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

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Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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:
20 September 2007

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: LIVER/PLASMA CONCENTRATION RATIO FOR DOSING HEPATITIS C VIRUS PROTEASE INHIBITOR

(57) Abstract: Compositions and therapeutic combinations are provided including at least one compound selected from the group consisting of compounds of Formulae I to XXVI as defined herein as well as methods of treatment, prevention or amelioration of one or more symptoms of hepatitis C, treating disorders associated with HCV virus, modulating activity of HCV protease, in which liver to plasma concentration ratio of the compound ranges from about 2:1 to about 10:1.

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/04 A61P21/00

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)
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, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/062265 A2 (SCHERING CORP [US]; CORVAS INT INC [US] SCHERING CORP [US]; DENDREON C) 31 July 2003 (2003-07-31) cited in the application the whole document especially p. 76, line 3 - . 82, line 7	1-40
X	WO 03/062228 A (SCHERING CORP [US]) 31 July 2003 (2003-07-31) cited in the application the whole document especially p. 36, line 2 - p. 42, line 13	1-3,6-40
X	US 2005/085425 A1 (CHEN KEVIN X [US] ET AL) 21 April 2005 (2005-04-21) cited in the application the whole document paragraphs [0210] - [0236]	1-3,6-40

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

[X] 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)

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"P" document published prior to the international filing date but later than the priority date claimed

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2007	25/07/2007

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/021116

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/08244 A2 (SCHERING CORP [US]; CORVAS INT INC [US]) 31 January 2002 (2002-01-31) the whole document especially p. 86, line 11 - p. 92, line 15	1-40
X	US 2005/020689 A1 (CHEN MINZHANG [US] ET AL) 27 January 2005 (2005-01-27) cited in the application the whole document	1-5
X	US 2005/059648 A1 (PARK JEONGHAN [US] ET AL) 17 March 2005 (2005-03-17) cited in the application the whole document	1-5
Y	ULRICH JAEHDE: "Lehrbuch der Klinischen Pharmazie" 1998, WISSENSCHAFTLICHE VERLAGSGESELLSCHAFT MBH , STUTTGART , XP002425073 pages 56-58	1-40
Y	NAVEAU S ET AL: "Interleukin-1 receptor antagonist plasma concentration is specifically increased by alpha-2A-interferon treatment." JOURNAL OF HEPATOLOGY AUG 1997, vol. 27, no. 2, August 1997 (1997-08), pages 272-275, XP002424832 ISSN: 0168-8278 the whole document	1-40
P,X	WO 2005/085275 A (SCHERING CORP [US]; BOGEN STEPHANE L [US]; PAN WEIDONG [US]; RUAN SUME) 15 September 2005 (2005-09-15) the whole document but see especially p. 124, line 6 to p. 129, line 14	1-3,6-40
P,X	WO 2005/087721 A (SCHERING CORP [US]; VENKATRAMAN SRIKANTH [US]; NJOROGE F GEORGE [US];) 22 September 2005 (2005-09-22) the whole document but see especially p. 44, line 29 - p. 50, line 17	1-3,6-40
P,X	WO 2005/087725 A (SCHERING CORP [US]; ARASAPPAN ASHOK [US]; NJOROGE F GEORGE [US]; PADIL) 22 September 2005 (2005-09-22) the whole document but see especially p. 56, line 20 - p. 62, line 6	1-3,6-40

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/021116

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 2005/085242 A (SCHERING CORP [US]; CHEN KEVIN X [US]; NJOROGE F GEORGE [US]; SANNIGRA) 15 September 2005 (2005-09-15) the whole document but see especially p. 44, line 4 - p. 50, line 5; and p. 209, line 1 to p. 211.	1-3,6-40
P,X	WO 2005/087731 A1 (SCHERING CORP [US]; BENNETT FRANK [US]; LOVEY RAYMOND G [US]; HUANG YU) 22 September 2005 (2005-09-22) the whole document but see especially p. 84, line 7 - p. 92, line 9	1-3,6-40
P,X	WO 2005/085197 A (SCHERING CORP [US]; BOGEN STEPHANE L [US]; PAN WEIDONG [US]; RUAN SUME) 15 September 2005 (2005-09-15) the whole document but see especially p. 47, line 27 - p. 54, line 5	1-3,6-40
P,X	US 2006/046956 A1 (SANNIGRAHI MOUSUMI [US] ET AL) 2 March 2006 (2006-03-02) the whole document	1-3,6-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/021116

Box 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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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 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.:

1-3,6-40(all in parts), 4,5

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

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

1. claims: 1-3, 6-40 (all in parts), 4,5

   A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formulae I, Ia, Ib, Ic, IV or VI.

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2. claims: 1-3, 6-40 (all in parts)

   A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula II.

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3. claims: 1-3,6-40 (all in parts)

   A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula III

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4. claims: 1-3,6-40 (all in parts)

   A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula V.

---

5. claims: 1-3,6-40 (all in parts)

   A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula VII, VIII or IX.

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6. claims: 1-3,6-40 (all in parts)

   A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formulae X, XI, XII, XIII, XIV, XVIII.

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7. claims: 1-3,6-40 (all in parts)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XV.

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8. claims: 1-3,6-40

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XVI.

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9. claims: 1-3,6.-40

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XIX.

---

10. claims: 1-3,6-40 (all in parts)

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XX or XXI.

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11. claims: 1-3,6-40

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XXII.

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12. claims: 1-3,6-40 (all in parts)

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XXIII.

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13. claims: 1-3,6-40 (all in parts)

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XXIV.

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14. claims: 1-3,6-40 (all in parts)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XXV

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15. claims: 1-3,6-40 (all in parts)

A method of treating disorders associated with hepatitis C virus (HCV) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula XXVI.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03062265 A2	31-07-2003	BR 0306931 A	19-04-2005
		CA 2473032 A1	31-07-2003
		CN 1633446 A	29-06-2005
		EP 1481000 A2	01-12-2004
		JP 2005524628 T	18-08-2005
		MX PA04006934 A	19-04-2005
		ZA 200405304 A	29-03-2006
WO 03062228 A	31-07-2003	CA 2473070 A1	31-07-2003
		CN 1692109 A	02-11-2005
		EP 1467989 A1	20-10-2004
		JP 2005515255 T	26-05-2005
		MX PA04007163 A	29-10-2004
		NZ 533861 A	31-03-2006
		TW 265927 B	11-11-2006
		ZA 200405341 A	09-09-2005
US 2005085425 A1	21-04-2005	NONE	
WO 0208244 A2	31-01-2002	AU 7698801 A	05-02-2002
		BR 0112540 A	24-06-2003
		CA 2410662 A1	31-01-2002
		CN 1498224 A	19-05-2004
		CZ 20030151 A3	14-05-2003
		EP 1385870 A2	04-02-2004
		HU 0401730 A2	28-12-2004
		JP 2004504404 T	12-02-2004
		MX PA03000627 A	30-07-2004
		NO 20030272 A	21-03-2003
		NZ 523782 A	28-10-2005
		PL 366063 A1	24-01-2005
		SK 752003 A3	05-08-2003
		ZA 200210312 A	29-03-2004
US 2005020689 A1	27-01-2005	US 2006030734 A1	09-02-2006
US 2005059648 A1	17-03-2005	NONE	
WO 2005085275 A	15-09-2005	AR 047901 A1	01-03-2006
		AU 2005219859 A1	15-09-2005
		CA 2557322 A1	15-09-2005
		CN 1950393 A	18-04-2007
		EP 1730165 A1	13-12-2006
		KR 20060124725 A	05-12-2006
WO 2005087721 A	22-09-2005	AR 047902 A1	01-03-2006
		AU 2005222055 A1	22-09-2005
		CA 2557247 A1	22-09-2005
		CN 1946691 A	11-04-2007
		EP 1748983 A2	07-02-2007
		KR 20060127162 A	11-12-2006
WO 2005087725 A	22-09-2005	AR 047903 A1	01-03-2006
		AU 2005222056 A1	22-09-2005
		CA 2557249 A1	22-09-2005
		CN 1972956 A	30-05-2007
		EP 1737881 A2	03-01-2007
		KR 20060124729 A	05-12-2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/021116

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005085242 A	15-09-2005	AR 048023 A1	22-03-2006
		AU 2005219824 A1	15-09-2005
		CA 2557304 A1	15-09-2005
		CN 1946718 A	11-04-2007
		EP 1730142 A1	13-12-2006
		KR 20070026394 A	08-03-2007
WO 2005087731 A1	22-09-2005	AR 048241 A1	12-04-2006
		AU 2005222060 A1	22-09-2005
		CA 2557495 A1	22-09-2005
		EP 1730110 A1	13-12-2006
		KR 20060134083 A	27-12-2006
WO 2005085197 A	15-09-2005	CA 2557301 A1	15-09-2005
		CN 1946690 A	11-04-2007
		EP 1742914 A1	17-01-2007
US 2006046956 A1	02-03-2006	NONE	