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see Notice of 22 April 2010

(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

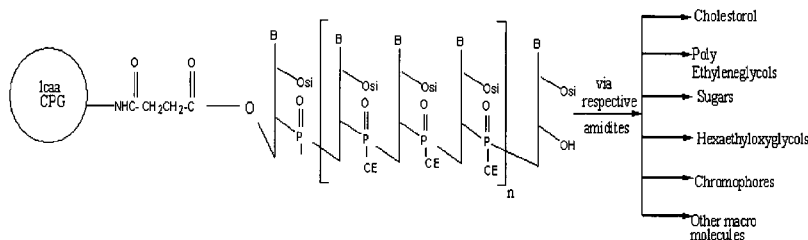


Fig.7. Diagrammatic Representation of 5'→3' RNA synthesis and application to 3'-modifications

(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 <sup>31</sup>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%.



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## INTERNATIONAL SEARCH REPORT

International 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	<p>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 ----- -/--</p>	1

 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

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## INTERNATIONAL SEARCH REPORT

International 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

# INTERNATIONAL SEARCH REPORT

International 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.

## 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  
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## 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  
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## 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  
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## 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  
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## 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  
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