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

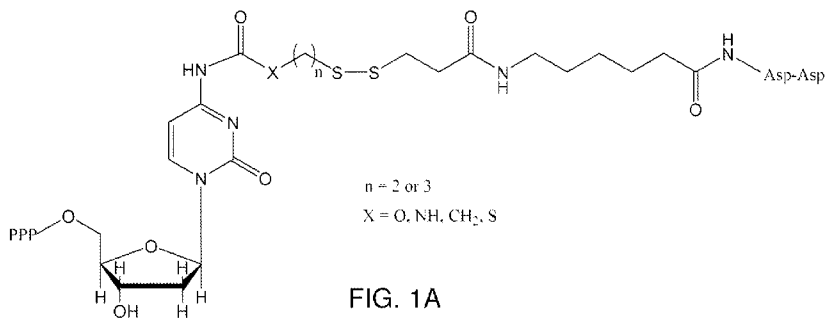


FIG. 1A

(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.

WO 2014/162307 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/061673

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2014.01)
CPC - C12Q 1/68 (2014.12)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07H 19/04, 19/10, 19/14, 19/20; C07K 9/00; C12P 19/34; C12Q 1/68 (2014.01)
USPC - 435/6.1, 91.1; 530/322; 536/26.26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C12N 9/1241, 9/1264: C12P 19/34; C12Q 1/68 (2014.12) (keyword delimited)

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

PatBase, Orbit, Google Patents, Google Scholar, STN V8.5.2.1
Search terms used: cleavable nucleotide analog disulfide terminator asp-asp (n3 OR azido) unlabelled automated oligonucleotide synthesis (aqueous OR enzymatic) flow reservoir well pin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages. | Relevant to claim No. |
|---|---|---|
| X<br>--<br>Y | US 2011/0081647 A1 (SIDDIQI et al) 07 April 2011 (07.04.2011) entire document | 32-34, 36-39, 42<br>----------<br>1-9, 14-31, 35, 40, 41 |
| Y | US 2004/0043396 A1 (MUELLER et al) 04 March 2004 (04.03.2004) entire document | 1-9, 14-31 |
| Y | US 2011/0124529 A1 (BRENNAN) 26 May 2011 (26.05.2011) entire document | 35, 40, 41 |
| A | WO 2008/144544 A1 (HELICOS BIOSCIENCES CORPORATION) 27 November 2008 (27.11.2008) entire document | 1-42 |
| 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 | 1-42 |
| A | US 2012/0040340 A1 (EFCAVITCH et al) 16 February 2012 (16.02.2012) entire document | 1-42 |
| A | US 8,808,989 B1 (EFCAVITCH et al) 19 August 2014 (19.08.2014) entire document | 1-42 |

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"A" document defining the general state of the art which is not considered to be of particular relevance
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"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 |
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