxycarbonyl (Fmoc), alkyl, aryl, and acetyl;

Z is a protecting group consisting of dimethoxy triphenyl (DMT), monomethoxy triphenyl (MMT) and trimethoxy triphenyl (TMT);

R_1 is an alkyl or aryl group;

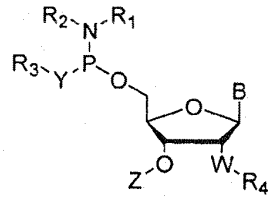
R_2 is an alkyl or aryl group;

R_3 is cyanoethyl, alkyl or aryl; and

B is hydrogen or a nucleobase which is optionally functionalized at each primary amine with an amine protecting group.

Shanghai Hongene Exhibit 1002

2. The phosphoramidite of Formula (1):



Formula (1)

wherein,

Y is oxygen or sulfur;

W is sulphur;

R_4 is benzoyl, acetyl or disulfide;

Z is a protecting group consisting of dimethoxy triphenyl (DMT), monomethoxy triphenyl (MMT) and trimethoxy triphenyl (TMT);

R_1 is an alkyl or aryl group;

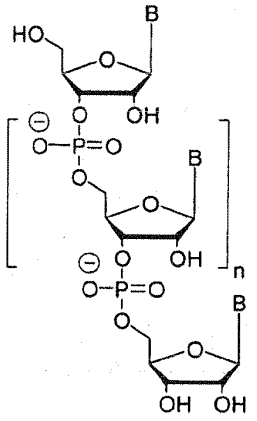
R_2 is an alkyl or aryl group;

R_3 is cyanoethyl, alkyl or aryl; and

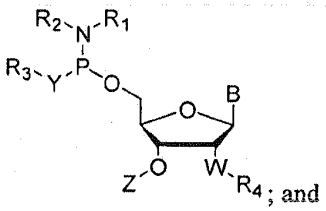
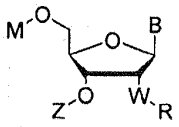
B is hydrogen or a nucleobase which is optionally functionalized at each primary amine with an amine protecting group.

3. A method of preparing an oligonucleotide by bond formations in the 5'- to 3'- direction for the synthesis of RNA oligomers represented by a structural formula selected from:

Shanghai Hongene Exhibit 1002



said method comprises the step of reacting a compound

 ; and 

wherein;

B is hydrogen or a nucleobase which is optionally functionalized at each primary amine with an amine protecting group;

n is 0 through 98

Y is oxygen or sulfur;

W is oxygen, nitrogen, sulfur or fluorine;

R_4 is silyl ether such as TBDMS, triisopropylsilyl oxymethylene, Fmoc, alkyl, aryl, or acetyl, when W is not sulphur; but in case when W is sulfur R_4 is benzoyl, acetyl or disulfide;

Z is DMT, MMT, TMT protecting group;

R_1 and R_2 are independently selected from an alkyl or aryl group;

R_3 is cyanoethyl, alkyl or aryl; and

M is a hydrogen radical or Y-CO-; wherein Y is a linker suitable for attaching to a solid support.

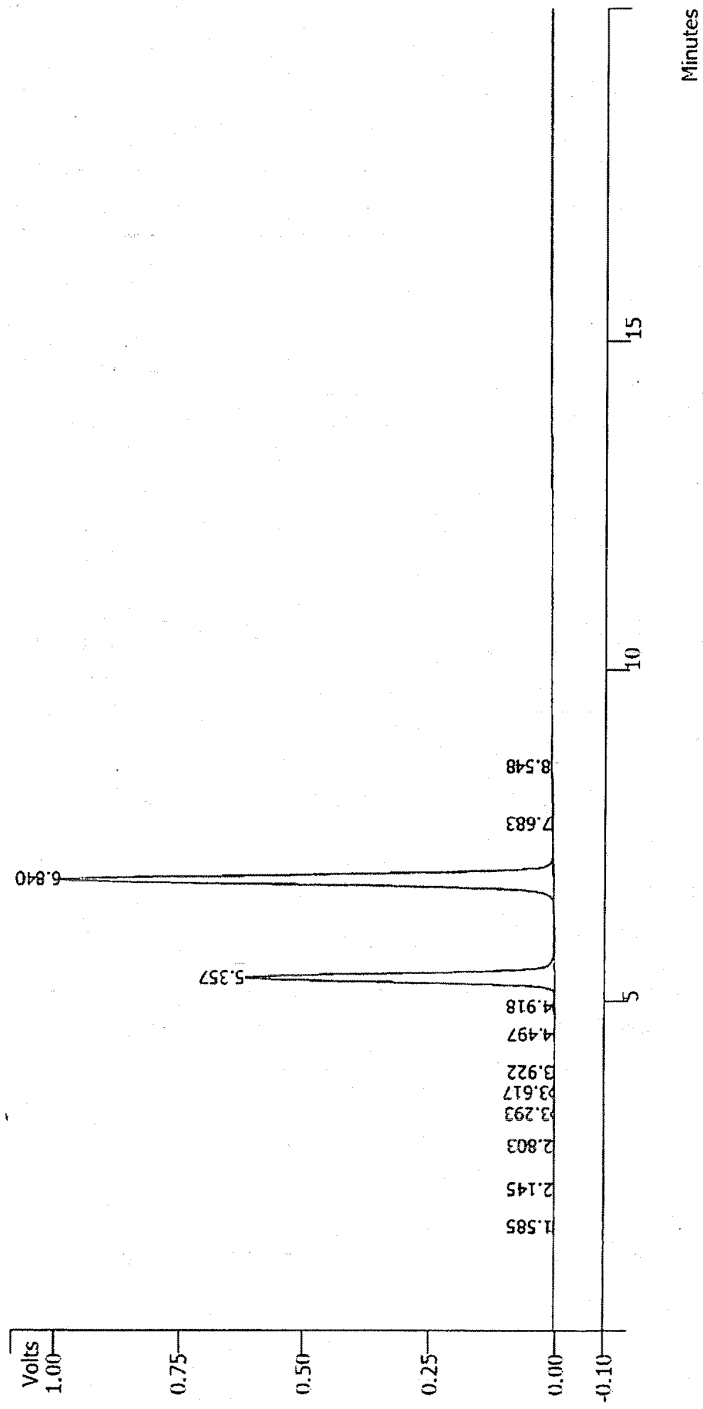


Fig.1. HPLC Chromatogram of the compound (16a)

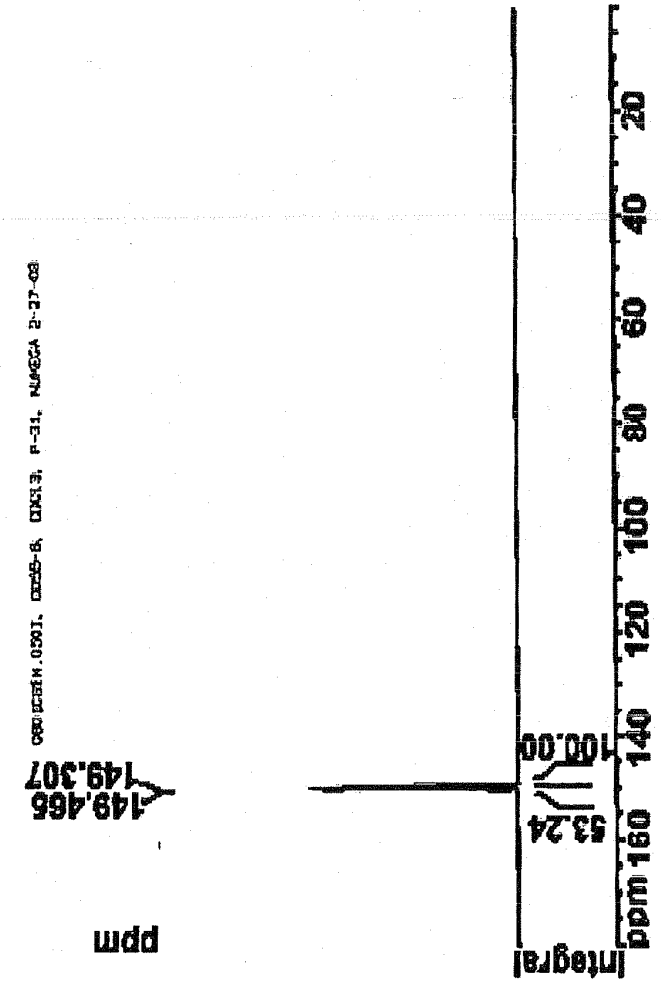


Fig.2. ^{31}P NMR spectrum of the compound (16a)

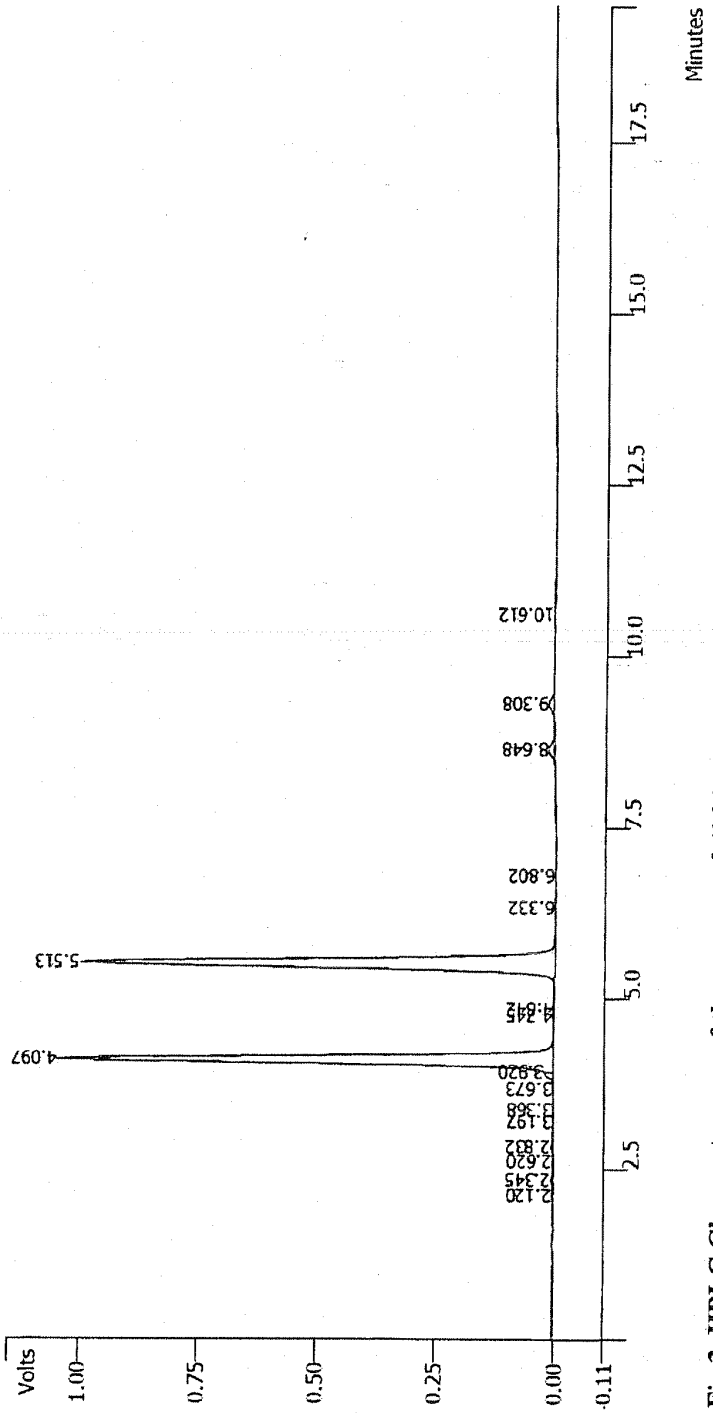


Fig.3. HPLC Chromatogram of the compound (16c)

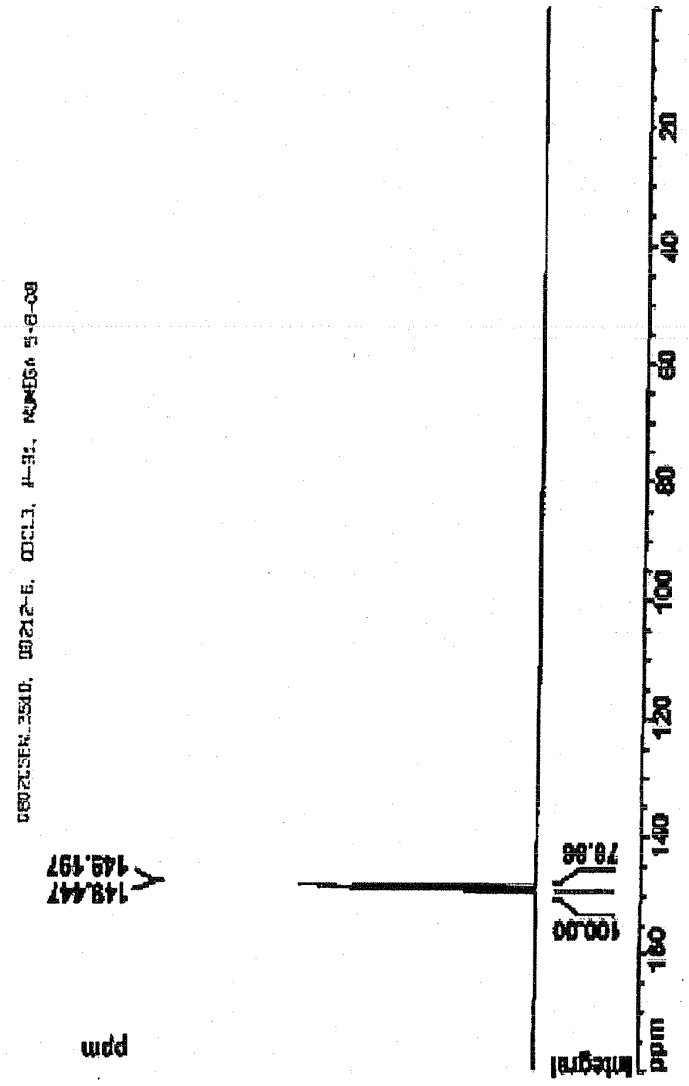


Fig.4. ^{31}P NMR spectrum of the compound (16c)

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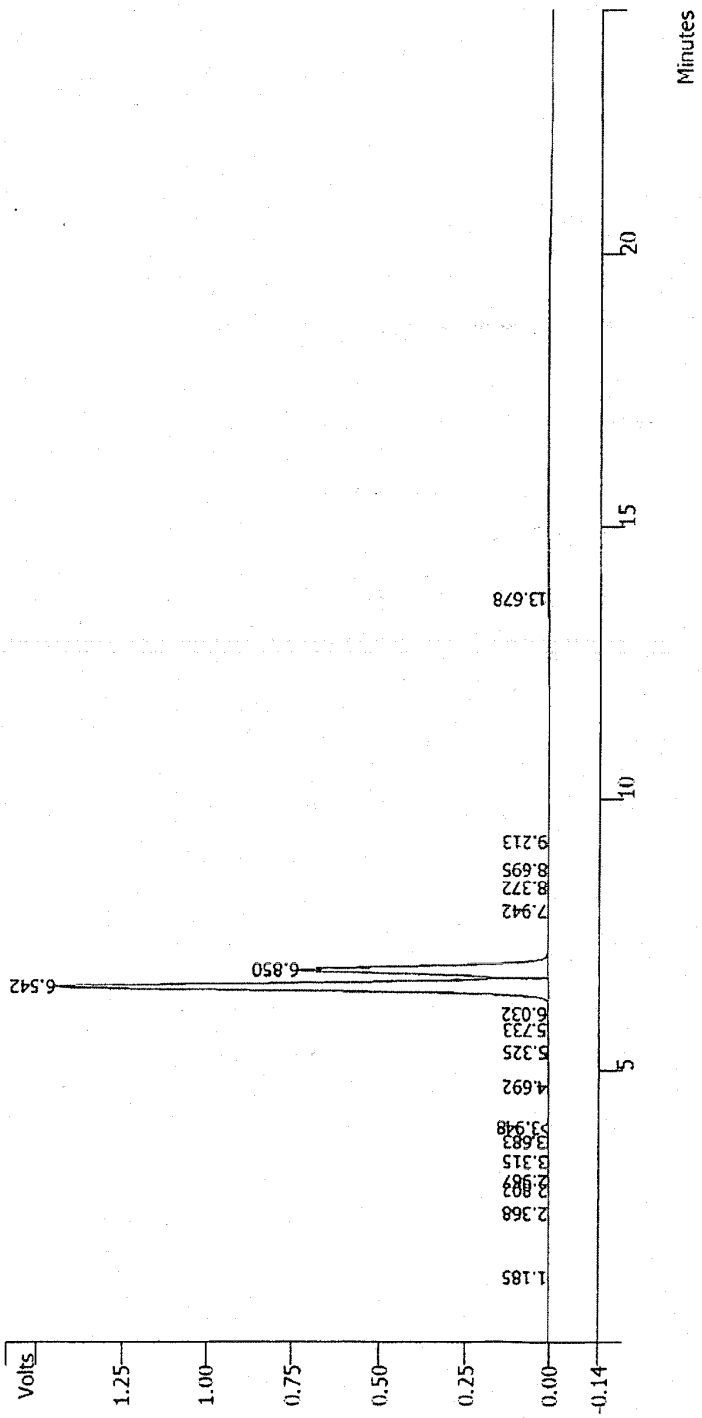


Fig.5. HPLC Chromatogram of the compound (16d)

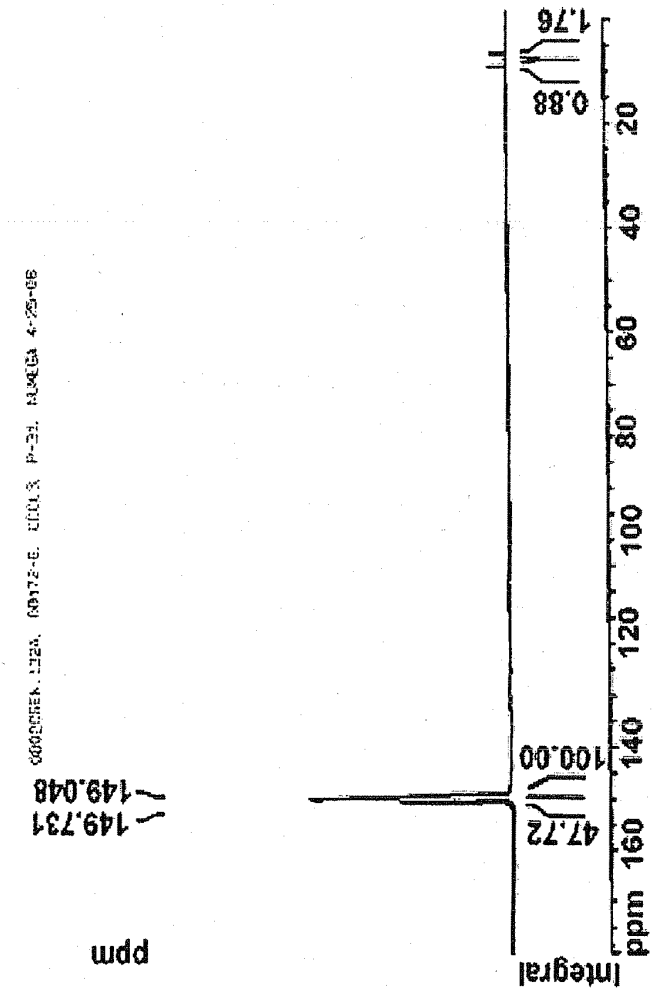


Fig.6. ^{31}P NMR spectrum of the compound (16d)

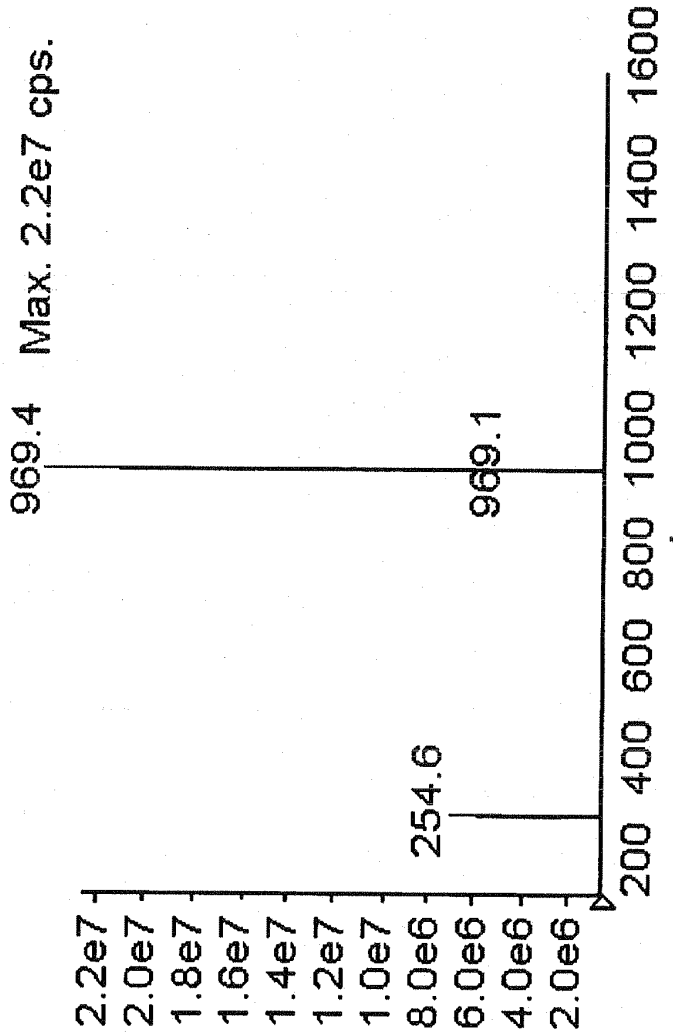


Fig.6a. Mass spectrum of the compound (16d)

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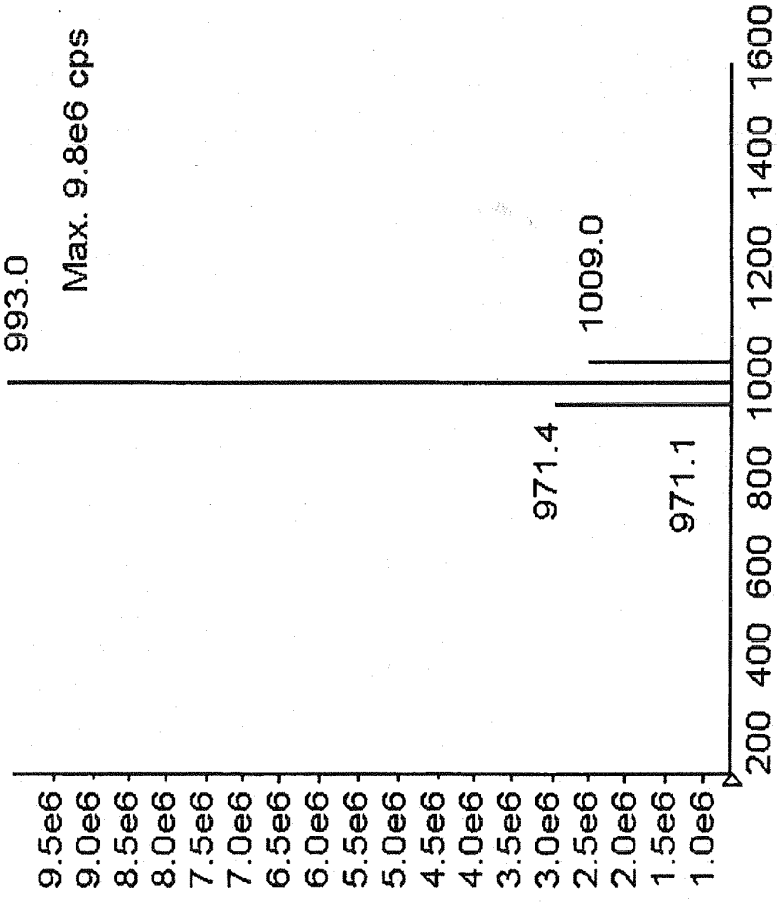


Fig.6b. Mass spectrum of the compound (16d)

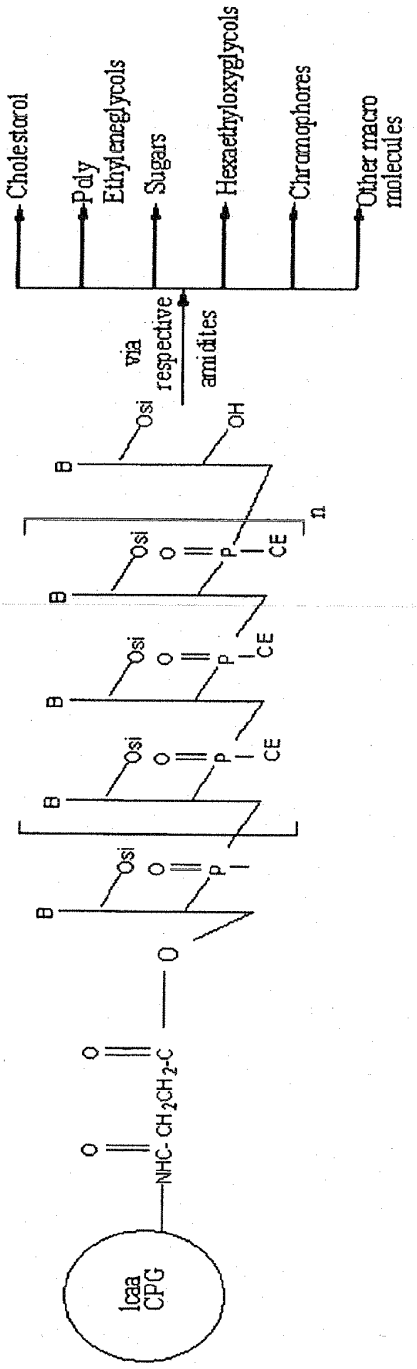


Fig.7. Diagrammatic Representation of 5'→3' RNA synthesis and application to 3'-modifications

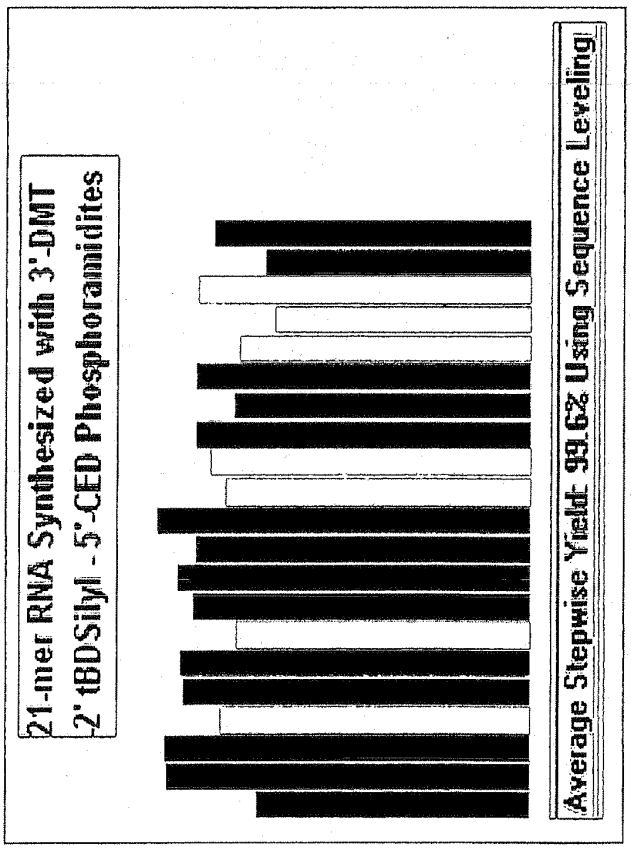


Fig. 8. Coupling Efficiency Trityl Histogram Notes (21 mer RNA Synthesis)

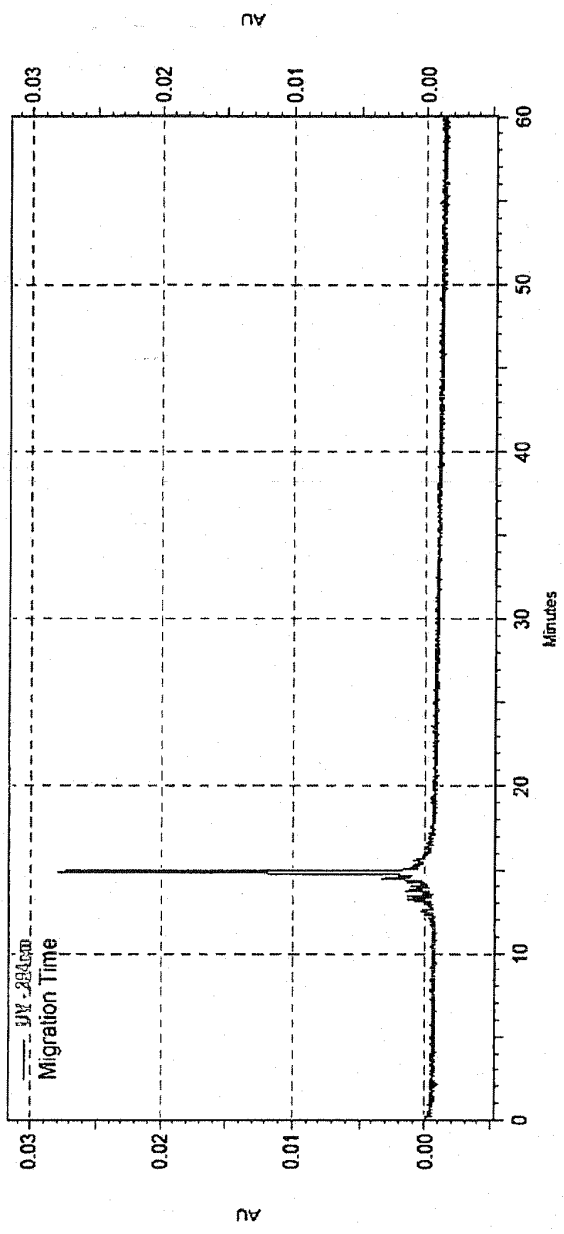


Fig. 9a. Electropherogram of the crude Oligonucleotide SEQ No.1 made by conventional method (3'-5'-direction)

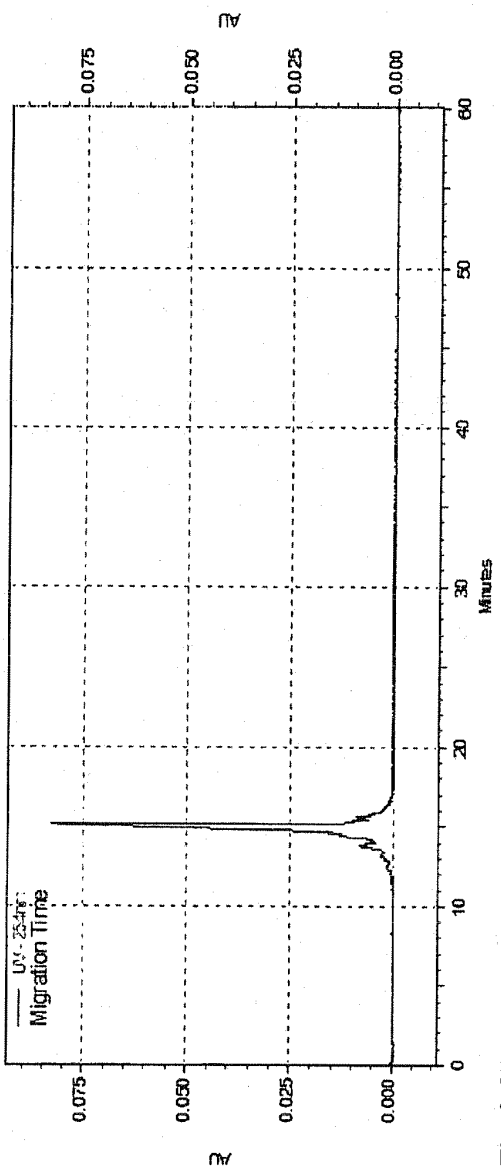


Fig. 9. Electropherogram of the purified Oligonucleotide SEQ No.1 made by conventional method (3'-5'-direction)

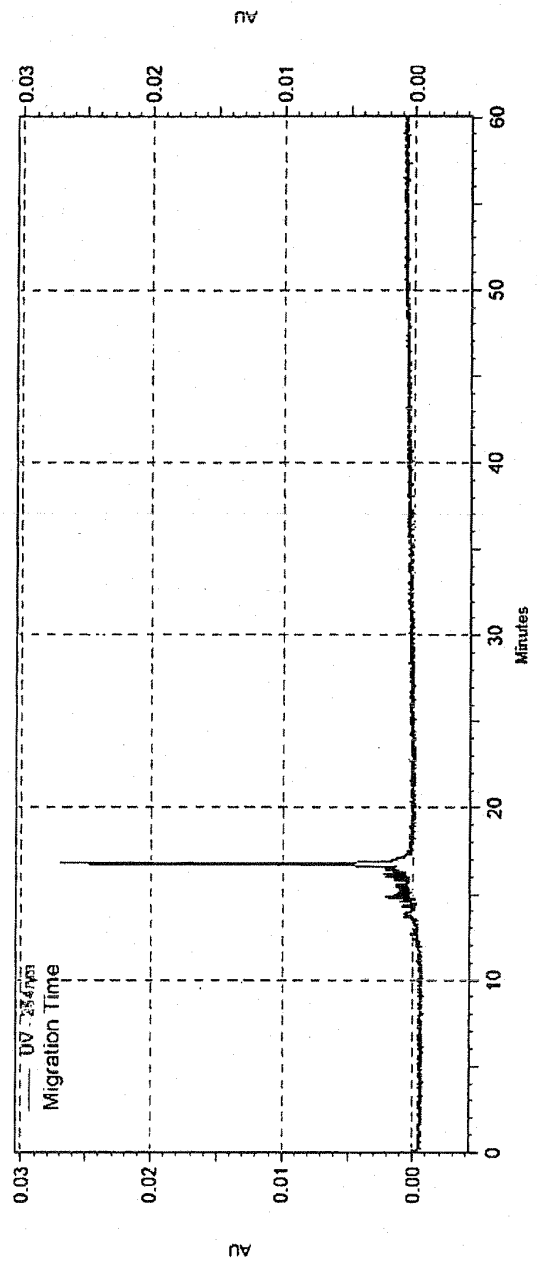


Fig.10 Electropherogram of the crude Oligonucleotide SEQ No.1 made by Reverse RNA synthesis

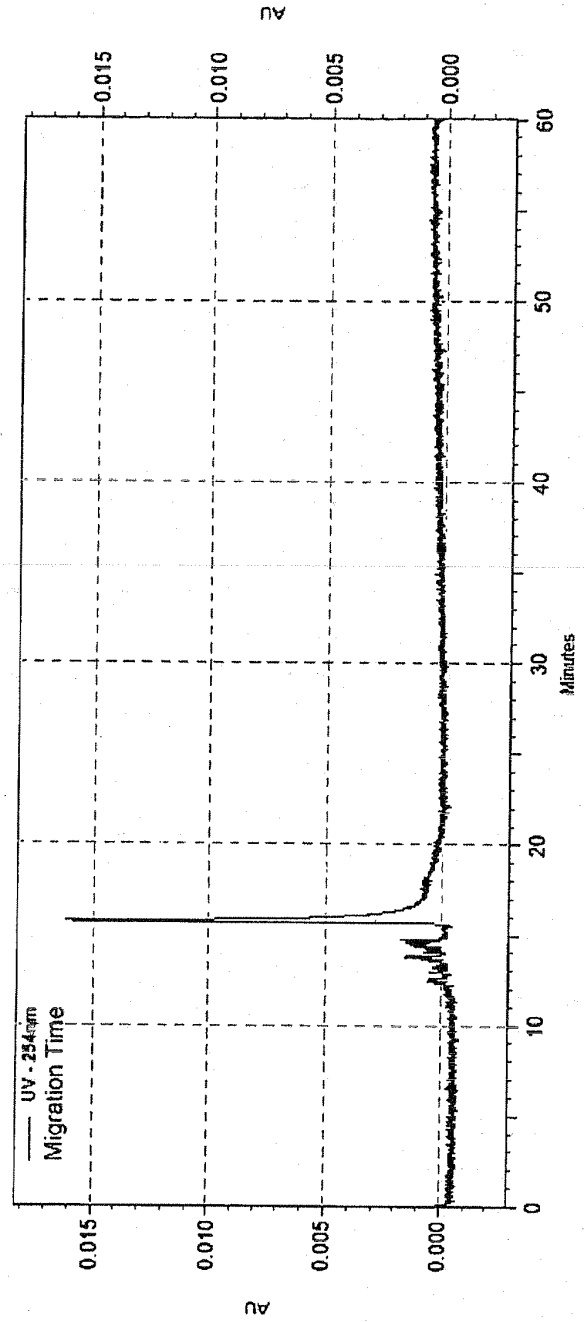


Fig. 11 Electropherogram of the crude oligonucleotide, SEQ ID No. 2 made by conventional method

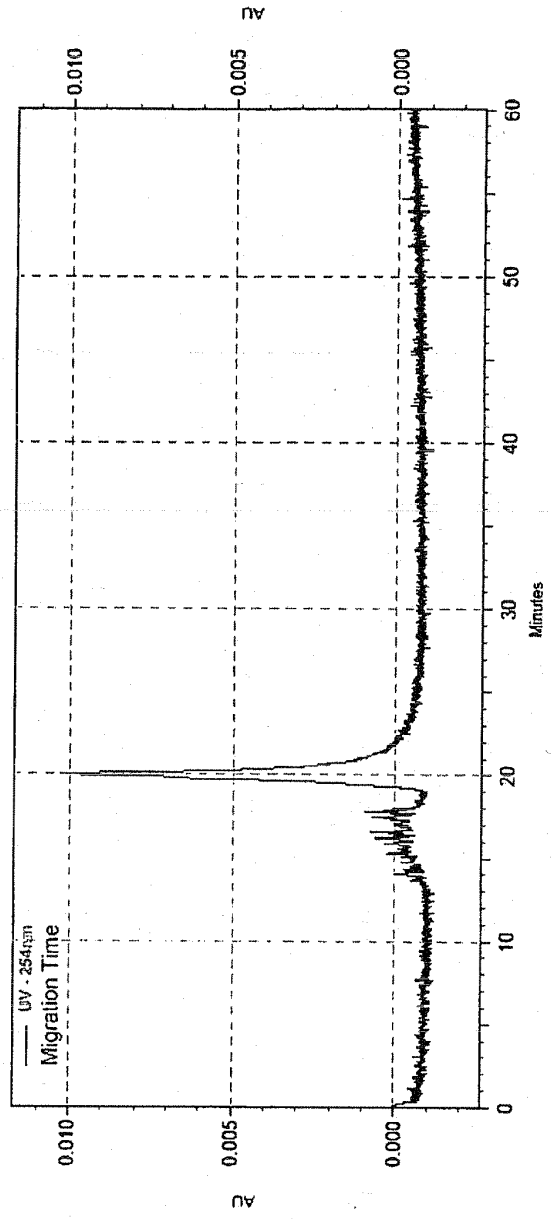


Fig. 12. Electropherogram of the crude oligonucleotide, SEQ ID No. 2 made by reverse RNA synthesis

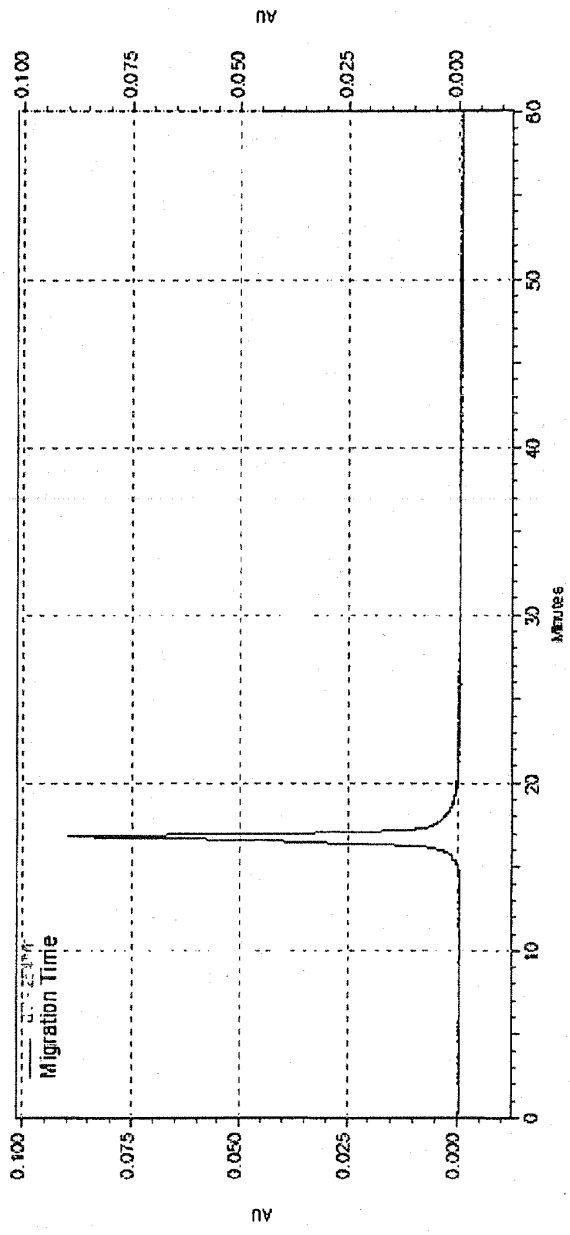


Fig. 13. 21- Mer RNA with 3'-Cholesterol-TEG linker Reverse direction (5'→3') synthesis and HPLC purification

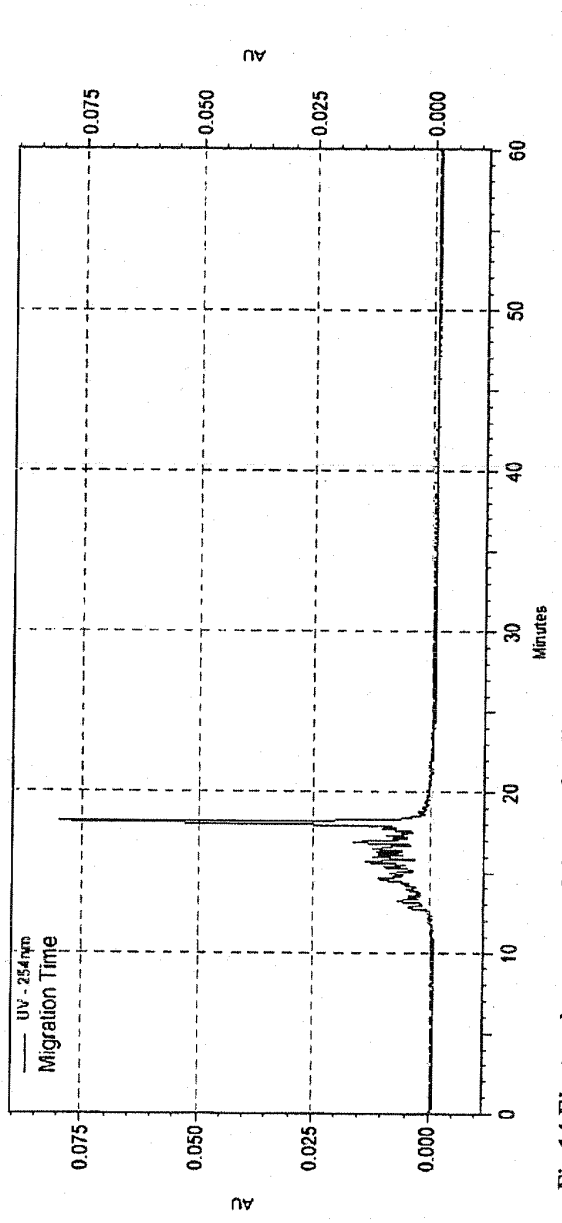


Fig.14 Electropherogram of the crude oligonucleotide, SEQ ID No. 3 made by reverse RNA synthesis

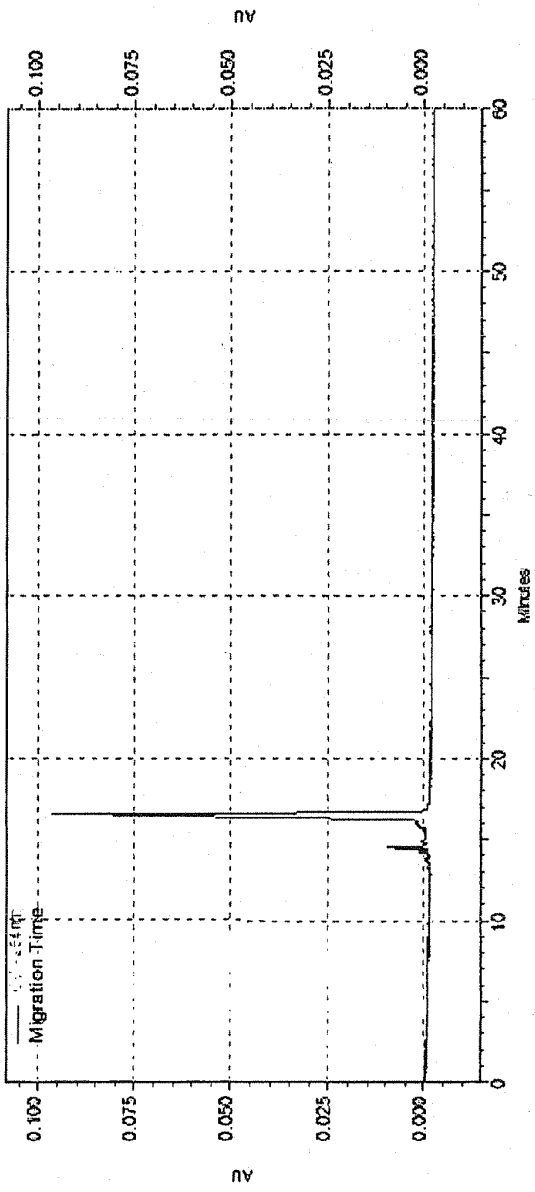


Fig.15 21-mer RNA synthesized by reverse direction (5'→3'), followed by HEG (Hexa-ethyloxyglycol) attachment

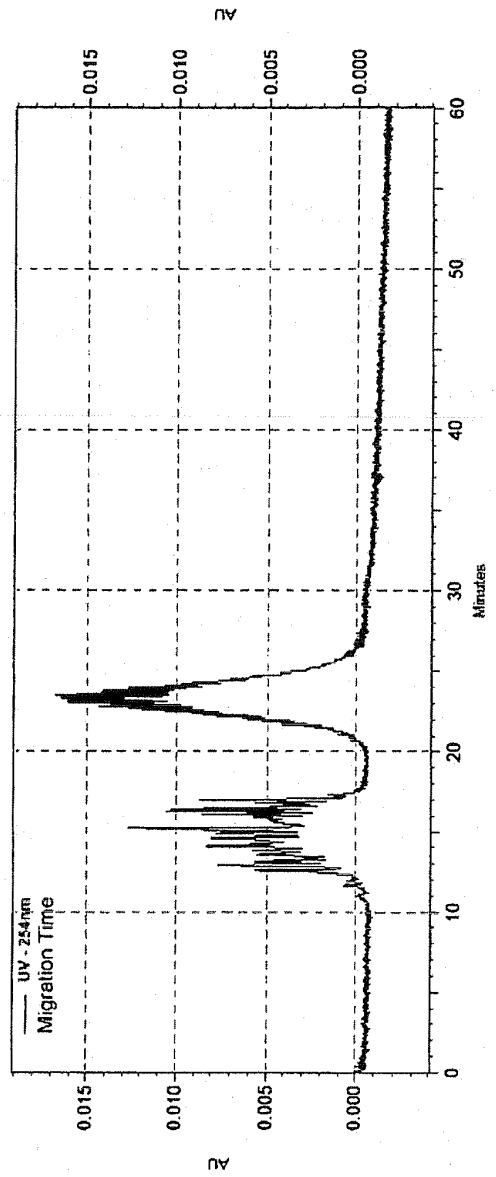


Fig. 16 Electropherogram of the crude oligonucleotide, SEQ ID No. 4 made by reverse RNA synthesis

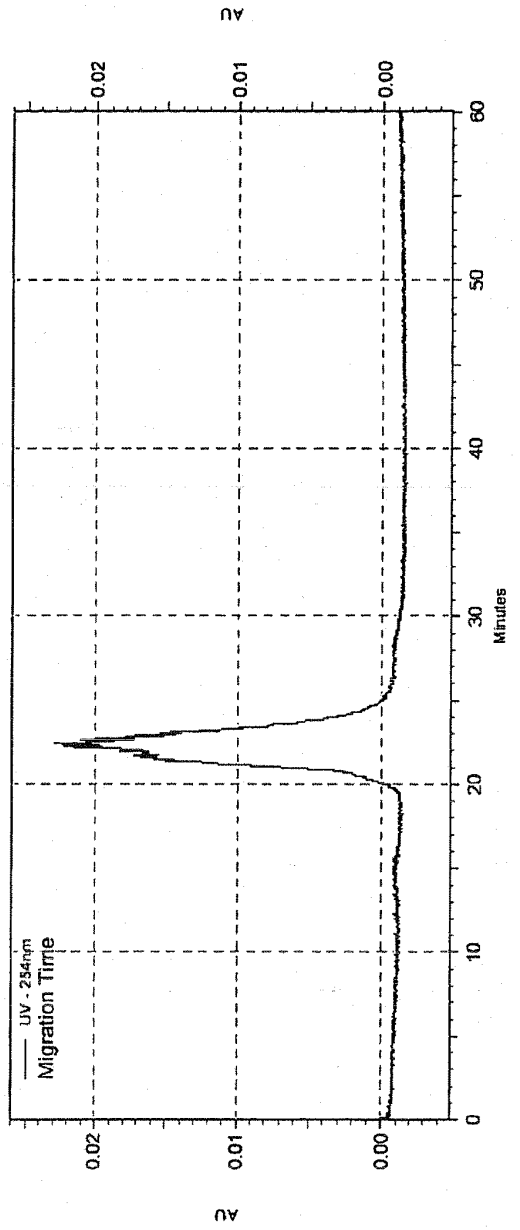


Fig. 17 Electropherogram of the crude oligonucleotide, SEQ ID No. 4 made by reverse RNA synthesis and purified by reverse-phase HPLC

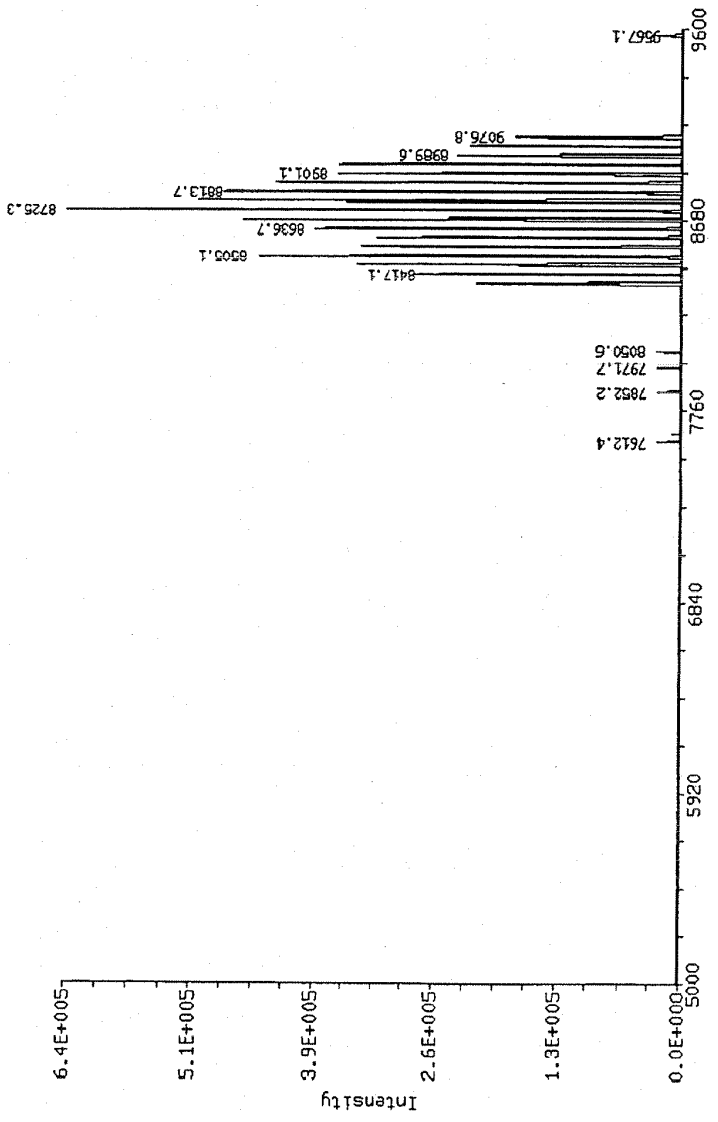


Fig. 18 ESI Mass Spectral analysis of 21-mer RNA with 3'-PEG-2000 attachment, purified RNA as shown in Fig. 17

PATENT COOPERATION TREAT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
CARROLL, Alice, O.
Hamilton, Brook, Smith & Reynolds,
P.C.
530 Virginia Road, P.O. Box 9133
Concord, MA 01742-9133
ETATS-UNIS D'AMERIQUE

RECEIVED
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
APR 26 2010

ATTORNEY/IFC/IAS
Docketed ✓ Already Docketed
Not Required
Initials 1st MH Initials 2nd CER

Date of mailing (day/month/year) RG 20/04/2010	
Applicant's or agent's file reference 4441.1001000	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2009/005063	International filing date (day/month/year) 08/09/2009
Applicant CHEMGENES CORPORATION	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer Federico Bonomelli

Form PCT/ISA/220 (July 2009)

(See notes on accompanying sheet)

C1

Shanghai Hongene Exhibit 1002

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annex B).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, International Phase, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Shanghai Hongene Exhibit 1002

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide,* National Chapters.

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
4441.1001000		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2009/005063	08/09/2009	06/09/2008
Applicant		
CHEMGENES CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [X] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 9/21
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [X] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (July 2009)

Shanghai Hongene Exhibit 1002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/005063

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. (means)

   [X] on paper

   [X] in electronic form

   b. (time)

   [ ] in the international application as filed

   [ ] together with the international application in electronic form

   [X] subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

national application No
PCT/US2009/005063

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07H21/02 C07H19/167 C07H19/067

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07H

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THOMAS WAGNER, WOLFGANG PFLEIDERER: "Nucleotides, Part LXV , Synthesis of 2'-Deoxyribonucleoside 5'-Phosphoramidites: New Building Blocks for the Inverse (5'-3')-Oligonucleotide Approach" HELVETICA CHIMICA ACTA, vol. 83, no. 8, 15 August 2000 (2000-08-15), pages 2023-2035, XP002569710 ISSN: 0018-019X page 2025; compounds 25-28 page 2028; figure 2; compounds 33-34 ----- -/--	1

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

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 2010	20/04/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Mezzato, Stefano

3

Form PCT/ISA/210 (second sheet) (April 2005)

Shanghai Hongene Exhibit 1002

INTERNATIONAL SEARCH REPORT

national application No
PCT/US2009/005063

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATYSIAK S ET AL: "Acetal oligonucleotide conjugates in antisense strategy" NUCLEOSIDES & NUCLEOTIDES, MARCEL DEKKER, INC, US, vol. 16, 1 January 1997 (1997-01-01), pages 855-861, XP002244702 ISSN: 0732-8311 page 856; figure 2; compound 4a	1
X	SCHWARTZ M E ET AL: "A Universal Adapter for Chemical Synthesis of DNA or RNA on any Single Type of Solid Support" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 36, no. 1, 2 January 1995 (1995-01-02), pages 27-30, XP004028936 ISSN: 0040-4039 page 28; figure 1; compound 7	1
X	RAVIKUMAR, VASULINGA T. ET AL: "Stereoselective Synthesis of Alkyl-Phosphonates: A Facile Rearrangement of Cyanoethyl-Protected Nucleoside Phosphoramidites" ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 8, no. 4, 22 May 2004 (2004-05-22), pages 603-608, XP002569711 ISSN: 1083-6160 page 604; figure 3; compound 3	1
X,P	SRIVASTAVA, SURESH C. ET AL: "RNA synthesis: phosphoramidites for RNA synthesis in the reverse direction. Highly efficient synthesis and application to convenient introduction of ligands, chromophores and modifications of synthetic RNA at the 3'-end" NUCLEIC ACIDS SYMPOSIUM SERIES, vol. 52, no. 1, 8 September 2008 (2008-09-08), pages 103-104, XP002569712 ISSN: 1746-8272 the whole document	1

3

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

Shanghai Hongene Exhibit 1002

INTERNATIONAL SEARCH REPORT

nternational application No.
PCT/US2009/005063

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This international Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

Shanghai Hongene Exhibit 1002

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claim: 1(partially)

a phosphoramidite of formula (1) of claim 1, wherein W is oxygen

---

2. claims: 1, 3(all partially)

a phosphoramidite of formula (1) of claim 1, wherein W is nitrogen and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite

---

3. claims: 1, 3(all partially)

a phosphoramidite of formula (1) of claim 1, wherein W is fluorine and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite

---

4. claim: 2(completely); 3(partially)

a phosphoramidite of formula (1) of claim 1, wherein W is sulphur and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite

---

5. claim: 3(partially)

a method of preparing RNA oligomers by bond formations in the 5' to 3' direction comprising the step of reacting a phosphoramidite of formula (1) of claim 1, wherein W is oxygen

---

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/005063	08.09.2009	06.09.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07H21/02 C07H19/167 C07H19/067

Applicant
CHEMGENES CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Mezzato, Stefano Telephone No. +49 89 2399-7387

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Shanghai Hongene Exhibit 1002

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☒ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☒ subsequently to this Authority for the purposes of search

4. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 2, 3(completely); 1(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 2, 3(completely); 1(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1(partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1(partially)
Industrial applicability (IA)	Yes:	Claims	1(partially)
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1 THOMAS WAGNER, WOLFGANG PFLEIDERER: "Nucleotides, Part LXV , Synthesis of 2'- Deoxyribonucleoside 5'- Phosphoramidites: New Building Blocks for the Inverse (5'-3')- Oligonucleotide Approach"HELVETICA CHIMICA ACTA, vol. 83, no. 8, 15 August 2000 (2000-08-15) , pages 2023-2035, XP002569710ISSN: 0018-019X

D2 MATYSIAK S ET AL: "Acetal oligonucleotide conjugates in antisense strategy"NUCLEOSIDES & NUCLEOTIDES, MARCEL DEKKER, INC, US, vol. 16, 1 January 1997 (1997-01-01) , pages 855-861, XP002244702ISSN: 0732-8311

D3 SCHWARTZ M E ET AL: "A Universal Adapter for Chemical Synthesis of DNA or RNA on any Single Type of Solid Support"TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 36, no. 1, 2 January 1995 (1995-01-02) , pages 27-30, XP004028936ISSN: 0040-4039

D4 RAVIKUMAR, VASULINGA T. ET AL: "Stereoselective Synthesis of Alkyl-Phosphonates: A Facile Rearrangement of Cyanoethyl- Protected Nucleoside Phosphoramidites"ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 8, no. 4, 22 May 2004 (2004-05-22) , pages 603-608, XP002569711ISSN: 1083-6160

D5 SRIVASTAVA, SURESH C. ET AL: "RNA synthesis: phosphoramidites for RNA synthesis in the reverse direction. Highly efficient synthesis and application to convenient introduction of ligands, chromophores and modifications of synthetic RNA at the 3'-end"NUCLEIC ACIDS SYMPOSIUM SERIES, vol. 52, no. 1, 8 September 2008 (2008-09-08) , pages 103-104, XP002569712ISSN: 1746-8272

Re Item II.

1 The attention of the Applicant is drawn to the fact that some documents are mentioned in the search report which might become relevant for novelty (see D5, made available to the public on 08/09/2008, indicated in the search report as a P-document).

This document will be novelty destroying, if the priority of the present application, which could not be checked, is not to be valid.

Re Item IV.

1 This Authority considers that there are 5 inventions covered by the claims indicated as follows:

1. claim: 1(all partially): a phosphoramidite of formula (1) of claim 1, wherein W is oxygen
2. claims: 1, 3 (all partially): a phosphoramidite of formula (1) of claim 1, wherein W is nitrogen and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite
3. claims: 1, 3 (all partially): a phosphoramidite of formula (1) of claim 1, wherein W is fluorine and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite
4. claims: 2 (completely); 3 (partially): a phosphoramidite of formula (1) of claim 1, wherein W is sulphur and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite
5. claim: 3 (all partially): a method of preparing RNA oligomers by bond formations in the 5' to 3' direction comprising the step of reacting a phosphoramidite of formula (1) of claim 1, wherein W is oxygen

2 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows.

According to Rule13.2 PCTin an international patent application the requirement of unity of invention as referred to in Rule 13.1 PCT is fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features, the latter expression designating those features which define a contribution which each of the claimed inventions considered as a whole makes over the prior art.

3 The prior art has been identified as documents:

- D1 (page 2025; compounds 25-28; page 2028; figure 2; compounds 33-34): deoxyribonucleoside 5'- phosphoramidites as building blocks for the (5'-3')- synthesis of oligonucleotides. Oligonucleotides 3'- conjugates carrying cholesterol and vitamin E are also disclosed.

- D2 (page 856; figure 2; compound 4a), D3 (page 28; figure 1; compound 7), D4 (page 604; figure 3; compound 3): ribonucleoside 5'-phosphoramidites of formula (1) of claim 1, wherein W is oxygen.

4 Therefore, the subject - matter of:

1. independent claim 1, as regards a phosphoramidite of formula (1), wherein W is oxygen does not differs from this known compounds of D2-D4;
2. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is nitrogen, differs from this known compounds of D2-D4 and the method of D1 in that W is nitrogen;
3. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is fluorine, differs from this known compounds of D2-D4 and the method of D1 in that W is fluorine;
4. independent claims 2 and 3, as regards a phosphoramidite of formula (1), wherein W is sulphur, differs from this known compounds of D2-D4 and the method of D1 in that W is sulphur;
5. independent claim 3, as regards a phosphoramidite of formula (1), wherein W is oxygen, differs from this known method of D1 in that W is oxygen.

5 Starting from the known compounds of D2- D4 and the method of D1, the subject-matter of:

1. independent claim 1, as regards a phosphoramidite of formula (1), wherein W is oxygen does not solve any problem; this claim does not have any special technical feature;
2. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is nitrogen, solves the problem of providing a process of reverse (5' -3') synthesis of oligonucleotide oligomers bearing nitrogen at position 2'; the special technical feature is the nitrogen at position 2';
3. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is fluorine, solves the problem of providing a process of reverse (5' -3') synthesis of oligonucleotide oligomers bearing fluorine at position 2'; the special technical feature is the fluorine at position 2';

4. independent claims 2 and 3, as regards a phosphoramidite of formula (1), wherein W is sulphur, solves the problem of providing a process of reverse (5' -3') synthesis of oligonucleotide oligomers bearing sulphur at position 2'; the special technical feature is the sulphur at position 2';

5. independent claim 3, as regards a phosphoramidite of formula (1), wherein W is oxygen, solves the problem of providing a process of reverse (5' -3') synthesis of RNA oligomers; the special technical feature is the use of ribonucleoside 5'-phosphoramidites as building blocks for the (5'-3')-synthesis of RNA.

6 Therefore, the special technical features are not the same. Moreover the special technical features have different effects and hence solve different problems, consequently they cannot be considered to be corresponding.

In conclusion, the groups of claims are not linked by common or corresponding special technical features and define 5 different inventions not linked by a single general inventive concept. The application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Invention 1
claim: 1(partially): a phosphoramidite of formula (1) of claim 1, wherein W is oxygen

Re Item V.

1 **Novelty**

1.1 Documents D2 (page 856; figure 2; compound 4a), D3 (page 28; figure 1; compound 7), D4 (page 604; figure 3; compound 3) all disclose:
ribonucleoside 5'- phosphoramidites of formula (1) of claim 1, wherein W is oxygen.

Consequently, the present application does not meet the criteria of Article 33 (1) PCT, because the subject-matter of claim 1, as regards the invention 1, is not new in the sense of Article 33(2) PCT.

2 **Inventive step**

2.1 The problem underlying the present invention is to provide ribonucleoside 5'-phosphoramidites of formula (1) of claim 1, wherein W is oxygen.

In view of the context of paragraph 1 above it is understood that subject-matter that is not novel is also regarded as not inventive, since D2-D4 provide the same solution to the same problem as the present application.

Therefore, claim 1 is not inventive (Art. 33(3) PCT).

Re Item VIII.

1 Claim 1 is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and drawings. The reasons therefor are the following: examples 1-4 on pages 29-36 of the description disclose only ribonuclosides having the following substitution pattern:

- 2'-O-TBDMS
- 3'-O-DMT
- 5'-cyanoethyl-N,N-diisopropyl-phosphoramidite

Therefore, the following definitions in claim 1 have too broad a scope and are not sufficiently supported:

- Y is sulphur

- R1, R2, R3, R4 are unspecified alkyl or aryl substituents of unspecified lenght.

2 The embodiment of the invention described in example 5 on pages 36-37 does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

DOCKET NO. 4441.1001-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Declaration for Patent Application

☐ Supplemental (37 CFR § 1.67)

As a named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated next to my name;

I believe I am the original, first and sole inventor (if only one name is listed) or an original, first and joint inventor (if plural names are listed in the signatory page(s) commencing at page 2 hereof) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

the specification of which:

☐ is attached hereto.

☒ was filed on February 19, 2010 as United States Application Number 12/708,827.

☐ was filed on [PCT filing date] as PCT International Application No. [PCT Appl'n No.] [and assigned United States Application No. [ ]].

☐ and was amended on [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment 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.

I hereby expressly authorize the filing of an International Patent Application under the Patent Cooperation Treaty which corresponds to and claims the priority of the above-identified application.

I hereby claim foreign priority benefits under 35 U.S.C. 119 or 365 of any foreign application(s) for patent or inventor's certificate, or 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 or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Not Claimed	Certified Copy Filed?	
				YES	NO
_____ (Number)	_____ (Country)	_____ (Day/Month/Year filed)	☐	☐	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year filed)	☐	☐	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year filed)	☐	☐	☐

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 Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of **sole or first** inventor: Suresh C. Srivastava

Inventor's Signature:

Residence: City	State	Country	Citizenship
Burlington	Massachusetts	US	US

Mailing Address (Business or Residential)

Street or P.O. Box: 7 Donald Road

City	State	ZIP	Country
Burlington	Massachusetts	01803	US

Full name of **second** joint inventor, if any: Naveen P. Srivastava

Inventor's Signature:

Residence: City	State	Country	Citizenship
Burlington	Massachusetts	US	India

Mailing Address (Business or Residential)

Street or P.O. Box: 4 Baron Park Lane, Apartment 10

City	State	ZIP	Country
Burlington	Massachusetts	01803	US

962020_1

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	12/708,827
Filing Date	February 19, 2010
First Named Inventor	Suresh C. Srivastava
Confirmation Number	5297
Group Art Unit	1614
Examiner Name	Not yet known
Attorney Docket Number	4441.1001-002

Title: Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

I hereby appoint

☒ Practitioners associated with **Customer No. 021005**

☐ Practitioner(s) named below:

as my/our attorneys/agents to prosecute the application identified above, including any continuation or divisional applications thereof, and to transact all business in the United States Patent and Trademark Office connected therewith.

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

☒ Customer Number 021005

Hamilton, Brook, Smith & Reynolds, P.C.

530 Virginia Road

P.O. Box 9133

Concord, Massachusetts 01742-9133

☐ Other

Please direct all telephone calls and facsimiles to:

Name Alice O. Carroll Tel. No. 978-341-0036 Fax No. 978-341-0136

I am the:

☐ Applicant/Inventor.

☒ Authorized representative of the Assignee, ChemGenes Corporation, of the entire interest. See 37 CFR § 3.71. A Statement under 37 CFR § 3.73(b) is enclosed.

☐ Authorized representative of the Assignee, [ ], together with [ ], of the entire interest. A Statement under 37 CFR § 3.73(b) is enclosed.

SIGNATURE of Applicant or Assignee of Record

Signature	
Name & Title	Suresh C. Srivastava, Ph.D., Chief Executive Officer
Date	06/29/2010

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Shanghai Hongene Exhibit 1002

STATEMENT UNDER 37 CFR § 3.73(b)

Applicant/Patentee: Suresh C. Srivastava and Naveen P. Srivastava

Application No./Patent No.: 12/708,827 Filed/Issue Date: February 19, 2010

For: Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

ChemGenes Corporation (Name of Assignee), a corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is

A. ☒ the assignee of the entire right, title and interest in the patent application identified above; or

B. ☐ an assignee together with [ ] of the entire right, title and interest in the patent application identified above.

The right, title and interest of the above-named assignee in the patent application identified above is established by virtue of:

A. ☒ An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel [ ], Frame [ ], or a copy thereof is attached.

OR

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

1. From: [ ] To: [ ]
The document was recorded in the United States Patent and Trademark Office at
Reel [ ], Frame [ ], or a copy thereof is attached.

2. From: [ ] To: [ ]
The document was recorded in the United States Patent and Trademark Office at
Reel [ ], Frame [ ], or a copy thereof is attached.

3. From: [ ] To: [ ]
The document was recorded in the United States Patent and Trademark Office at
Reel [ ], Frame [ ], or a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

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

Name: Suresh C. Srivastava, Ph.D.

Title: Chief Executive Officer

Date: 06/29/2010

962809_1

COPY

NOT FOR RECORDATION

Docket No. 4441.1001-002

Joint

ASSIGNMENT

WHEREAS, we, **Suresh C. Srivastava** and **Naveen P. Srivastava**, have invented a certain improvement in **Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA** described in an application for Patent,

☐ the specification of which is about to be filed in the United States Patent Office *(use for utility (37 CFR § 1.53(b)) and design filings only)*;

☐ is about to be filed in the United States Patent Office as a Provisional Application;

☒ the specification of which is United States Application No. **12/708,827**, filed **February 19, 2010**;

☐ the specification of which is a Patent Cooperation Treaty Application, International Application No. [ ], filed [ ], which designates the United States of America [and is assigned United States Application No. [ ]];

☐ which was patented under United States Patent No. [ ].

WHEREAS, **ChemGenes Corporation** (hereinafter "ASSIGNEE"), a corporation organized and existing under the laws of the **Commonwealth of Massachusetts**, and having a usual place of business at **33 Industrial Way, Wilmington, Massachusetts 01887** desires to acquire an interest therein in accordance with agreements duly entered into with us;

NOW, THEREFORE, to all whom it may concern be it known that for and in consideration of said agreements and of other good and valuable consideration, the receipt of which is hereby acknowledged, we have sold, assigned and transferred and by these presents do hereby sell, assign and transfer unto said ASSIGNEE, its successors, assigns and legal representatives, the entire right, title and interest in and throughout the United States of America, its territories and all foreign countries, in and to said invention as described in said application, together with the entire right, title and interest in and to said application and such Letters Patent as may issue on said invention; said invention, application and Letters Patent to be held and enjoyed by said ASSIGNEE for its own use and behalf and for its successors, assigns and legal representatives, to the full end of the term for which said Letters Patent may be granted as fully and entirely as the same would have been held by us had this assignment and sale not been made; we hereby convey all rights arising under or pursuant to any and all international agreements, treaties or laws relating to the protection of industrial property by filing any such applications for Letters Patent. We hereby acknowledge that this assignment, being of the entire right, title and interest in and to said invention, carries with it the right in ASSIGNEE to apply for and obtain from competent authorities in all countries of the world any and all Letters Patent by attorneys and agents of ASSIGNEE's selection and the right to procure the grant of all such Letters Patent to ASSIGNEE for its own name as assignee of the entire right, title and interest therein; we hereby expressly authorize the filing of an International Patent Application under the Patent

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Cooperation Treaty which corresponds to and claims the priority of the above-identified application;

AND, we hereby further agree for ourselves and our executors and administrators to execute upon request any other lawful documents and likewise to perform any other lawful acts which may be deemed necessary to secure fully the aforesaid invention to said ASSIGNEE, its successors, assigns and legal representatives, but at its or their expense and charges, including the execution of applications for patents in foreign countries, and the execution of any future applications including substitution, reissue, divisional or continuation applications, and preliminary or other statements and the giving of testimony in any interference or other proceeding in which said invention or any application or patent directed thereto may be involved;

AND, we do hereby authorize and request each Patent Office and the Commissioner of Patents of the United States to issue such Letters Patent as shall be granted upon said invention to said ASSIGNEE, its successors, assigns, and legal representatives.

IN TESTIMONY WHEREOF, we have hereunto set our hands and affixed our seals the date set forth below.

Inventor's Signature: _____
Suresh C. Srivastava

State/Commonwealth
of Massachusetts
County of Middlesex

On this June 18th day of June 2010, before me, the undersigned notary public, personally appeared Suresh C. Srivastava,

☐ personally known to me, or

☐ proved to me through satisfactory evidence of identification, which was

_____

to be the person whose name was signed on the foregoing instrument in my presence, and acknowledged that he/she signed the foregoing instrument as his/her free act and deed.

(SEAL)

Notary Public_____

_____(print name)

My Commission expires _____/_____/_____

COPY

NOT FOR RECORDATION

Docket No. 4441.1001-002

Inventor's Signature: _____

Naveen P. Srivastava

State/Commonwealth
of _____
County of _____

On this 18th day of June 2010, before me, the undersigned notary public, personally appeared Naveen P. Srivastava,

☐ personally known to me, or

☐ proved to me through satisfactory evidence of identification, which was

_____

to be the person whose name was signed on the foregoing instrument in my presence, and acknowledged that he/she signed the foregoing instrument as his/her free act and deed.

(SEAL)

Notary Public_____

_____(print name)

My Commission expires _____/_____/_____

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Shanghai Hongene Exhibit 1002

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

FEE TRANSMITTAL FOR PATENT APPLICATIONS	Attorney Docket Number	4441.1001-002
	Application Number	12/708,827
	First Named Inventor	Suresh C. Srivastava

CLAIM CALCULATION (includes any preliminary amendment)

CLAIMS	(1) FOR	(2) NUMBER FILED		(3) NUMBER EXTRA	(4) RATE			(5) CALCULATIONS
	TOTAL CLAIMS (37 CFR 1.16(c) or (j))	39	– 20 =	19	X $ 52 =	X $ 26 =	$	988
	INDEPENDENT CLAIMS (37 CFR 1.16(b) or (i))	5	– 3 =	2	X$220 =	X $110 =	$	440
	MULTIPLE DEPENDENT CLAIMS (if applicable) (37 CFR 1.16(d))				+ $390 =	+ $195 =	$	
				BASIC FEE (37 CFR1.16(a)(1)) Paper or Electronic Filing - Large Entity; Paper Filing - Small Entity; Electronic filing - Small Entity			$	330
	APPLICATION SIZE FEE $270/135 for each add'l 50 sheets exceeding 100 **IF FILED ELECTRONICALLY:** Total No. Pages/Sheets X .75 (If a fraction remains, add 1 page to the total thereby including the fraction). Using the total after calculation, the fee is $270/135 for each additional 50 sheets over 100.			Specification: 148 Pages; Drawings: 38 Sheets; Sequence Listing: 9 pages; Total No. Pages/Sheets **195** x .75 = 147			$	270
				SEARCH FEE (37 CFR 1.16(k))			$	540
				EXAMINATION FEE (37 CFR 1.16(o))			$	220
	Surcharge - Late Filing of Declaration or Filing Fees (37 CFR 1.16(f)) =						$	130
	Petition for Extension of Time Fee (37 CFR 1.17) =						$	490
	[Other]						$	
	Assignment Recordation Fee (37 CFR 1.21(h)) = (only when filed with application)						$	
	TOTAL =						$	3408

1. Small entity status:
   - a. ☐ A small entity statement is enclosed.
   - b. ☐ A small entity statement was filed in the prior non-provisional application and such status is still proper and desired.
   - c. ☐ Is no longer claimed.
2. ☒ Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380.
3. ☐ A check is enclosed for **$[ ]**. ☒ Please charge **$3408** to Deposit Account No. 08-0380.
4. ☐ Other: _____

Signature	Alice O. Carroll	Date	July 12, 2010
Submitted by Typed or Printed Name	Alice O. Carroll	Reg. Number	33,542

999564_1 – September 15, 2008

Shanghai Hongene Exhibit 1002

SCORE Placeholder Sheet for IFW Content

Application Number: 12708827 Document Date: 7/12/2010

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Drawings – Other than Black and White Line Drawings

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

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Form Revision Date: February 8, 2006

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/708,827	02/19/2010	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	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			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	39 minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 07/12/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 39	Minus	** 39	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	* 5	Minus	***5	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) 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))									
☐ 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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/PEGGY YARBOROUGH/

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.

Shanghai Hongene Exhibit 1002

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Sequence Listing could not be accepted.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Anne Corrigan
Timestamp: [year=2010; month=7; day=20; hr=12; min=52; sec=53; ms=960; ]
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<223> All c's, a's, g's and u's are ribonucleic acids.

<220>
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<222> (1)...(75)
<223> All a's are
      N6-Benzoyl-2'-O-TBDMS-3'-O-DMT-adenosine-OP;
      all c's are
      N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

<220>
<221> misc_feature
<222> (1)...(75)
<223> all g's are
      N2-Isobutryl-2'-O-TBDMS-3'-O-DMT-guanosine-OP;
      all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Artificial oligonucleotide

Since "Artificial" is already indicated in the above <213> response, please replace it with "Synthetic" in the <223> response.
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Validated By CRFValidator v 1.0.3

Application No: 12708827 Version No: 1.0

Input Set:

Output Set:

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Finished: 2010-07-12 16:47:19.667
Elapsed: 0 hr(s) 0 min(s) 2 sec(s) 72 ms
Total Warnings: 11
Total Errors: 0
No. of SeqIDs Defined: 11
Actual SeqID Count: 11

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Srivastava, Naveen P.

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the Reverse Direction, Efficient RNA Synthesis and
Convenient Introduction of 3'-End Ligands, Chromophores and
Modifications of Synthetic RNA

<130> 4441.1001-002

<140> 12708827
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N6-Benzoyl-2'-O-Me-3'-O-DMT-adenosine-OP

<220>
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<223> u is 2'-O-TBDMS-3'-O-DMT-uridine-OP

Shanghai Hongene Exhibit 1002

<220>
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N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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<223> all g's are
N2-Isobutryl-2'-O-TBDMS-3'-O-DMT-guanosine-OP;
all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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<223> Phosphorothioate internucleotide linkage

<220>
<221> misc_feature
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<220>
<221> misc_feature
<222> 21
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<222> (2)...(19)
<223> All a's are
N6-Benzoyl-2'-O-TBDMS-3'-O-DMT-adenosine-OP;
all c's are

N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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<223> all g's are
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all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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aacagcauac aucucgacca u 21

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all c's are
N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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N6-Benzoyl-2'-O-TBDMS-3'-O-DMT-adenosine-OP;
all c's are
N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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<222> (1)...(75)
<223> All a's are

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all c's are
N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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<223> all g's are
N2-Isobutryl-2'-O-TBDMS-3'-O-DMT-guanosine-OP;
all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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<220>
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<222> 1, 20
<223> Adenosine is
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<220>
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<222> 21
<223> u is 2'-O-TBDMS-3'-O-DMT-uridine-OP

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<223> All a's are
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all c's are
N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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all c's are
N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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<223> u is 2'-O-TBDMS-3'-O-DMT-uridine-OP

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all c's are
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all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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<210> 9
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all c's are
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<220>
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<222> (3)...(20)
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N2-Isobutryl-2'-O-TBDMS-3'-O-DMT-guanosine-OP;
all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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all c's are
N4-Acetyl-2'-O-TBDMS-3'-O-DMT-cytidine-OP

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all u's are 2'-O-TBDMS-3'-O-DMT-uridine-OP

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gcccggauag cucagucggu agagcaucag acuuuuuauc ugagggucca ggguucaagu 60
cccuguucgg gcgcca 76

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002

CONFIRMATION NO. 5297

POA ACCEPTANCE LETTER

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

OC000000042697776

Date Mailed: 07/23/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/12/2010.

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

/lchau/

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002

CONFIRMATION NO. 5297

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

FORMALITIES LETTER



Date Mailed: 07/23/2010

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

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

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings must be reasonably free from erasures and must be free from alterations, overwriting, interlineations, folds, and copy marks. See Figure(s) 2B,2D,3B,4B,4D,5B-5D,7,8,9,10,11A,14A, 16A,16B,17,18,19,20,21A-B, 22-24.
  - Numbers, letters, and reference characters on the drawings must measure at least 0.32 cm (1/8 inch) in height. See Figure(s) 1B,2B,2D,3B,4B,5B,7,8,9,10,11A, 15D-F, 16A-B, 17-20, 23.
- A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing." Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). Refer to attachment or PAIR document dated 07/20/2010.

To Download Patentin Software, visit http://www.uspto.gov/web/patents/software.htm
For questions regarding compliance to these requirements, please contact:

- **For Rules Interpretation, call (571) 272-0951**
- **For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.**
- **Send e-mail correspondence for Patentin Software Program Help to ebc@uspto.gov**

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

Replies should be mailed to:

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

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

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

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

/nfissha/

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/708,827	02/19/2010	1614	2918	4441.1001-002	39	5

CONFIRMATION NO. 5297

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

FILING RECEIPT

OC000000042706487

Date Mailed: 07/23/2010

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, Wilmington, MA

Power of Attorney: The patent practitioners associated with Customer Number 021005

Domestic Priority data as claimed by applicant

This application is a CIP of PCT/US2009/005063 09/08/2009
which claims benefit of 61/191,065 09/06/2008

Foreign Applications

If Required, Foreign Filing License Granted: 03/03/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/708,827**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

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NOT GRANTED

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002

CONFIRMATION NO. 5297

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

WITHDRAWAL NOTICE



Date Mailed: 07/23/2010

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 03/10/2010. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

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

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

If the reply is not filed electronically via EFS-Web, the reply must be accompanied by a copy of the new notice.

If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

/nfissha/

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

STATEMENT CLAIMING SMALL ENTITY STATUS
(37 CFR § 1.27(a))-SMALL BUSINESS CONCERN

DOCKET NUMBER: 4441.1001-002

Applicant or Patentee: Suresh C. Srivastava and Naveen P. Srivastava
Application or Patent No.: 12/708,827
Filed or Issued: February 19, 2010
Title: Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

I hereby state that I am

☐ the owner of the small business concern identified below:

☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN ChemGenes Corporation
ADDRESS OF SMALL BUSINESS CONCERN 33 Industrial Way, Wilmington, Massachusetts 01887

I hereby state that the above identified small business concern qualifies as a small business concern as defined in 13 CFR Part 121 for purposes of paying reduced fees to the United States Patent and Trademark Office. Questions related to size standards for a small business concern may be directed to: Small Business Administration, Size Standards Staff, 409 Third Street, SW, Washington, DC 20416 or you may call 202-205-6618.

I hereby state that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

☐ the specification filed herewith with title as listed above.

☒ the application identified above.

☐ the patent identified above.

If the rights held by the above identified small business concern are not exclusive, each person, concern or organization having rights in the invention must file separate statements as to their status as small entities. No rights to the invention are held by any person who would not qualify as a person under 37 CFR 1.27(a)(1), or by any concern which would not qualify as a small business concern under 37 CFR 1.27(a)(2), or a nonprofit organization under 37 CFR 1.27(a)(3).

Each additional person, concern or organization having any rights in the invention is listed below:

☒ no such person, concern, or organization exists.

☐ each such person, concern, or organization is listed below.

Separate statements are required from each named person, concern, or organization having rights to the invention stating their status as small entities.

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.27(g)(2))

NAME OF PERSON SIGNING Suresh C. Srivastava, Ph.D.

TITLE OF PERSON IF OTHER THAN OWNER Chief Executive Officer

ADDRESS OF PERSON SIGNING 33 Industrial Way, Wilmington, Massachusetts 01887

SIGNATURE _____ DATE 9/15/10

iManage\1015827.1

Shanghai Hongene Exhibit 1002

Electronic Acknowledgement Receipt

EFS ID:	8439507
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Kristin Lovett
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	17-SEP-2010
Filing Date:	19-FEB-2010
Time Stamp:	14:56:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	44411001002transmittalofses.PDF	48213 d299157fdf4773614548ab833238d24a93f3c786	no	1
Warnings:					
Information:					

Shanghai Hongene Exhibit 1002

2	Miscellaneous Incoming Letter	44411001002sesstatement.PDF	53873 95acb393f6256f2d6d21ef3b7f0b4f703d428916	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	102086	

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not Assigned
Confirmation No.:	5297		
For:	Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Mail Stop 16, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

Date _____ Signature _____

Typed or printed name of person signing certificate

TRANSMITTAL OF SMALL ENTITY STATEMENT
AND REQUEST FOR REIMBURSEMENT

Mail Stop 16
Director of the USPTO
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is a Small Entity Statement in the above-identified patent application. Applicant's Attorney respectfully requests a reimbursement of $1,787.00, one-half of the total fees paid on July 12, 2010 under EFS ID No. 7988480, including the discount applied for electronically filing the application to be deposited in Deposit Account No. 08-0380. This request is made within the three-month period allowed for such reimbursement.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____
Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: September 17, 2010

Shanghai Hongene Exhibit 1002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not Assigned

Confirmation No.: 5297

For: Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

_____ _____

Date Signature

_____

Typed or printed name of person signing certificate

TRANSMITTAL OF REPLACEMENT DRAWINGS AND SUBSTITUTE SEQUENCE LISTING IN REPLY TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

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

Sir:

In reply to the Notice to File Corrected Application Papers dated July 23, 2010, requesting submission of replacement drawings, please find enclosed 28 sheets of replacement drawings consisting of FIGs. 1B, 2B, 2D, 3B, 4B, 4D, 5B-5C, 7, 8, 9, 10, 11A, 14A, 15D-15F, 16A, 16B, 17, 18, 19, 20, 21A-21B and 22-24 for filing in the above-captioned application. The Notice also required replacement of FIG. 5D but this is in error since there is no FIG. 5D in the application.

Certain figures have been revised to delete unnecessary extraneous information. FIGs. 7-10, 11A and 14A have been annotated in red to show the deletions being made. Entry of the amended replacement drawings for FIGs. 7-10, 11A and 14A is respectfully requested.

In accordance with procedures regarding electronically filed applications containing a sequence listing in text format, Applicants state that the sequences contained in the substitute sequence listing include no new matter, as required by 37 CFR § 1.825(a). Additionally, it is understood that since the substitute sequence listing is being submitted electronically, the requirement for submission of a computer readable form under 37 CFR § 1.821(e) has been met.

☒ Applicants hereby petition to extend the time to respond to the Notice to Correct Application Papers dated July 23, 2010 for two months from September 23, 2010 to November 23, 2010.

☐ The appropriate fee of $[ ] is enclosed in the form of a check.

☒ Authorization is granted to charge Deposit Account No. 08-0380 for fees due in this matter.

Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No.: 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Date: November 23, 2010

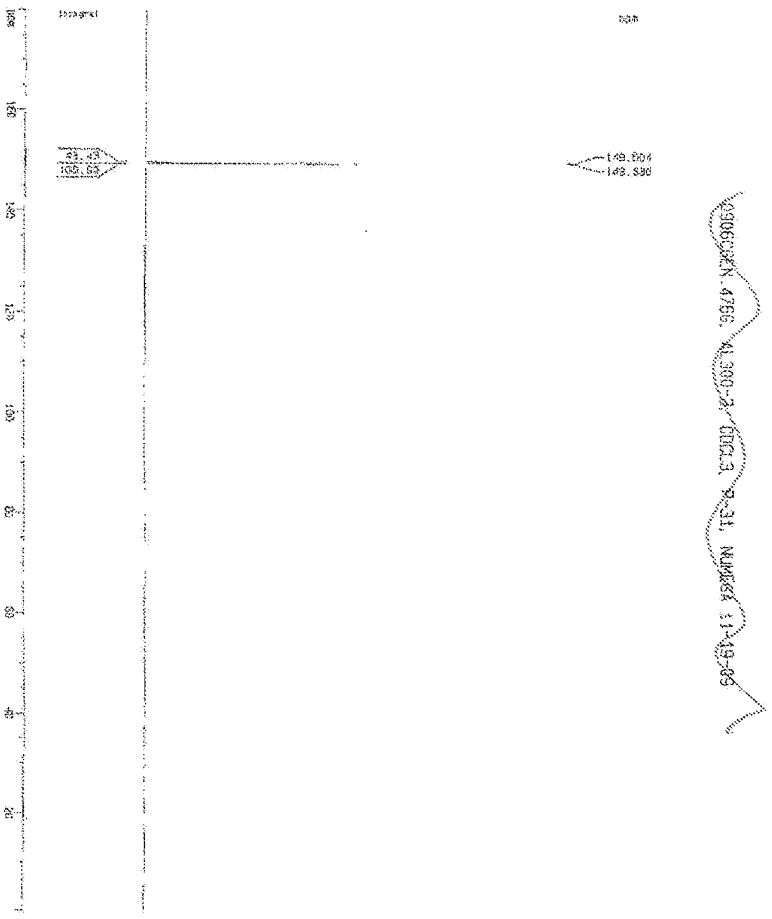


FIG. 7

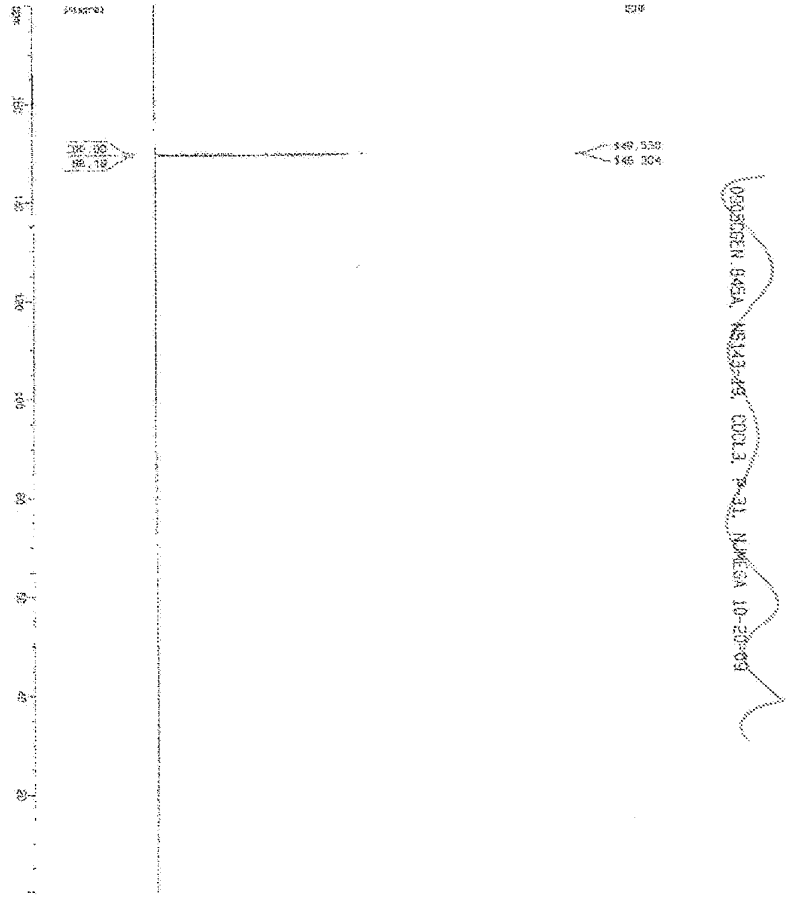


FIG. 8

Shanghai Hongene Exhibit 1002

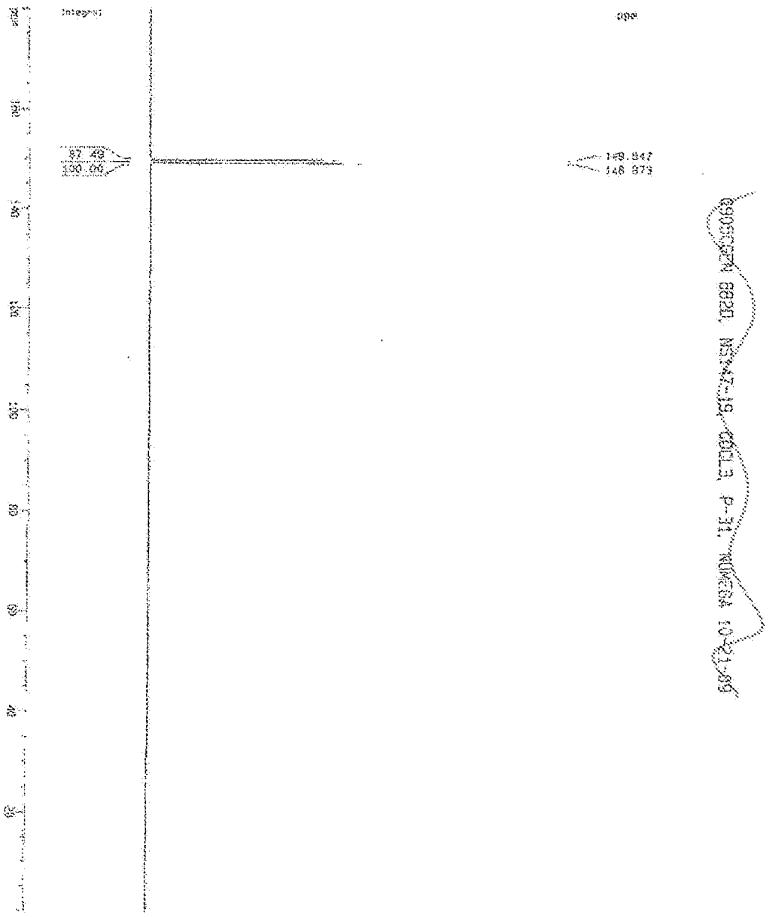


FIG. 9

Shanghai Hongene Exhibit 1002

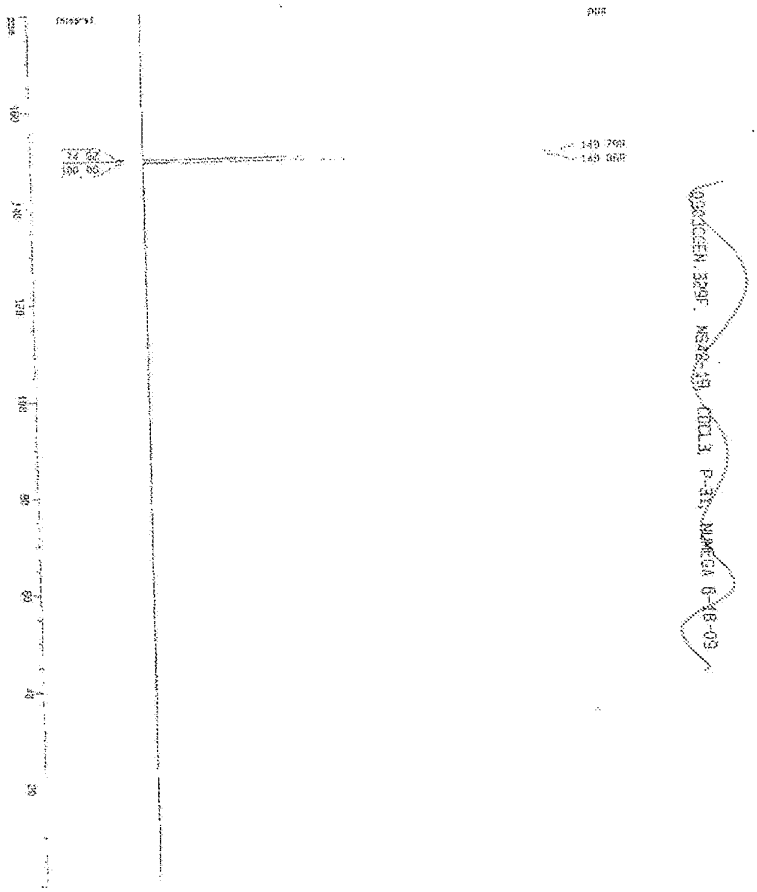


FIG. 10

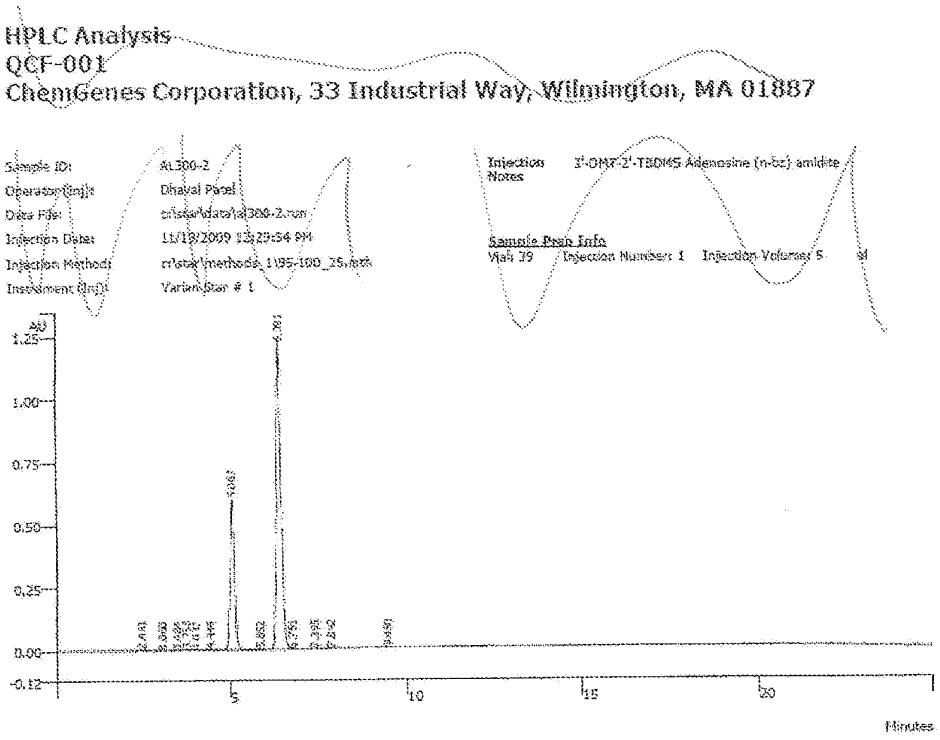

HPLC Analysis
QCF-001
ChemGenes Corporation, 33 Industrial Way, Wilmington, MA 01887
Sample ID: AL300-2
Operator(inj): Dhaval Patel
Data File: c:\star\data\al300-2.run
Injection Date: 11/19/2009 12:29:54 PM
Injection Method: c:\star\methods\1105-100_25.mth
Instrument (inj): Varian Star # 1
Injection Notes: 5'-DMT-2'-TBDMS Adenosine (n-bz) amidite
Sample Peak Info
Vial: 79 Injection Number: 1 Injection Volume: 5
AU
1.25
1.00
0.75
0.50
0.25
0.00
-0.12
5
10
15
20
Minutes

FIG. 11A

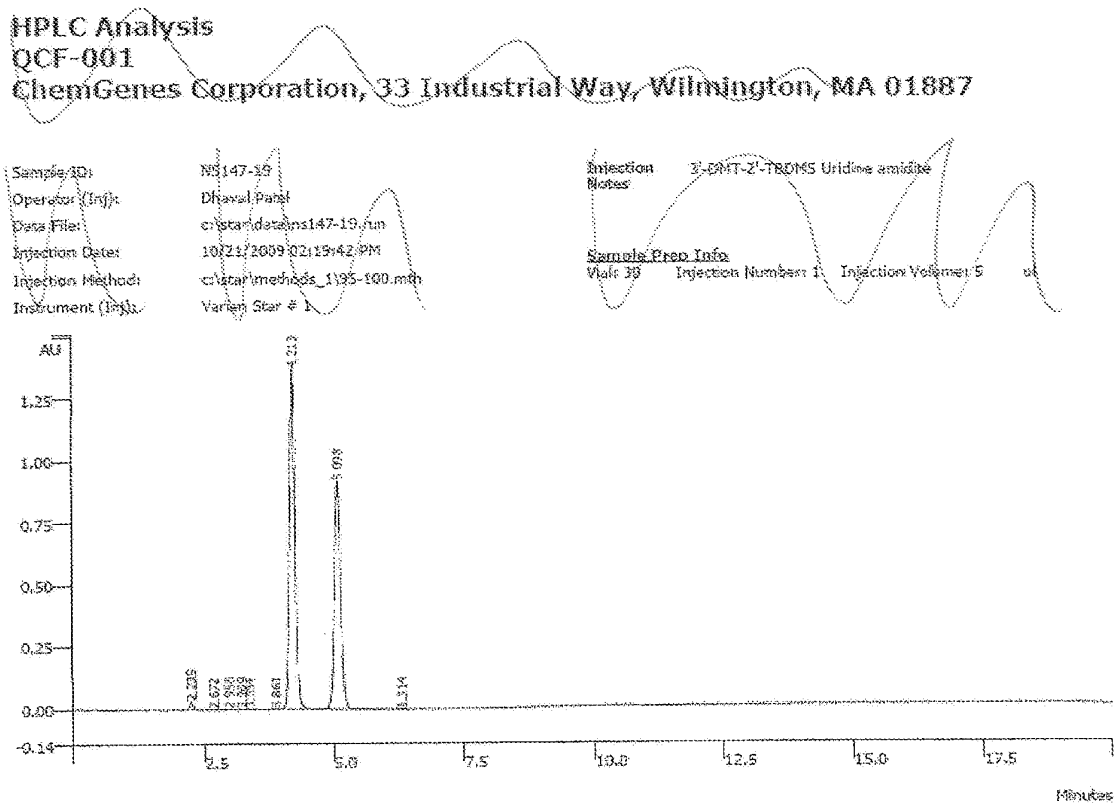

HPLC Analysis
QCF-001
ChemGenes Corporation, 33 Industrial Way, Wilmington, MA 01887
Sample ID: NS147-19
Operator (Inj): Dhaval Patel
Data File: c:\star\data\ns147-19.run
Injection Date: 10/21/2009 02:19:42 PM
Injection Method: c:\star\methods_1\95-100.mth
Instrument (Inj): Varian Star # 1
Injection Notes: 3'-OMT-2'-TBDMS Uridine amidite
Sample Prep Info
Vial: 39 Injection Number: 1 Injection Volume: 5
AU
1.25
1.00
0.75
0.50
0.25
0.00
-0.14
2.5
5.0
7.5
10.0
12.5
15.0
17.5
Minutes

FIG. 14A

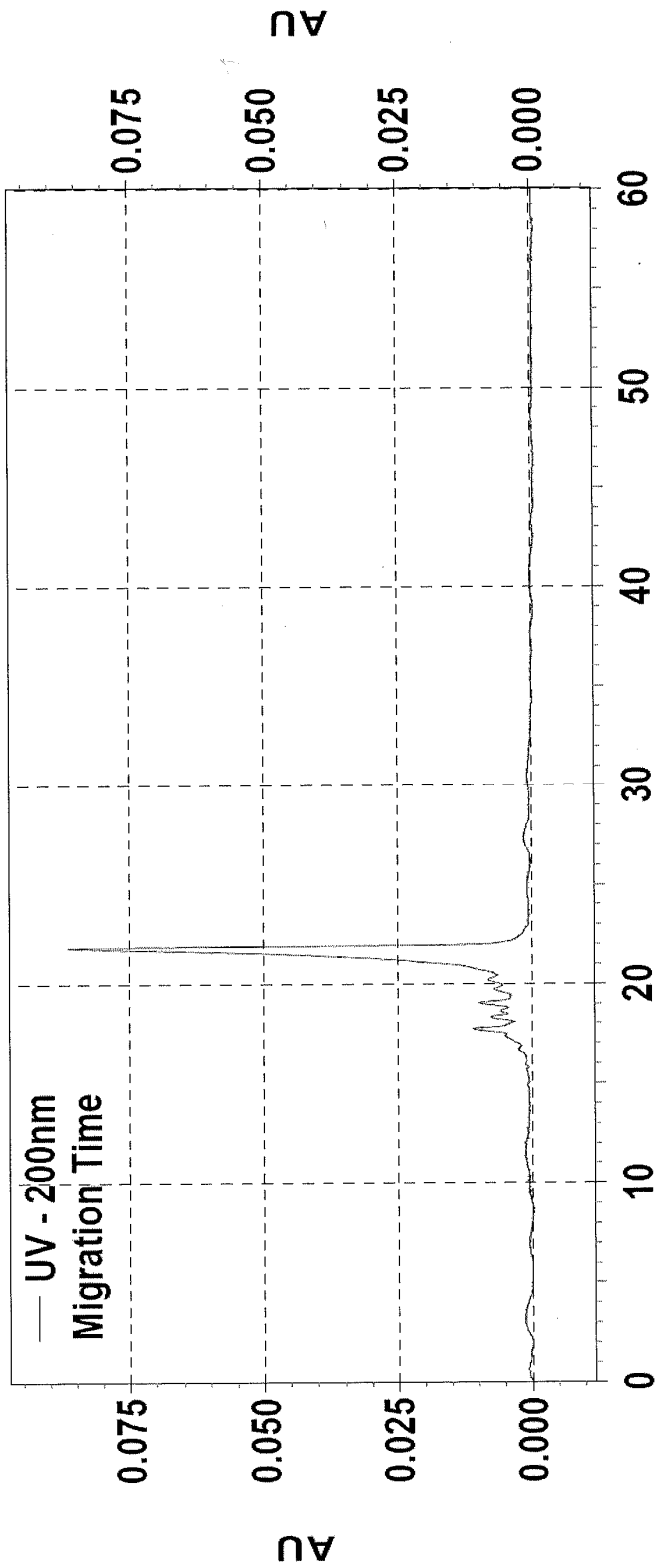


FIG. 1B

Shanghai Hongene Exhibit 1002

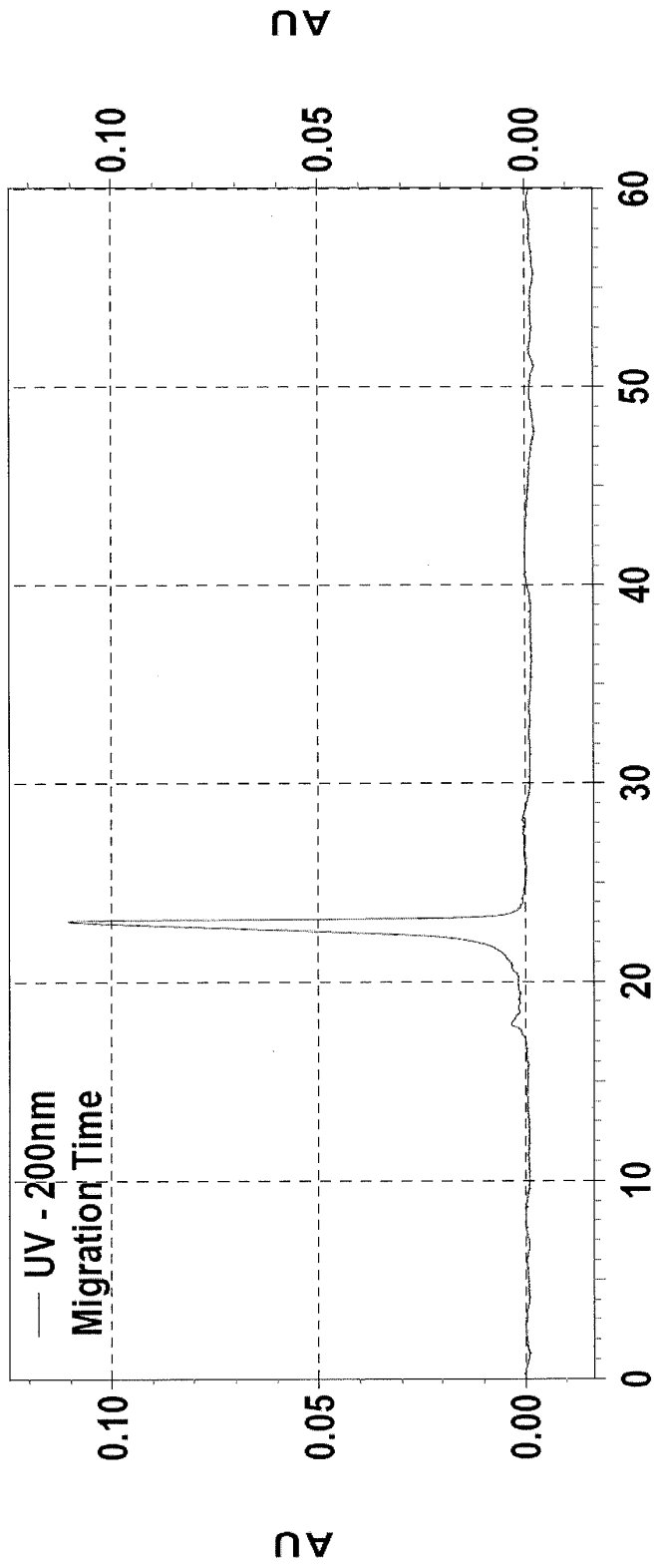


FIG. 2B

Shanghai Hongene Exhibit 1002

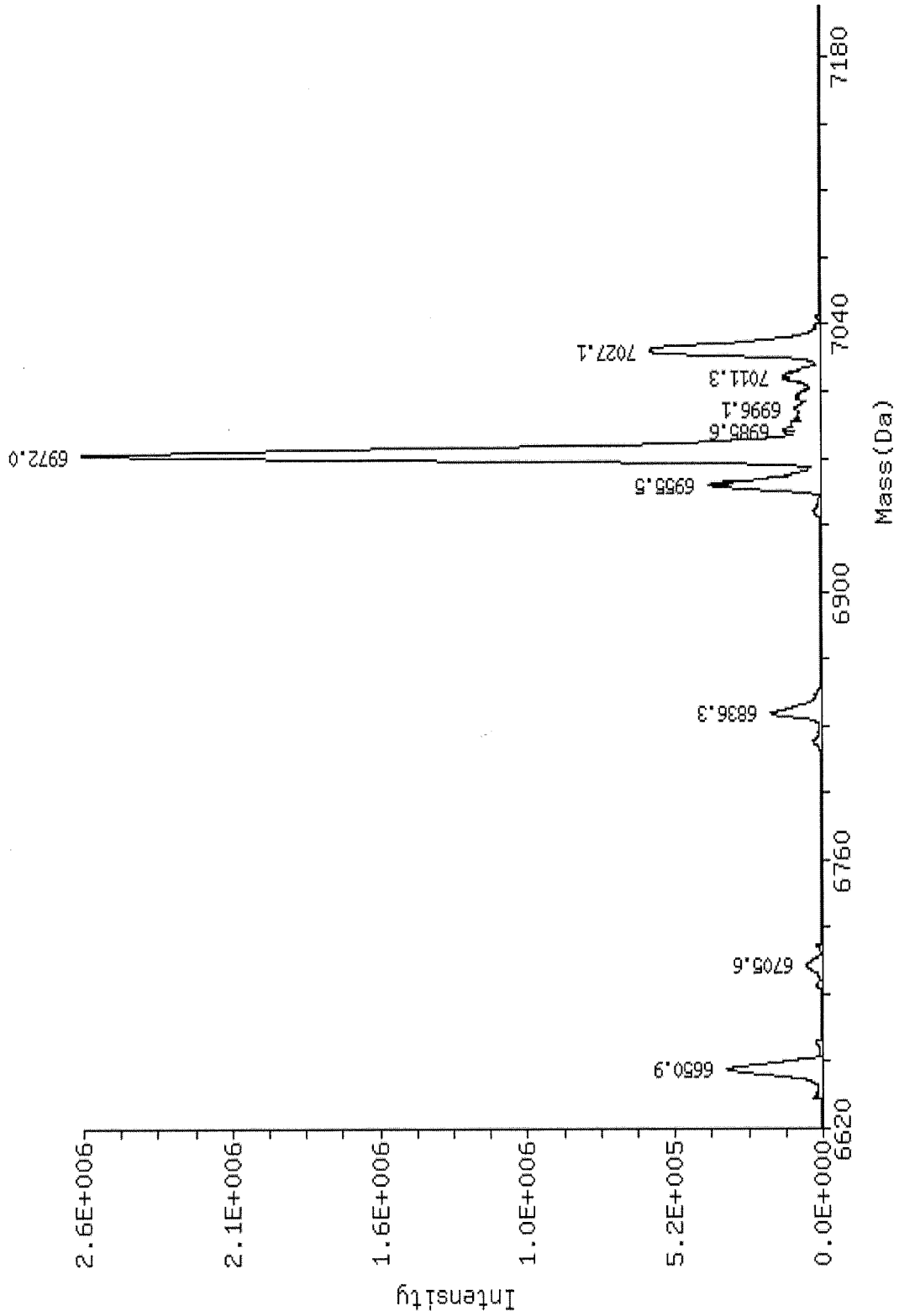


FIG. 2D

Shanghai Hongene Exhibit 1002

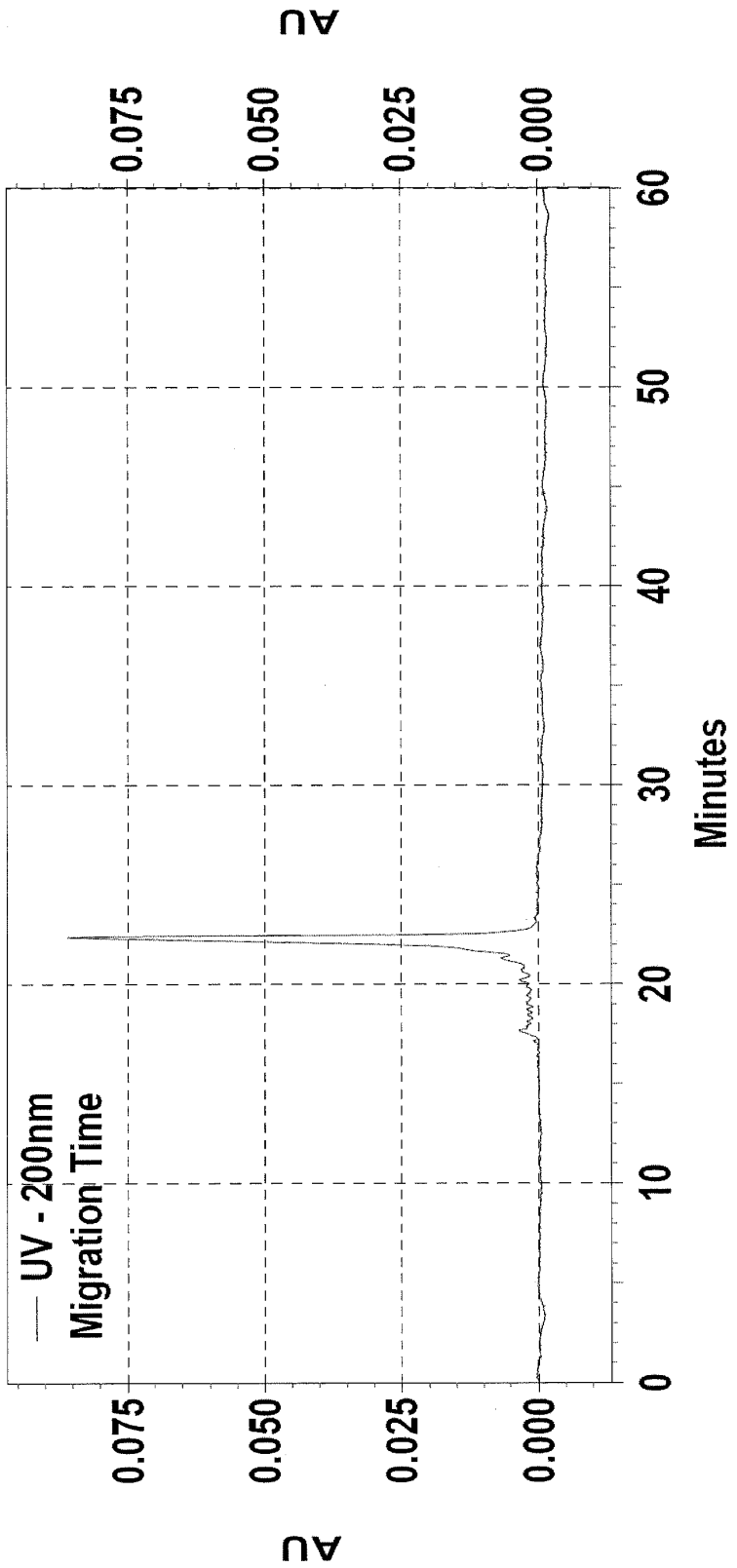


FIG. 3B

Shanghai Hongene Exhibit 1002

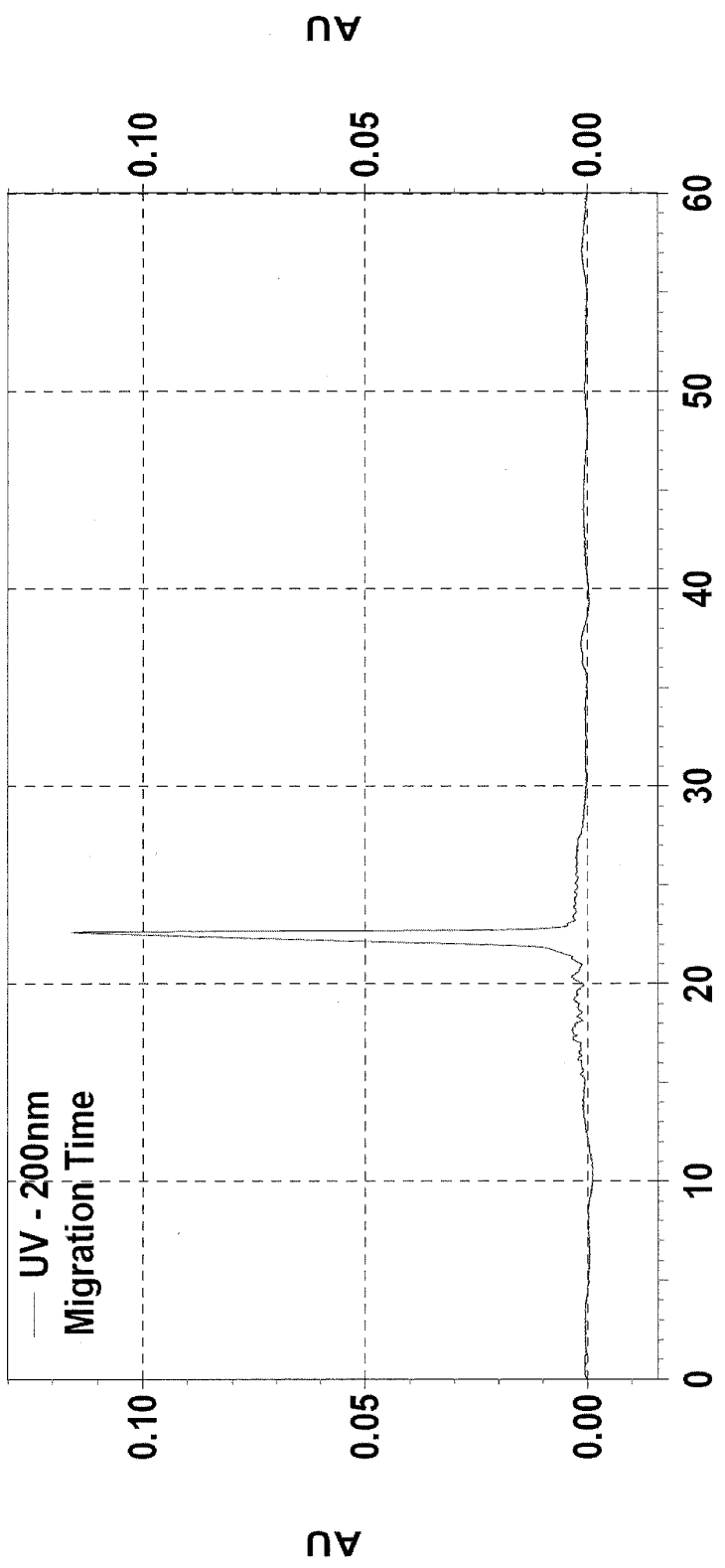


FIG. 4B

Shanghai Hongene Exhibit 1002

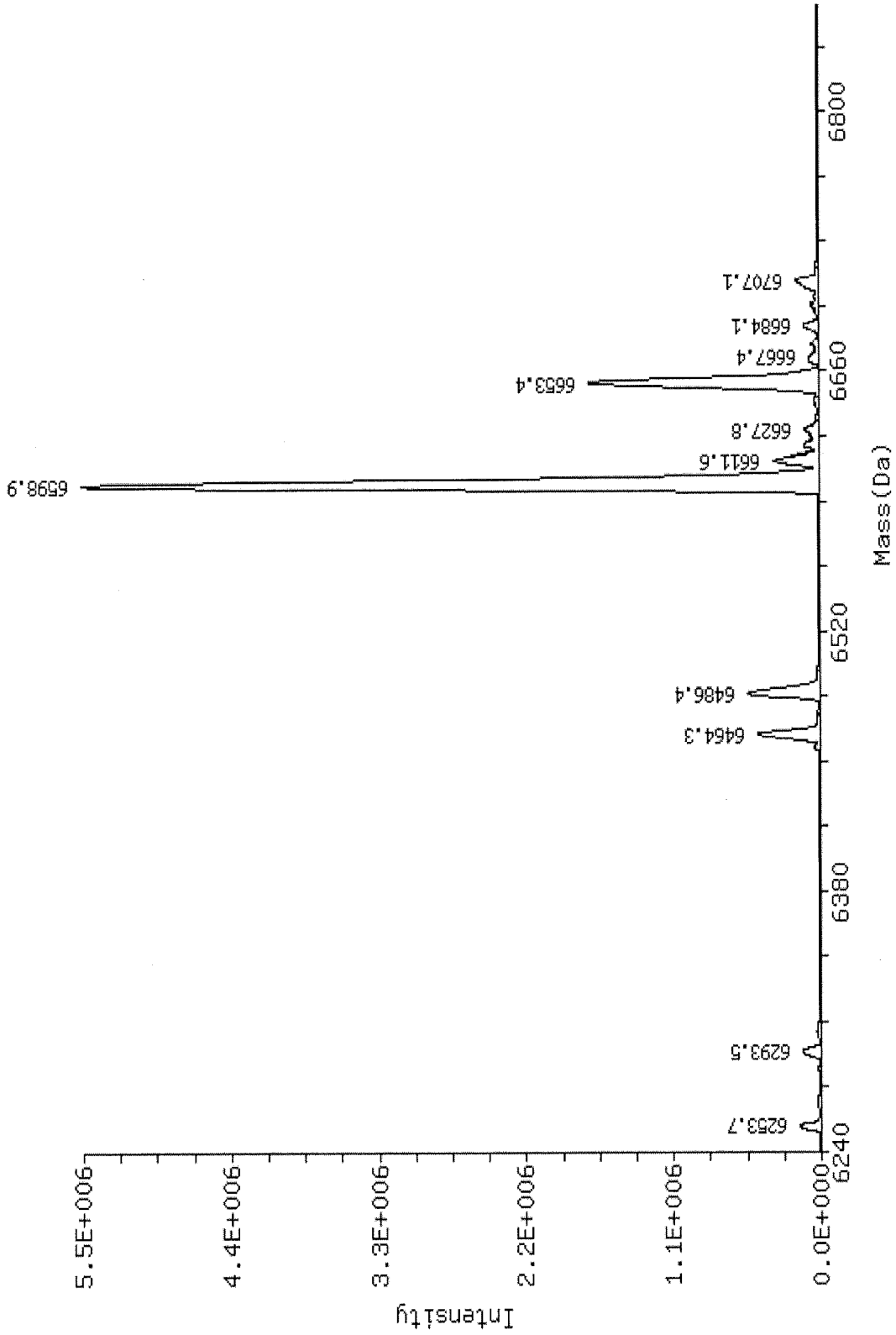


FIG. 4D

Shanghai Hongene Exhibit 1002

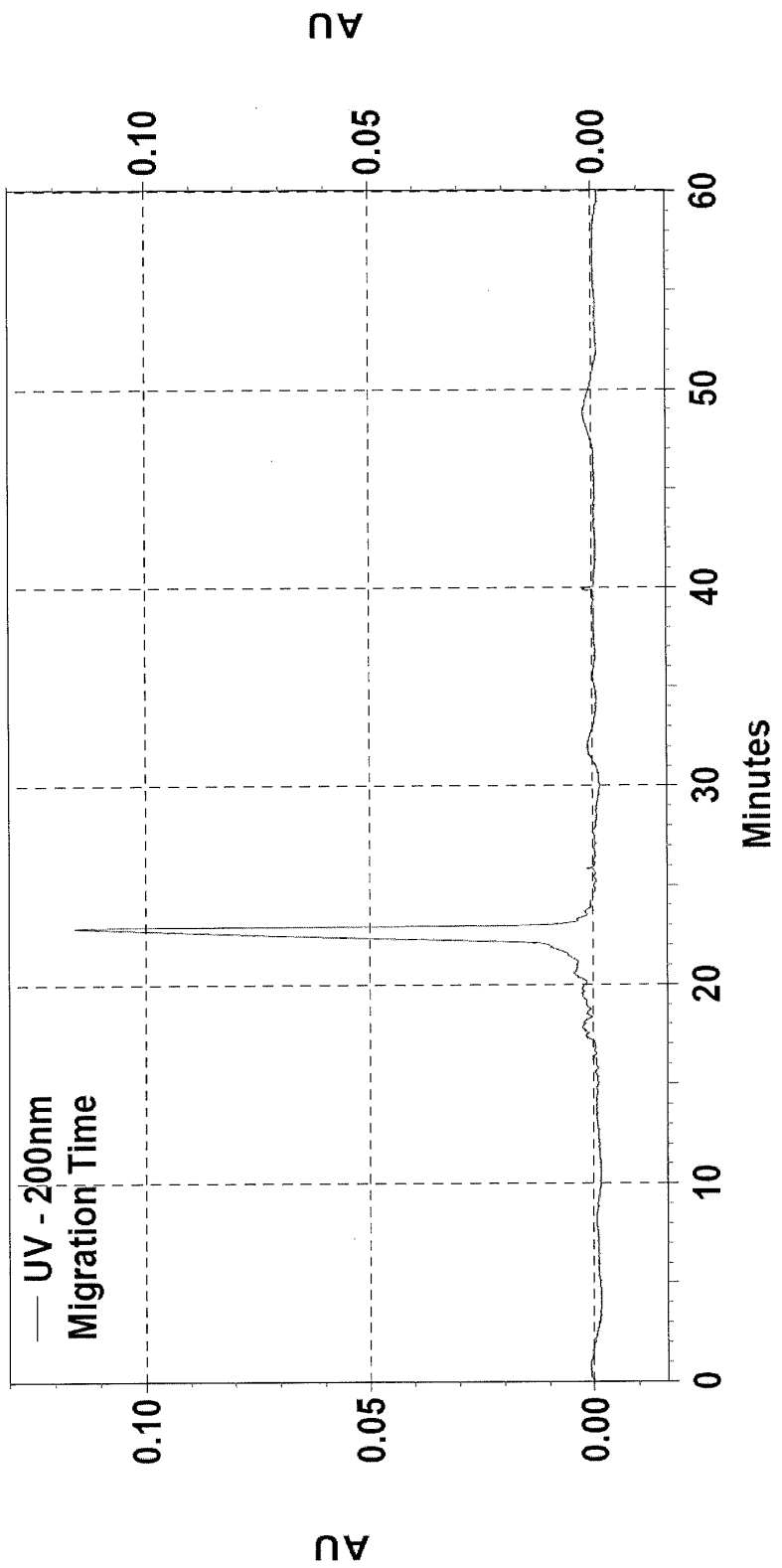


FIG. 5B

Shanghai Hongene Exhibit 1002

UV – 200nm
Results

Time	Height	Area	Area %
17.867	2612	124390	3.14
19.767	2308	125679	3.17
22.879	114213	3710219	93.69
Totals	119133	3960288	100.00

FIG. 5C

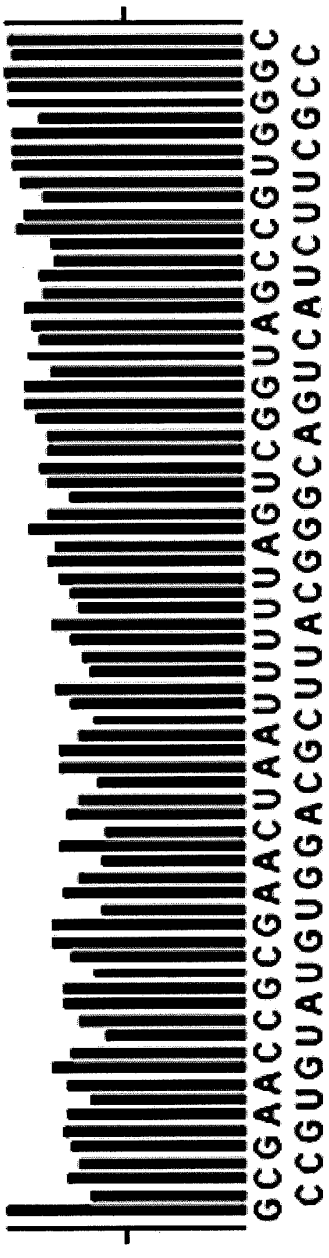


FIG. 6A

Shanghai Hongene Exhibit 1002

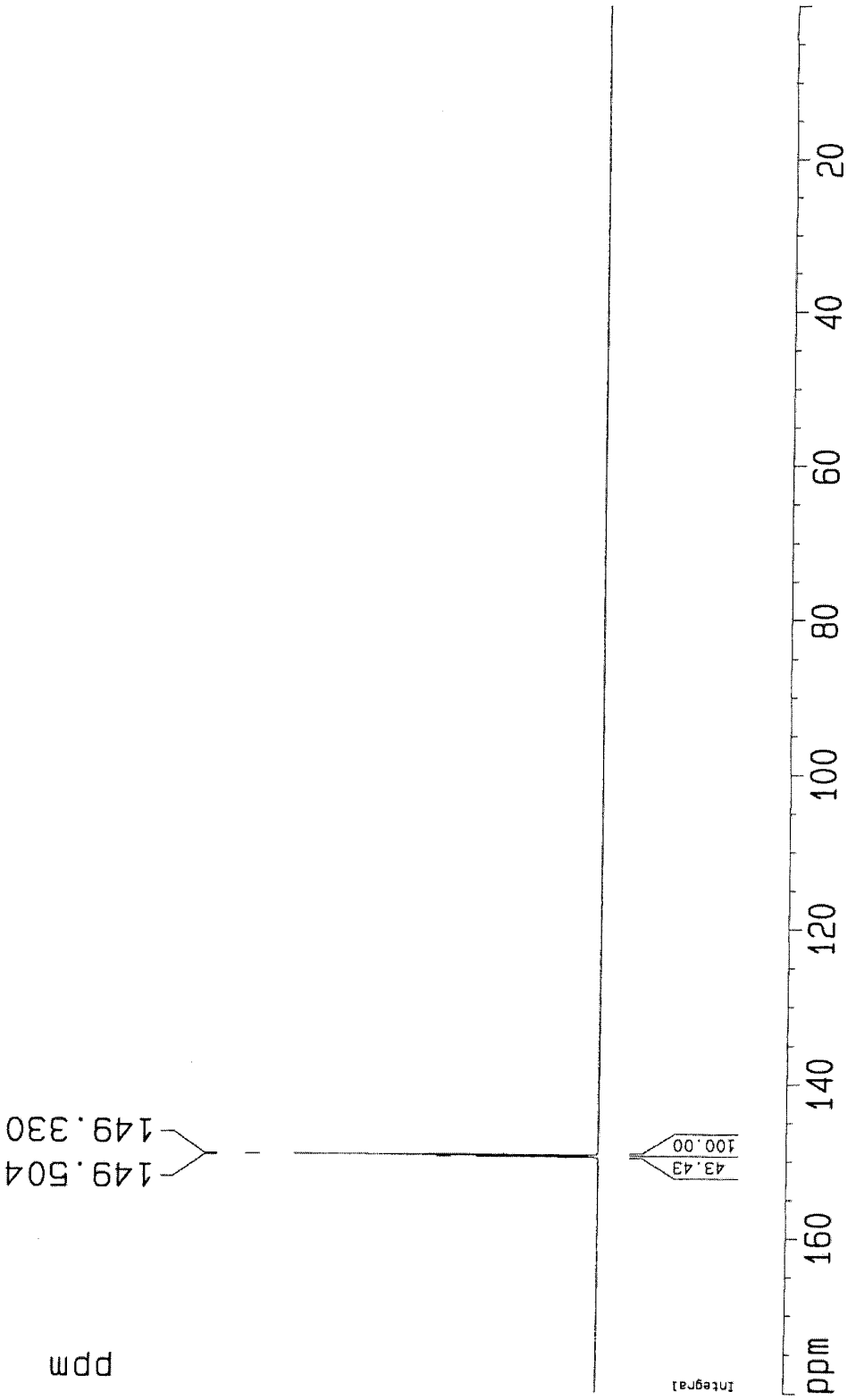


FIG. 7

Shanghai Hongene Exhibit 1002

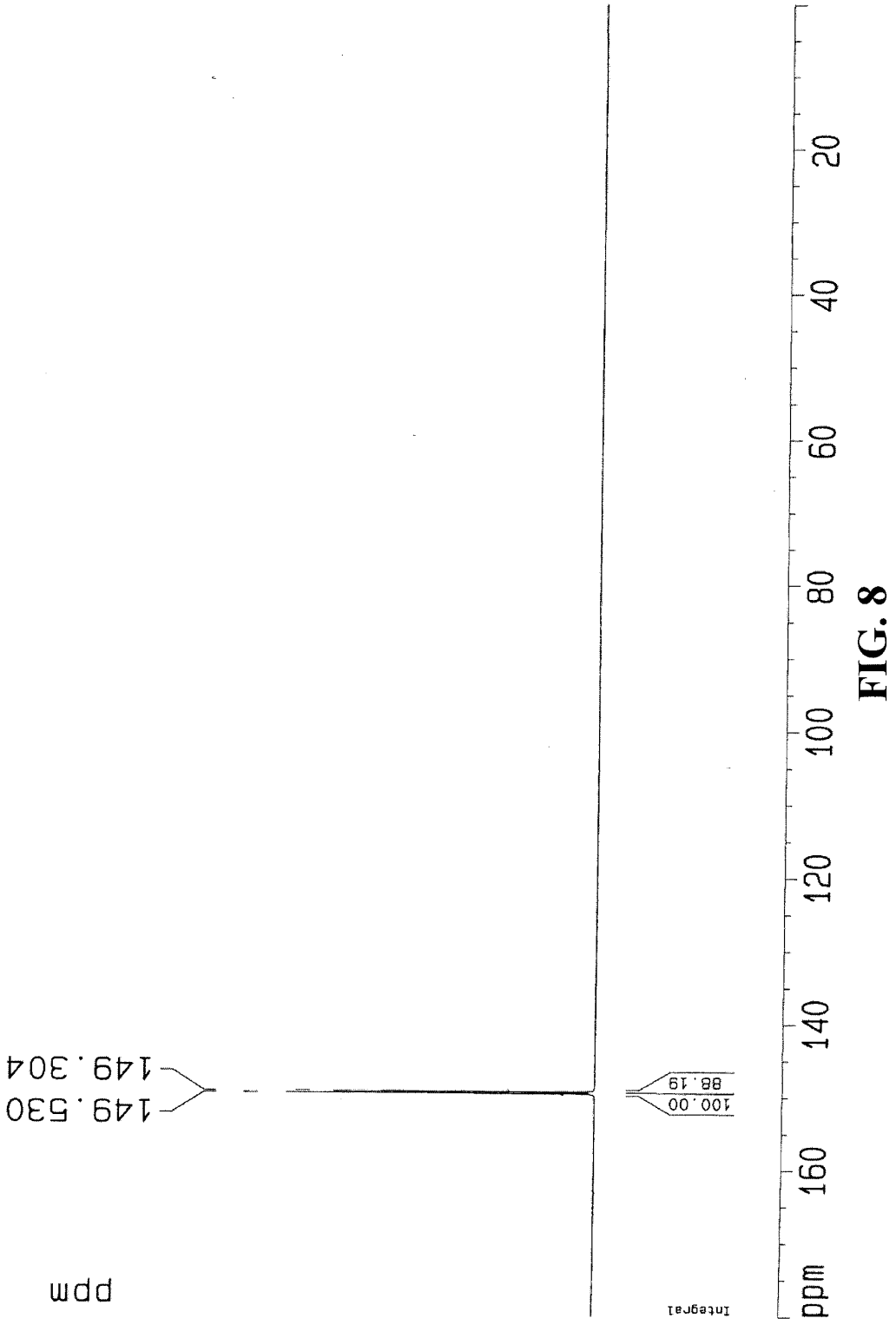


FIG. 8

Shanghai Hongene Exhibit 1002

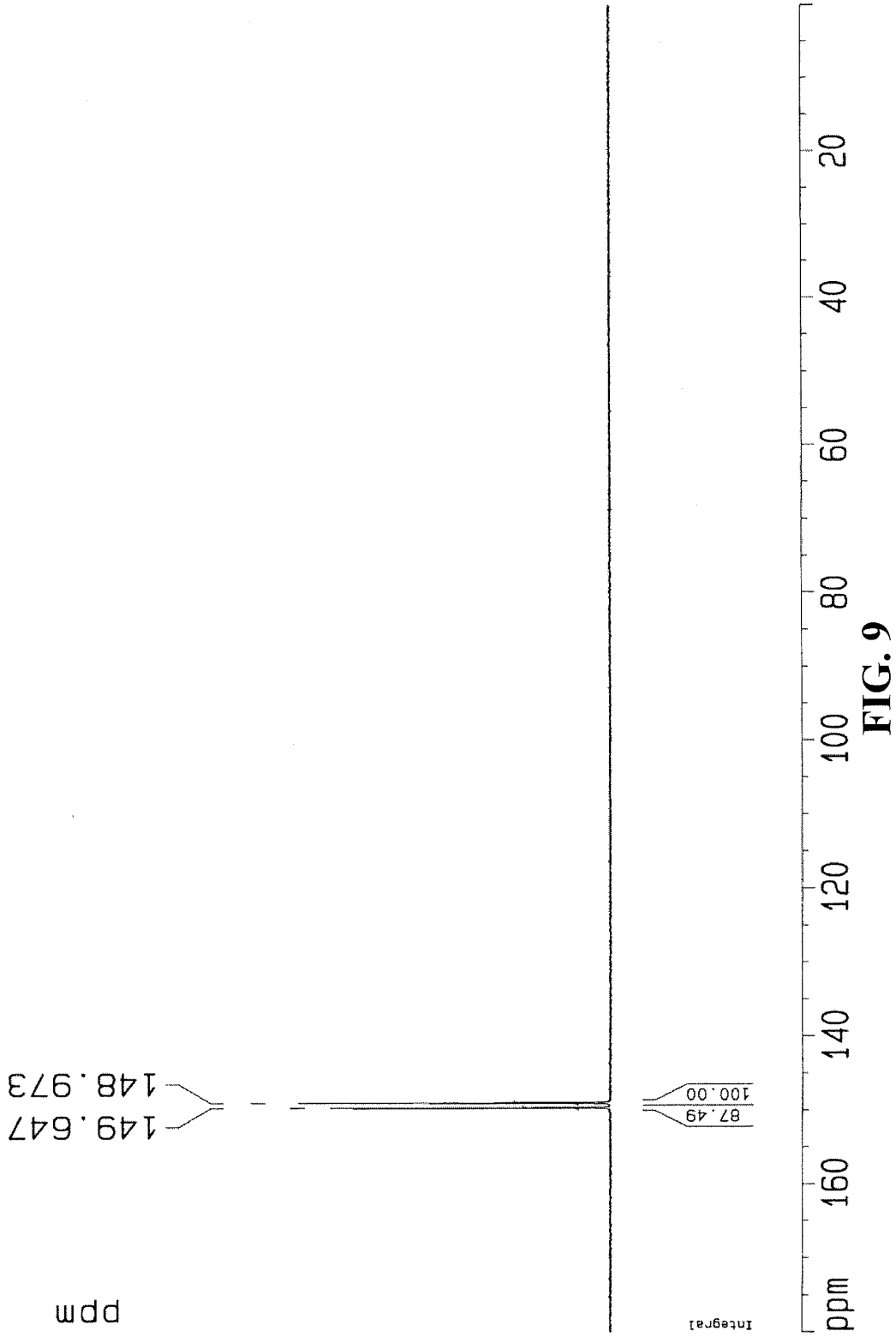


FIG. 9

Shanghai Hongene Exhibit 1002

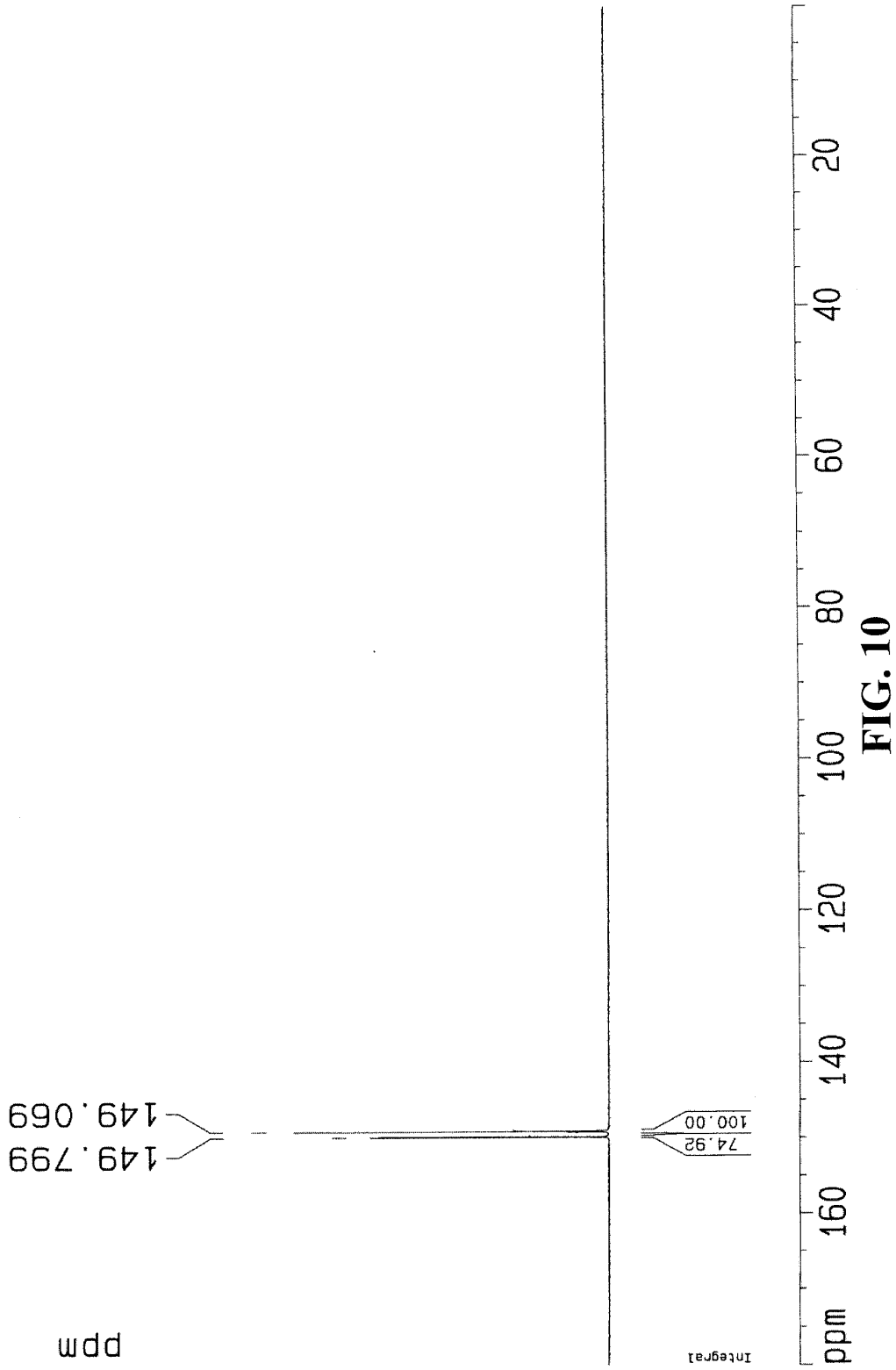


FIG. 10

Shanghai Hongene Exhibit 1002

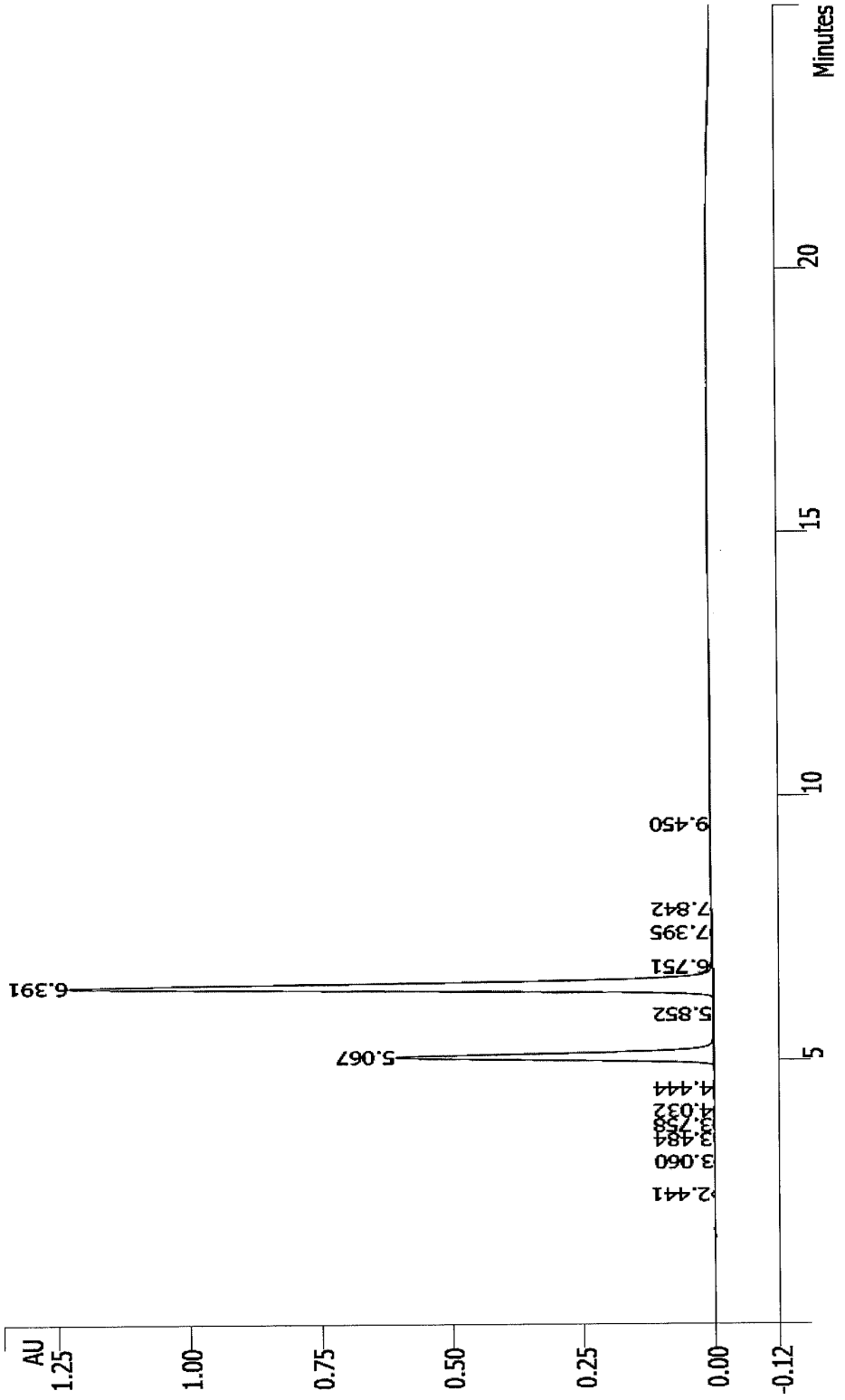


FIG. 11A

Shanghai Hongene Exhibit 1002

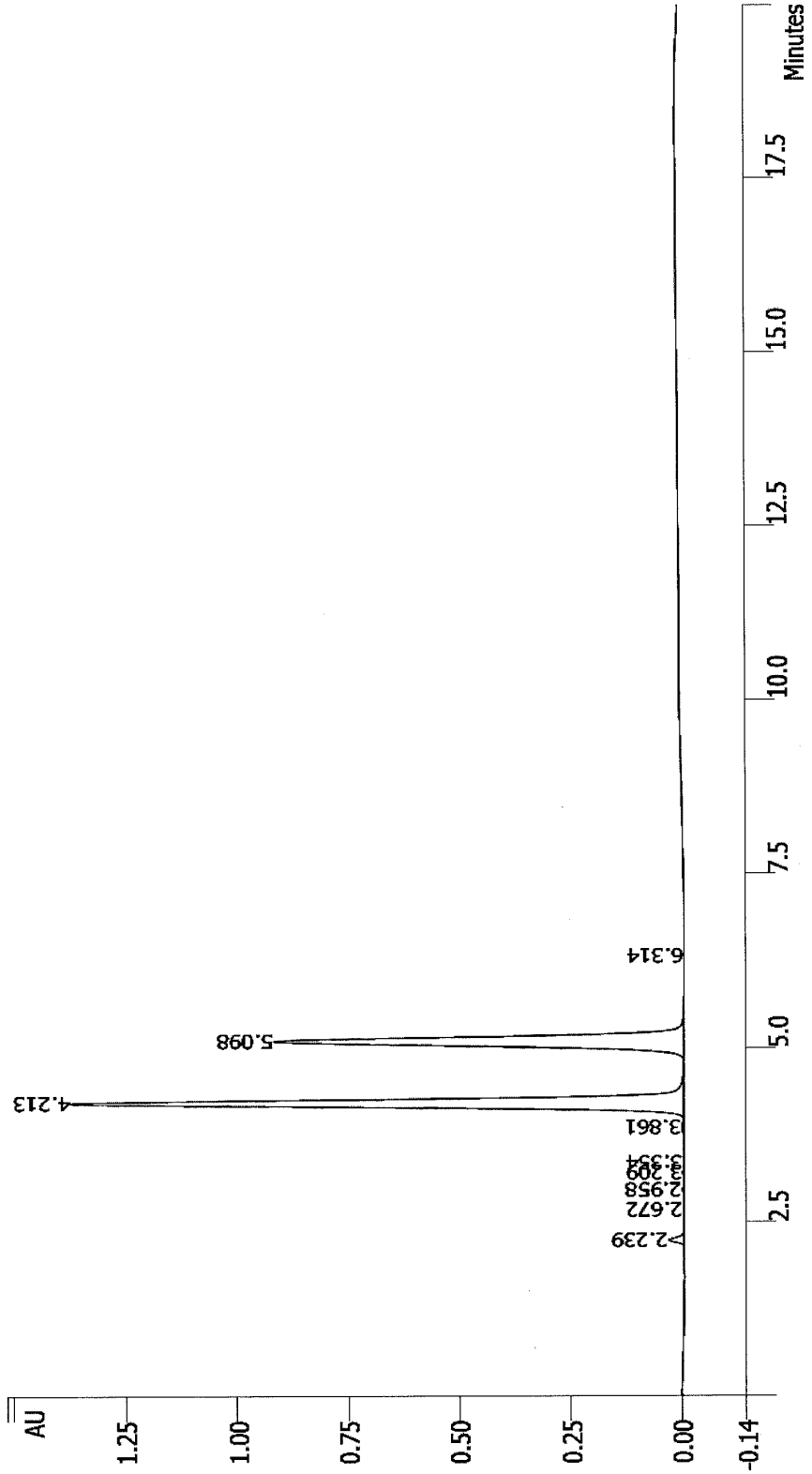


FIG. 14A

Shanghai Hongene Exhibit 1002

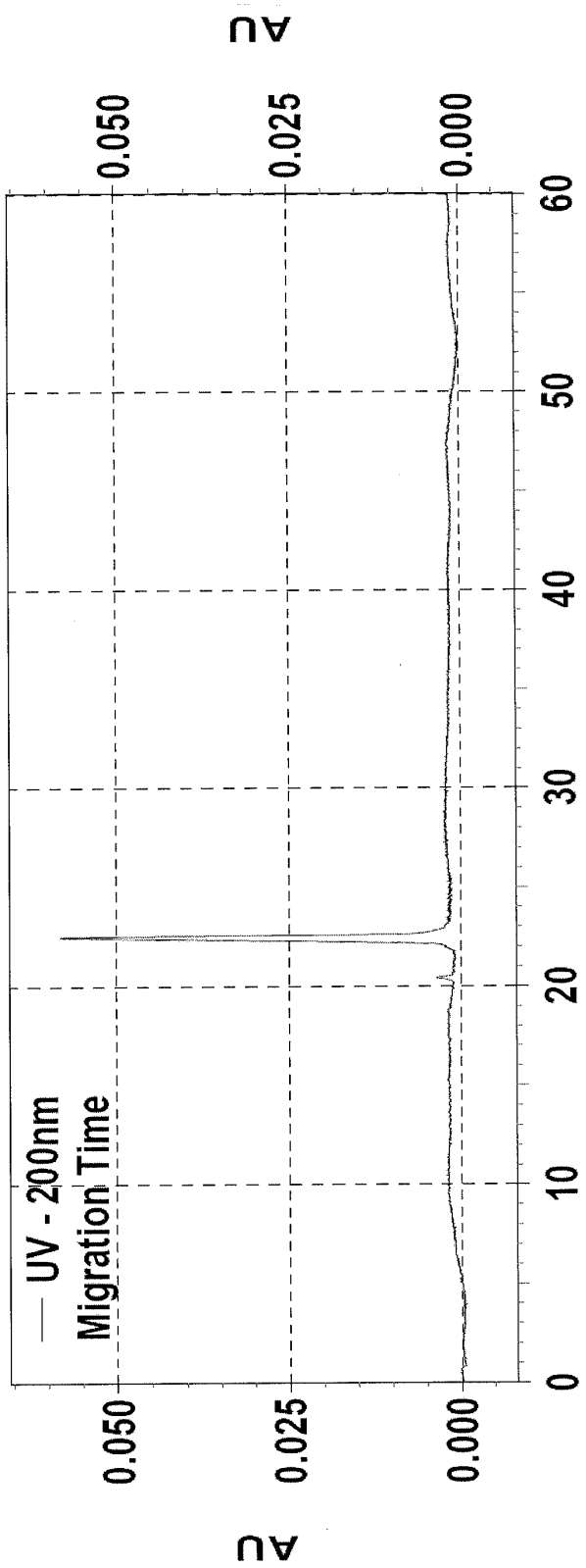
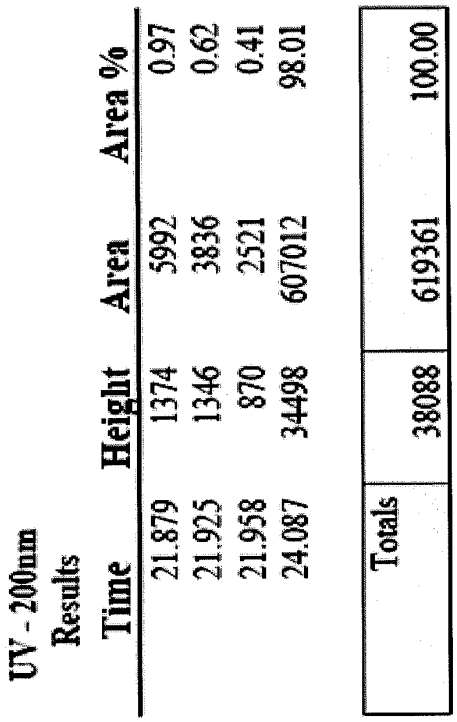


FIG. 15D

Shanghai Hongene Exhibit 1002



UV - 200nm
Results

Time	Height	Area	Area %
21.879	1374	5992	0.97
21.925	1346	3836	0.62
21.958	870	2521	0.41
24.087	34498	607012	98.01
Totals	38088	619361	100.00

FIG. 15E

Shanghai Hongene Exhibit 1002

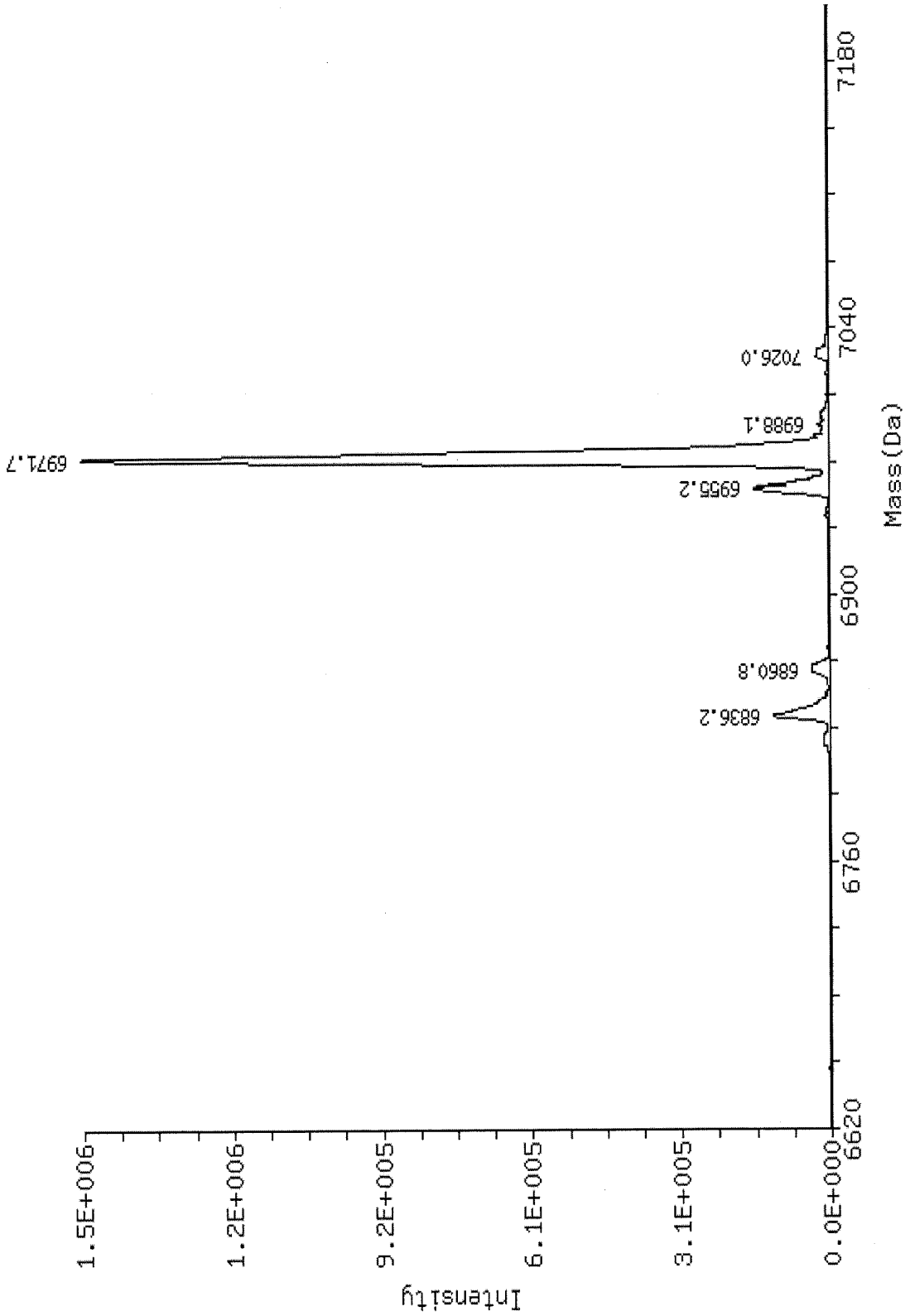


FIG. 15F

Shanghai Hongene Exhibit 1002

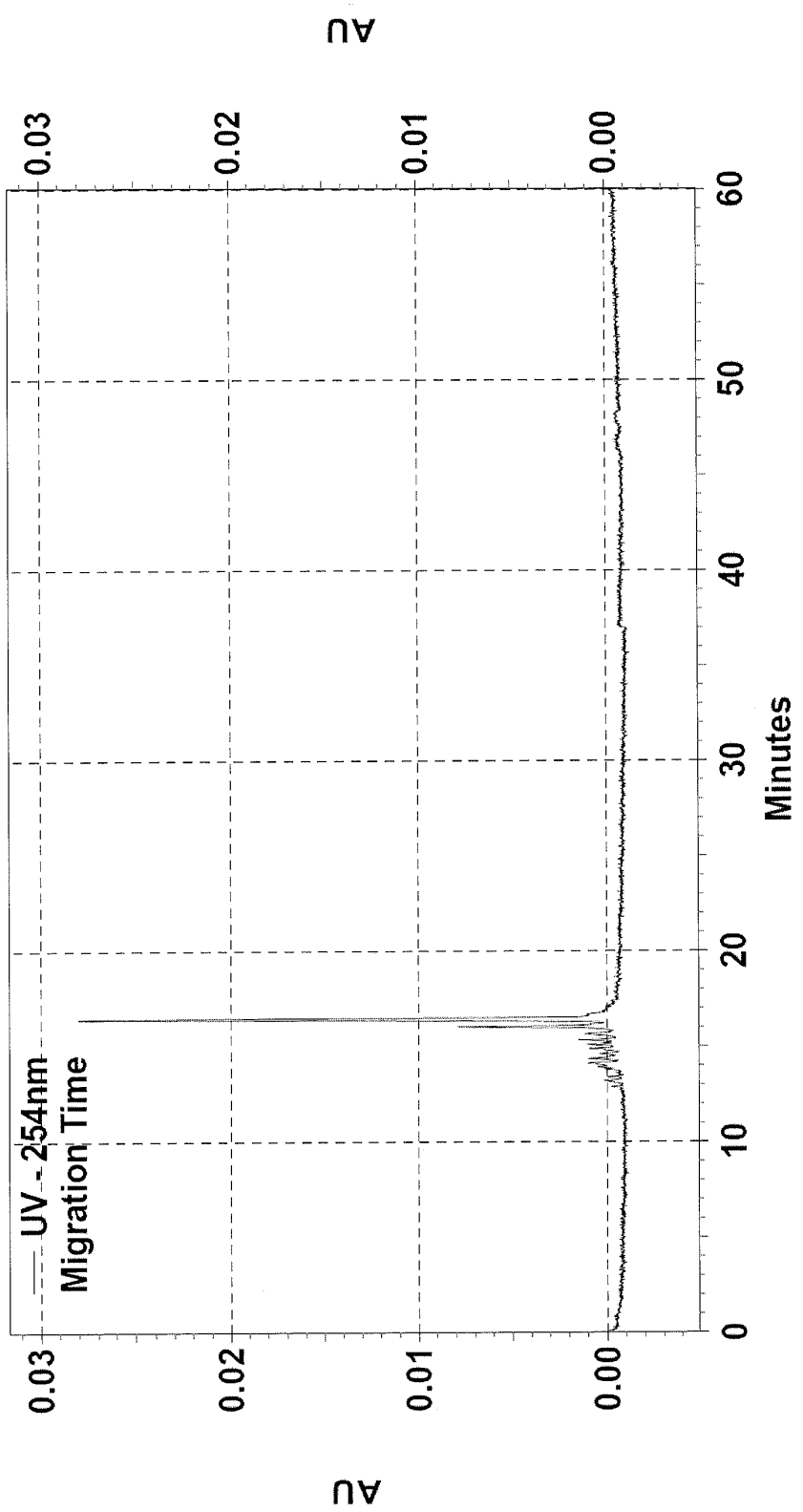


FIG. 16A

Shanghai Hongene Exhibit 1002

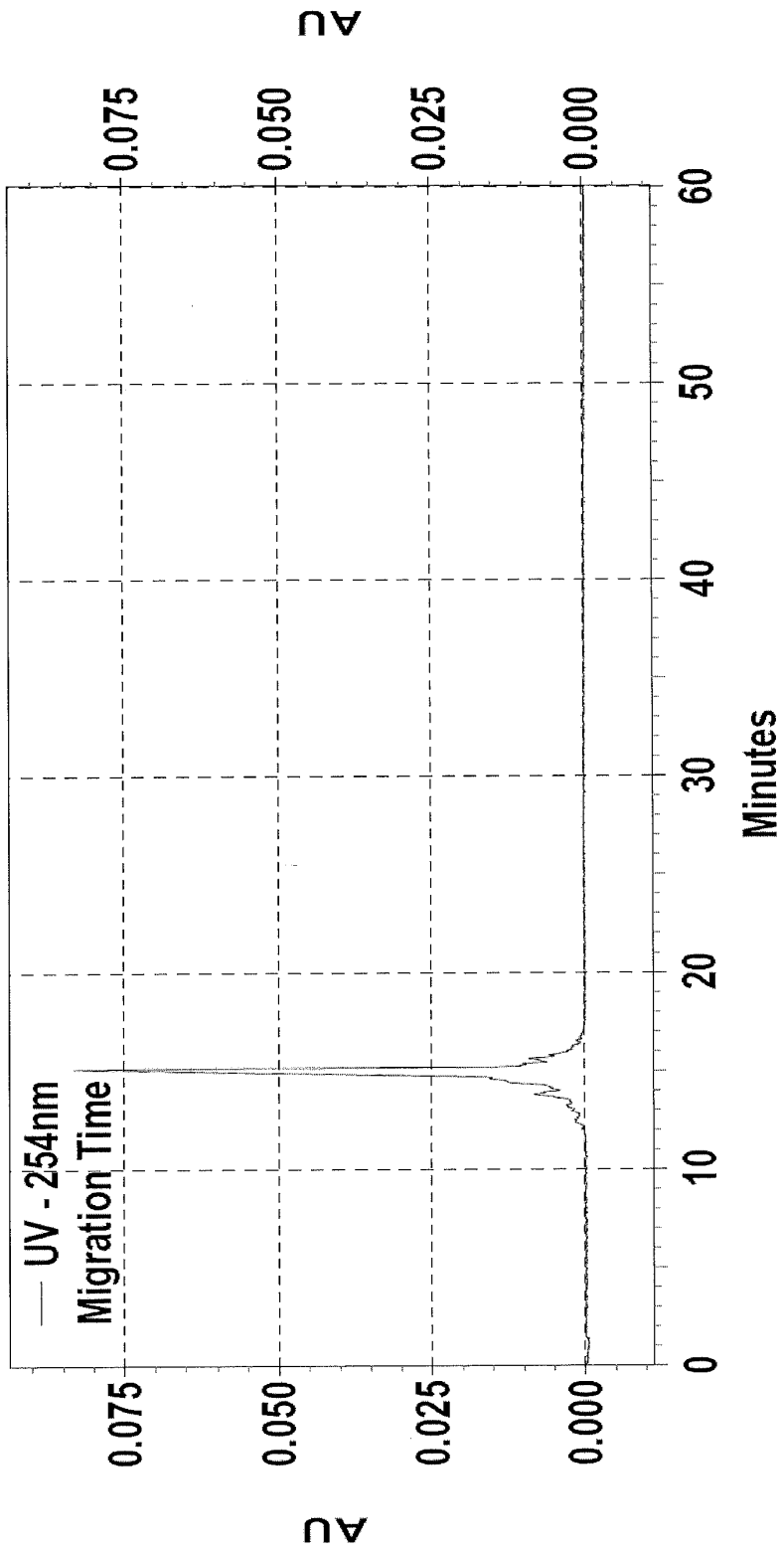


FIG. 16B

Shanghai Hongene Exhibit 1002

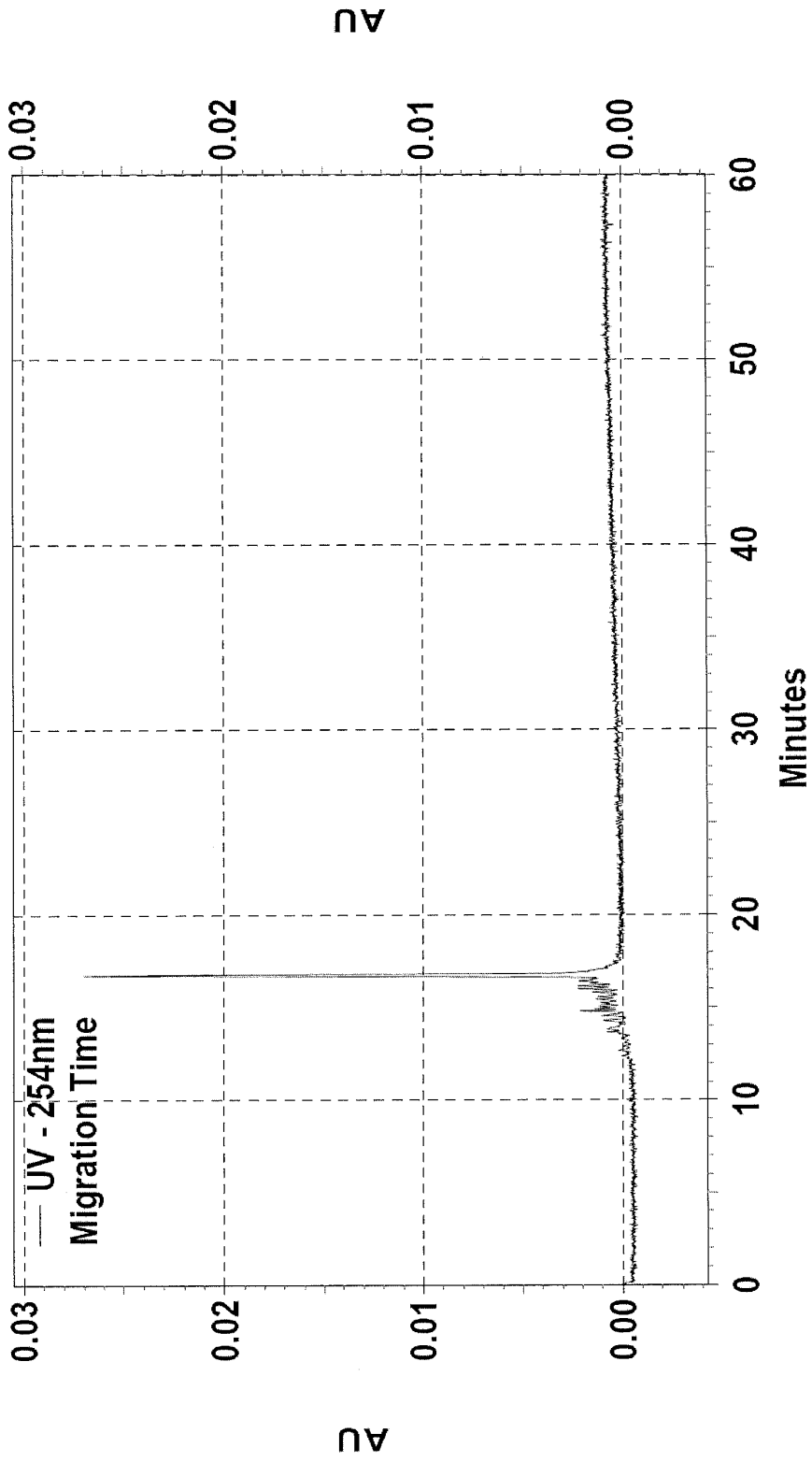


FIG. 17

Shanghai Hongene Exhibit 1002

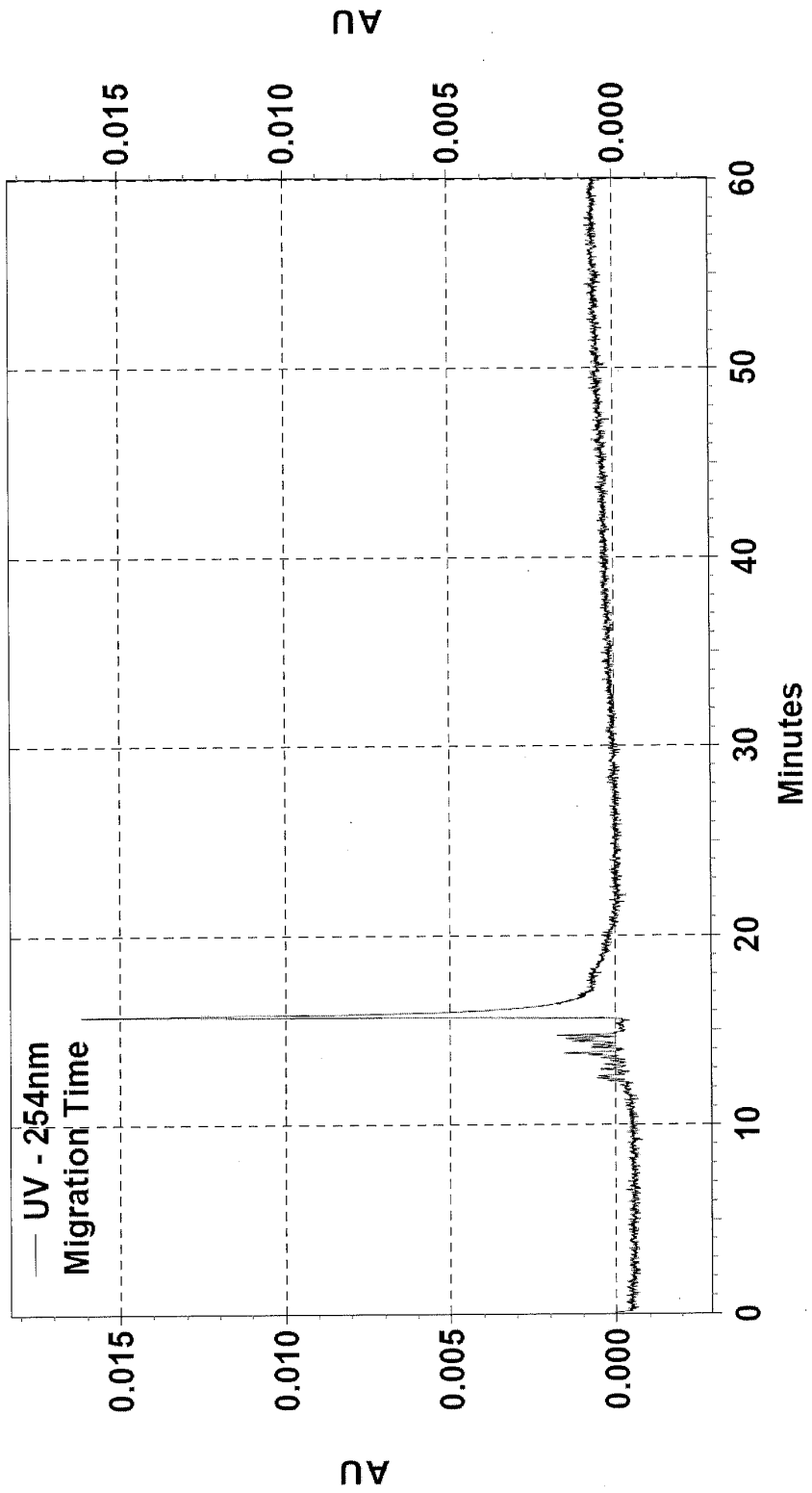


FIG. 18

Shanghai Hongene Exhibit 1002

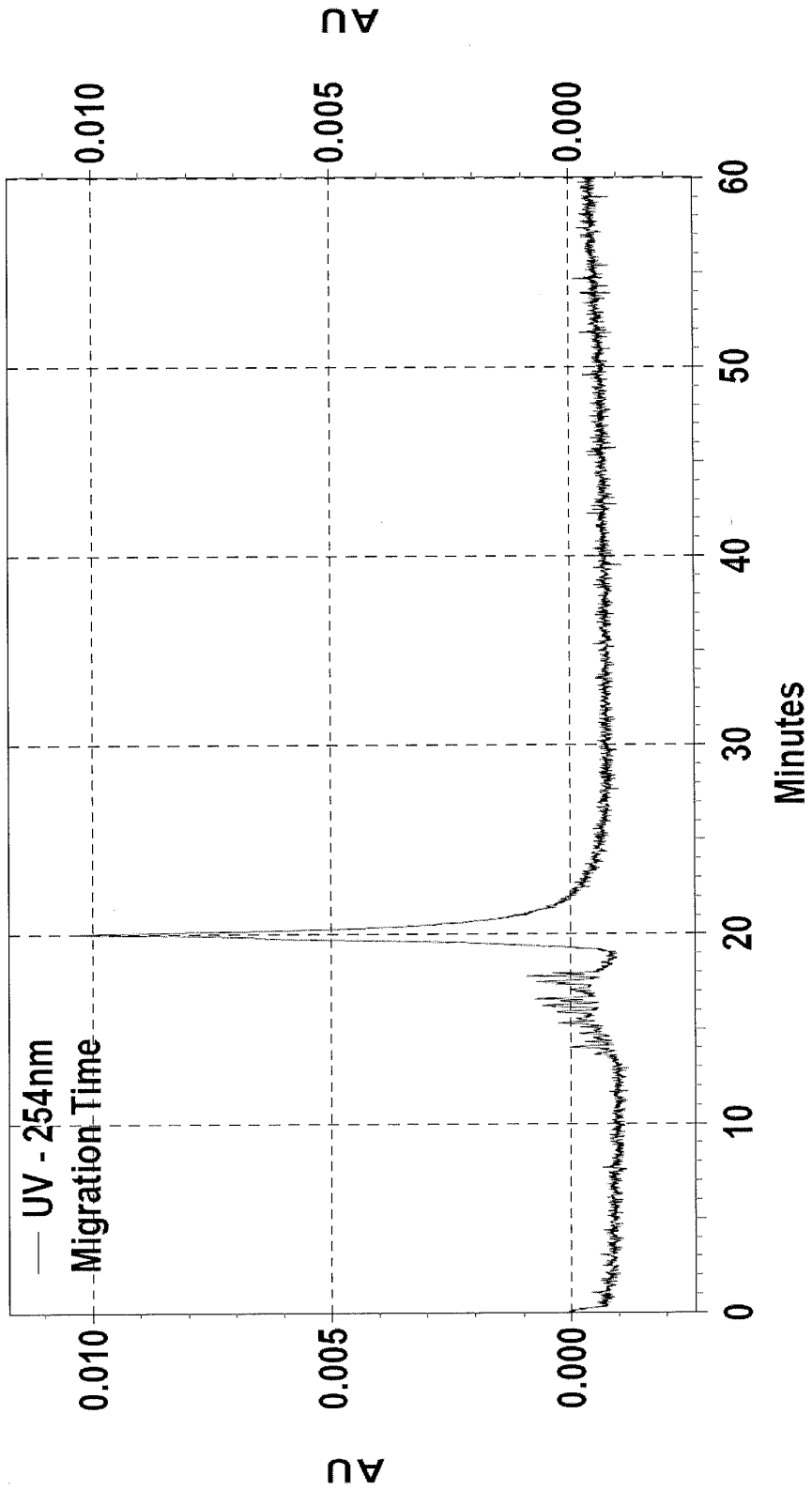


FIG. 19

Shanghai Hongene Exhibit 1002

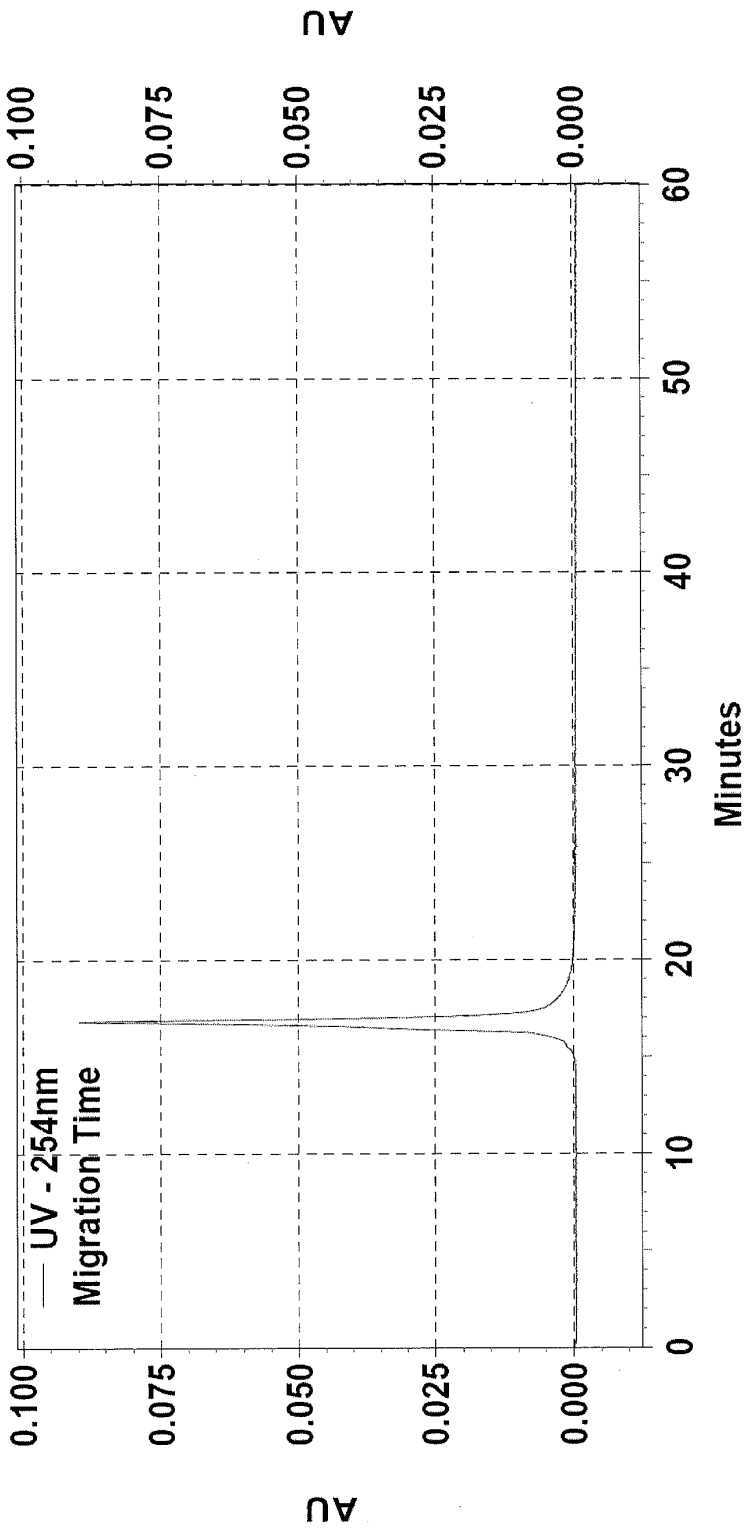


FIG. 20

Shanghai Hongene Exhibit 1002

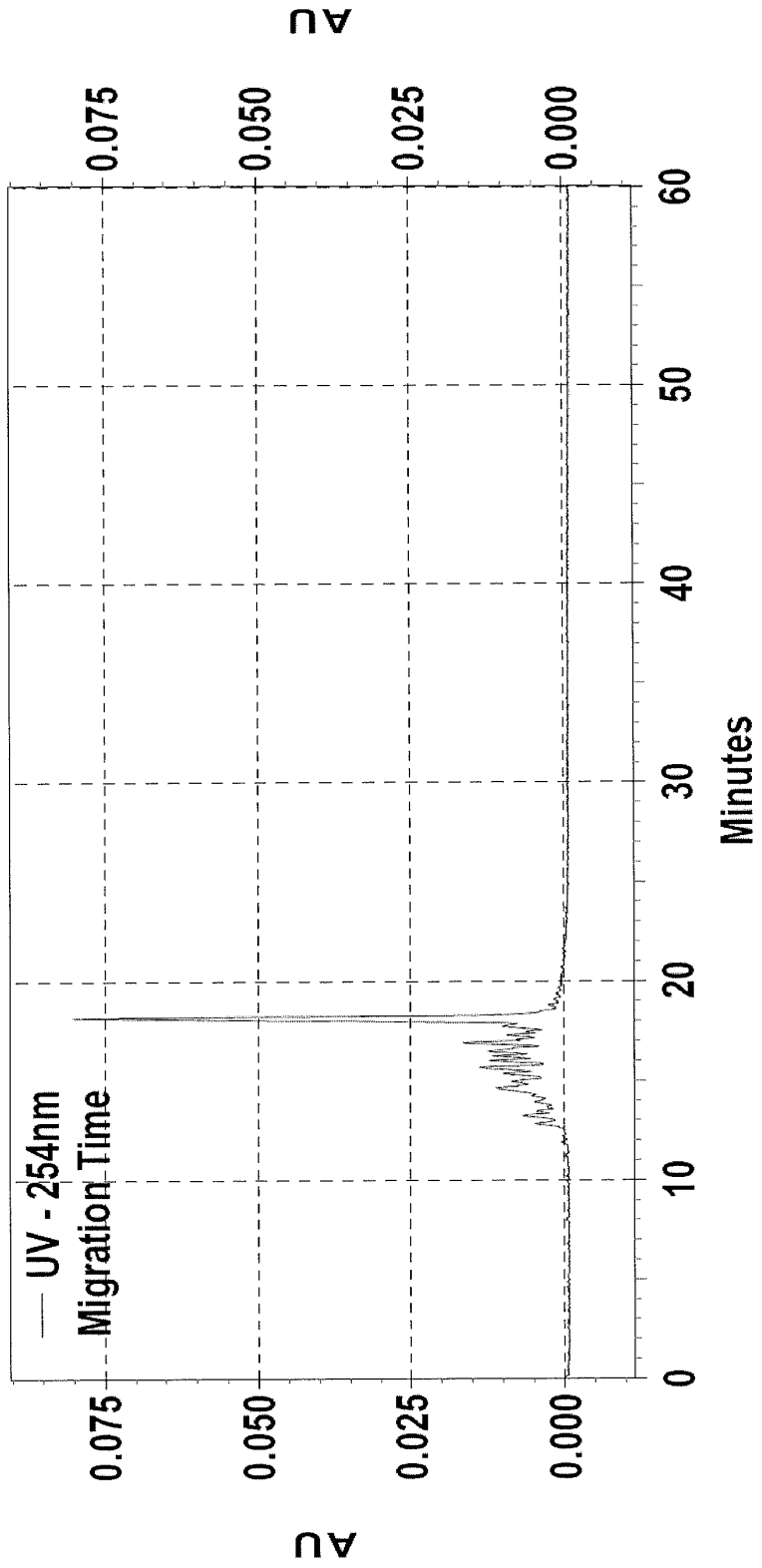


FIG. 21A

Shanghai Hongene Exhibit 1002

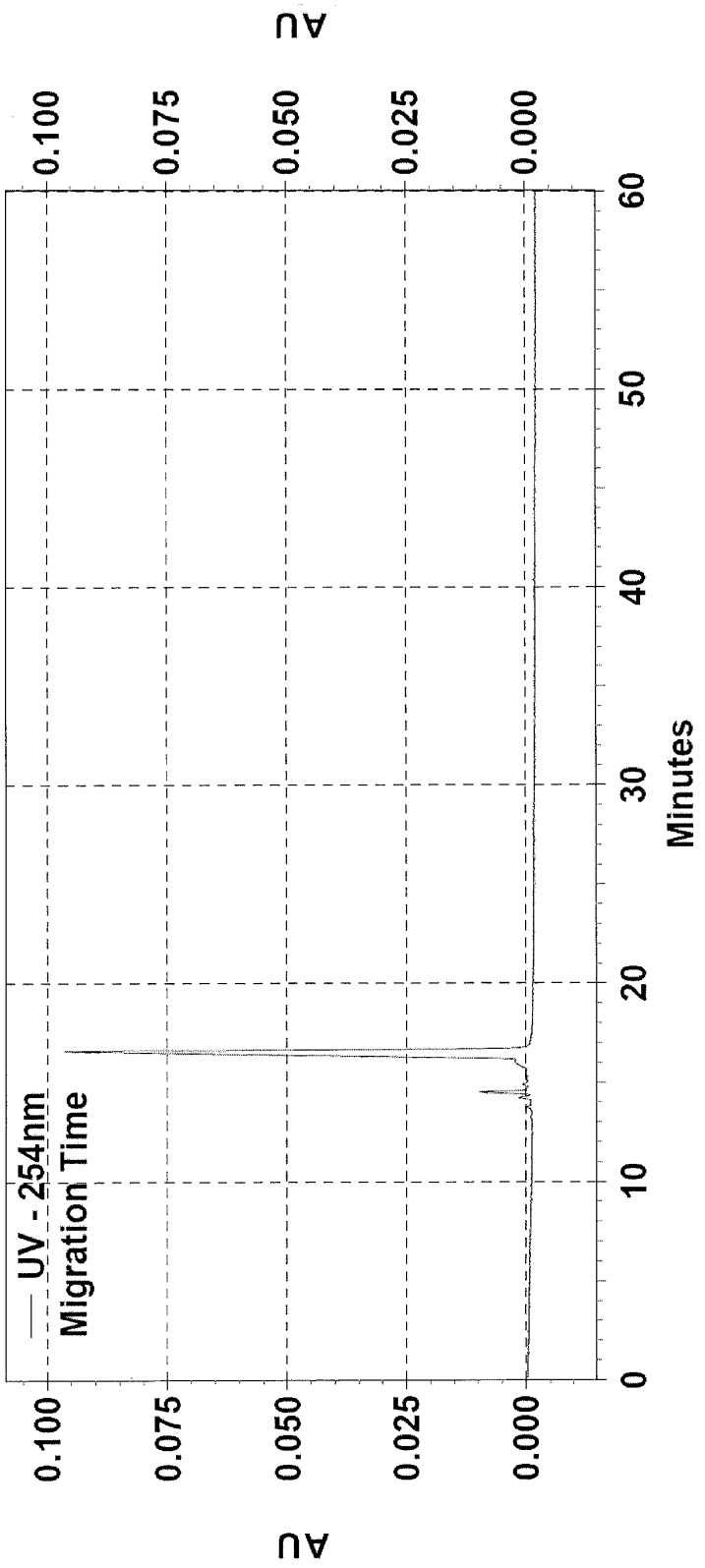


FIG. 21B

Shanghai Hongene Exhibit 1002

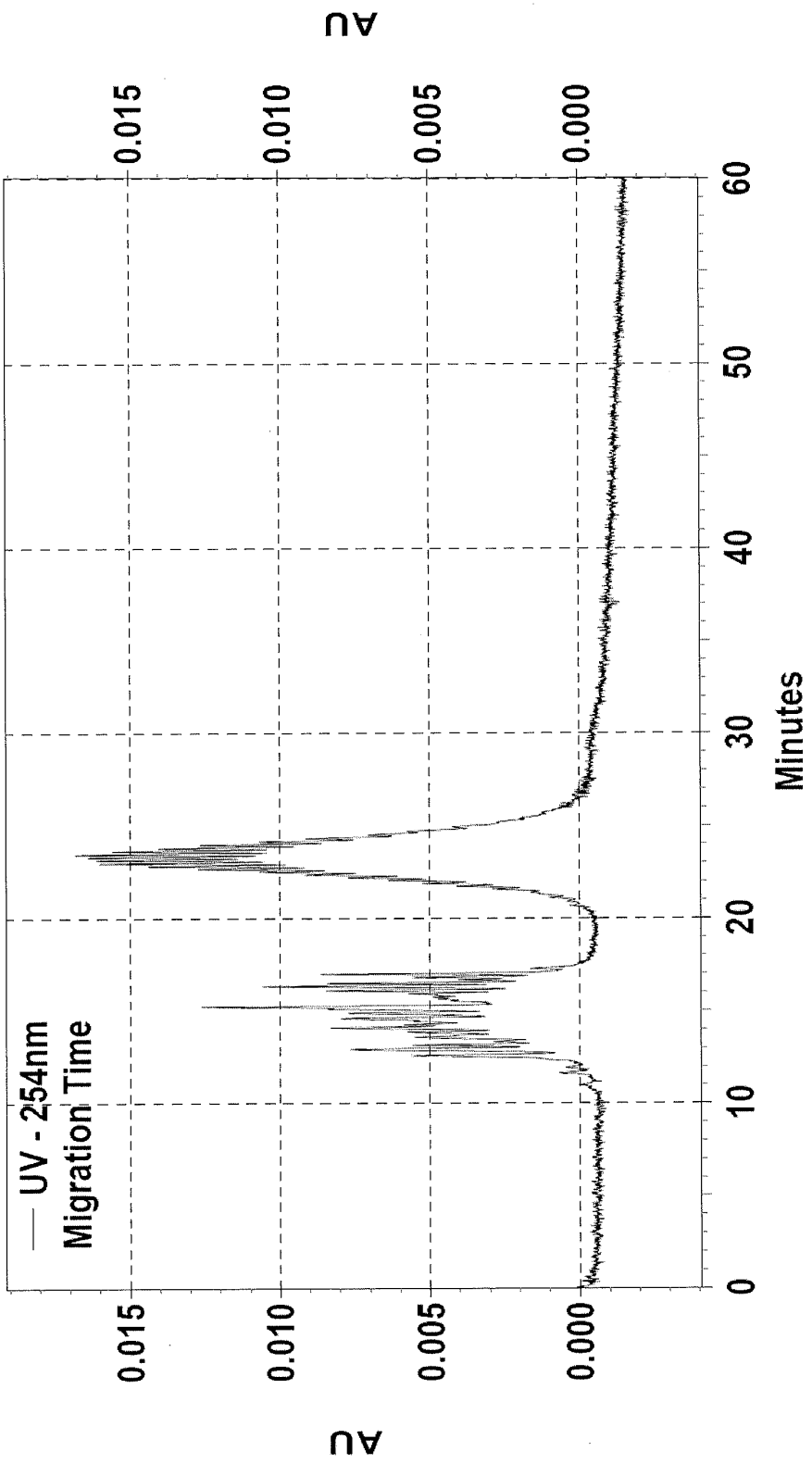


FIG. 22

Shanghai Hongene Exhibit 1002

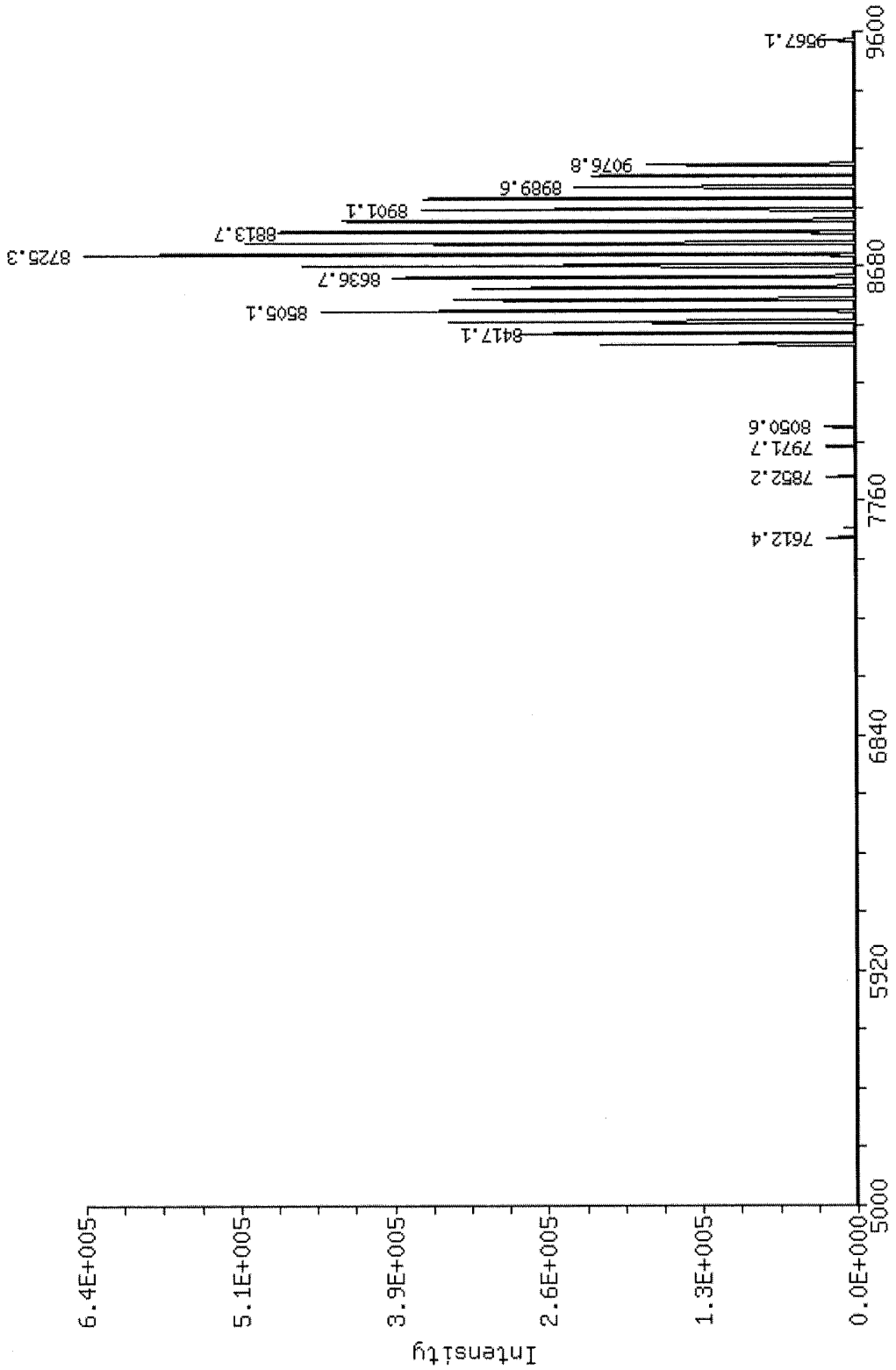


FIG. 23

Shanghai Hongene Exhibit 1002

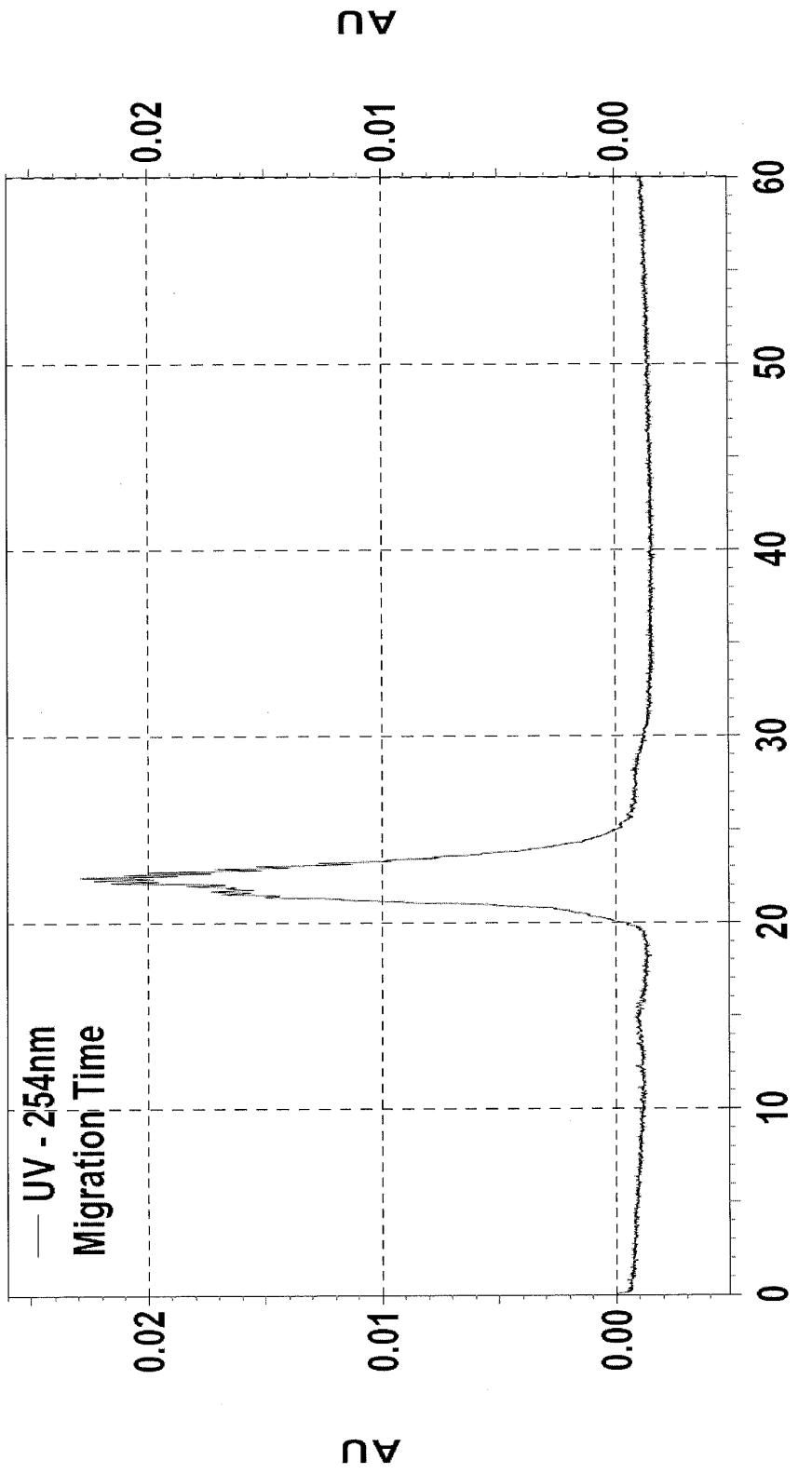


FIG. 24

Shanghai Hongene Exhibit 1002

Electronic Patent Application Fee Transmittal

Application Number:	12708827
Filing Date:	19-Feb-2010
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Filer:	Alice O. Carroll/Jane Morgan
Attorney Docket Number:	4441.1001-002

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	490	490

Shanghai Hongene Exhibit 1002

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**490**

Electronic Acknowledgement Receipt	
EFS ID:	8900217
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Jane Morgan
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	23-NOV-2010
Filing Date:	19-FEB-2010
Time Stamp:	15:26:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$490
RAM confirmation Number	2283
Deposit Account	080380
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Information:					
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Warnings:					
Information:					
3	Drawings-only black and white line drawings	44411001002Annotatedfigs.PDF	1240792 2272eac7fdc56fb38eb0f4d7cbd7b0282c2f6d32	no	6
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Information:					
4	Drawings-only black and white line drawings	44411001002replfigs.PDF	1334955 5318db439f0fcd12f36b542d5cbb86fd026a2d63	no	28
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Information:					
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Warnings:					
Information:					
		Total Files Size (in bytes):	2777350		

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

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

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

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 12708827 Document Date: 11/23/2010

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

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Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

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Form Revision Date: February 8, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not yet assigned

Confirmation No.: 5297

For: Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

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TRANSMITTAL OF ANNOTATED DRAWINGS

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

Sir:

Transmitted herewith are annotated drawings for Figs. 12A and 13A to show deletions that were made to the substitute drawings of those figures filed in the USPTO on July 12, 2010. Applicants inadvertently failed to submit the annotated drawings with the substitute drawings on July 12, 2010. The substitute drawings of Figs. 12A and 13A submitted on July 12, 2010 have been already accepted by the Office.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date: January 6, 2011

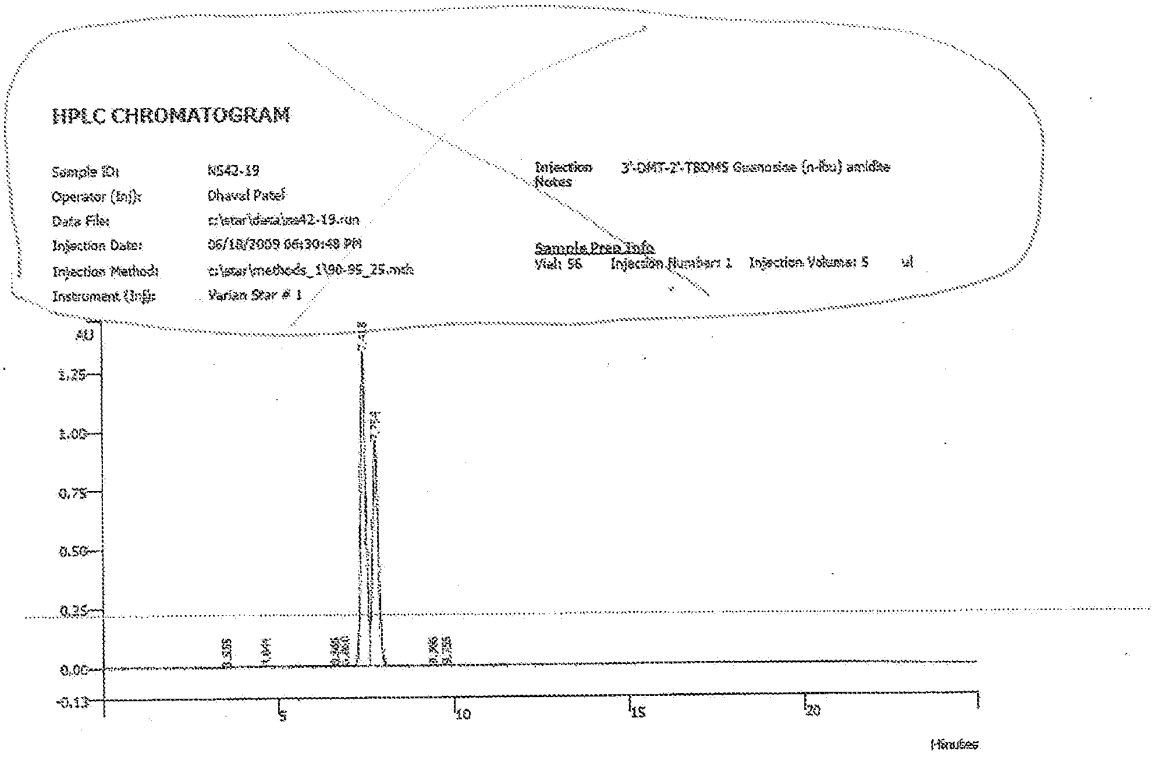


FIG. 12A

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		3.555	58277	0.02
2		4.644	162346	0.07
3		6.565	159521	0.07
4		6.860	314210	0.13
5	*3'-DMT-2'-TBDMS ibuG OP	7.418	136478726	56.37
6	*3'-DMT-2'-TBDMS ibuG OP	7.754	104749944	43.27
7		9.366	76431	0.03
8		9.755	99522	0.04
	Totals		242098968	100.00

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSolver 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 90% ACN in 0.1M TEAA (pH 7.5)
Eluent B- 95% ACN in 0.1M TEAA
Gradient: Increse B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

FIG. 12B

Annotated Sheet

HPLC Analysis
QCF-001
ChemGenes Corporation, 33 Industrial Way, Wilmington, MA 01887

Sample ID: HS143-19
Operator (Inj): Dhaval Patel
Data File: c:\star\data\hs143-19.run
Injection Date: 10/20/2009 01:29:03 PM
Injection Method: c:\star\methods_1355-100.meth
Instrument (Inj): Varian Star # 1

Injection Notes: 5'-DMT-2'-TBDMS Cytidine (n-acetyl) amidite

Sample Prep Info
Vial: 23 Injection Number: 1 Injection Volume: 5 ul

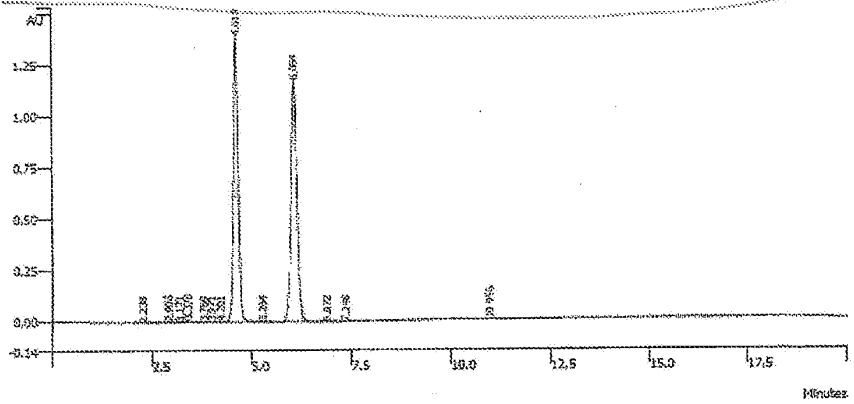


FIG. 13A

Peak No	Peak Name	Ret Time (min)	Peak Area (counts)	Result (Area %)
1		2.238	51545	0.02
2		2.906	257959	0.11
3		3.171	73365	0.03
4		3.378	761764	0.32
5		3.769	326242	0.14
6		3.971	178872	0.08
7		4.201	291630	0.12
8	5'-DMT-2'-TBDMS Cytidine (n-ac) CP	4.618	118156432	49.60
9		5.264	101551	0.04
10	3'-DMT-2'-TBDMS Cytidine (n-ac) CP	6.064	117767928	49.44
11		6.872	112221	0.05
12		7.346	67182	0.03
13		10.956	51805	0.02
	Totals		238199696	100.00

Method Notes
Column: ChromSep SS (4.6 x 250mm) with ChromSep Guard Column OmniSphier 5 C18.
Detection: UV @ 254 nm
Solvent System:
Eluent A- 95% ACN in 0.1M TEAA (pH 7.5)
Eluent B- ACN
Gradient: Increase B (0-50%) in 20 min
Dissolved in: ACN
Flow Rate: 1.5 ml/min

Sample Amount (mg): _____
Solvent Amount (ml): _____
Solvent: _____
Lot Number: _____
Exp. Date: _____

Analyst Initials: _____
PASS / FAIL

FIG. 13B

Electronic Acknowledgement Receipt

EFS ID:	9178792
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Jane Morgan
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	06-JAN-2011
Filing Date:	19-FEB-2010
Time Stamp:	15:39:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Warnings:					
Information:					

2	Drawings-only black and white line drawings	44411001002AnnotatedDRW.PDF	619712 3688131e6bd23e1333f1c54ed7aebd69b6931604	no	2

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New Applications Under 35 U.S.C. 111
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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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

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Sequence Listing was accepted.
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217-9197 (toll free).
Reviewer: Anne Corrigan
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Application No: 12708827 Version No: 2.1

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Finished: 2011-02-14 10:47:12.668
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Total Errors: 0
No. of SeqIDs Defined: 11
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Srivastava, Naveen P.

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<140> 12708827
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<151> 2009-09-08

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all c's are
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 12/708,827

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	39 minus 20 =	* 19	x 26 =	494	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	* 2	x 110 =	220			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due 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).			135			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1311		TOTAL	

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Shanghai Hongene Exhibit 1002

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/708,827	02/19/2010	1614	1376	4441.1001-002	39	5

CONFIRMATION NO. 5297

UPDATED FILING RECEIPT

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

OC000000046203512

Date Mailed: 02/25/2011

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, Wilmington, MA

Power of Attorney: The patent practitioners associated with Customer Number 021005

Domestic Priority data as claimed by applicant

This application is a CIP of PCT/US2009/005063 09/08/2009
which claims benefit of 61/191,065 09/06/2008

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: 03/03/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/708,827**

Projected Publication Date: 06/09/2011

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **

Title

PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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

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

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

NOT GRANTED

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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
12708827	

Applicant(s) Suresh Srivastava

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
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Total Indep	5		0		0	
Total Depend	34	↵	0	↵	0	↵
Total Claims	39		0		0	

	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
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Shanghai Hongene Exhibit 1002

1015845
AOC/kml/(dc)
09/17/2010

PATENT APPLICATION
Docket No.: 4441.1001-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not Assigned
Confirmation No.:	5297		
For:	Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Mail Stop 16, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

Date _____ Signature _____

Typed or printed name of person signing certificate

TRANSMITTAL OF SMALL ENTITY STATEMENT
AND REQUEST FOR REIMBURSEMENT

Mail Stop 16
Director of the USPTO
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

02/25/2011 MTEKLEMI 00000014 080380 12708827

01 FC:4011 82.00 DA
02 FC:2111 270.00 DA
03 FC:2311 110.00 DA
04 FC:2202 494.00 DA
05 FC:2201 220.00 DA
06 FC:2051 65.00 DA
07 FC:2081 135.00 DA
08 FC:2252 245.00 DA

Enclosed is a Small Entity Statement in the above-identified patent application. Applicant's Attorney respectfully requests a reimbursement of $1,787.00, one-half of the total fees paid on July 12, 2010 under EFS ID No. 7988480, including the discount applied for electronically filing the application to be deposited in Deposit Account No. 08-0380. This request is made within the three-month period allowed for such reimbursement.

Adjustment Date: 02/25/2011 MTEKLEMI
07/13/2010 INTEFSW 00003391 080380 12708827
01 FC:1011 330.00 CR
02 FC:1111 540.00 CR
03 FC:1311 220.00 CR
04 FC:1081 270.00 CR
05 FC:1202 988.00 CR
06 FC:1201 440.00 CR
07 FC:1051 130.00 CR
08 FC:1252 490.00 CR

Adjustment date: 02/25/2011 MTEKLEMI
11/24/2010 INTEFSW 00002283 080380 12708827
01 FC:1252 490.00 CR

02/25/2011 MTEKLEMI 00000015 080380 12708827
01 FC:1252 245.00 DA

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____
Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: September 17, 2010

Shanghai Hongene Exhibit 1002

Substitute for form 1449B/PTO **SUPPLMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **March 24, 2011** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not yet assigned	CONFIRMATION NO. 5297	GROUP 1614

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C7	International Preliminary Report on Patentability for International Application No.: PCT/US2009/005063 dated March 8, 2011.

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR**

EXAMINER	DATE CONSIDERED

1073517.1

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

ADVANCE E-MAIL

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

CARROLL, Alice, O.
Hamilton, Brook, Smith & Reynolds, P.C.
530 Virginia Road, P.O. Box 9133
Concord, MA 01742-9133
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 17 March 2011 (17.03.2011)	
Applicant's or agent's file reference 4441.1001001	IMPORTANT NOTICE

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/005063	08 September 2009 (08.09.2009)	06 September 2008 (06.09.2008)

Applicant: CHEMGENES CORPORATION et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

RECEIVED
HAMILTON, BROOK,
SMITH & REYNOLDS, P.C.

MAR 17 2011

ATTORNEY/IPC/IAC
Docketed ✓ Already Docketed
Not Required
Initials 1st Initials 2nd

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Simin Baharlou

e-mail: pt09.pct@wipo.int

Form PCT/IB/326 (January 2004)

C7

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 4441.1001001	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2009/005063	International filing date *(day/month/year)* 08 September 2009 (08.09.2009)	Priority date *(day/month/year)* 06 September 2008 (06.09.2008)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHEMGENES CORPORATION		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 08 March 2011 (08.03.2011)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/005063	08.09.2009	06.09.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07H21/02 C07H19/167 C07H19/067

Applicant
CHEMGENES CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Mezzato, Stefano Telephone No. +49 89 2399-7387

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Shanghai Hongene Exhibit 1002

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/005063

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☒ on paper

      ☒ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☒ subsequently to this Authority for the purposes of search

4. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 2, 3(completely); 1(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 2, 3(completely); 1(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1(partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1(partially)
Industrial applicability (IA)	Yes:	Claims	1(partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1 THOMAS WAGNER, WOLFGANG PFLEIDERER: "Nucleotides, Part LXV , Synthesis of 2'- Deoxyribonucleoside 5'- Phosphoramidites: New Building Blocks for the Inverse (5'-3')- Oligonucleotide Approach"HELVETICA CHIMICA ACTA, vol. 83, no. 8, 15 August 2000 (2000-08-15) , pages 2023-2035, XP002569710ISSN: 0018-019X

D2 MATYSIAK S ET AL: "Acetal oligonucleotide conjugates in antisense strategy"NUCLEOSIDES & NUCLEOTIDES, MARCEL DEKKER, INC, US, vol. 16, 1 January 1997 (1997-01-01), pages 855-861, XP002244702ISSN: 0732-8311

D3 SCHWARTZ M E ET AL: "A Universal Adapter for Chemical Synthesis of DNA or RNA on any Single Type of Solid Support"TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 36, no. 1, 2 January 1995 (1995-01-02) , pages 27-30, XP004028936ISSN: 0040-4039

D4 RAVIKUMAR, VASULINGA T. ET AL: "Stereoselective Synthesis of Alkyl-Phosphonates: A Facile Rearrangement of Cyanoethyl- Protected Nucleoside Phosphoramidites"ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 8, no. 4, 22 May 2004 (2004-05-22) , pages 603-608, XP002569711ISSN: 1083-6160

D5 SRIVASTAVA, SURESH C. ET AL: "RNA synthesis: phosphoramidites for RNA synthesis in the reverse direction. Highly efficient synthesis and application to convenient introduction of ligands, chromophores and modifications of synthetic RNA at the 3'-end"NUCLEIC ACIDS SYMPOSIUM SERIES, vol. 52, no. 1, 8 September 2008 (2008-09-08) , pages 103-104, XP002569712ISSN: 1746-8272

Re Item II.

1 The attention of the Applicant is drawn to the fact that some documents are mentioned in the search report which might become relevant for novelty (see D5, made available to the public on 08/09/2008, indicated in the search report as a P-document).

This document will be novelty destroying, if the priority of the present application, which could not be checked, is not to be valid.

Re Item IV.

1 This Authority considers that there are 5 inventions covered by the claims indicated as follows:

1. claim: 1 (all partially): a phosphoramidite of formula (1) of claim 1, wherein W is oxygen
2. claims: 1, 3 (all partially): a phosphoramidite of formula (1) of claim 1, wherein W is nitrogen and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite
3. claims: 1, 3 (all partially): a phosphoramidite of formula (1) of claim 1, wherein W is fluorine and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite
4. claims: 2 (completely); 3 (partially): a phosphoramidite of formula (1) of claim 1, wherein W is sulphur and a method of preparing an oligonucleotide by bond formations in the 5' to 3' direction comprising the step of reacting such phosphoramidite
5. claim: 3 (all partially): a method of preparing RNA oligomers by bond formations in the 5' to 3' direction comprising the step of reacting a phosphoramidite of formula (1) of claim 1, wherein W is oxygen

2 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows.

According to Rule13.2 PCTin an international patent application the requirement of unity of invention as referred to in Rule 13.1 PCT is fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features, the latter expression designating those features which define a contribution which each of the claimed inventions considered as a whole makes over the prior art.

3 The prior art has been identified as documents:

- D1 (page 2025; compounds 25-28; page 2028; figure 2; compounds 33-34): deoxyribonucleoside 5'- phosphoramidites as building blocks for the (5'-3')- synthesis of oligonucleotides. Oligonucleotides 3'- conjugates carrying cholesterol and vitamin E are also disclosed.

- D2 (page 856; figure 2; compound 4a), D3 (page 28; figure 1; compound 7), D4 (page 604; figure 3; compound 3): ribonucleoside 5'-phosphoramidites of formula (1) of claim 1, wherein W is oxygen.

4 Therefore, the subject - matter of:

1. independent claim 1, as regards a phosphoramidite of formula (1), wherein W is oxygen does not differs from this known compounds of D2-D4;
2. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is nitrogen, differs from this known compounds of D2-D4 and the method of D1 in that W is nitrogen;
3. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is fluorine, differs from this known compounds of D2-D4 and the method of D1 in that W is fluorine;
4. independent claims 2 and 3, as regards a phosphoramidite of formula (1), wherein W is sulphur, differs from this known compounds of D2-D4 and the method of D1 in that W is sulphur;
5. independent claim 3, as regards a phosphoramidite of formula (1), wherein W is oxygen, differs from this known method of D1 in that W is oxygen.

5 Starting from the known compounds of D2- D4 and the method of D1, the subject-matter of:

1. independent claim 1, as regards a phosphoramidite of formula (1), wherein W is oxygen does not solve any problem; this claim does not have any special technical feature;
2. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is nitrogen, solves the problem of providing a process of reverse (5' -3') synthesis of oligonucleotide oligomers bearing nitrogen at position 2'; the special technical feature is the nitrogen at position 2';
3. independent claims 1 and 3, as regards a phosphoramidite of formula (1), wherein W is fluorine, solves the problem of providing a process of reverse (5' -3') synthesis of oligonucleotide oligomers bearing fluorine at position 2'; the special technical feature is the fluorine at position 2';

4. independent claims 2 and 3, as regards a phosphoramidite of formula (1), wherein W is sulphur, solves the problem of providing a process of reverse (5' -3') synthesis of oligonucleotide oligomers bearing sulphur at position 2'; the special technical feature is the sulphur at position 2';

5. independent claim 3, as regards a phosphoramidite of formula (1), wherein W is oxygen, solves the problem of providing a process of reverse (5' -3') synthesis of RNA oligomers; the special technical feature is the use of ribonucleoside 5'- phosphoramidites as building blocks for the (5'-3')-synthesis of RNA.

6 Therefore, the special technical features are not the same. Moreover the special technical features have different effects and hence solve different problems, consequently they cannot be considered to be corresponding.

In conclusion, the groups of claims are not linked by common or corresponding special technical features and define 5 different inventions not linked by a single general inventive concept. The application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Invention 1
claim: 1(partially): a phosphoramidite of formula (1) of claim 1, wherein W is oxygen

Re Item V.

1 **Novelty**

1.1 Documents D2 (page 856; figure 2; compound 4a), D3 (page 28; figure 1; compound 7), D4 (page 604; figure 3; compound 3) all disclose:
ribonucleoside 5'-phosphoramidites of formula (1) of claim 1, wherein W is oxygen.

Consequently, the present application does not meet the criteria of Article 33 (1) PCT, because the subject-matter of claim 1, as regards the invention 1, is not new in the sense of Article 33(2) PCT.

2 **Inventive step**

2.1 The problem underlying the present invention is to provide ribonucleoside 5'-phosphoramidites of formula (1) of claim 1, wherein W is oxygen.

In view of the context of paragraph 1 above it is understood that subject-matter that is not novel is also regarded as not inventive, since D2-D4 provide the same solution to the same problem as the present application.

Therefore, claim 1 is not inventive (Art. 33(3) PCT).

Re Item VIII.

1 Claim 1 is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and drawings. The reasons therefor are the following: examples 1-4 on pages 29-36 of the description disclose only ribonuclosides having the following substitution pattern:

- 2'-O-TBDMS
- 3'-O-DMT
- 5'-cyanoethyl-N,N-diisopropyl-phosphoramidite

Therefore, the following definitions in claim 1 have too broad a scope and are not sufficiently supported:

- Y is sulphur

- R1, R2, R3, R4 are unspecified alkyl or aryl substituents of unspecified lenght.

2 The embodiment of the invention described in example 5 on pages 36-37 does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not yet assigned
Confirmation No.:	5297		

For: Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

_____ _____
Date Signature

_____
Typed or printed name of person signing certificate

TRANSMITTAL LETTER FOR SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

Sir:

This Supplemental Information Disclosure Statement is submitted:

☒ under 37 CFR 1.97(b), or
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application; or before the mailing date of a first office action on the merits; or before the mailing of a first office action after the filing of a Request for Continued Examination).

☐ under 37 CFR 1.97(c) together with either:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, or
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(After the 37 CFR 1.97(b) time period, but before any of a final action, notice of allowance, or an action that closes prosecution, whichever occurs first)

☐ under 37 CFR 1.97(d) together with:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, and
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(Filed after final action, notice of allowance, whichever occurs first, or if prosecution otherwise closes, but on or before payment of the issue fee)

☐ under 37 CFR 1.97(i):
Applicant requests that the IDS and cited reference(s) be placed in the application file.
(Filed after payment of issue fee)

Statement Under 37 CFR 1.97(e)

☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)
Applies to original applications (other than design) filed on or after May 29, 2000

☐ Each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the Information Disclosure Statement.

☒ Enclosed herewith is a Listing of References. Copies of the cited references are enclosed except as indicated below or in the attached Listing of References.

☐ Copies of the cited references submitted with an Information Disclosure Statement in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed, are not required under 37 CFR 1.98(d)(1) and (2) and are thus not provided.

☒ The listed references were cited in the enclosed Search Report in counterpart foreign application PCT/US2009/005063, which is listed in the attached Listing of References.

☐ The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

- ☐ the explanation provided on the attached sheet.
- ☐ the explanation provided in the Specification.
- ☐ submission of the enclosed International Search Report.
- ☐ submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.
- ☐ the enclosed English language abstract.

Method of payment:

☐ Authorization is NOT granted to charge any fees which may be due in this matter to our Deposit Account.

☐ Please charge Deposit Account 08-0380 in the amount of $[ ].

☐ A check for the fee noted above is enclosed, or the fee has been included in the check with the accompanying Reply.

☒ Please charge any deficiency in fees and credit any overpayment to Deposit Account 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: March 24, 2011

Electronic Acknowledgement Receipt

EFS ID:	9730247
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Kristin Lovett
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	24-MAR-2011
Filing Date:	19-FEB-2010
Time Stamp:	17:01:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed (SB/08)	44411001002Listingofreferences.PDF	80433 6ccf00723239802558c48411de20b5b5239d1773	no	1

Warnings:

Information:

This is not an USPTO supplied IDS fillable form					
2	Foreign Reference	44411001002RefC7.PDF	984453 4678b9161e3db8458c10082fee8742768ab46d65	no	13
Warnings:					
Information:					
3	Transmittal Letter	44411001002SIDStrans.PDF	236114 a817e93d0efe97350b656093d4d7fbff463887da	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	1301000		

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002

CONFIRMATION NO. 5297

21005
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

PUBLICATION NOTICE

OC000000048116125

Title:PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

Publication No.US-2011-0137010-A1
Publication Date:06/09/2011

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

Substitute for form 1449B/PTO **SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **December 5, 2011** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not yet assigned	CONFIRMATION NO. 5297	GROUP 1614

U.S. PATENT DOCUMENTS

Examiner's Initials	Ref. No.	DOCUMENT NUMBER Number-Kind Code (if known)	ISSUE DATE / PUBLICATION DATE MM-DD-YYYY	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	A2	US 2010/0324278 A1	12-23-2010	Srivastava, *et al.*
	A3	US 2011/0015382 A1	01-20-2011	Srivastava, *et al.*
	A4			
	A5			
	A6			
	A7			
	A8			
	A9			
	A10			
	A11			
	A12			
	A13			
	A14			
	A15			
	A16			
	A17			
	A18			
	A19			
	A20			

Copies of issued U.S. Patents and Published U.S. Applications are not required and are not being provided. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.

EXAMINER	DATE CONSIDERED

Shanghai Hongene Exhibit 1002

Substitute for form 1449B/PTO **SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **December 5, 2011** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not yet assigned	CONFIRMATION NO. 5297	GROUP 1614

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C8	Notification of Transmittal of the International Search Report and Written Opinion of the International Searching Authority from counterpart International Application Number PCT/US2011/025488, date of mailing: November 18, 2011.
	C9	
	C10	
	C11	
	C12	
	C13	
	C14	
	C15	
	C16	
	C17	
	C18	
	C19	
	C20	
	C21	
	C22	
	C23	
	C24	
	C25	

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.**

EXAMINER	DATE CONSIDERED

Shanghai Hongene Exhibit 1002

Electronic Acknowledgement Receipt

EFS ID:	11559696
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/ann giso
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	07-DEC-2011
Filing Date:	19-FEB-2010
Time Stamp:	15:22:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	44411001002_SIDSTransmittal.PDF	261176 9175d58ae628db13c701cdea46d0b888aec95c6f	no	3
Warnings:					
Information:					

2	Non Patent Literature	44411001002_RefC8.PDF	908578 433102bf1e755a5150ec3835ab0d9dd108c7116c	no	11
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	44411001002_ListingofRefs.PDF	188746 a5c775dea36432e5be31be1668ba4ad70d4959b9	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
			Total Files Size (in bytes):	1358500	

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1614
Filed:	February 19, 2010	Examiner:	Not yet assigned
Confirmation No.:	5297		
For:	Phosphoramidites for Synthetic RNA in the Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'-End Ligands, Chromophores and Modifications of Synthetic RNA		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

Date _____ Signature _____

Typed or printed name of person signing certificate

TRANSMITTAL LETTER FOR SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

Sir:

This Supplemental Information Disclosure Statement is submitted:

☒ under 37 CFR 1.97(b), or
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application; or before the mailing date of a first office action on the merits; or before the mailing of a first office action after the filing of a Request for Continued Examination).

☐ under 37 CFR 1.97(c) together with either:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, or
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(After the 37 CFR 1.97(b) time period, but before any of a final action, notice of allowance, or an action that closes prosecution, whichever occurs first)

☐ under 37 CFR 1.97(d) together with:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, and
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(Filed after final action, notice of allowance, whichever occurs first, or if prosecution otherwise closes, but on or before payment of the issue fee)

☐ under 37 CFR 1.97(i):
Applicant requests that the IDS and cited reference(s) be placed in the application file.
(Filed after payment of issue fee)

Statement Under 37 CFR 1.97(e)

☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)
Applies to original applications (other than design) filed on or after May 29, 2000

☐ Each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the Information Disclosure Statement.

☒ Enclosed herewith is a Listing of References. Copies of the cited references are enclosed except as indicated below or in the attached Listing of References.

☐ Copies of the cited references submitted with an Information Disclosure Statement in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed, are not required under 37 CFR 1.98(d)(1) and (2) and are thus not provided.

☒ The listed references were cited in the enclosed Search Report in counterpart foreign application PCT/US2011/025488, which is listed in the attached Listing of References.

☐ The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

- ☐ the explanation provided on the attached sheet.
- ☐ the explanation provided in the Specification.
- ☐ submission of the enclosed International Search Report.
- ☐ submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.
- ☐ the enclosed English language abstract.

Method of payment:

☐ Authorization is NOT granted to charge any fees which may be due in this matter to our Deposit Account.

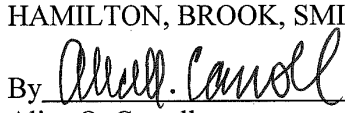
☐ Please charge Deposit Account 08-0380 in the amount of $[ ].

☐ A check for the fee noted above is enclosed, or the fee has been included in the check with the accompanying Reply.

☒ Please charge any deficiency in fees and credit any overpayment to Deposit Account 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: December 6, 2011

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

CARROLL ALICE O.

HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530
VIRGINIA RD, P.O. BOX 9133 CONCORD MA 01742-9133
USA

NOV 28 2011

AOC/RG

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 4441.1001003	Date of mailing *(day/month/year)* 18 NOVEMBER 2011 (18.11.2011) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2011/025488**	International filing date *(day/month/year)* **18 FEBRUARY 2011 (18.02.2011)**

Applicant

CHEMGENES CORPORATION et al

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19months.

For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the PCT Applicant's Guide, National Chapters.

Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer COMMISSIONER Telephone No. 82-42-481-8752

Form PCT/ISA/220 (July 2010)

C8

Shanghai Hongene Exhibit 1002

* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for three months from the date of mailing of the international search report.

http://www.kipo.go.kr/en/ => PCT Services => PCT Services

ID : PCT international application number
PW : **QCG8Z9LD**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: http://www.ipkcenter.com
Email: ipkc@ipkcenter.com
Phone: +1 703 388 1066
Fax: +1 703 388 1084

Notes to Form PCT/ISA/220 (July 2010)

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
4441.1001003		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2011/025488	**18 FEBRUARY 2011 (18.02.2011)**	19 FEBRUARY 2010 (19.02.2010)

Applicant

CHEMGENES CORPORATION et al

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figure is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

Shanghai Hongene Exhibit 1002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/025488

A. CLASSIFICATION OF SUBJECT MATTER

C07H 19/10(2006.01)i, C07H 19/20(2006.01)i, C07H 19/067(2006.01)i, C07H 19/167(2006.01)i, C07H 21/02(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07H 19/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: phosphoramidite, RNA, reverse.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RNA Synthesis: Phosphoramidites for RNA synthesis in the reverse direction. Highly efficient synthesis and application to convenient introduction of ligands, chromophores and modifications of synthetic RNA at the 3`-end., Nucleic Acids Symposium Series, Srivastava, S. C. et al., 08 September 2008, No.52, pages 103-104.	1-16,20,22,23,27,39
PX	US2010/0324278A1(SRIVASTAVA, S. C. et al.) 23 December 2010 See [0109]-[0152];claims 1,2.	1-16,27,39
PA	US2011/0015382A1(SRIVASTAVA, S. C. et al.) 20 January 2011 See [0036]-[0105]; claims 1-5.	1-39

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 NOVEMBER 2011 (16.11.2011)	**18 NOVEMBER 2011 (18.11.2011)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer KIM, Bumsu Telephone No. 82-42-481-8289

Form PCT/ISA/210 (second sheet) (July 2009)

Shanghai Hongene Exhibit 1002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2011/025488

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US2010/0324278A1	23.12.2010	CA 2735251 A1	11.03.2010
		EP 2326656 A2	01.06.2011
		KR 10-2011-0099680 A	08.09.2011
		US 2011-0137010 A1	09.06.2011
		WO 2010-027512 A2	11.03.2010
		WO 2010-027512 A3	10.06.2010
		WO 2010-027512 A4	02.09.2010
		WO 2010-027512 A9	11.03.2010
		WO 2010-103468 A2	25.08.2011
US2011/0015382A1	20.01.2011	WO 2010-062404 A3	14.10.2010
		WO 2010-062404 A3	03.06.2010

Form PCT/ISA/210 (patent family annex) (July 2009)

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
CARROLL ALICE O.

HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530
VIRGINIA RD, P.O. BOX 9133 CONCORD MA 01742-9133
USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**18 NOVEMBER 2011 (18.11.2011)**
Applicant's or agent's file reference 4441.1001003	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2011/025488	**18 FEBRUARY 2011 (18.02.2011)**	19 FEBRUARY 2010 (19.02.2010)

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

C07H 19/10(2006.01)i, C07H 19/20(2006.01)i, C07H 19/067(2006.01)i, C07H 19/167(2006.01)i, C07H 21/02(2006.01)i

Applicant

CHEMGENES CORPORATION et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	16 NOVEMBER 2011 (16.11.2011)	KIM, Bumsu Telephone No.82-42-481-8289

Form PCT/ISA/237 (cover sheet) (July 2011)

Shanghai Hongene Exhibit 1002

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/025488

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/025488

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	17-19,21,24-26,28-38	YES
	Claims	1-16,20,22-23,27,39	NO
Inventive step (IS)	Claims	17-19,21,24-26,28-38	YES
	Claims	1-16,20,22-23,27,39	NO
Industrial applicability (IA)	Claims	1-39	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following document

D1: Nucleic Acids Symposium Series, Srivastava, S. C. et al., 08 September 2008, No.52, pages 103-104.

1. Novelty and inventive step

1-1. D1, which is considered to represent the most relevant state of the art, discloses a compound of formula (Ia) or (Ib)(e.g. J=cyanoethylphosphoramidite, Bn=substituted nuclobase, R^4=TBDMS, R^6=O-DMT; see 103page, right column and figure 1 in D1). As all of the features of claims 1-16 are disclosed in D1, claims 1-16 are anticipated by D1. Therefore, claims 1-16 lack novelty under PCT Article 33(2).

1-2. The subject matters of claims 17-19 and 21 differ from these prior art documents in that the pendant groups of compounds are specified(especially, ester pendant groups). And it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, claims 17-19 and 21 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

1-3. D1, which is considered to represent the most relevant state of the art, discloses compounds(e.g. Q=Icaa-CPG-NHC(=O)-CH_2-CH_2, Bn=substituted nuclobase, R^4=TBDMS, Z=DMT; see figure 1 in D1). As all of the features of claims 20, 22, and 23 are disclosed in D1, claims 20, 22, and 23 are anticipated by D1. Therefore, claims 20, 22, and 23 lack novelty under PCT Article 33(2).

1-4. The subject matters of claims 24-26 differ from these prior art documents in that the structure of compounds is specified. And it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, claims 24-26 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

(Continued on supplemental box)

Shanghai Hongene Exhibit 1002

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/025488

Box No. VI Certain documents cited

1. Certain published documents (Rule 43bis.1 and 70.10)

	Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
P,X	US2010/0324278	23/12/2010	08/09/2009	06/09/2008

US2010/0324278A1 does not constitute prior art within the meaning of PCT Rule 64.3, but appears to disclose all features of claims 1-16,27 and 39. In case the priority of the present application is not valid, this document is relevant for assessing novelty and inventive step.

2. Non-written disclosures (Rule 43bis.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/025488

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

It is not clear what the meaning of R14 in the chemical formula of claim 17 is (PCT Article 6).

Claim 37 relates to a method, but claim 38 dependent on claim 37 relates to a compound. As claim 38 does not clearly define the matter for which protection is sought, this claim does not meet the requirement of PCT Article 6.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of :

(Box No.V)

1-5. D1, which is considered to represent the most relevant state of the art, discloses a synthetic RNA molecule with a purity exceeding 97% and synthesized from a 5' phosphoramidite nucleoside. As all of the features of claim 27 is disclosed in D1, claim 27 is anticipated by D1. Therefore, claim 27 lacks novelty under PCT Article 33(2).

1-6. The subject matters of claims 28-38 differ from these prior art documents in that all steps to synthesize RNA in the reverse direction are specified. And it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, claims 28-38 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

1-7. D1, which is considered to represent the most relevant state of the art, discloses a synthetic RNA molecule with purity exceeding 97%. As all of the features of claim 39 is disclosed in D1(because claim 39 is a product-by-process claim), claim 39 is anticipated by D1. Therefore, claim 39 lacks novelty under PCT Article 33(2).

2. Industrial applicability

Claims 1-39 meet the criteria of PCT Article 33(4), because the claimed invention can be used in its related industry.

Shanghai Hongene Exhibit 1002

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002	5297

21005 7590 06/13/2012

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
LEWIS, PATRICK T	
ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
06/13/2012	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.	Applicant(s)	
	12/708,827	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	PATRICK LEWIS	1623	

-- 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 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 _____.

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) *1-39* 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) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-39* are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *19 February 2010* 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).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12072011; 03242011; 07122010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-23, drawn to a compound of Formula Ia or Ib, classified in class 536, subclass 22.1.

II. Claims 1-3 and 5-11, drawn to a compound of Formula Ic or Id, classified in class 536, subclass 22.1.

III. Claims 24-27 and 38-39, drawn to an oligonucleotide, classified in class 536, subclass 23.1.

IV. Claims 28-37, drawn to a method of preparing an oligonucleotide, classified in class 536, subclass 25.3.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, II and III are directed to related products. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, do not overlap in scope and are not obvious variants. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

3. Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product of Invention I could be used in a method for inhibiting HCV as demonstrated by Carroll et al. The Journal of Biological Chemistry (2003), Vol. 278, No. 14, pages 11979-11984 (Carroll).

4. Inventions II and IV are directed to an unrelated product and process. Product and process inventions are unrelated if it can be shown that the product cannot be used in, or made by, the process. See MPEP § 802.01 and § 806.06. In the instant case, the product of Invention II is not used in or made by the process of Invention IV.

5. Inventions IV and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product of Invention III could be made by the process described by Matteucci et al. JACS (1981), Vol. 103, pages 3185-3191 (Matteucci).

6. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above

and there would be a serious search and/or examination burden if restriction were not required because at least the following reason(s) apply:

The searches are not coextensive.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

7. Claim(s) 1-23 is/are generic to the following disclosed patentably distinct species: a single, specific compound of Formula Ia, Ib, Ic, or Id wherein each variable is explicitly set forth such as the compounds depicted in Scheme 1 of the specification. The species are independent or distinct because they have a materially different design, do not overlap in scope and are not obvious variants. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

The searches are not coextensive.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election

shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached on Monday - Thursday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. 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 T. Lewis/
Primary Examiner, Art Unit 1623

/PL/

Notice of References Cited	Application/Control No. 12/708,827	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	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	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Matteucci et al. JACS (1981), Vol. 103, pages 3185-3191.
	V	Carroll et al. The Journal of Biological Chemistry (2003), Vol. 278, No. 14, pages 11979-11984.
	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.

Substitute for form 1449B/PTO **SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **December 5, 2011** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not yet assigned	CONFIRMATION NO. 5297	GROUP 1614

U.S. PATENT DOCUMENTS

Examiner's Initials	Ref. No.	DOCUMENT NUMBER Number-Kind Code (if known)	ISSUE DATE / PUBLICATION DATE MM-DD-YYYY	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	A2	US 2010/0324278 A1	12-23-2010	Srivastava, *et al.*
	A3	US 2011/0015382 A1	01-20-2011	Srivastava, *et al.*
	A4			
	A5			
	A6			
	A7			
	A8			
	A9			
	A10			
	A11			
	A12			
	A13			
	A14			
	A15			
	A16			
	A17			
	A18			
	A19			
	A20			

Copies of issued U.S. Patents and Published U.S. Applications are not required and are not being provided. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.

EXAMINER /Patrick Lewis/ (05/31/2012)	DATE CONSIDERED

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (05/31/2012)

Shanghai Hongene Exhibit 1002

Substitute for form 1449B/PTO **SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **December 5, 2011** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not yet assigned	CONFIRMATION NO. 5297	GROUP 1614

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C8	Notification of Transmittal of the International Search Report and Written Opinion of the International Searching Authority from counterpart International Application Number PCT/US2011/025488, date of mailing: November 18, 2011.
	C9	
	C10	
	C11	
	C12	
	C13	
	C14	
	C15	
	C16	
	C17	
	C18	
	C19	
	C20	
	C21	
	C22	
	C23	
	C24	
	C25	

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.**

EXAMINER /Patrick Lewis/ (05/31/2012)	DATE CONSIDERED

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (05/31/2012)

Shanghai Hongene Exhibit 1002

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor, GOOGLE (oligonucleotide synthesis)	6/12/2012	/PL/

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

UNITED STATES PATENT AND TRADEMARK OFFICE

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P.O. Box 1450
Alexandria, Virginia 22313-1450
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BIB DATA SHEET

CONFIRMATION NO. 5297

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/708,827	02/19/2010 RULE	514	1623	4441.1001-002

APPLICANTS

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

**** CONTINUING DATA **************************

This application is a CIP of PCT/US2009/005063 09/08/2009
which claims benefit of 61/191,065 09/06/2008

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
03/03/2010

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
❑ Yes ☑ No	❑ Yes ☑ No	/PATRICK T LEWIS/ Examiner's Signature	❑ Initials	MA	38	39	5

ADDRESS

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133
UNITED STATES

TITLE

PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

FILING FEE RECEIVED		
1376	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

BIB (Rev. 05/07).

Shanghai Hongene Exhibit 1002

Substitute for form 1449B/PTO **SUPPLMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **March 24, 2011** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not yet assigned	CONFIRMATION NO. 5297	GROUP 1614

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
/P.L./	C7	International Preliminary Report on Patentability for International Application No.: PCT/US2009/005063 dated March 8, 2011.

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR**

EXAMINER	DATE CONSIDERED
/Patrick Lewis/ (05/31/2012)	

1073517.1

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

✓	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	06/12/2012								
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	3	÷								
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	36	÷								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	06/12/2012								
	37	÷								
	38	÷								
	39	÷								

Substitute for form 1449B/PTO **INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **July 12, 2010** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not assigned	CONFIRMATION NO. 5297	GROUP 1614

U.S. PATENT DOCUMENTS

Examiner's Initials	Ref. No.	DOCUMENT NUMBER Number-Kind Code (if known)	ISSUE DATE / PUBLICATION DATE MM-DD-YYYY	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	A1	6,043,353	03-28-2000	Pon *et al.*
	A2			
	A3			

FOREIGN PATENT DOCUMENTS

Examiner's Initials	Ref. No.	DOCUMENT NUMBER Country Code-Number-Kind Code (if known)	DATE MM-DD-YYYY	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	B1	WO 2010/027512 A2	03-11-2010	Chemgenes Corporation
	B2			
	B3			

We are not listing separately any prior U.S. Patent Office communications regarding the cited application(s) because the Examiner has access to any such actions through PAIR.

EXAMINER /Patrick Lewis/ (05/31/2012)	DATE CONSIDERED

993039_1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (05/31/2012)

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Substitute for form 1449B/PTO **INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** **July 12, 2010** (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Not assigned	CONFIRMATION NO. 5297	GROUP 1614

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C1	Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, PCT/US2009/005063, mailed 04-20-10
	C2	Wagner, T. and W. Pfleiderer, "Nucleotides, Part LXV, Synthesis of 2'-Deoxyribonucleoside 5'-Phosphoramidites: New Building Blocks for the Inverse (5'-3')-Oligonucleotide Approach," *Helvetica Chimica ACTA,* 83(8):2023-2035 (Aug. 2000)
	C3	Matysiak, S., *et al.*, "Acetal Oligonucleotide Conjugates in Antisense Strategy," *Nucleotides & Nucleotides*, 16(5&6):855-861 (Jan. 1997)
	C4	Schwartz, M.E., *et al.*, "A Universal Adapter for Chemical Synthesis of DNA or RNA on Any Single Type of Solid Support," *Tetrahedron Letters*, 36(1):27-30 (Jan. 1995)
	C5	Ravikumar, V.T. and R.K. Kumar, "Stereoselective Synthesis of Alkylphosphonates: A Facile Rearrangement of Cyanoethyl-Protected Nucleoside Phosphoramidites," *Organic Process Research & Development*, 8(4):603-608 (May 2004)
	C6	Srivastava, S.C., *et al.*, "RNA Synthesis: Phosphoramidites for RNA Synthesis in the Reverse Direction. Highly Efficient Synthesis and Application to Convenient Introduction of Ligands, Chromophores and Modifications of Synthetic RNA at the 3'-End," *Nucleic Acids Symposium Series*, 52(1):103-104 (Sep. 2008)
	C7	
	C8	
	C9	
	C10	
	C11	
	C12	
	C13	
	C14	
	C15	

EXAMINER	DATE CONSIDERED
/Patrick Lewis/ (05/31/2012)	

993039_1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (05/31/2012)

Shanghai Hongene Exhibit 1002

AOC/kml
September 12, 2012

PATENT APPLICATION
Docket No.: 4441.1001-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Suresh C. Srivastava and Naveen P. Srivastava

Application No.: 12/708,827 Group: 1623

Filed: February 19, 2010 Examiner: Patrick T. Lewis

Confirmation No.: 5297

For: Phosphoramidites For Synthetic RNA In The Reverse Direction, Efficient RNA Synthesis And Convenient Introduction Of 3'-End Ligands, Chromophores And Modifications Of Synthetic RNA

CERTIFICATE OF MAILING OR TRANSMISSION
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Date Signature

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Typed or printed name of person signing certificate

REPLY TO RESTRICTION REQUIREMENT

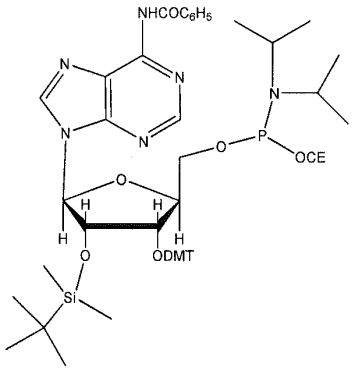
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Responsive to the Restriction Requirement dated June 13, 2012, the claims of Group I (Claims 1-23) drawn to a compound of Formula 1a or 1b are elected for prosecution. Applicants reserve the right to file a continuing application or take such other appropriate action as deemed necessary to protect the non-elected inventions. Applicants do not hereby abandon or waive any rights in the non-elected inventions.

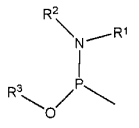
With regard to a species for searching purposes, Applicants elect the following compound: 3'-DMT-2'-TBDMS-B-L-rA-n-bz-5'-cyanoethyl phosphoramidite having the structural formula noted below (Structure 1A).

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(Structure 1A)

This sub class has been described in the specification on pages 58-60. See the last structure in Scheme 2. With respect to Claim 1, the elected species falls under Formula 1b and the substituents are, as follows:

Where J is 

B^n joining to the ribose moiety Where  represents B-L stereochemistry of joining of nucleobase with ribose moiety.
B^n is N6-benzoyladenine
R^1 is isopropyl amino group;
R^2 is isopropyl amino group;
R^3 is a phosphate protecting group, $CNCH_2CH_2$ (OCE) ;
R^4 is O-Si $(R^{11})_3$; where R^{11} is tertiary butyl dimethyl silyl, referred to as TBDMS in the formula (structure 1A);
R^6 is O-Z; where Z is an acid labile protecting group, DMT (dimethoxytrityl).

Claims readable on the elected species are 1-5, 7, 8, 10-16 from Group I. Claims readable on the elected species with regard to Group III are Claims 24 and 27.

An extension of time to respond to the Restriction Requirement is respectfully requested. A Petition for an Extension of Time and the appropriate fee are being filed concurrently.

The requirement is being traversed for the reasons set forth in detail below.

The inventions of I and III are related as combination/subcombination under 806.05(c). The combination (an oligonucleotide comprising the compound of formula 1a repeatedly linked to each other) requires the particulars of the subcombination (the compound of formula 1a or 1b). Because two way distinctness cannot be shown for the combination, the claims of inventions I and III should be examined together. Furthermore, a search of the subcombination would necessarily be overlapping with a search of the combination. Thus, there is not a search burden placed on the Examiner if inventions I and III were combined.

For the reasons presented above, Applicants respectfully request that the Claims of invention III be combined into Group I.

Rejoinder

Alternatively, Applicants respectfully note that rejoinder of the inventions set forth in Groups III and IV may be applicable upon an indication of allowability of the claims of Group I, provided that they are amended commensurate in scope with the allowed claims.

Applicants' Invention

Applicants respectfully pointed out the prior art citations of DNA/RNA or oligonucleotide synthesis of which they are aware, either provide or assume that the compounds are synthesized *in the 3'-5' direction.*

The distinction between 3'-5' direction synthesis and 5'-3' (reverse) direction is not a mere stylistic difference, but is a significant one as to the utility of the compounds. The methodology and the process of 5'→3' direction RNA synthesis disclosed in this invention opens up a whole new and broadly practical approach for various applications, especially in therapeutic applications.

RNA synthesis in the 3'-5' direction is well established and used for synthesis and development of a vast variety of RNA aptamers, tRNA's, siRNA and biologically active RNA molecules. This approach utilizes a ribonucleoside with suitable N-protecting group, for example, a 5'-Protecting group, a 2'-protecting group, or a 3'-phosphoramidite (component 1). This component is then coupled with a nucleoside with a suitable N-protecting group, a 2' or 3' succinate of a ribonucleoside attached to a solid support (component 2), followed by oxidation.

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However, the synthesis of RNA in the reverse direction (5'-3' direction) had not been achieved until the present invention. To the best of the inventors' knowledge 2'- silyl protected ribonucleoside-5'- phosphoramidites have not been known in the prior art, and similarly no oligonucleotide using reverse RNA synthesis had been recorded. The level of success or the predictability in the 5'-→ 3' direction synthesis was not apparent prior to the current invention.

Based on steric consideration the coupling between 3'- free hydroxyl group with a 5'-phosphoramidite is expected to be lower and due to the 3' hydroxyl being secondary in nature, thus less nucleophilic. The steric factor will be more pronounced in the 5'-nucleoside component due to the neighboring -2'- tertiary butyl dimethyl silyl (t-BPAC) protecting group. But reverse direction synthesis offers a practical and convenient introduction of a number of groups required for selective introduction at 3'-end. Applicants have observed higher coupling efficiency per step during automated oligo synthesis with the reverse RNA amidites, resulting in a greater ability to achieve higher purity and produce *very long* oligos.

Surprisingly, very high coupling efficiency per step for reverse direction 5'→ 3'-direction was observed using the methods of the invnetion as compared to 3'→ 5' direction synthesis. Thus, in the case of 5'→ 3' direction RNA synthesis greater than 99% coupling takes place within 2-4 minutes in the oligonucleotide synthesizer. While in the case of conventional 3'→ 5' direction oligonucleotide synthesis during 2-4 minutes coupling time in the oligonucleotide synthesizer, between 3'- phosphoramidite and 5'- hydroxyl group does not even begin and it takes approx 10 minutes to get approx 98% coupling efficiency.

Thus, the synthesis of RNA in the reverse direction (5'-3' direction) offers highly desirable properties. Applicants also demonstrated that the process of this invention leads to oligonucleotides free of M+1 species. Such species lead to closer impurities as shoulder of desired peak during HPLC analysis or purification or Gel purification.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on July 12, 2010, March 24, 2011 and December 7, 2011. A Supplemental Information Disclosure Statement is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

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CONCLUSION

In view of the above Reply to Restriction Requirement and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Date: September 13, 2012

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1623
Filed:	February 19, 2010	Examiner:	Patrick T. Lewis
Confirmation No.:	5297		
For:	Phosphoramidites For Synthetic RNA In The Reverse Direction, Efficient RNA Synthesis And Convenient Introduction Of 3'-End Ligands, Chromophores And Modifications Of Synthetic RNA		

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Commissioner:

This Supplemental Information Disclosure Statement is submitted:

☒ under 37 CFR 1.97(b), or
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application; or before the mailing date of a first office action on the merits; or before the mailing of a first office action after the filing of a Request for Continued Examination).

☐ under 37 CFR 1.97(c) together with either:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, or
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(After the 37 CFR 1.97(b) time period, but before any of a final action, notice of allowance, or an action that closes prosecution, whichever occurs first)

☐ under 37 CFR 1.97(d) together with:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, and
- ☐ a $180.00 fee under 37 CFR 1.17(p), or

(Filed after final action, notice of allowance, whichever occurs first, or if prosecution otherwise closes, but on or before payment of the issue fee)

☐ under 37 CFR 1.97(i):
Applicant requests that the IDS and cited reference(s) be placed in the application file.
(Filed after payment of issue fee)

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Statement Under 37 CFR 1.97(e)

☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)
Applies to original applications (other than design) filed on or after May 29, 2000

☐ (1) A paper containing only an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section if it is accompanied by a statement that each item of information contained in the information disclosure statement:

☐ (i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in §1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

☐ (ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in §1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☒ Enclosed herewith is a Listing of References. Copies of the cited references are enclosed except as indicated below or in the attached Listing of References.

☐ Copies of the cited references submitted with an Information Disclosure Statement in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed, are not required under 37 CFR 1.98(d)(1) and (2) and are thus not provided.

☐ The listed references were cited in the enclosed Search Report in counterpart foreign application [add application number], which is listed in the attached Listing of References.

☐ The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

- ☐ the explanation provided on the attached sheet.
- ☐ the explanation provided in the Specification.
- ☐ submission of the enclosed International Search Report.
- ☐ submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.
- ☐ the enclosed English language abstract.

Method of payment:

☐ Authorization is NOT granted to charge any fees which may be due in this matter to our Deposit Account.

☐ Please charge Deposit Account 08-0380 in the amount of $[ ].

☐ A check for the fee noted above is enclosed, or the fee has been included in the check with the accompanying Reply.

☒ Please charge any deficiency in fees and credit any overpayment to Deposit Account 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: September 10, 2012

Substitute for form 1449B/PTO **SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** September 5, 2012 (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Patrick T. Lewis	CONFIRMATION NO. 5297	GROUP 1623

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C9	Van Boom, *et al.*, "Chemical Synthesis of Small Oligoribonucleotides in Solution," Ch. 7 in Oligonucleotide Synthesis – A Practical Approach, M.J. Gait (ed), IRLS Press, Washington, DC, 1984, only pages 153-183 supplied.
	C10	Becket, *et al.*, "Enzymatic synthesis of Oligoribonucleotides," Ch. 8 in Oligonucleotide Synthesis – A Practical Approach, M. J. Gait (ed), IRLS Press, Washington, DC, 1984, only pages 184-197 supplied.
	C11	Guzaev, *et al.*, "A Conformationally Preorganized Universal Solid Support for Efficient Oligonucleotide Synthesis," *J. Amer. Chec. Soc.*, 125(9): 2380-2381 (2003): CAPlus Abstract No. 2003:98281, CA Doc. No. 138: 287895; see CAPLUS search of record for Abstract and structure.
	C12	Anon, Sigma Catalog – Biochemicals and Reagents, St. Louis, MO, 2002-2003: only page 1424 supplied, see items R 4142 and R 6895.
	C13	*Non-Office Action mailed March 23, 2011 for U.S. Application No. 12/584,625, "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".
	C14	*Final Office Action mailed December 5, 2011 for U.S. Application No. 12/584,625, "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".
	C15	*Notice of Allowance mailed June 29, 2012 for U.S. Application No. 12/584,625, "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".
	C16	International Preliminary Report on Patentability from counterpart International Application Number PCT/US2011/025488, "Phosphoramidites For Synthetic RNA In The Reverse Direction", Dated February 19, 2010.

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.**

EXAMINER	DATE CONSIDERED

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PATENT COOPERATION TREATY

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NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
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To:

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Hamilton, Brook, Smith & Reynolds, P.C.
530 Virginia Rd, P.O. Box 9133
Concord, MA 01742-9133
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 30 August 2012 (30.08.2012)		
Applicant's or agent's file reference 4441.1001003	IMPORTANT NOTICE	
International application No. PCT/US2011/025488	International filing date *(day/month/year)* 18 February 2011 (18.02.2011)	Priority date *(day/month/year)* 19 February 2010 (19.02.2010)
Applicant CHEMGENES CORPORATION et al		

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

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Form PCT/IB/326 (January 2004)

C16

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 4441.1001003	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2011/025488	International filing date *(day/month/year)* 18 February 2011 (18.02.2011)	Priority date *(day/month/year)* 19 February 2010 (19.02.2010)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHEMGENES CORPORATION		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 21 August 2012 (21.08.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt03.pct@wipo.int

Form PCT/IB/373 (January 2004)

Shanghai Hongene Exhibit 1002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
CARROLL ALICE O.

HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530
VIRGINIA RD, P.O. BOX 9133 CONCORD MA 01742-9133
USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**18 NOVEMBER 2011 (18.11.2011)**
Applicant's or agent's file reference 4441.1001003	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2011/025488	**18 FEBRUARY 2011 (18.02.2011)**	19 FEBRUARY 2010 (19.02.2010)

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

C07H 19/10(2006.01)i, C07H 19/20(2006.01)i, C07H 19/067(2006.01)i, C07H 19/167(2006.01)i, C07H 21/02(2006.01)i

Applicant

CHEMGENES CORPORATION et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	16 NOVEMBER 2011 (16.11.2011)	KIM, Bumsu Telephone No.82-42-481-8289

Form PCT/ISA/237 (cover sheet) (July 2011)

Shanghai Hongene Exhibit 1002

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/025488

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/025488

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	17-19,21,24-26,28-38	YES
	Claims	1-16,20,22-23,27,39	NO
Inventive step (IS)	Claims	17-19,21,24-26,28-38	YES
	Claims	1-16,20,22-23,27,39	NO
Industrial applicability (IA)	Claims	1-39	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following document

D1: Nucleic Acids Symposium Series, Srivastava, S. C. et al., 08 September 2008, No.52, pages 103-104.

1. Novelty and inventive step

1-1. D1, which is considered to represent the most relevant state of the art, discloses a compound of formula (Ia) or (Ib)(e.g. J=cyanoethylphosphoramidite, Bn=substituted nuclobase, R^4=TBDMS, R^6=O-DMT; see 103page, right column and figure 1 in D1). As all of the features of claims 1-16 are disclosed in D1, claims 1-16 are anticipated by D1. Therefore, claims 1-16 lack novelty under PCT Article 33(2).

1-2. The subject matters of claims 17-19 and 21 differ from these prior art documents in that the pendant groups of compounds are specified(especially, ester pendant groups). And it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, claims 17-19 and 21 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

1-3. D1, which is considered to represent the most relevant state of the art, discloses compounds(e.g. Q=Icaa-CPG-NHC(=O)-CH_2-CH_2, Bn=substituted nuclobase, R^4=TBDMS, Z=DMT; see figure 1 in D1). As all of the features of claims 20, 22, and 23 are disclosed in D1, claims 20, 22, and 23 are anticipated by D1. Therefore, claims 20, 22, and 23 lack novelty under PCT Article 33(2).

1-4. The subject matters of claims 24-26 differ from these prior art documents in that the structure of compounds is specified. And it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, claims 24-26 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

(Continued on supplemental box)

Shanghai Hongene Exhibit 1002

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/025488

Box No. VI Certain documents cited

1. Certain published documents (Rule 43bis.1 and 70.10)

	Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
P,X	US2010/0324278	23/12/2010	08/09/2009	06/09/2008

US2010/0324278A1 does not constitute prior art within the meaning of PCT Rule 64.3, but appears to disclose all features of claims 1-16,27 and 39. In case the priority of the present application is not valid, this document is relevant for assessing novelty and inventive step.

2. Non-written disclosures (Rule 43bis.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2011/025488

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

It is not clear what the meaning of R14 in the chemical formula of claim 17 is (PCT Article 6).

Claim 37 relates to a method, but claim 38 dependent on claim 37 relates to a compound. As claim 38 does not clearly define the matter for which protection is sought, this claim does not meet the requirement of PCT Article 6.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of :

(Box No.V)

1-5. D1, which is considered to represent the most relevant state of the art, discloses a synthetic RNA molecule with a purity exceeding 97% and synthesized from a 5' phosphoramidite nucleoside. As all of the features of claim 27 is disclosed in D1, claim 27 is anticipated by D1. Therefore, claim 27 lacks novelty under PCT Article 33(2).

1-6. The subject matters of claims 28-38 differ from these prior art documents in that all steps to synthesize RNA in the reverse direction are specified. And it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, claims 28-38 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

1-7. D1, which is considered to represent the most relevant state of the art, discloses a synthetic RNA molecule with purity exceeding 97%. As all of the features of claim 39 is disclosed in D1(because claim 39 is a product-by-process claim), claim 39 is anticipated by D1. Therefore, claim 39 lacks novelty under PCT Article 33(2).

2. Industrial applicability

Claims 1-39 meet the criteria of PCT Article 33(4), because the claimed invention can be used in its related industry.

Shanghai Hongene Exhibit 1002

AOC/kml
September 5, 2012

PATENT APPLICATION
DOCKET NO.: 4441.1001-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1623
Filed:	February 19, 2010	Examiner:	Patrick T. Lewis
Confirmation No.:	5297		
For:	Phosphoramidites For Synthetic RNA In The Reverse Direction, Efficient RNA Synthesis And Convenient Introduction Of 3'-End Ligands, Chromophores And Modifications Of Synthetic RNA		

Date:_____

EXPRESS MAIL LABEL NO._____

PETITION FOR EXTENSION OF TIME

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

Commissioner:

Applicants hereby petition the Commissioner for Patents to extend the time for filing a Reply to the Office Action (Restriction Requirement) dated June 13, 2012 for two months from July 13, 2012 to September 13, 2012 under 37 CFR § 1.136(a).

	Small Entity	Other than Small Entity
1 month	☐ $ 75	☐ $ 150
2 months	☒ $ 280	☐ $ 560
3 months	☐ $ 635	☐ $1,270
4 months	☐ $ 990	☐ $1,980
5 months	☐ $1,345	☐ $2,690

☐ A check is enclosed in the amount of the extension fee indicated above, or the extension fee has been included in the check with the accompanying Reply.

☒ Please charge Deposit Account No. 08-0380 in the amount of $280 to cover the cost of the extension fee.

Any deficiency or overpayment should be charged or credited to Deposit Account No. 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No.: 33,542
Telephone: (978) 341-0036
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Concord, MA 01742-9133
Dated: September 13, 2012

–Rev/Fee Schedule September 26, 2011

1333700.1

Shanghai Hongene Exhibit 1002

Electronic Patent Application Fee Transmittal

Application Number:	12708827
Filing Date:	19-Feb-2010
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Filer:	Alice O. Carroll/Kristin Lovett
Attorney Docket Number:	4441.1001-002

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Extension - 2 months with $0 paid	2252	1	280	280

Shanghai Hongene Exhibit 1002

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**280**

Electronic Acknowledgement Receipt	
EFS ID:	13737085
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Karen Kenney
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	13-SEP-2012
Filing Date:	19-FEB-2010
Time Stamp:	17:43:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$280
RAM confirmation Number	5923
Deposit Account	080380
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:					
Document Number	**Document Description**	**File Name**	**File Size(Bytes)/ Message Digest**	**Multi Part /.zip**	**Pages (if appl.)**
1	Response to Election / Restriction Filed	44411001002Replytorr.pdf	412619 c5f6b85b6a75e58e737e53a1ba72e76499ce641c	no	5
Warnings:					
Information:					
2	Transmittal Letter	44411001002SIDStransmittal.pdf	281583 346929dc279df9a998a36f5f62949912f185904b	no	3
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	44411001002listingofreferences.pdf	143922 6c583d7a856444026a0229e54f08c59b1fe98627	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Non Patent Literature	44411001002RefC9.pdf	2016876 60f765d17100b3d33875e5357e646895c486928d	no	34
Warnings:					
Information:					
5	Non Patent Literature	44411001002RefC10.pdf	931226 100b4a12d93d97a722f9f217ec5f5b1abb670d76	no	16
Warnings:					
Information:					
6	Non Patent Literature	44411001002RefC11.pdf	189275 077af0118bbdad36c9ad6f7e9be755f13ba5b002	no	2
Warnings:					
Information:					
7	Non Patent Literature	44411001002RefC12.pdf	374752 c32d6817dacdcc3553574ef1ac4361be6f3f2ae9	no	2
Warnings:					
Information:					
8	Non Patent Literature	44411001002RefC16.pdf	606642 f208e0f8216a3c1a34ec3dd5ba74aa404ece649e	no	8
Warnings:					
Information:					

9	Extension of Time	44411001002extensionoftime.pdf	84826 35291dac56315a8988be5261d2a0e9dc439d6c81	no	1
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	30818 58682c2393412fe0d780632812ceb004f643baef	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	5072539	

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002	5297

21005 7590 10/26/2012

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
LEWIS, PATRICK T	
ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
10/26/2012	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.	Applicant(s)	
	12/708,827	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	PATRICK LEWIS	1623	

-- 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* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *13 September 2012*.

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) *1-39* is/are pending in the application.

5a) Of the above claim(s) *6,9 and 17-39* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-5,7,8 and 10-16* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *19 February 2010* 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).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09132012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-23) wherein 3'-DMT-2'-TBDMS-B-L-rA-n-bz-5'-cyanoethyl phosphoramidite in the reply filed on September 13, 2012 is acknowledged. The traversal is on the ground(s) that Groups I and III are related as combination/subcombination. This is not found persuasive because Group III (combination) does not require the details of Group I (subcombination) as claimed. For example, variable R6 of Group I is not required by Group III.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 6, 9 and 17-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 13, 2012.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 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 of this title, 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 negatived by the manner in which the invention was made.

4. 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 35 U.S.C. 103(a) are summarized as follows:

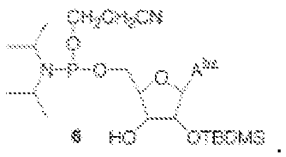
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 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 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-5, 7, 8 and 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. Organic Letters (2001), Vol. 3, pages 795-797 (Lin); Ogilvie et al. Can. J. Chem. (1978), Vol. 56, pages 2768-2780 (Ogilvie); and Aramini et al. Biochemistry (1996), Vol. 35, pages 9355-9365 (Aramini) in combination.

Claims 1-5, 7, 8 and 10-16 are drawn to a compound of Formula Ia, Ib, Ic or Id.

Lin teaches compound **6** having the structure

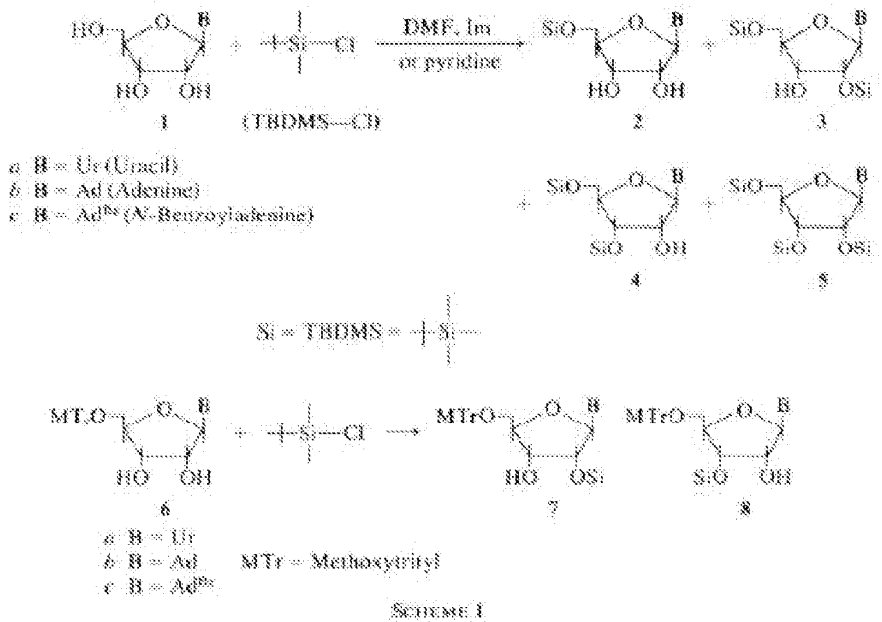


.

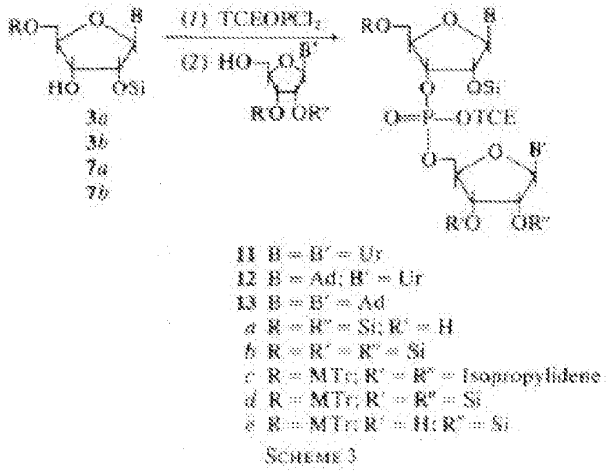
Lin differs from the instantly claimed compound in that Lin does not teach protection of the 3'-OH with an acid labile protecting group; however, this deficiency would have been obviuos in view of the teaching of Ogilvie and Aramini.

Ogilvie teaches that there are two important challenges in the chemical synthesis of oligonucleotides: the synthesis of oligodeoxynucleotides leading ultimately to the synthesis of genetic material and the synthesis of oligoribonucleotides leading ultimately to the synthesis of molecules such as transfer RNA and messenger RNA (page 2768). Developments in these two areas are similar in that the methods used to date to condense protected monomers into oligomers are virtually the same for both cases. However, they differ greatly in the availability of suitably protected monomers. The lack of procedures for the rapid synthesis of suitably protected ribonucleotides is the major reason that while the chemical synthesis of oligodeoxynucleotides has contributed significantly to the synthesis of a gene no development of equivalent magnitude has occurred in the ribose area.

Ogilvie has been exploring new methods for protection deprotection of ribonucleotides and methods for condensation. Efforts in exploiting the alkyl silyl protecting groups for ribonucleotides and use of fluoride ion to not only remove silyl groups but phosphate protecting groups as well, when combined with the Letsinger phosphite condensation procedure, have allowed for a versatile route to oligoribonucleotides.



Scheme 1



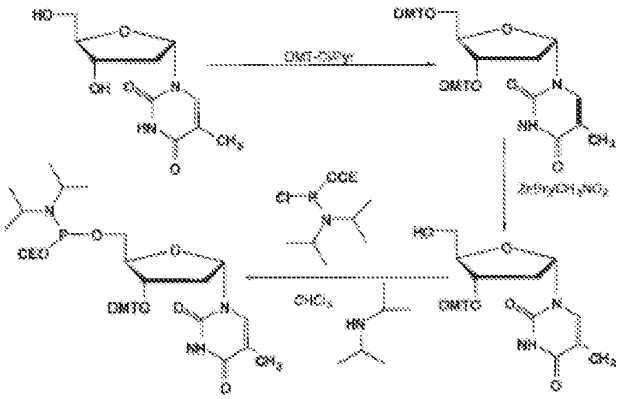
Scheme 3

The major advantage of the TBMDCl reagent is that it rapidly converts the ribonucleoside (Scheme 1) into derivatives that can be directly used in forming nucleotides (page 2769). One excellent synthetic feature of the silylated nucleosides is

that isomeric compounds, e.g., **3** and **4**, separate very cleanly on silica gel chromatography. Consequently the products can rapidly be obtained by thick-layer chromatography or by shor column chromatography often in solvents such as ether and hexane. Products containing silyl groups on exocyclic amino groups are not obtained in any quantity in these reactions.

Since there are several phosphorylating procedures that require N-protection, Ogilvie also prepared the silylated derivatives of N-benzoyl adenosine. From Table 2 it can be seen that N-protection causes a remarkable increase in the separation of isomers such as **3c** and **4c**. The silyl groups are also completely compatible with the methoxytrityl group and together they provide an ideal protection system for nucleosides.

Aramini teaches the synthesis of 5'-phosphoramidite-4'-DMT derivative of a-anomeric thymidine used for the preparation of the αT decamer.



It would have been obvious to protect the hydroxyl group of compound **6** of Lin with a trityl group in order to produce a protected monomer for subsequent

condensation reactions to form oligoribonucleotides as demonstrated by Ogilvie or Aramini which used analogous deoxoyribonuclosides.

Conclusion

7. Claims 1-39 are pending. Claims 6, 9 and 17-39 are withdrawn from further consideration as being drawn to a nonelected invention or species. Claims 1-5, 7, 8 and 10-16 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached on Monday - Thursday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. 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 T. Lewis/
Primary Examiner, Art Unit 1623

/PL/

Notice of References Cited	Application/Control No. 12/708,827	Applicant(s)/Patent Under Reexamination SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	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	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Lin et al. Organic Letters (2001), Vol. 3, pages 795-797.
	V	Ogilvie et al. Can. J. Chem. (1978), Vol. 56, pages 2768-2780.
	W	Aramini et al. Biochemistry (1996), Vol. 35, pages 9355-9365.
	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.

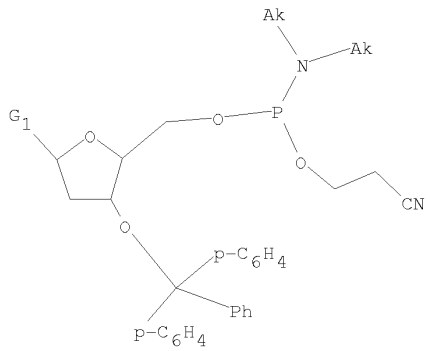
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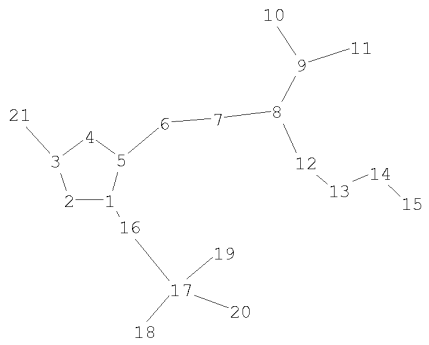
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L1              STRUCTURE UPLOADED
L2            0 S L1 SSS SAM
L3            2 S L1 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 05:28:41 ON 16 OCT 2012
L4            6 S L3

     FILE 'STNGUIDE' ENTERED AT 05:30:01 ON 16 OCT 2012
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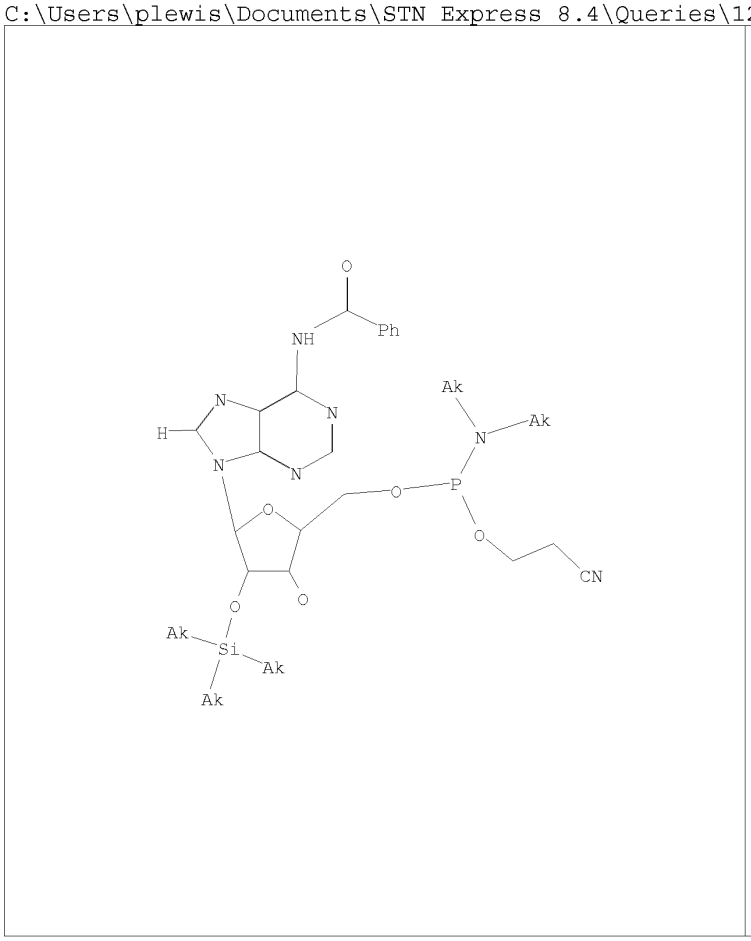


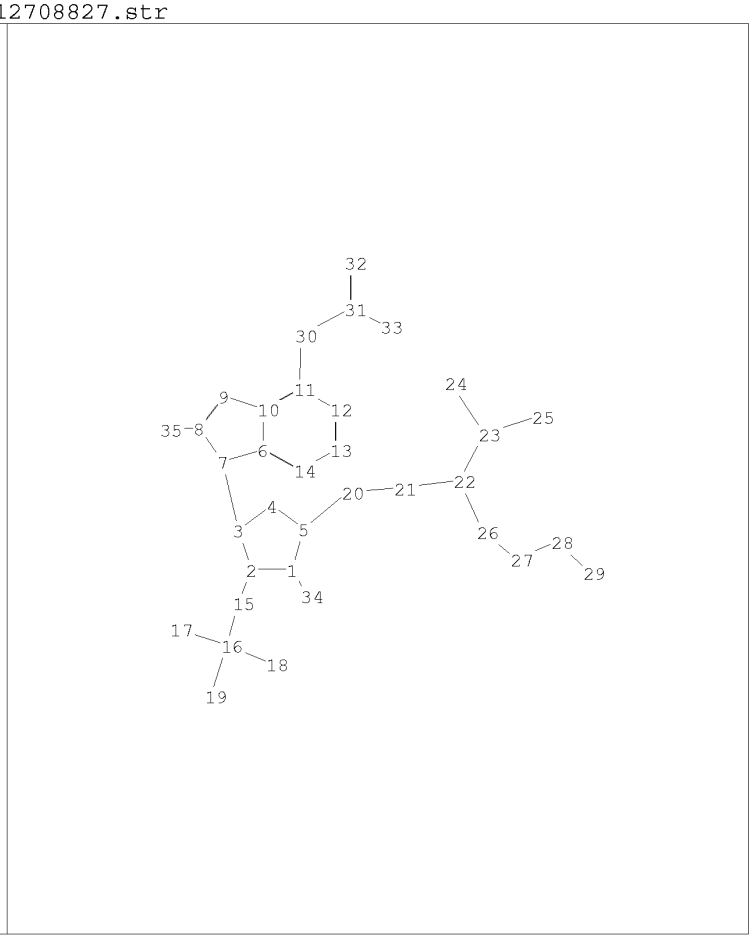
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6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
ring nodes :
1 2 3 4 5
chain bonds :
1-16 3-21 5-6 6-7 7-8 8-9 8-12 9-10 9-11 12-13 13-14 14-15 16-17 17-18 17-19
17-20
ring bonds :
1-2 1-5 2-3 3-4 4-5
exact/norm bonds :
1-2 1-5 1-16 2-3 3-4 3-21 4-5 6-7 7-8 8-9 8-12 9-10 9-11 12-13 16-17
exact bonds :
5-6 13-14 14-15 17-18 17-19 17-20

G1:H,Hy

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:CLASS 19:CLASS 20:CLASS
21:CLASS

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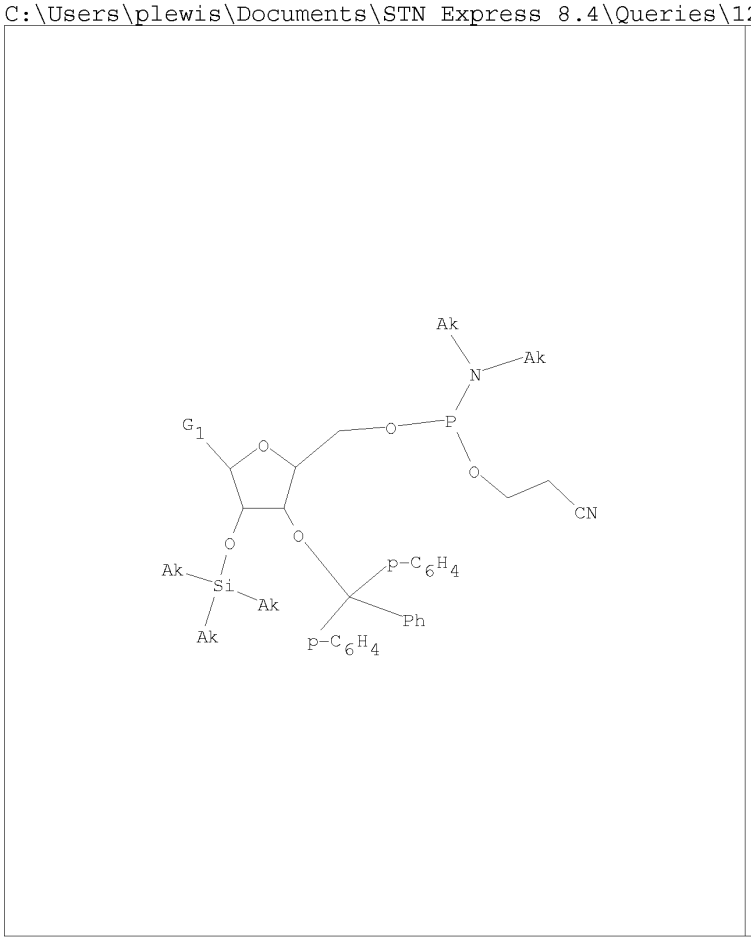


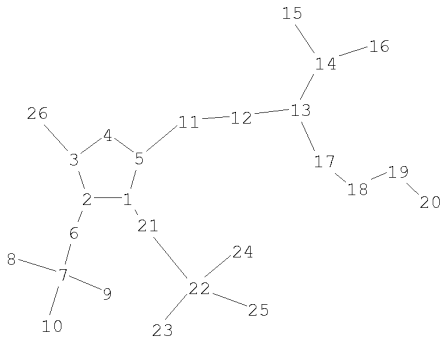
chain nodes :
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
ring nodes :
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chain bonds :
1-34 2-15 3-7 5-20 8-35 11-30 15-16 16-17 16-18 16-19 20-21 21-22 22-23 22-26
23-24 23-25 26-27 27-28 28-29 30-31 31-32 31-33
ring bonds :
1-2 1-5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

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS
22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS
31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:CLASS

Shanghai Hongene Exhibit 1002

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```
chain nodes :
    6  7  8  9  10  11  12  13  14  15  16  17  18  19  20  21  22  23  24  25  26
ring nodes :
    1  2  3  4  5
chain bonds :
    1-21  2-6  3-26  5-11  6-7  7-8  7-9  7-10  11-12  12-13  13-14  13-17  14-15  14-16  17-18
    18-19  19-20  21-22  22-23  22-24  22-25
ring bonds :
    1-2  1-5  2-3  3-4  4-5
exact/norm bonds :
    1-2  1-5  1-21  2-3  2-6  3-4  3-26  4-5  7-8  7-9  7-10  11-12  12-13  13-14  13-17  14-15
    14-16  17-18  21-22
exact bonds :
    5-11  6-7  18-19  19-20  22-23  22-24  22-25


G1:H,Hy

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:CLASS  19:CLASS  20:CLASS
    21:CLASS  22:CLASS  23:CLASS  24:CLASS  25:CLASS  26:CLASS
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Shanghai Hongene Exhibit 1002

Substitute for form 1449B/PTO	ATTORNEY DOCKET NO.	APPLICATION NO.	
SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION	4441.1001-002	12/708,827	
	FIRST NAMED INVENTOR	FILING DATE	
	Suresh C. Srivastava	February 19, 2010	
LISTING OF REFERENCES	EXAMINER	CONFIRMATION NO.	GROUP
September 5, 2012	Patrick T. Lewis	5297	1623
(Use several sheets if necessary)			

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C9	Van Boom, *et al.*, "Chemical Synthesis of Small Oligoribonucleotides in Solution," Ch. 7 in Oligonucleotide Synthesis – A Practical Approach, M.J. Gait (ed), IRLS Press, Washington, DC, 1984, only pages 153-183 supplied.
	C10	Becket, *et al.*, "Enzymatic synthesis of Oligoribonucleotides," Ch. 8 in Oligonucleotide Synthesis – A Practical Approach, M. J. Gait (ed), IRLS Press, Washington, DC, 1984, only pages 184-197 supplied.
	C11	Guzaev, *et al.*, "A Conformationally Preorganized Universal Solid Support for Efficient Oligonucleotide Synthesis," *J. Amer. Chec. Soc.*, 125(9): 2380-2381 (2003): CAPlus Abstract No. 2003:98281, CA Doc. No. 138: 287895; see CAPLUS search of record for Abstract and structure.
	C12	Anon, Sigma Catalog – Biochemicals and Reagents, St. Louis, MO, 2002-2003: only page 1424 supplied, see items R 4142 and R 6895.
	C13	*Non-Office Action mailed March 23, 2011 for U.S. Application No. 12/584,625, "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".
	C14	*Final Office Action mailed December 5, 2011 for U.S. Application No. 12/584,625, "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".
	C15	*Notice of Allowance mailed June 29, 2012 for U.S. Application No. 12/584,625, "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".
	C16	International Preliminary Report on Patentability from counterpart International Application Number PCT/US2011/025488, "Phosphoramidites For Synthetic RNA In The Reverse Direction", Dated February 19, 2010.

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.**

EXAMINER	DATE CONSIDERED
/Patrick Lewis/ (10/15/2012)	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (10/15/2012)

Shanghai Hongene Exhibit 1002

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor, GOOGLE (oligonucleotide synthesis)	6/12/2012	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	10/20/2012	/PL/

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

✓	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	06/12/2012	10/20/2012							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
	5	÷	✓							
	6	÷	N							
	7	÷	✓							
	8	÷	✓							
	9	÷	N							
	10	÷	✓							
	11	÷	✓							
	12	÷	✓							
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	33	÷	N							
	34	÷	N							
	35	÷	N							
	36	÷	N							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

✓	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	06/12/2012	10/20/2012							
	37	÷	N							
	38	÷	N							
	39	÷	N							

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1623
Filed:	February 19, 2010	Examiner:	Lewis, Patrick T.
Confirmation No:	5297		
For:	Phosphoramidites For Synthetic RNA In The Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'- End Ligands, Chromophores And Modifications Of Synthetic RNA		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

_____ _____
Date Signature

_____
Typed or printed name of person signing certificate

AMENDMENT

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

Commissioner:

This Amendment is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on October 26, 2012 in the above-identified application. Reconsideration and further examination are requested.

An extension of time to respond to the Office Action is respectfully requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently with this Amendment.

Please amend the application as follows:

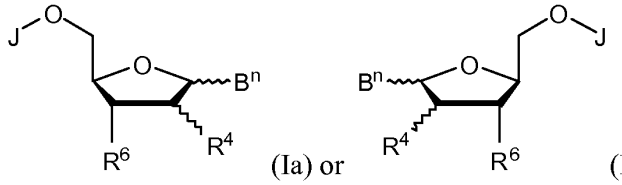
Amendments to the Claims

Please cancel Claims 4, 5, 24-27 and 39. Please amend Claims 1-3, 6-8, 10, 11, 15, 17-19, 21, 28, 31, 33, 35, 37 and 38. The Claim Listing below will replace all prior versions of the claims in the application:

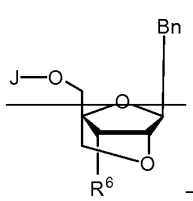
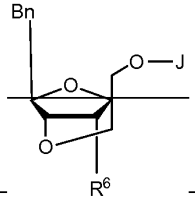
Claim Listing

What is claimed is:

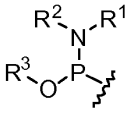
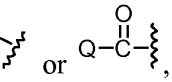
1. (Currently Amended) A compound of Formula Ia[[,]] or Ib~~, Ic, or Id~~:


(Ia) or

(Ib)[[;]]


~~(Ic) or~~

~~(Id)~~,

or a salt thereof, wherein:

J is H,  or  , wherein ≀ indicates where J is attached to the O atom;

Q is ~~a)~~ a support comprised of: a) a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl;

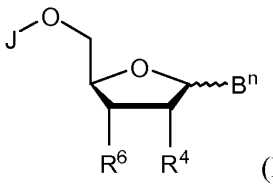
R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

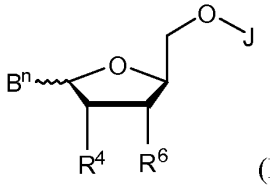
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

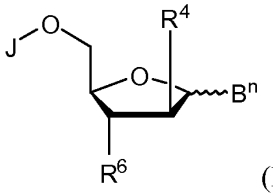
R^4 is a [[-]]-halo, [[-]]-R^5, [[-]]-NR^7R^8, -OR^9, [[-]]-SR^{10}, or 2'-blocking group[[,]]; or when Structural Formula Ia or Ib is:



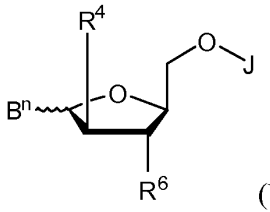
(II), or



(III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:



(IV), or



(V); R^4 is further selected from -OC(=O)R^{12};

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with –NR^7R^8, (C_1-

C_4)alkylamino, di(C_1-C_4)alkylamino, -OR^9, (C_1-C_6)alkoxy, benzyl or substituted benzyl, -SR^{10}; or -S-(C_1-C_6)alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)$-phthalimide; -C(=O)-$(CH_2)_{1-16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, -C(=O)-$(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl ~~an acid labile protecting group~~;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6,N6-dimethyl adenine, ~~N6-benzoyladenine,~~ N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7-deaza-7-iodoadenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with $-C\equiv C(CH_2)_{1\text{-}8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6-methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5- methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with –C≡C-CH_2-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, ~~4-thiouracil,~~ N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoromethyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl;

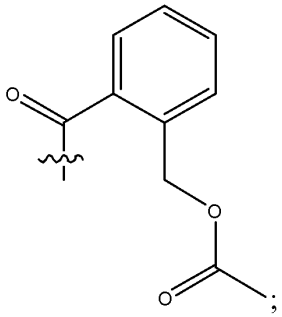
-C(=O)$CH_2CH_2CH=CH_2$[[l]]; -C(=O)(C_1-C_{16})alkylene-C(=O)OH;

-C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; =CR^8N(C_1-C_6)alkyl)$_2$;

-C(=O)-NR^8-$(CH_2)_{1-16}NR^8C(=O)CF_3$; -C(=O)-$(CH_2)_{1-16}NR^8C(=O)CF_3$;

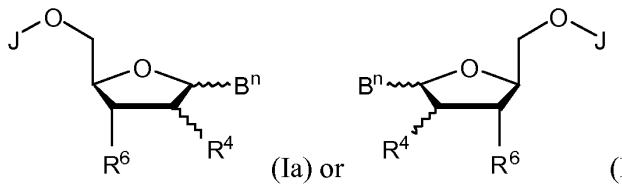
-C(=O)-$NR^8(CH_2)_{1-16}NR^8$C(=O)-phthalimide;

-C(=O)-$(CH_2)_{1-16}$-phthalimide; and

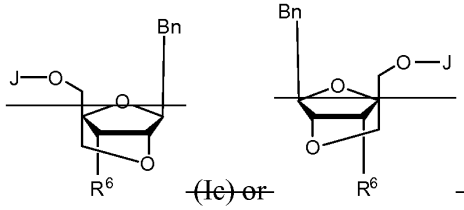


wherein any substitutable oxygen atom within the nucleobase is optionally substituted with –C(=O)N(C_1-C_6alkyl)$_2$ or –C(=O)N(phenyl)$_2$.

2. (Currently Amended) A compound of Formula Ia[[,]] or Ib~~, Ic, or Id~~:

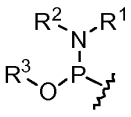
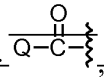


(Ia) or (Ib)[[;]]



~~(Ic) or~~ ~~(Id)~~,

or a salt thereof, wherein:

J is H[[,]] or  ~~, or~~  ~~, wherein ≀ indicates where J is attached to the O atom~~;

~~Q is a) a support comprised of a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl;~~

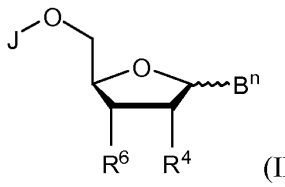
R^1 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^2 is a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

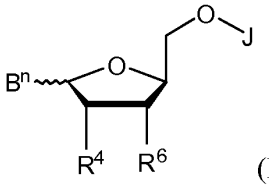
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

R^3 is a phosphate protecting group;

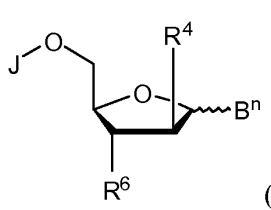
R^4 is a [[-]]-halo, [[-]]-R^5, [[-]]-NR^7R^8, -OR^9, [[-]]-SR^{10}, or 2'-blocking group[[,]]; or when Structural Formula Ia or Ib is:



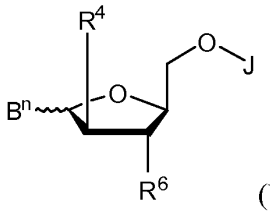
(II), or



(III); wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when Structural Formula Ia or Ib is:



(IV), or



(V); R^4 is further selected from $-OC(=O)R^{12}$;

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with $–NR^7R^8$, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, $-OR^9$, (C_1-C_6)alkoxy, benzyl or substituted benzyl, $-SR^{10}$; or -S-(C_1-C_6)alkyl group;

R^6 is –H or –O-Z;

each R^7 is independently a fluorenylmethyloxycarbonyl; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)$-phthalimide; $-C(=O)-(CH_2)_{1-16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently –S(C_1-C_6) alkyl, $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or

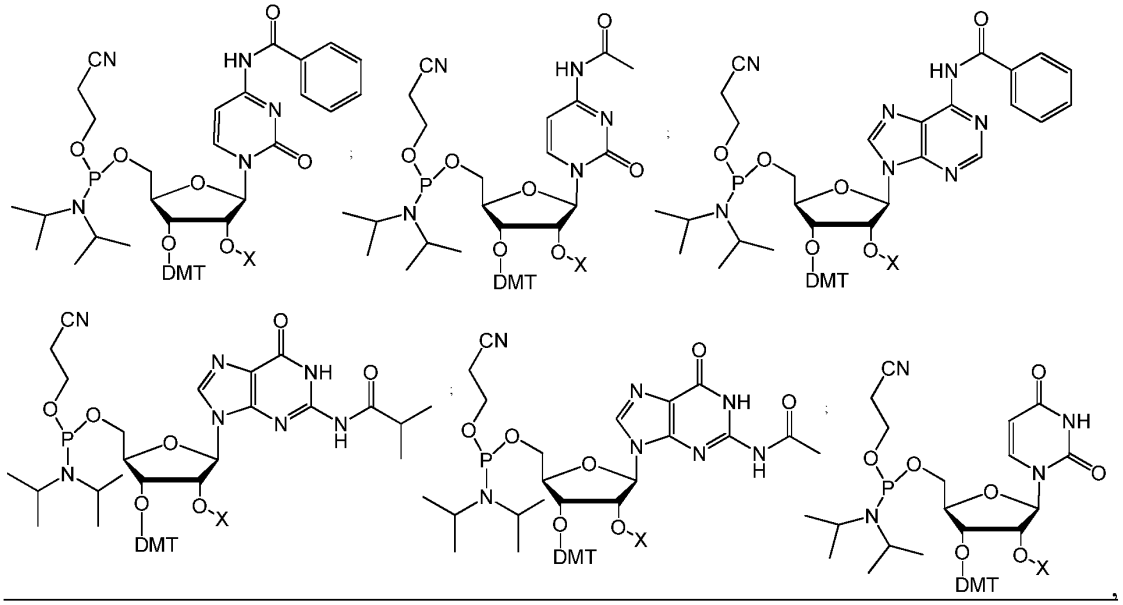
unsubstituted (C_2-C_{12})alkynyl group; provided that if R^4 is –O-Si(R^{11})$_3$, and two R^{11} groups are both methyl, the other is not t-butyl or if R^4 is -O-CH_2-Si(R^{11})$_3$, then the three R^{11} groups cannot all be isopropyl;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

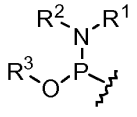
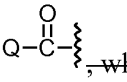
Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl ~~an acid labile protecting group~~;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group,

provided that the compound is not represented by one of the following structural formulas:



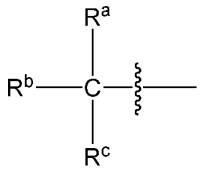
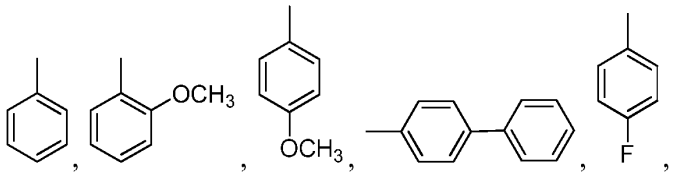
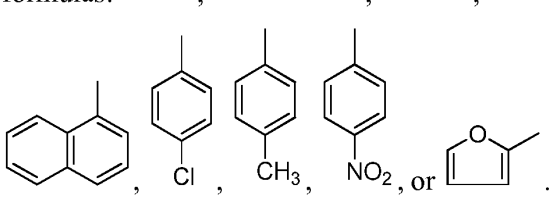
wherein X is tert-butyldimethylsilyl or triisopropylsiloloxymethyl.

3. (Currently Amended) The compound of Claim 1, wherein J is  [[,]] or  , ~~wherein ≀ indicates where J is attached to the O atom~~.

4.-5. (Cancelled).

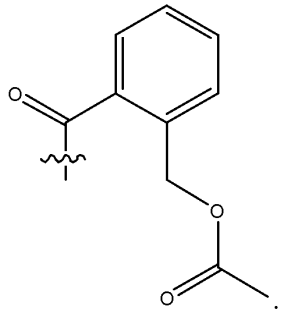
6. (Withdrawn - Currently Amended) The compound of Claim [[5]] 1, wherein Z is di-p-anisylphenyl methyl, p-fluorophenyl-1- naphthylphenyl methyl, p-anisyl-1- naphthylphenyl methyl, di-o-anisyl-1- naphthyl methyl, di-o-anisylphenyl methyl, p-tolyldiphenylmethyl, di-p-anisylphenylmethyl, di-o-anisyl-1- naphthylmethyl, di-p-anisylphenyl methyl, di-o-anisyl phenyl methyl, di-p-anisylphenyl methyl, or p-tolyldiphenylmethyl.

7. (Currently Amended) The compound of Claim [[5]] 1, wherein Z is represented by the following structural formula:

 , wherein ≀ indicates attachment to the 3' oxygen atom and R^a, R^b, and R^c are independently selected from the following structural formulas:  ,  .

8. (Currently Amended) The compound of Claim [[5]] 1, wherein Z is 4-methoxytrityl, 4,4'-dimethoxytrityl, or 4,4',4"-trimethoxytrityl.

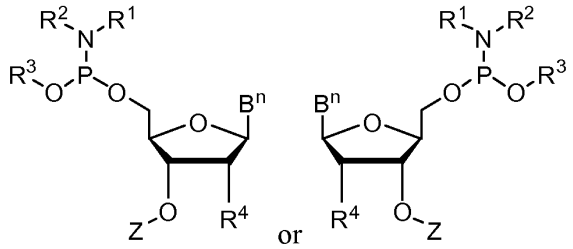
9. (Withdrawn) The compound of Claim 1, wherein the substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with $=CHN(CH_3)_2$; $C(=O)CH(CH_3)_2$; $-C(=O)CH_3$, $=C(CH_3)N(CH_3)_2$; $-C(=O)OPh$; $-C(=O)CH_2CH_2CH=CH_2$; $-C(=O)CH_2CH_2-C(=O)O(C_1-C_6)$alkyl; $-C(=O)-NR^8-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-NR^8(CH_2)_{1-16}NR^8C(=O)$-phthalimide; $-C(=O)-(CH_2)_{1-16}$-phthalimide

and  .

10. (Currently Amended) The compound of Claim [[4]] 1, wherein R^3 is $-CH_2CH_2CN$, $-CH_2CH_2-Si(CH3)_2C_6H_5$, $-CH_2CH_2-S(O)_2-CH_2CH_3$, $-CH_2CH_2-C_6H_4-NO_2$, $-CH_2CH_2-NH-C(O)-C_6H_5$, or $-CH_2CH_2-O-C_6H_4-C(O)CH_3$, and R^4 is [[-]]-O-Si$(R^{11})_3$ or –O-CH_2-Si$(R^{11})_3$.

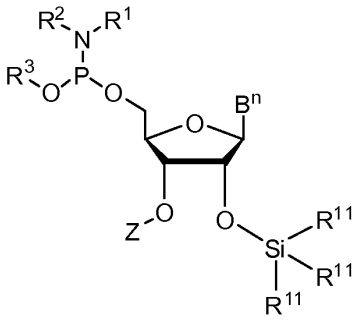
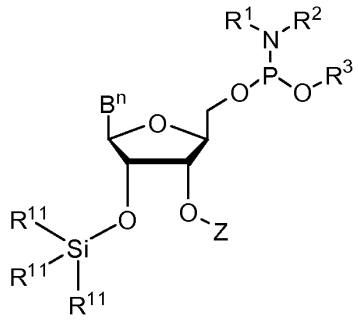
11. (Currently Amended) The compound of Claim 10, wherein R^4 is –O-$Si(CH_3)_2(C(CH_3)_3)$ or -O-CH_2-$Si(CH(CH_3)_2)_3$[[)]].

12. (Original) The compound of Claim 1, wherein the compound is represented by one of the following structural formulas :


or

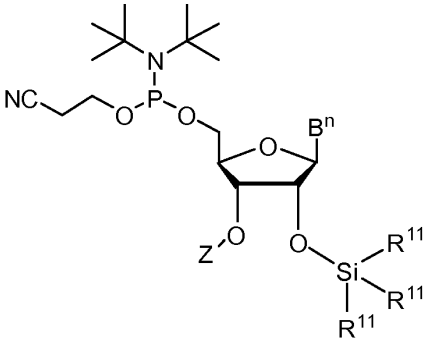
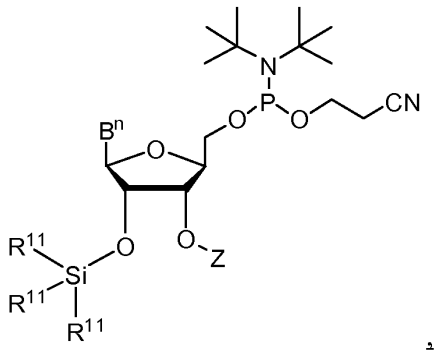
or a salt thereof.

13. (Original) The compound of Claim 12, wherein the compound is represented by one of the following structural formulas:


or

, or a salt thereof.

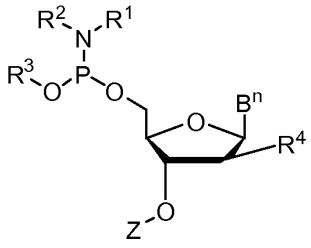
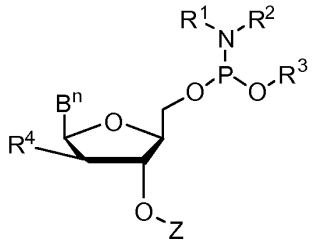
14. (Original) The compound of Claim 13, wherein R^3 is $-CH_2CH_2CN$.

15. (Currently Amended) The compound of Claim 14, wherein the compound is represented by one of the following structural formulas:

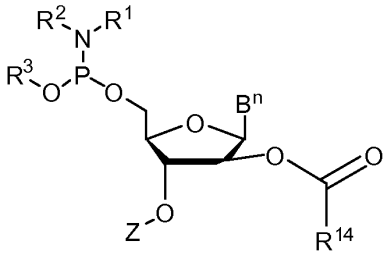
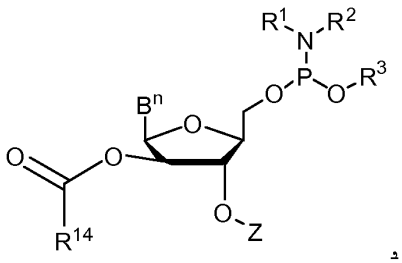

[[,]] or

.

or a salt thereof.

16. (Original) The compound of Claim 1, wherein the compound is represented by one of the following structural formulas:


or

, or a salt thereof.

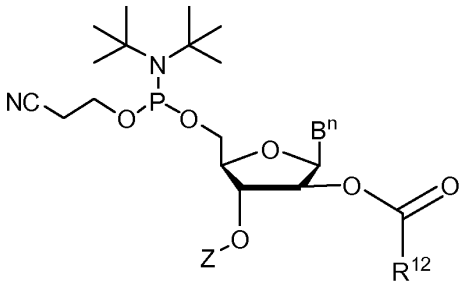
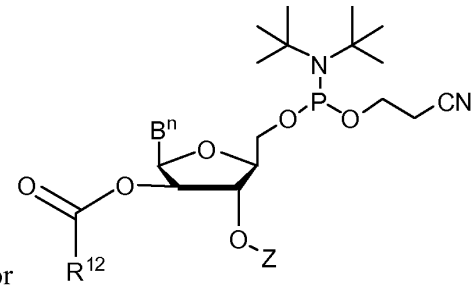
17. (Currently Amended) The compound of Claim 16, wherein the compound is represented by one of the following structural formula:


[[,]] or

,

or a salt thereof.

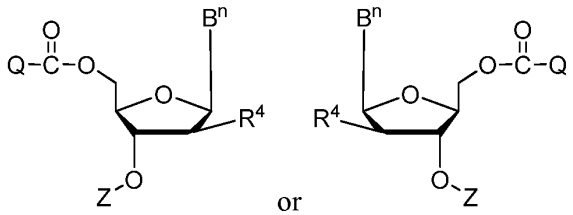
18. (Currently Amended) The compound of Claim 17, wherein R^3 is -CH_2CH_2CN.

19. (Currently Amended) The compound of Claim 18, wherein the compound is represented by one of the following structural formulas:


[[,]] or

,

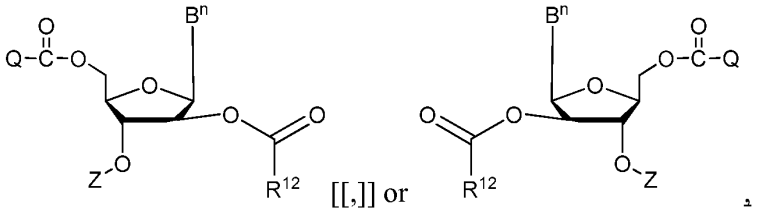
or a salt thereof.

20. (Original) The compound of Claim 1, wherein the compound is represented by one of the following structural formulas :



or , or a salt thereof.

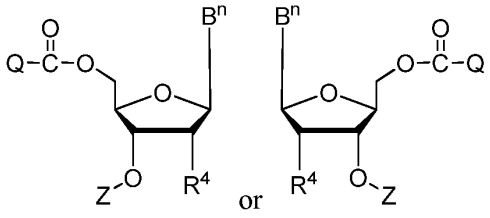
21. (Currently Amended) The compound of Claim 20, wherein the compound is represented by one of the following structural formulas:



[[,]] or ,

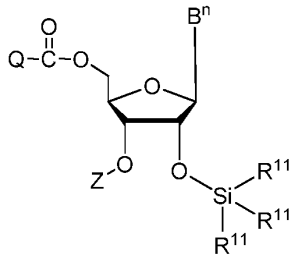
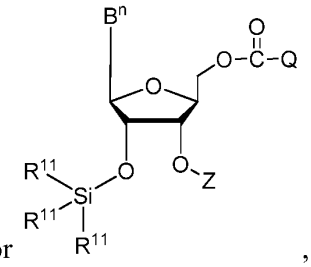
or a salt thereof.

22. (Original) The compound of Claim 1, wherein the compound is represented by one of the following structural formulas:



or , or a salt thereof.

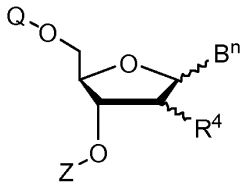
23. (Original) The compound of Claim 22, wherein the compound is represented by one of the following structural formulas:

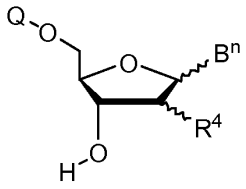

or

, or a salt thereof.

24.-27. (Cancelled).

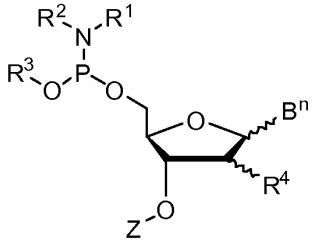
28. (Withdrawn) A method of preparing an oligonucleotide by bond formations in the 5'- to 3'- direction for the synthesis of RNA oligomers and enantiomers thereof, said method comprises the following steps

a) cleavage of ~~the~~ Z ~~protecting group~~ from a compound ~~attached to the support~~ represented by the following structural formula:

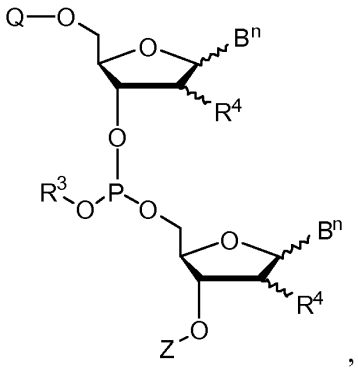

, thereby forming a compound represented by structural formula (XX):


(XX);

b) reacting the compound represented by structural formula XX with a compound of structural formula XXI:



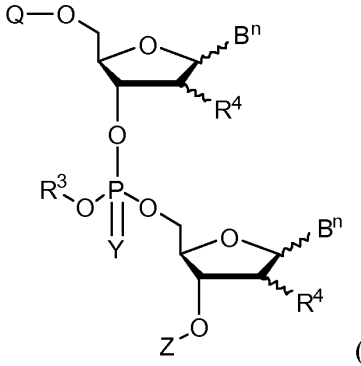
(XXI), thereby forming 2-mer compound represented by the following structural formula:



,

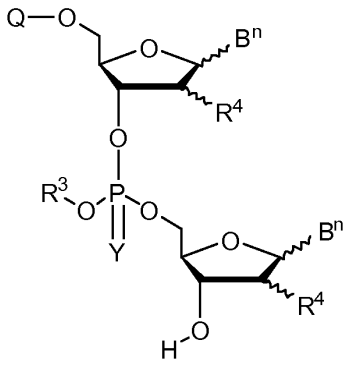
c) reacting the 2-mer compound with a capping agent;

d) oxidizing or sulfurizing ~~sulfurization of~~ the trivalent phosphorous group of the 2-mer compound to form a compound of structural formula XXII:



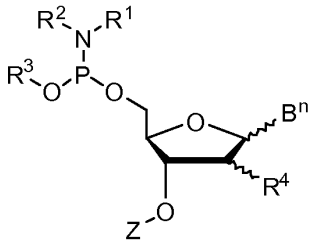
(XXII);

e) cleavage of ~~the~~ Z ~~protecting group~~ from ~~a~~ the compound represented by ~~the~~ structural formula XXII, thereby forming a compound of structural formula XXIII:

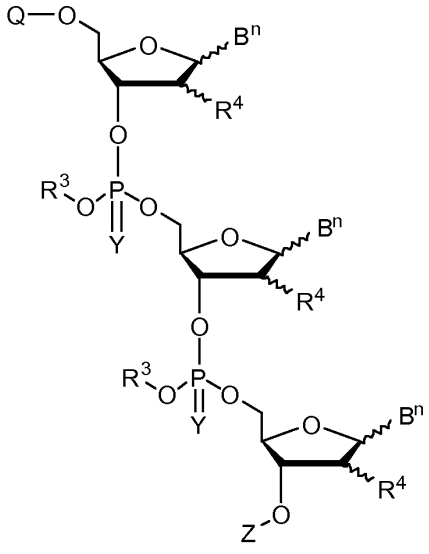


(XXIII);

f) reacting the compound represented by structural formula XXIII with a compound represented by the following structural formula:



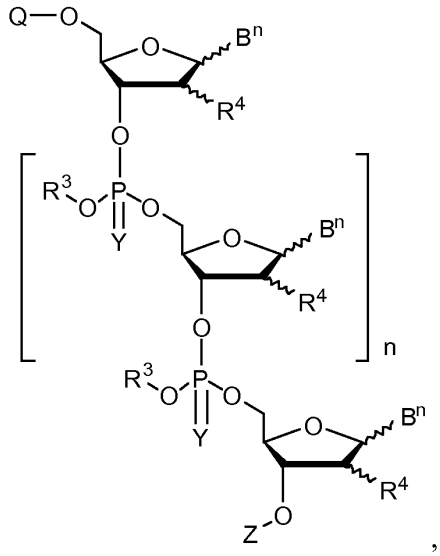
, thereby forming a 3-mer represented by the following structural formula XXIV:



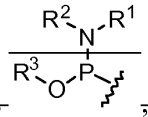
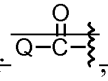
XXIV;

e) cleavage of ~~the~~ Z ~~protecting group~~ from ~~a~~ the compound represented by structural formula XXIV;

g) repeating steps a) through e) n times, thereby forming a oligonucleotide represented by the following structural formula:



, or a salt thereof, wherein:

~~J is~~  ~~, or~~  ~~, wherein indicates where J is attached to the O atom;~~

Q is ~~a)~~ a support comprised of: a) a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl;

each R^1 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

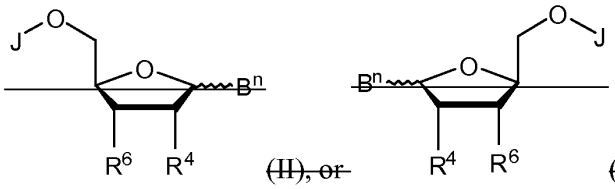
each R^2 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_3-C_{20})cycloalkyl group, or a substituted or unsubstituted (C_3-C_{20})cycloalkyl(C_1-C_{12})alkyl group, wherein the alkyl or

cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

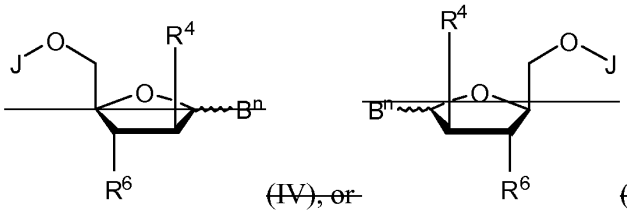
or each occurrence of R^1 and R^2 taken together with the nitrogen atom to which they are bound independently forms a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, NR^7, O and S;

each R^3 is independently a phosphate protecting group;

each R^4 is independently a [[-]]-halo, [[-]]-R^5, [[-]]-NR^7R^8, -OR^9, [[-]]-SR^{10}, or 2'-blocking group[[,]]; or when a 1-mer is in the β-D-ribose, β-L-ribose, α-D-ribose or α-L-ribose configuration, ~~Structural Formula Ia or Ib is:~~



~~(II), or~~ ~~(III);~~ wherein R^4 is further selected from O-Si(R^{11})$_3$ or O-CH_2-Si(R^{11})$_3$; or when a 1-mer is in the β-D-arabinose, β-L-arabinose, α-D-arabinose or α-L-arabinose configuration, ~~Structural Formula Ia or Ib is:~~



~~(IV), or~~ ~~(V);~~ R^4 is further selected from -OC(=O)R^{12};

each R^5 is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5, O and S; and may optionally terminate with –NR^7R^8, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, -OR^9, (C_1-C_6)alkoxy, benzyl or substituted benzyl, -SR^{10}; or -S-(C_1-C_6)alkyl group;

~~R^6 is H or O-Z;~~

each R^7 is independently a fluorenylmethyloxycarbonyl; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)CF_3$; $-C(=O)-(CH_2)_{1-16}NR^8C(=O)$-phthalimide; $-C(=O)-(CH_2)_{1-16}$–phthalimide; $NR^8C(=O)$-phthalimide; a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^8 is independently H or a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^9 is independently $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{10} is independently $-S(C_1-C_6)$ alkyl, $-C(=O)-(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{11} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group;

each R^{12} is independently a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_2-C_{12})alkenyl group, or a substituted or unsubstituted (C_2-C_{12})alkynyl group, or a substituted or unsubstituted aryl group;

each Z is independently an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl ~~an acid labile protecting group~~;

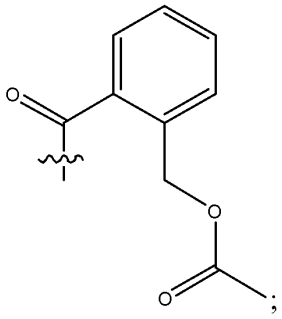
each B^n is independently hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is independently selected from:

N6,N6-dimethyl adenine, ~~N6-benzoyladenine,~~ N-1-methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7-deaza-7-iodoadenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with $-C\equiv C(CH_2)_{1\text{-}8}$-pthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6-methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C_1-C_6)alkylcytosine, N-3(C_1-C_6)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C_1-C_6)alkylcytosine, 5-aryl(C_1-C_6)alkylcytosine, 5-trifluoromethylcytosine, 5- methylcytosine, ethenocytosine, cytosine and uracil substituted with –CH=CH-C(=O)NH(C_1-C_6)alkyl, cytosine and uracil substituted with $-C\equiv C\text{-}CH_2$-phthalimide, NH(C_1-C_6)alkyl, 4-thiouracil, 2-thiouracil, N^3-thiobenzoylethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, ~~4-thiouracil,~~ N-3-(C_1-C_6) alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C_1-C_6)alkyluracil, 5-aryl(C_1-C_6)alkyluracil, 5-trifluoromethyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally <u>and independently</u> substituted with fluorenylmethyloxycarbonyl; -C(=O)OPh; -C(=O)(C_1-C_{16})alkyl; $-C(=O)CH_2CH_2CH=CH_2$l; -C(=O)(C_1-C_{16})alkylene-C(=O)OH; -C(=O)(C_1-C_{16})alkylene-C(=O)O(C_1-C_6)alkyl; $=CR^8N(C_1\text{-}C_6\text{alkyl})_2$; $-C(=O)\text{-}NR^8\text{-}(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$; $-C(=O)\text{-}(CH_2)_{1\text{-}16}NR^8C(=O)CF_3$;

-C(=O)-$NR^8(CH_2)_{1-16}NR^8C(=O)$-phthalimide;

-C(=O)-$(CH_2)_{1-16}$-phthalimide; and



wherein any substitutable oxygen atom within the nucleobase is optionally and independently substituted with –C(=O)N(C_1-C_6alkyl)$_2$ –C(=O)N(phenyl)$_2$; and

n is 1 to 150[[;]]

~~or a salt thereof~~.

29. (Withdrawn) The method of Claim 28, wherein each Y group is independently introduced via sulfurization to form a phosphorothioate linkage or via oxidation to form a phosphate linkage.

30. (Withdrawn) The method of Claim 29, wherein the R^3 group is eliminated after oxidation to form a phosphate linkage.

31. (Withdrawn – Currently Amended) The method of Claim 29, wherein the R^3 group is eliminated after sulfurization ~~sulfurazation~~ to form a phosphorothioate linkage.

32. (Withdrawn) The method of Claim 31, wherein the nucleobase protecting groups are deprotected with a base.

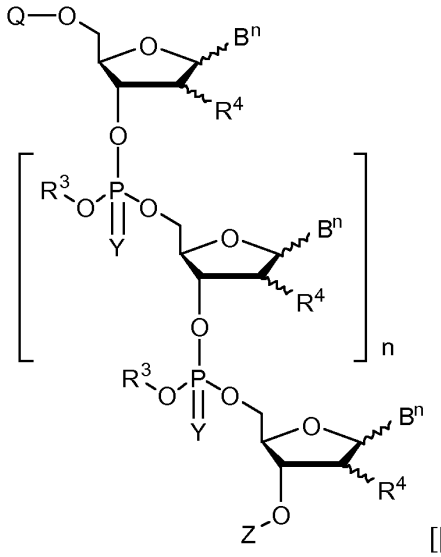
33. (Withdrawn – Currently Amended) The method of Claim 32, wherein the base is selected from aqueous ammonia, methanolic ammonia, or ethanolic ammonia.

34. (Withdrawn) The method of Claim 32, wherein R^4 is $-OSi(R^{11})_3$.

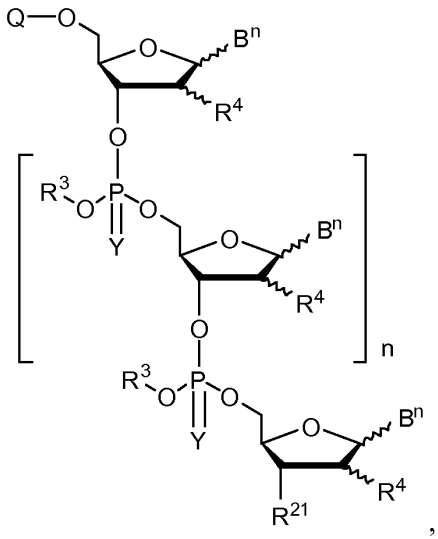
35. (Withdrawn – Currently Amended) The method of Claim 34, wherein the method further comprises the step of cleaving $-Si(R^{11})_3$ from $-OSi(R^{11})_3$ with a fluoride salt.

36. (Withdrawn) The method of Claim 35, wherein the fluoride salt is tetraethylammonium fluoride.

37. (Withdrawn – Currently Amended) The method of Claim 28, further comprising the step of reacting the compound represented by the following structural formula:



[[,]] with a 3' functional group, thereby forming a compound ~~of~~ represented by the following structural formula[[;]] :



, wherein R^{21} is the 3' functional group or a salt thereof.

38. (Withdrawn – Currently Amended) The method ~~compound~~ of Claim 37, wherein R^{21} is

a) cyanoethyl phosphate-polyethylene glycols^{v}, where v is 2-100 and is number of glycol units;

b) cyanoethyl phosphate –linker attached with cholesterol, biotin, fluorescein[[s]], cyanine dye[[s]], psoralen, tetramethylrhodamine dye, dabcyl dye, C-3 disulfide, C-6 disulfide, symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}), symmetrical and asymmetrical hydrocarbon chain (C_2-C_{50}) with a terminal amino group protected with CF3C(=O) or phthalamido or FMOC, (C_1-C_{16})alkylene-amine protected with a amine protecting group, (C_1-C_5)alkylene-amine protected with an azide group; (C_1-C_5)alkylene-amine protected ~~amine protected~~ with ~~an acetylene (C triple bond CH)~~ a C≡CH group;

c) cyanoethyl phosphate –ethane-2-ol- protected with DMT group or other acid labile group[[s]], cyanoethyl phosphate –propane -3-ol- protected with DMT group or other acid labile group[[s,]] ;

d) (C_1-C_{50})alkylene with a terminal hydroxy;

e) lipid[[s]], carboxyl group[[s]], or peptide; or

f) a branched phosphoramidite.

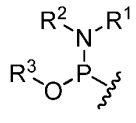
39. (Cancelled).

REMARKS

Claims 1-39 are pending. Claims 6, 9 and 17-39 are withdrawn. Claims 4, 5, 24-27 and 39 are cancelled herein.

Amendments to the Claims

Claim 1 has been amended to delete withdrawn subject matter, to clarify claim language, to incorporate the subject matter of Claim 5, and to delete N6-benzoyladenine from the list of nucleobases. Support for the amendments to Claim 1 can be found, for example, in original Claim 5.

Claim 2 has been amended to delete withdrawn subject matter, to incorporate the subject matter of Claim 5, to indicate that J is hydrogen or  , and to include a proviso. Support for the amendments to Claim 2 can be found, for example, at page 99, line 20 to page 100, line 1, and in original Claim 5.

Claims 3, 11, 15, 17-19, 21, 31 and 37 have been amended to simplify claim wording and/or to correct typographical errors.

Claims 6-8 and 10 have been amended to depend from Claim 1 in view of the cancellation of Claims 4 and 5. Claim 10 has also been amended to indicate that R^4 is $-O-Si(R^{11})_3$ or $-O-CH_2-Si(R^{11})_3$. Support for the amendments to Claim 10 can be found, for example, at page 24, lines 9-10.

Claim 28 has been amended to require all of the limitations of Claim 1, as amended, to clarify claim language and to indicate that the variables in each monomer can be selected independently of one another. Support for the amendments to Claim 28 can be found, for example, at page 45, lines 2-10 and at page 110, line 26 to page 117, line 32.

Claims 33, 35 and 38 have been amended to clarify claim wording.

The amendments are made to expedite prosecution of this application. Applicant is not conceding that the claims prior to amendment are not patentable. No inference should be made that Applicant is disclaiming any subject matter of the present application, and Applicant

reserves the right to pursue the unamended claims or any other broader or narrower claims supported by the disclosure at a later date, including in one or more continuing applications.

Entry of the amendments to Claims 1-3, 6-8, 10, 11, 15, 17-19 and 21 is respectfully requested. In addition, upon allowance of Claim 1, Applicant respectfully requests rejoinder of Claims 28-38.

Rejection of Claims 1-5, 7, 8, and 10-16 under 35 U.S.C. § 103(a)

Claims 1-5, 7, 8 and 10-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lin *et al.* Organic Letters (2001), Vol. 3, pages 795-797 (hereinafter "Lin"); Ogilvie *et al.* Can. J. Chem. (1978), Vol. 56, pages 2768-2780 (hereinafter "Ogilvie"); and Aramini *et al.* Biochemistry (1996), Vol. 35, pages 9355-9365 (hereinafter "Aramini"). The Examiner stated that it would have been obvious to protect the hydroxyl group of Compound 6 of Lin with a trityl group in order to produce a protected monomer for subsequent condensation reactions to form oligoribonucleotides as demonstrated by Ogilvie or Aramini.

Lin discloses a procedure for the synthesis of a 3',5'-cyclic boranomonophosphate. The procedure includes treating Compound 6 with tetrazole to induce intramolecular cyclization of the 3'-hydroxyl group onto the 5'-phosphoramidite. The intramolecular cyclization relies on the 3'-hydroxyl group being nucleophilic.

Ogilvie discloses the synthesis of oligoribonucleotides in the 3'→5' direction.

Aramini discloses the synthesis and spectroscopic study of a self-complementary DNA decamer. Aramini does not disclose RNA.

Claims 4 and 5 have been cancelled. Claims 1 and 2, as amended, are drawn to a compound of Formula Ia or Ib, or a salt thereof, wherein R^6 is hydrogen or -O-Z, and Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl.

The MPEP at 2143.01(V) states, "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984)." In *In re Gordon*, the Board ruled that there was no motivation to turn a prior art apparatus

upside-down in the absence of an indication in the prior art of the desirability to do so. In fact, according to the Board, the prior art reference actually taught away from the claimed invention because if the prior art apparatus were turned upside-down, it would not work for its intended purpose.

The combination of Lin with Ogilvie and Aramini, each alone or in combination, would render Lin's Compound 6 inoperable for its intended purpose. Compound 6 is an intermediate in the synthesis of a 3',5'-cyclic boranomonophosphate and, in the presence of tetrazole and under dilute conditions, undergoes intramolecular cyclization to form a cyclic phosphate triester. The success of the cyclization depends on the 3'-hydroxyl group being nucleophilic. A protected hydroxyl group, including a protected 3'-hydroxyl group in Lin's Compound 6, is not nucleophilic. Therefore, a 3'-hydroxyl-protected version of Lin's Compound 6 would not be useful for its intended purpose, namely to undergo intramolecular cyclization upon treatment with tetrazole.

Because the proposed modification (*i.e.*, protecting the hydroxyl group of Compound 6 of Lin with a trityl group) would render Compound 6 unsatisfactory for its intended purpose (*i.e.*, as an intermediate in the synthesis of a 3',5'-cyclic boranomonophosphate), there is no suggestion or motivation to make the proposed modification. In fact, according to the *Gordon* Board, there is a teaching away from the proposed modification. Because Lin teaches away from the proposed modification, there is no suggestion or motivation to make the proposed modification and thereby arrive at a compound of Formula Ia or Ib wherein R^6 is hydrogen or -O-Z and Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl, the subject matter of Claims 1 and 2, as amended.

Similarly, protection of the 3'-hydroxyl of Compounds 3 and 7 of Ogilvie would render Ogilvie's Compound 3 and 7 inoperable for their intended purpose – serving as building blocks for the synthesis of an oligoribonucleotide. Because Ogilvie's synthesis of oligoribonucleotides proceeds in the 3'→5' direction, compounds such as Compounds 3 and 7 must have a free 3'-hydroxyl group. It is this 3'-hydroxyl group that is converted first to a phosphate diester chloride and then to a phosphate triester that serves as the linkage between individual

ribonucleotides in the oligoribonucleotide. Because the proposed modification (*i.e.*, protecting the hydroxyl group of Compounds 3 and 7 of Ogilvie) would render Compounds 3 and 7 unsatisfactory for their intended purposes (*i.e.*, as building blocks in the synthesis of an oligoribonucleotide), there is no suggestion or motivation to make the proposed modification and thereby arrive at the subject matter of Claims 1 and 2, as amended. Therefore, like Lin, Ogilvie teaches away from the claimed subject matter.

With respect to the ribonucleotide at the 3'-terminus of the oligonucleotide, Ogilvie teaches, "We feel that in general it is best to protect the 3'-hydroxyl during chain extension, whether units are being added one at a time or in blocks…For stepwise chain extension the use of compounds ***9c*** and ***10c*** containing silyl groups on both 2'- and 3'-positions at the 3'-terminus of the growing chain is ideal" (Ogilvie, p. 2775, right colum). Thus, even when Ogilvie teaches protection of the 3'-hydroxyl group, the suggestion is to protect it with a silyl group, not an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl, as recited in amended Claims 1 and 2. The difference between having silyl groups on both the 2'- and 3'-positions at the 3'-terminus and having orthogonal groups at R^4 and R^6 is significant because, in order to achieve reverse RNA synthesis (*e.g.*, 5'→3' synthesis), such as that disclosed in the instant application, the groups used to protect the 2'- and 3'-hydroxyl groups need to be independently removable. There is no teaching or suggestion in Ogilvie that the silyl groups on both 2'- and 3'-positions at the 3'-terminus are independently removable, such that one might be removed without affecting the other. Thus, Ogilvie does not teach or suggest the subject matter of amended Claims 1 and 2, either alone or in combination with Lin.

Because there is no 2'-substituent in DNA, there is also no teaching or suggestion in Aramini to have orthogonal groups at R^4 and R^6. As stated above, having orthogonal substituents at R^4 and R^6 is significant because, in order to achieve reverse RNA synthesis, such as that disclosed in the instant application, the groups used to protect the 2'- and 3'-hydroxyl groups need to be independently removable. Because Aramini does not provide the teaching or suggestion missing from Lin and Ogilvie to differentially protect the 2'- and 3'-hydroxyl groups,

Aramini does not rectify the deficiencies of Lin and Ogilvie or overcome the teaching away of Lin and Ogilvie.

Therefore, Claims 1 and 2, as amended, are patentable under 35 U.S.C. § 103(a) in view of Lin, Ogilvie and Aramini. Because Claim 1, as amended, is patentable under 35 U.S.C. § 103(a) in view of Lin, Ogilvie and Aramini, and Claims 3, 7, 8 and 10-16 depend, directly or indirectly, from Claim 1, Claims 3, 7, 8 and 10-16 are also patentable under 35 U.S.C. § 103(a) in view of Lin, Ogilvie and Aramini.

Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By /Alice O. Carroll, Reg. No. 33,542/
Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Date: April 26, 2013

1374090.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Group:	1623
Filed:	February 19, 2010	Examiner:	Lewis, Patrick T.
Confirmation No.:	5297		
For:	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		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

_____ _____
Date Signature

_____
Typed or printed name of person signing certificate

TRANSMITTAL LETTER FOR SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

Commissioner:

This Information Disclosure Statement is submitted:

☐ under 37 CFR 1.97(b), or
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application; or before the mailing date of a first office action on the merits; or before the mailing of a first office action after the filing of a Request for Continued Examination).

☒ under 37 CFR 1.97(c) together with either:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, or
- ☒ a $90 fee under 37 CFR 1.17(p), or
(After the 37 CFR 1.97(b) time period, but before any of a final action, notice of allowance, or an action that closes prosecution, whichever occurs first)

☐ under 37 CFR 1.97(d) together with:
- ☐ a Statement under 37 CFR 1.97(e), as checked below, and
- ☐ a $[180/90/45] fee under 37 CFR 1.17(p), or
(Filed after final action, notice of allowance, whichever occurs first, or if prosecution otherwise closes, but on or before payment of the issue fee)

Shanghai Hongene Exhibit 1002

☐ under 37 CFR 1.97(i):
Applicant requests that the IDS and cited reference(s) be placed in the application file.
(Filed after payment of issue fee)

Statement Under 37 CFR 1.97(e)

☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)
Applies to original applications (other than design) filed on or after May 29, 2000

☐ (1) A paper containing only an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section if it is accompanied by a statement that each item of information contained in the information disclosure statement:

☐ (i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in §1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

☐ (ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in §1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☒ Enclosed herewith is a Listing of References. Copies of the cited references are enclosed except as indicated below or in the attached Listing of References.

☐ Copies of the cited references submitted with an Information Disclosure Statement in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed, are not required under 37 CFR 1.98(d)(1) and (2) and are thus not provided.

☐ The listed references were cited in the enclosed Search Report in counterpart foreign application [add application number], which is listed in the attached Listing of References.

☐ The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

- ☐ the explanation provided on the attached sheet.
- ☐ the explanation provided in the Specification.
- ☐ submission of the enclosed International Search Report.
- ☐ submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.
- ☐ the enclosed English language abstract.

Method of payment:

☐ Authorization is NOT granted to charge any fees which may be due in this matter to our Deposit Account.

☒ Please charge Deposit Account 08-0380 in the amount of $90.

☐ A check for the fee noted above is enclosed, or the fee has been included in the check with the accompanying Reply.

☒ Please charge any deficiency in fees and credit any overpayment to Deposit Account 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By /Alice O. Carroll, Reg. No. 33,542/
Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: April 26, 2013

Substitute for form 1449B/PTO **SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** April 26, 2013 (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Lewis, Patrick T.	CONFIRMATION NO. 5297	GROUP 1623

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	C17	Srivastava, S.C., *et al.,* "RNA Synthesis by Reverse Direction Process: Phosphoramidites and High Purity RNAs and Introduction of Ligands, Chromophores, and Modifications at 3'-End:, *Current Protocols in Nucleic Acid Chemistry,* 3.20.1-3.20.39 (June 2011).
	C18	
	C19	
	C20	
	C21	
	C22	
	C23	
	C24	
	C25	
	C26	
	C27	
	C28	
	C29	
	C30	
	C31	
	C32	
	C33	
	C34	

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.**

EXAMINER	DATE CONSIDERED

Shanghai Hongene Exhibit 1002

Electronic Patent Application Fee Transmittal

Application Number:	12708827
Filing Date:	19-Feb-2010
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Filer:	Alice O. Carroll/Claudia Fagan
Attorney Docket Number:	4441.1001-002

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Extension - 3 months with $0 paid	2253	1	700	700

Shanghai Hongene Exhibit 1002

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**790**

Electronic Acknowledgement Receipt	
EFS ID:	15621341
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Claudia Fagan
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	26-APR-2013
Filing Date:	19-FEB-2010
Time Stamp:	18:28:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$790
RAM confirmation Number	7400
Deposit Account	080380
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	44411001002RefC17.pdf	2733032 dc6c8f23126fbbd0fd5a4ce9ea44a481d2a5178e	no	20
Warnings:					
Information:					
2	Transmittal Letter	44411001002AmendTransmittal.pdf	104407 26d30d3d8aa68cf04d3fff9525e99bc8c8d7b7e7	no	3
Warnings:					
Information:					
3		44411001002Amendment.pdf	251898 0d42ff9dfc1a2f32a51438e3e8fd29842ea92b3b	yes	30

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	25
Applicant Arguments/Remarks Made in an Amendment	26	30

Warnings:					
Information:					
4	Transmittal Letter	44411001002IDSTransmittal.pdf	75059 55bc776c09c93717845aaa72d3ecd11b87ef0854	no	3
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	44411001002ListReferences.pdf	79582 0035ddf59ee26e442f94530829c72a7b66919df2	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
6	Fee Worksheet (SB06)	fee-info.pdf	32649 516e57fd5ee43ebce74dd3dd21c38c1619fab403	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3276627		

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Suresh C. Srivastava and Naveen P. Srivastava

Application No.: 12/708,827 Group: 1623

Filed: February 19, 2010 Examiner: Lewis, Patrick T.

Confirmation No.: 5297

For: Phosphoramidites For Synthetic RNA In The Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'- End Ligands, Chromophores And Modifications Of Synthetic RNA

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

_____ _____
Date Signature

_____
Typed or printed name of person signing certificate

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

Commissioner:

Transmitted herewith is and Amendment for filing in the above-identified application.

☒ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a Small Entity Statement previously submitted.

☐ A Small Entity Statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.

☐ The Assignee hereby claims small entity status of the above-identified application under 37 CFR 1.27. This statement is being executed on behalf of the Assignee pursuant to 1.27(c)(2).
(Use if large entity and changing to small entity.)

☐ Applicant qualifies for and claims micro entity status. A Certification of Micro Entity Status **[Option** (Gross Income Basis)(Institution of Higher Education Basis)**]** is enclosed.

The claims fee has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	LARGE ENTITY RATE	LARGE ENTITY ADDIT. FEE
TOTAL	32	MINUS	* 39		X $80	$
INDEP	3	MINUS	** 5		X $420	$
☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+ $780	$

* not fewer than 20
** not fewer than 3

TOTAL OF ABOVE = $ 0

☐ Applicant claims small entity status. Fees above are reduced by 50%. MINUS $ 0

☐ Applicant claims micro entity status. Fees above are reduced by 75%. MINUS $ 0

TOTAL CLAIMS FEE $ 0

The Application Size Fee has been calculated as shown below:
(Effective for cases filed on or after December 8, 2004)

Actual Sheets (Including current amendment)	Highest No. of Sheets Paid For (At least 100)	No. of Additional Units Required (Increments of 50 sheets)	LARGE ENTITY Rate	LARGE ENTITY Total Amount Owed	Payment Sufficient for up to
195	150		X $400	$[ ]	150 Sheets

☐ Applicant claims small entity status. Fees above are reduced by 50%. MINUS $ 0

☐ Applicant claims micro entity status. Fees above are reduced by 75%. MINUS $ 0

TOTAL APPLICATION SIZE FEE $ 0

Petition for Extension of Time

☒ Applicant hereby petitions to extend the time to respond to the Office Action dated October 26, 2012 for 3 month(s) from January 26, 2013 to April 26, 2013. The appropriate fee is set forth below.

☐ *[For action-specific language in an extension of time, select the appropriate option from the Firm Templates]*

Please charge Deposit Account No. 08-0380 for the following fees:

☒	Petition for 3 month Extension of Time	$ 700
☐	Claims Fee	$
☐	Application Size Fee	$
☒	Other Fees:	
	Supplemental Information Disclosure Statement	$ 90
		$
	TOTAL:	$ 790

A check is enclosed in payment of the following fees:

☐	Petition for [ ] month Extension of Time	$
☐	Claims Fee	$
☐	Application Size Fee	$
☐	Other Fees:	
		$
		$
	TOTAL:	$

☒ Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By /Alice O. Carroll, Reg. No. 33,542/
Alice O. Carroll
Registration No.: 33,542
Telephone (978) 341-0036
Facsimile (978) 341-0136

Concord, Massachusetts 01742-9133
Dated: April 26, 2013

–Rev/Fee Schedule March 19, 2013

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/708,827	Filing Date 02/19/2010	☐ 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

AMENDMENT	04/26/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 32	Minus	** 39	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***5	= 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

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) 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.

LIE
/SHOWANE SMITH/

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.

Shanghai Hongene Exhibit 1002

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

21005 7590 05/22/2013

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER
LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 05/22/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002	5297

TITLE OF INVENTION: PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	08/22/2013

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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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)

21005 7590 05/22/2013
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

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.
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002	5297

TITLE OF INVENTION: PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	08/22/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1621	536-025300

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 _____
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 credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

PTOL-85 (Rev. 02/11)

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	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.
❑ Applicant changing to regular undiscounted fee 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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002	5297

21005 7590 05/22/2013

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 05/22/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 165 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 165 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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. 12/708,827	Applicant(s) SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	Art Unit 1621	AIA (First Inventor to File) 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 4/26/13*.
   ☐ 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 *1-3,6-23 and 28-38*. 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: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been 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)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 04262013
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Patrick T. Lewis/
Primary Examiner, Art Unit 1621

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION									
CLASS	**SUBCLASS**	**CLAIMED**					**NON-CLAIMED**				
536	25.3	C	0	7	H	21 / 00 (2006.01.01)					
CROSS REFERENCE(S)											
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**										
536	25.31	26.7	26.8	27.1	27.13						
536	27.2										

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	32	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621	5/20/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No. 20130520

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	32	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621	5/20/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No. 20130520

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17		33										
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	3		19		35										
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	11		27												
	12		28												
	13		29												
	14		30												
	15		31												
	16		32												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 32	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621 (Primary Examiner)	5/20/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office Part of Paper No. 20130520

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

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, GOOGLE (oligonucleotide synthesis)	6/12/2012	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	10/20/2012	/PL/
Updated Inventor, REGISTRY, CAPLUS, MEDLINE searches	5/20/2013	/PL/

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
536	25.3, 25.31, 26.7, 26.8, 27.1, 27.13, 27.2	5/20/2013	/PL/

WEST Search History

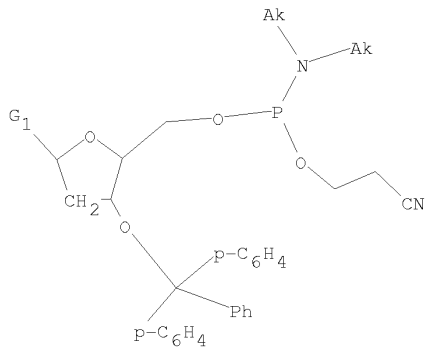
Hide Items | Restore | Clear | Close

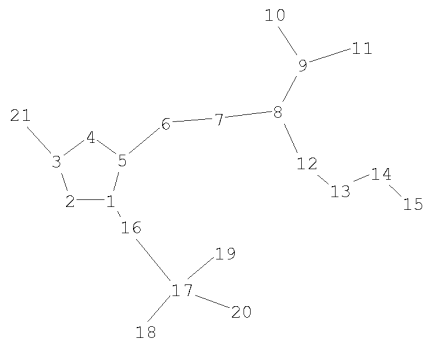
DATE: Monday, May 20, 2013

Hide?	Set Name	Query	Hit Count
Interference			
DB=PGPB,USPT; PLUR=YES; OP=ADJ			
☐	L8	L7 and fluoride	74
☐	L7	L6 and sulfurization	140
☐	L6	L5 and oxidation	550
☐	L5	L4 and trityl	760
☐	L4	L2 and protecting group	1300
☐	L3	L2 and phosphorathioate	2
☐	L2	L1 and phosphoramidite	1690
☐	L1	(536/25.3,25.31,26.7,26.8,27.1,27.13,27.2)![CCLS]	3666

END OF SEARCH HISTORY

C:\Users\plewis\Documents\STN Express 8.4\Queries\12708827-4.str






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chain nodes :
    6  7  8  9  10  11  12  13  14  15  16  17  18  19  20  21
ring nodes :
    1  2  3  4  5
chain bonds :
    1-16  3-21  5-6  6-7  7-8  8-9  8-12  9-10  9-11  12-13  13-14  14-15  16-17  17-18  17-19
    17-20
ring bonds :
    1-2  1-5  2-3  3-4  4-5
exact/norm bonds :
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exact bonds :
    5-6  13-14  14-15  17-18  17-19  17-20


G1:H,Hy

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:CLASS  19:CLASS  20:CLASS
    21:CLASS
```

Substitute for form 1449B/PTO **SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION** **LISTING OF REFERENCES** April 26, 2013 (Use several sheets if necessary)	ATTORNEY DOCKET NO. 4441.1001-002	APPLICATION NO. 12/708,827	
	FIRST NAMED INVENTOR Suresh C. Srivastava	FILING DATE February 19, 2010	
	EXAMINER Lewis, Patrick T.	CONFIRMATION NO. 5297	GROUP 1623

Examiner's Initials	Ref. No.	**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
/P.L./	C17	Srivastava, S.C., *et al.*, "RNA Synthesis by Reverse Direction Process: Phosphoramidites and High Purity RNAs and Introduction of Ligands, Chromophores, and Modifications at 3'-End:, *Current Protocols in Nucleic Acid Chemistry*, 3.20.1-3.20.39 (June 2011).
	C18	
	C19	
	C20	
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	C25	
	C26	
	C27	
	C28	
	C29	
	C30	
	C31	
	C32	
	C33	
	C34	

***Copies of any U.S. Office Communications or non-published U.S. Patent Applications are not being provided because the examiner has access to such documents through PAIR. We are not listing separately any prior U.S. Patent Office communications regarding the cited documents because the Examiner has access to any such actions through PAIR.**

EXAMINER /Patrick Lewis/ (05/04/2013)	DATE CONSIDERED

Shanghai Hongene Exhibit 1002

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1621

✓	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	06/12/2012	10/20/2012	05/20/2013						
	1	÷	✓	=						
	2	÷	✓	=						
	3	÷	✓	=						
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	7	÷	✓	=						
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	35	÷	N	=						
	36	÷	N	=						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1621

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☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	06/12/2012	10/20/2012	05/20/2013						
	37	÷	N	=						
	38	÷	N	=						
	39	÷	N	-						

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002	5297

21005 7590 08/08/2013

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
LEWIS, PATRICK T	
ART UNIT	**PAPER NUMBER**
1621	

NOTIFICATION DATE	DELIVERY MODE
08/08/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing.department@hbsr.com
helpdesk@hbsr.com

Corrected Notice of Allowability	**Application No.** 12/708,827	**Applicant(s)** SRIVASTAVA ET AL.	
	Examiner PATRICK LEWIS	**Art Unit** 1621	**AIA (First Inventor to File) 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 _____.
   ☐ 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 *1-3, 6-23 and 28-38*. 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)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Patrick T. Lewis/
Primary Examiner, Art Unit 1621

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Becky Simmons on August 2, 2013.

The application has been amended as follows:

In claim 28, line27, the term "e)" has been deleted and the term ---g)--- has been inserted therefor; in line 29, the text "g) repeating steps a) through e)" has been deleted and the text --- h) repeating steps a) through g)--- has been inserted therefor.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached on Monday - Thursday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Wu-Cheng W. Shen can be reached on 571-272-3157. 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 T. Lewis/
Primary Examiner, Art Unit 1621

/PL/

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12708827	SRIVASTAVA ET AL.
Examiner	**Art Unit**
PATRICK LEWIS	1621

CPC

Symbol	Type	Version
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CPC Combination Sets

Symbol	Type	Set	Ranking	Version
/				
/				

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 32
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621 (Primary Examiner)	8/2/2013 (Date)	O.G. Print Claim(s): 1 O.G. Print Figure: None

U.S. Patent and Trademark Office — Part of Paper No. 20130802

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS					CLAIMED						NON-CLAIMED				
536	25.3					C	0	7	H	21 / 00 (2006.01.01)						
CROSS REFERENCE(S)																
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
536	25.31	26.7	26.8	27.1	27.13											
536	27.2															

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 32	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621 (Primary Examiner)	8/2/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office — Part of Paper No. 20130802

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	**Art Unit**
	PATRICK LEWIS	1621

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17		33										
	2		18		34										
	3		19		35										
	4		20		36										
	5		21		37										
	6		22		38										
	7		23		39										
	8		24												
	9		25												
	10		26												
	11		27												
	12		28												
	13		29												
	14		30												
	15		31												
	16		32												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 32	
/PATRICK LEWIS/ Primary Examiner.Art Unit 1621 (Primary Examiner)	8/2/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office Part of Paper No. 20130802

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1621

✓	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	06/12/2012	10/20/2012	05/20/2013	08/02/2013					
	1	÷	✓	=	=					
	2	÷	✓	=	=					
	3	÷	✓	=	=					
	4	÷	✓	-	-					
	5	÷	✓	-	-					
	6	÷	N	=	=					
	7	÷	✓	=	=					
	8	÷	✓	=	=					
	9	÷	N	=	=					
	10	÷	✓	=	=					
	11	÷	✓	=	=					
	12	÷	✓	=	=					
	13	÷	✓	=	=					
	14	÷	✓	=	=					
	15	÷	✓	=	=					
	16	÷	✓	=	=					
	17	÷	N	=	=					
	18	÷	N	=	=					
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	28	÷	N	=	=					
	29	÷	N	=	=					
	30	÷	N	=	=					
	31	÷	N	=	=					
	32	÷	N	=	=					
	33	÷	N	=	=					
	34	÷	N	=	=					
	35	÷	N	=	=					
	36	÷	N	=	=					

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1621

✓	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	06/12/2012	10/20/2012	05/20/2013	08/02/2013					
	37	÷	N	=	=					
	38	÷	N	=	=					
	39	÷	N	-	-					

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12708827	SRIVASTAVA ET AL.
	Examiner	Art Unit
	PATRICK LEWIS	1623

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, GOOGLE (oligonucleotide synthesis)	6/12/2012	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	10/20/2012	/PL/
Updated Inventor, REGISTRY, CAPLUS, MEDLINE searches	5/20/2013	/PL/
Updated Inventor, REGISTRY, CAPLUS, MEDLINE searches	8/2/2013	/PL/

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
536	25.3, 25.31, 26.7, 26.8, 27.1, 27.13, 27.2	5/20/2013	/PL/

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)

21005 7590 05/22/2013
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

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.
12/708,827	02/19/2010	Suresh C. Srivastava	4441.1001-002	5297

TITLE OF INVENTION: PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	08/22/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1621	536-025300

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 Hamilton, Brook, Smith & Reynolds, P.C.
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 _____

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 credit any overpayment, to Deposit Account Number 08-0380 (enclose an extra copy of this form).

PTOL-85 (Rev. 02/11)

Shanghai Hongene Exhibit 1002

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

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.

☐ Applicant changing to regular undiscounted fee 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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Alice Carroll Date August 21, 2013

Typed or printed name Alice O. Carroll Registration No. 33,542

This collection of information 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.

Electronic Patent Application Fee Transmittal

Application Number:	12708827
Filing Date:	19-Feb-2010
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Filer:	Alice O. Carroll/ann giso
Attorney Docket Number:	4441.1001-002

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Utility Appl Issue Fee	2501	1	890	890
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Shanghai Hongene Exhibit 1002

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1190**

Electronic Acknowledgement Receipt	
EFS ID:	16645321
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/ann giso
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	21-AUG-2013
Filing Date:	19-FEB-2010
Time Stamp:	16:21:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1190
RAM confirmation Number	3322
Deposit Account	080380
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

Shanghai Hongene Exhibit 1002

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	44411001002_IssueFee.pdf	201870 84c6e3c89e2f1daffae3abc4a2f86d1a0819a630	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31964 27d9e0be18d2c2a004d60e1a3f0776bad42990be	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	233834		

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,827	09/24/2013	8541569	4441.1001-002	5297

21005 7590 09/04/2013

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

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 382 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;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Suresh C. Srivastava and Naveen P. Srivastava		
Application No.:	12/708,827	Filed:	February 19, 2010
Patent No.:	8,541,569	Issued:	September 24, 2013
Title:	Phosphoramidites For Synthetic RNA In The Reverse Direction, Efficient RNA Synthesis and Convenient Introduction of 3'- End Ligands, Chromophores And Modifications Of Synthetic RNA		

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

_____ _____
Date Signature

_____
Typed or printed name of person signing certificate

REQUEST FOR CERTIFICATE OF CORRECTION

Commissioner for Patents
Office of Patent Publication
ATTN: Certificate of Correction Branch
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Pursuant to 35 U.S.C. § 254, we hereby request that a Certificate of Correction be issued for the above-referenced U.S. Letters Patent to correct errors as shown on the attached PTO/SB/44 form.

Since the errors were made by the U.S. Patent and Trademark Office and not by Patentee or Patentee's Attorney/Agent, it is understood that no additional fees are due for the requested Certificate of Correction.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll
Alice O. Carroll
Registration No.: 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: April 22, 2014

1520878.v1

Shanghai Hongene Exhibit 1002

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
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.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,541,569 B2

APPLICATION NO.: 12/708,827

ISSUE DATE : September 24, 2013

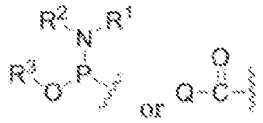
INVENTOR(S) : Suresh C. Srivastava, Naveen P. Srivastava

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

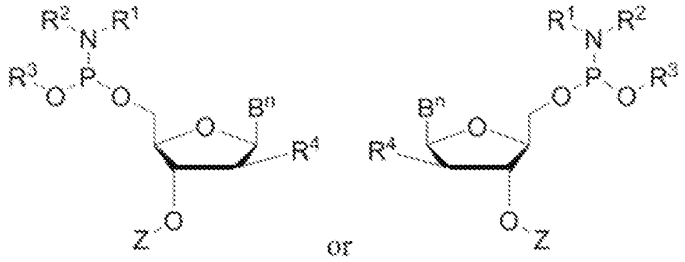
Claim 1, Column 113, line 46, delete "N-1 methyladenine" and insert -- N-1-methyladenine --.

Claim 1, column 114, line 12, delete "—" before the semicolon.

Claim 3, Column 117, lines 54 - 60, delete the structures and replace them with:



Claim 14, Column 120, Lines 20 - 40, delete the structures and replace them with:



MAILING ADDRESS OF SENDER (Please do not use customer number below):
Hamilton, Brook, Smith & Reynolds, P.C.
530 Virginia Road, P.O. Box 9133
Concord, MA 01742-9133

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 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: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
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.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,541,569 B2

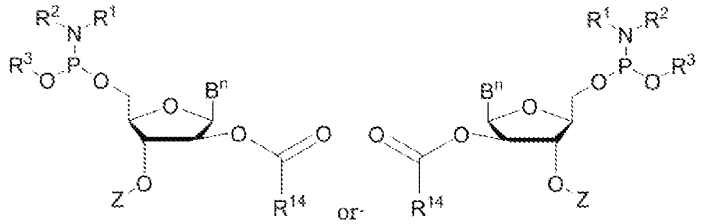
APPLICATION NO.: 12/708,827

ISSUE DATE : September 24, 2013

INVENTOR(S) : Suresh C. Srivastava, Naveen P. Srivastava

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 15, Column 120, lines 45 - 65, delete the structures and replace them with:



Claim 22, Column 126, Line 33, delete " NR^S " and insert -- NR^5 --.

Claim 22, column 127, line 7, delete "N1 methyladenine" and insert --N1-methyladenine --.

Claim 32, Column 129, Line 2, delete "glycols'" and insert -- glycols^v --.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Hamilton, Brook, Smith & Reynolds, P.C.

530 Virginia Road, P.O. Box 9133

Concord, MA 01742-9133

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 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: Attention Certificate of Corrections Branch, 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.

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 Acknowledgement Receipt

EFS ID:	18825627
Application Number:	12708827
International Application Number:	
Confirmation Number:	5297
Title of Invention:	PHOSPHORAMIDITES FOR SYNTHETIC RNA IN THE REVERSE DIRECTION, EFFICIENT RNA SYNTHESIS AND CONVENIENT INTRODUCTION OF 3'-END LIGANDS, CHROMOPHORES AND MODIFICATIONS OF SYNTHETIC RNA
First Named Inventor/Applicant Name:	Suresh C. Srivastava
Customer Number:	21005
Filer:	Alice O. Carroll/Kellie Varno
Filer Authorized By:	Alice O. Carroll
Attorney Docket Number:	4441.1001-002
Receipt Date:	22-APR-2014
Filing Date:	19-FEB-2010
Time Stamp:	15:57:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	44411001002ReqforCertofCorr.PDF	742171 cc3de4b35559eae5fd47ed81b3e40e82158b553a	no	4
Warnings:					
Information:					

Total Files Size (in bytes):	742171

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

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

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

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

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

Paper No.:20140604

DATE : June 04, 2014

TO SPE OF : ART UNIT 1672

SUBJECT : Request for Certificate of Correction on Patent No.: 8541569

A response is requested with respect to the accompanying request for a certificate of correction.

Please complete this form and return with file, within **7** days to:
Certificates of Correction Branch - ST (South Tower) 9A22
Palm location **7590** - Tel. No. (703) 305-8309

With respect to the change(s) requested, correcting Office and/or Applicant's errors, should the patent read as shown in the certificate of correction? No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Thank You For Your Assistance **Certificates of Correction Branch**

The request for issuing the above-identified correction(s) is hereby:

Note your decision on the appropriated box.

☒ **Approved** All changes apply.

☐ **Approved in Part** Specify below which changes **do not** apply.

☐ **Denied** State the reasons for denial below.

Comments:

/BRANDON FETTEROLF/
Supervisory Patent Examiner.Art Unit 1672

PTOL-306 (Rev. 7/03) U.S. DEPARTMENT OF COMMERCE Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,541,569 B2
APPLICATION NO. : 12/708827
DATED : September 24, 2013
INVENTOR(S) : Suresh C. Srivastava and Naveen P. Srivastava

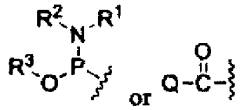
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

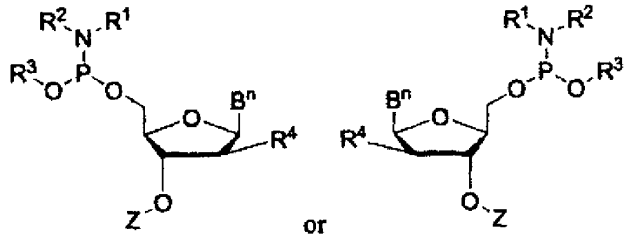
Claim 1, Column 113, Line 46, delete "N-1 methyladenine" and insert -- N-1-methyladenine --.

Claim 1, Column 114, Line 12, delete "—" before the ";".

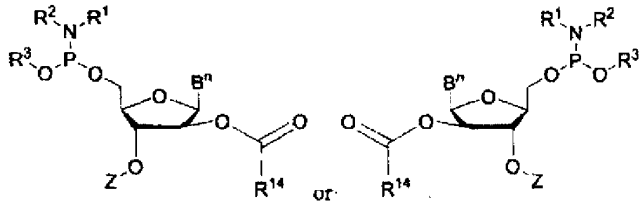
Claim 3, Column 117, Lines 54 - 60, delete the structures and replace them with:



Claim 14, Column 120, Lines 20 - 40, delete the structures and replace them with:



Claim 15, Column 120, Lines 45 - 65, delete the structures and replace them with:



Signed and Sealed this
First Day of July, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

Shanghai Hongene Exhibit 1002

Claim 22, Column 126, Line 33, delete "NR^S" and insert -- NR^5 --.

Claim 22, Column 127, Line 7, delete "N1 methyladenine" and insert -- N1-methyladenine --.

Claim 32, Column 129, Line 2, delete "glycols'" and insert -- $glycols^v$ --.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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.	DATE FILED	U.S. DISTRICT COURT
1:22-10290	02/18/2022 Format m/d/yyyy	Massachusetts
PLAINTIFF ChemGenes Corporation		DEFENDANT Hongene Biotchnology Ltd.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,309,707	11/13/2012 Format m/d/yyyy	ChemGenes Corporation
2 8,541,569	09/24/2013 Format m/d/yyyy	ChemGenes Corporation
3 9,884,885	02/06/2018 Format m/d/yyyy	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	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
Format m/d/yyyy TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	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

Copy 1---Upon initiation of action, mail this copy to Director Copy 3---Upon termination of action, mail this copy to Director
Copy 2---Upon filing document adding patent(s), mail this copy to Director Copy 4---Case file copy

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