

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 September 2003 (04.09.2003)

PCT

(10) International Publication Number
WO 2003/072586 A3

(51) International Patent Classification⁷: **C07B 47/00**,
C07F 9/24, C07H 19/10, 19/20, 21/00

(21) International Application Number:
PCT/US2003/005682

(22) International Filing Date: 24 February 2003 (24.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/359,124 22 February 2002 (22.02.2002) US
60/362,320 7 March 2002 (07.03.2002) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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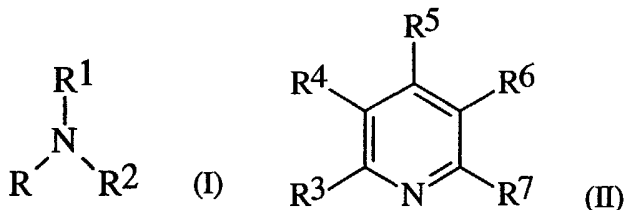
Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
8 April 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS OF PRODUCING PHOSPHITYLATED COMPOUNDS



heteroalkyl, or C₁-C₁₀ heteroaryl; (2) acid-base complexes derived from an amine base of Formula (II) wherein R³, R⁴, R⁵, R⁶, and are independently hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ cycloalkyl, C₁-C₁₀ aryl, C₁-C₁₀ aralkyl, C₁-C₁₀ heteroalkyl, or C₁-C₁₀ heteroaryl, and at least one of R³, R⁴, R⁵, R⁶, and R⁷ is not hydrogen.; (3) acid-base complexes derived from a diazabicyclo amine base; (4) zwitterionic amine complexes; and (5) combinations of two or more thereof, to produce a phosphitylated compound.

(57) Abstract: Provided are methods of producing phosphitylated compounds, including 3'-O-phosphoramidites, comprising the step of reacting a hydroxyl-containing compound with a phosphitylating agent in the presence of a phosphitylation activator selected from the group consisting of (1) acid-base complexes derived from an amine base of Formula (I) wherein R, R¹, and R² are independently C₁-C₁₀ alkyl, C₁-C₁₀ cycloalkyl, C₁-C₁₀ aryl, C₁-C₁₀ aralkyl, C₁-C₁₀

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/05682

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07B47/00 C07F9/24 C07H19/10 C07H19/20 C07H21/00

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 7 C07B C07F 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. BEIER, W. PFLEIDERER: "Nucleotides. Part LXII. Pyridinium salts - An effective class of catalysts for nologonucleotide synthesis" HELV. CHIM. ACTA, vol. 82, 1999, pages 879-887, XP002259404	28,31
Y	the whole document	1-6, 15-27, 29,30
X	----- US 4 725 677 A (KOESTER HUBERT ET AL) 16 February 1988 (1988-02-16)	28,31
Y	column 8 the whole document	1-6, 15-27, 29,30
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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

3 November 2003

Date of mailing of the international search report

11 02. 2004

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/05682

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 274 725 B1 (MANOHARAN MUTHIAH ET AL) 14 August 2001 (2001-08-14) figure 1 abstract	28,31
X	----- GRYAZNOV S M ET AL: "SELECTIVE O-PHOSPHITILATION WITH NUCLEOSIDE PHOSPHORAMIDITE REAGENTS" NUCLEIC ACIDS RESEARCH, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 20, no. 8, 1992, pages 1879-1882, XP002032929 ISSN: 0305-1048 page 1882	28,31
X	----- ZHANG Z ET AL: "NOVEL PHOSPHITYLATING REAGENT FOR IN SITU GENERATION OF DEOXYRIBONUCLEOSIDE PHOSPHORAMIDITES" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 3, 1996, pages 331-334, XP000612187 ISSN: 0040-4039 page 333	28,31
X	----- SINHA N D ET AL: "Polymer support oligonucleotide synthesis XVIII: use of beta-cyanoethyl-N,N-dialkylamino-/N-morpho lino phosphoramidite of deoxynucleosides for the synthesis of DNA fragments simplifying deprotection and isolation of the final product" NUCLEIC ACIDS RESEARCH, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 12, no. 11, 1984, pages 4539-4557, XP002134520 ISSN: 0305-1048 page 4541 -----	28,31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/05682

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 II Observations where unity of invention is lacking (Continuation of item 2 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 fee, this Authority did not invite payment of any additional fee.
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/part), 2-6, 15-22 (part), 23-31

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ 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. claims: 1 (in part), 2-6 (in full), 15-22 (in part), 23-31 (in full)

A method of producing a phosphitylated compound as in claim 1 where the phosphitylation activator is an acid-base complex derived from an amine base of Formula I of claim 1 or a combination of activators containing at least one activator as above as in claim 1(5), and compounds and oligomers pertaining thereto.

2. claims: 1 (in part), 7-11 (in full), 15-22 (in part)

A method of producing a phosphitylated compound as in claim 1 where the phosphitylation activator is an acid-base complex derived from an amine base of Formula II of claim 1 or a combination of activators containing at least one activator as above as in claim 1(5) and not falling within the previous subject.

3. claims: 1 (in part), 12 (in full), 15-22 (in part)

A method of producing a phosphitylated compound as in claim 1 where the phosphitylation activator is an acid-base complex derived from a diazabicyclo amine base or a combination of activators containing at least one activator as above as in claim 1(5) and not falling within one of the previous subjects.

4. claims: 1 (in part), 13-14 (in full), 15-22 (in part)

A method of producing a phosphitylated compound as in claim 1 where the phosphitylation activator is a zwitterionic amine complex.

5. claims: 32-35 (in full)

A method of purifying a phosphitylated compound as in claim 32.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/05682

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4725677	A	16-02-1988	DE 3329892 A1	07-03-1985
			AT 38386 T	15-11-1988
			AU 3313784 A	12-03-1985
			CA 1234060 A1	15-03-1988
			DE 3474964 D1	08-12-1988
			WO 8500816 A1	28-02-1985
			EP 0152459 A1	28-08-1985
			IT 1198910 B	21-12-1988
			JP 1301691 A	05-12-1989
			JP 1725624 C	19-01-1993
			JP 4011555 B	28-02-1992
			JP 60502102 T	05-12-1985
			JP 62050479 B	24-10-1987
			US RE34069 E	15-09-1992

US 6274725	B1	14-08-2001	AU 739468 B2	11-10-2001
			AU 4413599 A	20-12-1999
			CA 2330192 A1	09-12-1999
			EP 1084134 A1	21-03-2001
			JP 2002517404 T	18-06-2002
			WO 9962922 A1	09-12-1999
			US 2003191304 A1	09-10-2003
