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60/840,353 25 August 2006 (25.08.2006) US
- (71) **Applicants (for all designated States except US):** WYETH [US/US]; Five Giralda Farms, Madison, NJ 07940 (US). VIOPHARMA INCORPORATED [US/US]; 397 Eagleview Boulevard, Exton, PA 19392 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** HOWE, Anita, Y., M. [CA/US]; 344 Paoli Woods, Paoli, PA 19301 (US). CHOPRA, Rajiv [GB/US]; 94 Poor Street, Andover, MA 01810 (US).
- (74) **Agents:** PIERONI, Joseph, P. et al.; Fitzpatrick, Cella, Harper & Scinto, 30 Rockefeller Plaza, New York, NY 10112-3801 (US).

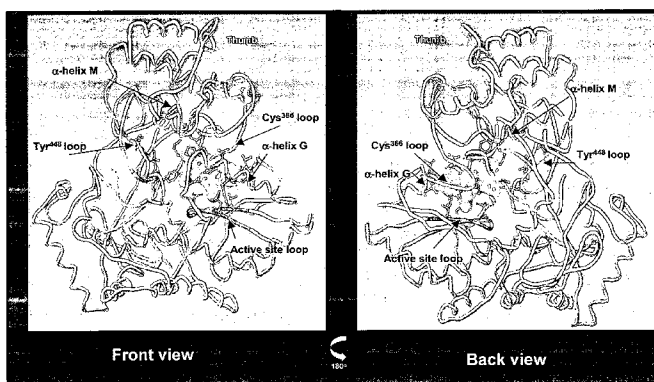
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
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- (88) **Date of publication of the international search report:**  
24 December 2008

(54) **Title:** IDENTIFICATION AND CHARACTERIZATION OF HCV REPLICON VARIANTS WITH REDUCED SUSCEPTIBILITY TO HCV-796, AND METHODS RELATED THERETO



(57) **Abstract:** The present invention provides methods of decreasing the frequency of emergence, decreasing the level of resistance, and delaying the emergence of a treatment-resistant Hepatitis C viral infection, by administering to a subject, either in combination or in series, an inhibitor of the Hepatitis C RNA-dependent RNA polymerase NS5B, e.g., a benzofuran, such as 5-cyclopropyl-2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-N-methyl-1-benzofuran-3-carboxamide (HCV-796), and at least one additional anti-Hepatitis C agent, e.g., a ribavirin product or an immunomodulator, such as an interferon product. Additionally, the invention relates to methods of monitoring the course of treatment of a Hepatitis C viral infection, methods of monitoring and prognosing a Hepatitis C viral infection, and methods of identifying an individual with a decreased likelihood of responding to an anti-Hepatitis C viral therapy. These methods use the sequence and/or structure of the Hepatitis C RNA-dependent RNA polymerase NS5B to identify the emergence of a treatment-resistant Hepatitis C viral infection, particularly a benzofuran (e.g., HCV-796) treatment-resistant Hepatitis C viral infection.

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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/076408

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. G01N33/68 A61K31/343

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)  
G01N 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)

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	WO 2005/067900 A (ACHILLION PHARMACEUTICALS INC [US]; THURKAUF ANDREW [US]; CHEN DAWEI [ ] 28 July 2005 (2005-07-28) whole document; in particular claim 46	1-5
X	US 2003/216325 A1 (SAKSENA ANIL K [US] ET AL SAKSENA ANIL K [US] ET AL) 20 November 2003 (2003-11-20) whole document; in particular paragraph [0135].	1-10
X	WO 2004/041201 A (VIROPHARMA INC [US]; WYETH CORP [US]; BURNS CHRISTOPHER J [US]; DEL VE) 21 May 2004 (2004-05-21) whole document; in particular claims 23 and 24.	1-10
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Further documents are listed in the continuation of Box C.

See patent family 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.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

23 April 2008

Date of mailing of the international search report

03/11/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Lüdemann, Susanna

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/076408

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/092645 A (SCHERING CORP [US]; VIROPHARMA INC [US]; WYETH CORP [US]; EMINI EMILIO) 16 August 2007 (2007-08-16) whole document; in particular claims 1 and 5	1-10
A	----- FRANCESCO DE R ET AL: "Challenges and successes in developing new therapies for hepatitis C" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 436, 18 August 2005 (2005-08-18), pages 953-960, XP002351157 ISSN: 0028-0836 whole document; in particular box 1, p. 956, left col., last paragraph - right col. second paragraph, p. 958, right col., last paragraph.	1-10
P,X	----- BEAULIEU PIERRE L: "Non-nucleoside inhibitors of the HCV NS5B polymerase: progress in the discovery and development of novel agents for the treatment of HCV infections" CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 8, no. 8, August 2007 (2007-08), pages 614-634, XP009099040 ISSN: 1472-4472 whole document; in particular p. 624, right col.-p.625, left col. and ref. 72	1-10
X	& DATABASE CLINICALTRIALS.GOV NIH; 21 August 2006 (2006-08-21), retrieved from HTTP://CLINICALTRIALS.GOV/CT2/SHOW/RECORD/ NCT00367887 abstract	1-10

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2007/076408

## 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.: 1-10  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
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 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:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2.  As all searchable claims could be searched without effort justifying an 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.:

see additional sheet(s)

### 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-10 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box II.1

Claims Nos.: 1-10

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10

a method of decreasing the frequency of emergence of a treatment-resistant hepatitis C viral (HCV) infection by a combination therapy administering a benzofuran inhibitor and an additional anti-hepatitis C virus agent.

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2. claims: 11-28

Methods of identifying individuals with a decreased likelihood of responding to an anti-HCV therapy or methods for monitoring, diagnosing or prognosing a treatment-resistant HCV infection, or monitoring the course of treatment of a HCV infection in a subject by determining the amino acid sequence or structure of the benzofuran/HCV-796 binding pocket in time or before and after a binding event.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2007/076408
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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