(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/055097 A3

(51) International Patent Classification[7]: A61K 38/00

(21) International Application Number: PCT/EP02/00435

(22) International Filing Date: 7 January 2002 (07.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2001A000027 10 January 2001 (10.01.2001) IT

(71) Applicant *(for all designated States except US)*: **UNIVERSITA' DI BOLOGNA** [IT/IT]; Dipartimento di Patologia Sperimentale, Via San Giacomo, 14, I-40126 Bologna (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FIUME, Luigi** [IT/IT]; Via Dante, 7, I-40100 Bologna (IT). **DI STEFANO, Giuseppina** [IT/IT]; Via C.A. Pizzardi, 16, I-40100 Bologna (IT). **BUSI, Corrado** [IT/IT]; Via Berretta Rossa, 68, I-40100 Bologna (IT).

(74) Agents: **PISTOLESI, Roberto** et al.; Dragotti & Associati SRL, Galleria San Babila, 4/C, I-20122 Milano (IT).

(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, 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, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

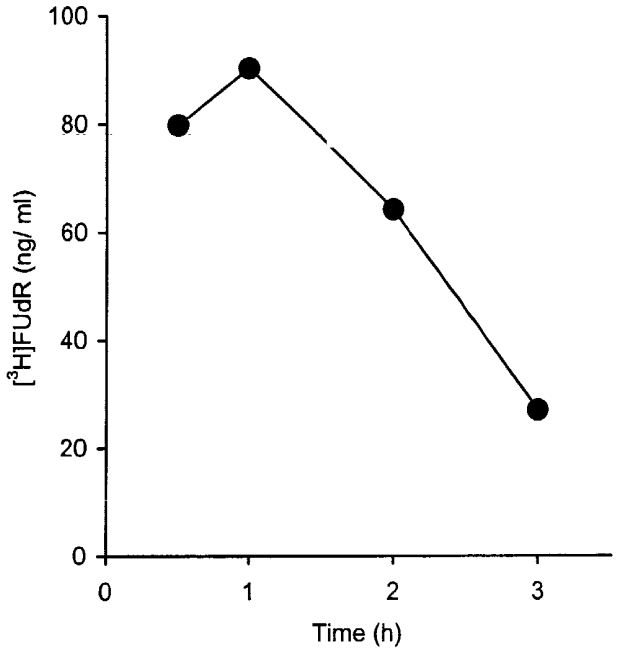
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,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

Declarations under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

[Continued on next page]

(54) **Title:** CONJUGATES OF NUCLEOSIDES WITH LACTOSAMINATED HUMAN ALBUMINE



(57) **Abstract:** Pharmaceutical compositions containing as active compound conjugates of lactosaminated albumin with antiblastic nucleosides (and their analogs) are here described. These compositions are particularly useful to increase the efficacy of the antiblastic nucleosides (and their analogs) on liver micrometastases. They preferably consist of aqueous solutions administered by parenteral route, preferably by intravenous injection. The antiblastic nucleoside of choice is 5-fluoro-2'-deoxyuridine (FUdR).

WO 02/055097 A3

— *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:
3 October 2002

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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/00435

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/00

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 A61K

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)
MEDLINE, BIOSIS, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FIUME L ET AL: "Liver targeting of nucleoside analogues coupled to galactosyl terminating macromolecules: a new approach to the treatment of a chronic viral hepatitis." ITALIAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY. ITALY JUN 1997, vol. 29, no. 3, June 1997 (1997-06), pages 275-280, XP008004174 ISSN: 1125-8055 page 276, left-hand column page 276, right-hand column page 277, Clinical studies --- -/--	1,2,4-6

[X] Further documents are listed in the continuation of box C.

[X] 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	Date of mailing of the international search report
12 June 2002	20/08/2002

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FIUME L ET AL: "Liver targeting of antiviral nucleoside analogues through the asialoglycoprotein receptor." JOURNAL OF VIRAL HEPATITIS. ENGLAND 1997, vol. 4, no. 6, 1997, pages 363-370, XP008004173 ISSN: 1352-0504 page 368, Conclusions ---	1,2,4-6
X	FIUME L ET AL: "The pathogenesis of vacuoles produced in rat and mouse liver cells by a conjugate of adenine arabinoside monophosphate with lactosaminated albumin." JOURNAL OF HEPATOLOGY, vol. 15, no. 3, 1992, pages 314-322, XP008004165 ISSN: 0168-8278 page 321, last paragraph ---	1,2,4-6
X	FIUME L ET AL: "Coupling of antiviral nucleoside analogs to lactosaminated human albumin by using the imidazolides of their phosphoric esters." ANALYTICAL BIOCHEMISTRY. UNITED STATES 1 AUG 1993, vol. 212, no. 2, 1 August 1993 (1993-08-01), pages 407-411, XP000371938 ISSN: 0003-2697 page 407, left-hand column page 410, right-hand column ---	1,2,4-6
A	PONZETTO A ET AL: "ARA AMP AND ACYCLOVIR MONOPHOSPHATE COUPLED TO LACTOSAMINATED ALBUMIN REDUCE WOODCHUCK HEPATITIS VIRUS VIREMIA AT DOSES LOWER THAN DO THE UNCONJUGATED DRUGS" HEPATOLOGY, vol. 14, no. 1, 1991, pages 16-24, XP000800471 ISSN: 0270-9139 the entire document ---	
A	US 5 594 110 A (MATTIOLI ALESSANDRO ET AL) 14 January 1997 (1997-01-14) the entire document ---	

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DI STEFANO G ET AL: "Enhanced liver blood concentrations of adenine arabinoside accomplished by lactosaminated poly-L-lysine coupling: implications for regional chemotherapy of hepatic micrometastases." BIOCHEMICAL PHARMACOLOGY. ENGLAND 1 FEB 2000, vol. 59, no. 3, 1 February 2000 (2000-02-01), pages 301-304, XP001074753 ISSN: 0006-2952 the entire document	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/00435

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.: 1,2, 4 - 8, 10
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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:

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.:

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

Continuation of Box I.2

Claims Nos.: 1,2, 4 - 8, 10

Present claims 1, 2, 4 - 8 and 10 relate to a large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos
that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely 5-fluoro-2'-deoxyuridine conjugated to lactosaminated human albumine.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/00435

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5594110 A	14-01-1997	IT 1256110 B	28-11-1995
		AT 190504 T	15-04-2000
		AU 5626294 A	22-06-1994
		DE 69328082 D1	20-04-2000
		DE 69328082 T2	24-08-2000
		DK 624098 T3	05-06-2000
		EP 0624098 A1	17-11-1994
		GR 3033611 T3	31-10-2000
		WO 9412218 A1	09-06-1994
		ES 2144046 T3	01-06-2000
		PT 624098 T	31-08-2000