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- (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, BN, BR, BW, BY,

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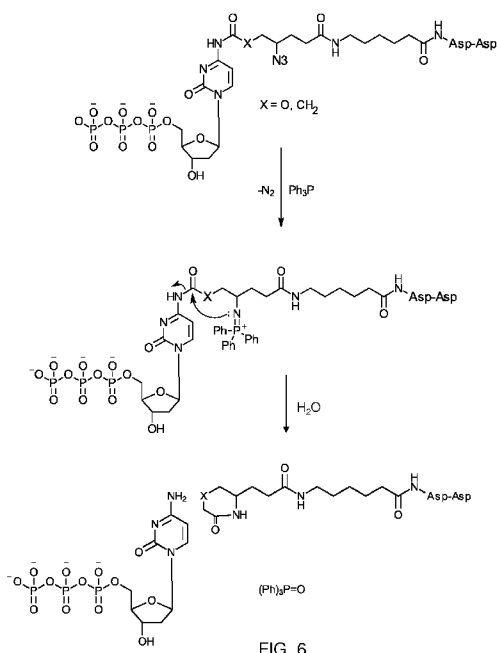
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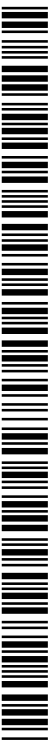
- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

[Continued on next page]

(54) Title: METHODS AND APPARATUS FOR SYNTHESIZING NUCLEIC ACIDS



(57) Abstract: The invention provides improved methods for synthesizing polynucleotides, such as DNA and RNA, using enzymes and specially designed nucleotide analogs. Using the methods of the invention, specific sequences of polynucleotides can be synthesized de novo, base by base, in an aqueous environment, without the use of a nucleic acid template. Because the nucleotide analogs have an unmodified 3' OH, i.e., as found in "natural" deoxyribose and ribose molecules, the analogs result in natural polynucleotides suitable for incorporation into biological systems.





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- with information concerning request for restoration of the right of priority in respect of one or more priority claims (Rules 26bis.3 and 48.2(b)(vii))
- with sequence listing part of description (Rule 5.2(a))
- (88) Date of publication of the international search report:
20 November 2014

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/033811

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12P 19/34

USPC - 435/91.1

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07H 21/00, 21/04; C12N 15/09; C12P 19/34; C12Q 1/48, 1/68; C40B 50/08 (2014.01)
USPC - 435/6.1, 91.1; 536/24.33, 25.4, 25.6Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C07B 2200/11; C12N 15/1068; C12P 19/34; C12Q 1/6811, 1/6853 (2014.06)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google, PubMed, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2011/0201002 A1 (GELFAND et al) 18 August 2011 (18.08.2011) entire document	1-3, 6-9, 14-19, 21-30, 32, 34, 35, 37-40 ----- 4, 5, 20, 31, 33, 36
Y	US 2004/0043396 A1 (MUELLER et al) 04 March 2004 (04.03.2004) entire document	4, 5
Y	US 8,071,755 B2 (EFCAVITCH et al) 06 December 2011 (06.12.2011) entire document	20, 33
Y	WO 1994/14972 A1 (HYMAN et al) 07 July 1994 (07.07.94) entire document	31, 36
A	WO 2007/022493 A2 (LEMAON et al) 22 February 2007 (22.02.2007) entire document	1-40
A	WO 2008/144544 A1 (SIDDIQI et al) 27 November 2008 (27.11.2008) entire document	1-40
A	BOWERS et al. 'Virtual Terminator nucleotides for next generation DNA sequencing' Nat Methods, 01 August 2009 (01.08.2009), Vol. 6, Pgs. 593-595. entire document	1-40
T, X	US 8,808,989 B1 (EFCAVITCH et al) 19 August 2014 (19.08.2014) entire document	1-40

 Further documents are listed in the continuation of Box C.

* 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 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

08 September 2014

Date of mailing of the international search report

30 SEP 2014

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/033811

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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

2. 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.

3. Additional comments:

SEQ ID NOs:1-6 were searched.