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**Published**:

— *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))*

(88) Date of publication of the international search report:
26 March 2015

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(54) Title: NUCLEOSIDE PHOSPHORAMIDATES AND PHOSPHORAMIDITES

(57) Abstract: The invention provides phosphoramidate prodrugs of chemotherapeutlc and/or antiviral agents for targeting and treating liver disease, including liver cancer, hepatocellular carcinoma, and hepatitis. The prodrugs are suitable for oral administration which makes the treatment available to a large population of patients worldwide, without expensive and limiting treatments only provided by clinics.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/47721

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/7076; C07H 19/20; A61P 31/14 (2014.01)

CPC - C07H 19/20; A61K 31/70; A61K 31/7076; C07H 19/10; C07H 21/00; C07H 19/06

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): A61K 31/7076; C07H 19/20; A61P 31/14 (2014.01)
CPC: C07H 19/20; A61K 31/70; A61K 31/7076; C07H 19/10; C07H 21/00; C07H 19/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/47; 536/26.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Web, PubChem
phosphoramidates, phosphoramidites, conjugate, floxuridine, nucleoside, liver cancer, hepatitis C, hepatocellular carcinoma, metastasis, cirrhosis

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 | WO 2012/142093 A2 (Girijavallabhan et al.) 18 October 2012 (18.10.2012) pg 125, ln 28 - pg 126, ln 2; pg 2, ln 26-29; pg 3, ln 9; pg 14, ln 18; pg 144, ln 8-9; pg 127, ln 8-10 | 1, 5/1<br>----------<br>2-3, 5/2, 10-15 |
| Y | US 2007/0037891 A1 (Esfand et al.) 15 February 2007 (15.02.2007) para [0106], [0116] | 2-3, 5/2, 10-15 |
| Y | US 2012/0294945 A1 (Hahn et al.) 22 November 2012 (22.11.2012) para [0124], para [0172] | 11 |

☐ 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 | Date of mailing of the international search report |
|---|---|
| 07 January 2015 (07.01.2015) | 22 JAN 2015 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/47721

**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.: 8-9 and 16-19
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:
--Please see attached 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 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.:
Claims 1-3, 5 and 10-15

**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.

Attachment to Box.No.III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-7, 10-15 and 20-22 directed to a method of treating liver disease selected from liver cancer and hepatitis, the method comprising, administering an effective amount of a compound of formula (III), or a pharmaceutically acceptable thereof to a subject in need of such treatment, in a dosage and for a time effective to treat the liver disease, wherein the compound of formula (III) is not sofosbuvir or PSI-7851 and wherein the compound of formula (III) is represented by structurally different compounds wherein R22 is a monovalent substituent group of a chemotherapeutic agent, or is a monovalent substituent group of an antiviral agent including compounds of formula (Ic), formula (IIa) and formula (IIIa).

Group I+ will be searched to the extent that it reads on a compound of formula (Ic), without any additional fee. It is believed that claims 1 -3, 5 and 10-15 read on this first-named invention. Applicants must indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

Applicant is invited to elect one or more additional inventions for the payment of an additional fee for each elected invention (see item 2). An exemplary election of a second invention would be a compound of Formula IIIa (i.e., claims 1-2, 4-5, 7 and 20-22). An exemplary election of a third invention would be a compound of Formula IIa (i.e. claims 1-2, 5-6).

The inventions listed as Group I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features:

Each invention of Group I+ includes the technical feature of a unique chemical compound not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a method of treating liver disease selected from liver cancer and hepatitis, the method comprising, administering an effective amount of a compound of formula (III), or a pharmaceutically acceptable thereof to a subject in need of such treatment, in a dosage and for a time effective to treat the liver disease, wherein the compound of formula (III) is not sofosbuvir or PSI-7851.

This shared technical feature, however, does not provide a contribution over the prior art as being anticipated by WO 2012/142093 A2 to Girijavallabhan et al. which teaches a method of treating liver disease selected from hepatitis, the method comprising administering an effective amount of a compound of formula (III), or a pharmaceutically acceptable thereof (pg 7, ln 24-32; pg 37, ln 23-28), wherein, R22 is a monovalent substituent group of an antiviral agent; and xD is O, wherein the compound of formula (III) is not sofosbuvir or PSI-7851 (pg 116, compound 195); to a subject in need of such treatment, in a dosage and for a time effective to treat the liver disease (pg 7, ln 24-32; pg 139, ln 27-pg 140, ln 7; pg 144, ln 31-pg 145, ln 1).

As said method was known in the art at the time of the invention this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+, thus lack unity under PCT Rule 13.2, because they do not share a same or corresponding special technical feature providing a contribution over the prior art.

Note reg. Item 4: Claims 8-9 and 16-19 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are, therefore, not included in the above analysis.