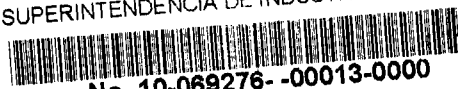


SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-069276- -00013-0000

Fecha: 2013-11-28 18:08:22 Dep. 2020 DIR.NUEVASCR
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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente No. PCT/10-69276

TÍTULO SOLICITADO: "COMPUESTOS QUE CONTIENEN QUINOXALINA ENLAZADA POR UN PUENTE CON EL ANILLO DE TETRAHIDROPIRROLIDINA ACTIVOS COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C"

PUBLICACIÓN: Gaceta 628 del 20/05/2011, N° de publicación 441.

SOLICITANTE: ENANTA PHARMACEUTICALS, INC.

APODERADO: MARGARITA CASTELLANOS A.

TRÁMITE: Recurso de Reposición y en subsidio el de apelación en contra de la Resolución 60386 de octubre 17 de 2013 por la cual se concede una patente de invención tramitada bajo el número de expediente PCT/10-69276.

TITO NOÉ PARRA MURILLO, mayor de edad, identificado como aparece al pie de mi firma, reconocido apoderado de la sociedad LAFRANCOL S.A.S. en el asunto de la referencia, de manera respetuosa, y dentro de los términos de ley, presento Recurso de Reposición y en subsidio de apelación contra la Resolución 60386 de octubre 17 de 2013 por la cual se concedió a la solicitud PCT/10-69276 el privilegio de patente de invención.

TOTAL #
10
1

I. PETICIÓN

Sírvase, Señor Superintendente, reponer íntegramente la Resolución 60386 de octubre 17 de 2013, por la cual se declaró infundada la oposición presentada y se otorgó el privilegio de patente solicitado en el expediente de la referencia, y en su remplazo emitir otra que, con fundamento en los argumentos expuestos en el escrito de observación y en el presente escrito, declare fundada dicha oposición y niegue el privilegio de patente mencionado, procediendo luego al definitivo archivo del expediente en cuestión.

II. ARGUMENTOS SOBRE LOS FUNDAMENTOS DE LA CONCESIÓN Y MOTIVOS DE INCONFORMIDAD

La Resolución 60386 de octubre 17 de 2013, que concede el privilegio de patente de invención solicitado para el capítulo reivindicatorio del expediente 11-112331 titulado **“Compuestos que contienen Quinoxalina enlazada por un puente con el anillo de tetrahidropirrolidina activos como inhibidores del virus de la Hepatitis C”**, viola flagrantemente la Decisión 486 si se tiene en cuenta que existían motivos suficientes para afectar los requisitos de novedad y nivel inventivo de la solicitud en mención. Es evidente que el solicitante y la Resolución cometen un error cuando afirman que la oposición presentada por mi representada no muestra ningún tipo de argumento soportado técnicamente, ni desvirtúa la patentabilidad del objeto de estudio, declarándola infundada por cuanto, al momento de presentación del escrito de oposición se dejó en claro que para el presente caso nos encontramos frente a una combinación de compuestos, lo cual indudablemente afecta el requisito de nivel inventivo, éste mismo indispensable para acceder a cualquier beneficio patentario.

Así las cosas, me permito reiterar que la concesión de patente objeto del presente escrito se ve afectada por los documentos del estado del arte que fueron presentados inicialmente en el escrito de observación, por lo cual, basado en lo siguiente, solicito respetuosamente a ese Despacho dar análisis completo y a cabalidad sobre los siguientes documentos, los cuales sin lugar a dudas objetan la concesión en mención, toda vez que develan de manera expresa y sucinta lo que se pretende proteger en la presente solicitud.

Dicho así, me permito manifestar que agentes tales como Ribavirina, Amantadina, Ritonavir, Interferón, entre muchos otros, han sido ampliamente divulgados en el sector químico-farmacéutico, y concretamente se han develado materias muy similares, las cuales ruego a ese Despacho analizar, en los siguientes documentos:

- **DE 2220246**
- **US 3798209**
- **WO 9414436**
- **US 5541206**

Así como resulta imprescindible manifestar que los anteriores documentos deben ser analizados a profundidad y cabalidad para así determinar finalmente si afectan o no la novedad y nivel inventivo de la presente solicitud, toda vez que en nuestra opinión se revelan materias muy similares, también es necesario reiterar que la solicitud de la referencia pretende proteger mediante el derecho patentario objetos que no son considerados invenciones. Es claro que una invención es toda creación humana que permita transformar la materia o energía que existe en la naturaleza, para su aprovechamiento por los seres humanos y satisfacer sus necesidades concretas. De igual modo, como ya se mencionó, según los parámetros de la Decisión 486 y normas concordantes, serán patentables las invenciones que cumplan con los requisitos de novedad, nivel inventivo y aplicación industrial. No obstante, puede observarse que la solicitud en comento pretende reivindicar combinaciones, las cuales no se consideran invenciones. En este sentido, la mezcla (Combinaciones) de productos (Moléculas) conocidos y su variación, bien sea en uso, forma, dimensión o de materia, NO se consideran invenciones por cuanto no son susceptibles de aplicación industrial, nivel inventivo y novedad, luego NO pueden acceder a beneficios patentarios. Por lo tanto, se suma una circunstancia más que imposibilita definitivamente la concesión de la solicitud en mención.

Y sobre el particular, es imprescindible señalar que un efecto sinérgico nuevo no se considera inventivo como tal, dado que puede ser obvio para una persona versada en la materia, cosa que sucede en el presente caso. En palabras del Doctor Carlos Correa, *“El efecto sinérgico entre dos o más drogas se puede considerar un “descubrimiento” y no una “invención”, dado que la sinergia ocurre en el cuerpo y se descubre a través de ensayos clínicos. Asimismo, cabe destacar que, en algunos casos, las reivindicaciones de combinaciones pueden equivaler, en términos prácticos, a reivindicaciones sobre tratamientos médicos (cuya patentabilidad está excluida en la mayoría de los países), cuando sólo brindan un método para administrar una combinación de drogas conocidas. Asimismo, la combinación de drogas para evitar la resistencia particular a una de ellas es una práctica normal en el desarrollo farmacéutico y, por lo general, es evidente para el hombre del oficio de nivel medio”* (Pautas para el examen de patentes farmacéuticas,

CEIDIE, Pág. 8). En estos términos, está claro que nos encontramos frente a un tema totalmente sensible que merece toda la evaluación por cuanto las combinaciones deben considerarse excluidas de beneficios de patente.

Adicionalmente, valga señalar que las moléculas propuestas en la presente solicitud son comúnmente utilizadas en las formulaciones igualmente descritas. Dicho así, debe enfatizarse en que las formulaciones que involucran moléculas como las propuestas son totalmente conocidas y obvias por lo cual se ven afectados los requisitos de novedad y nivel inventivo. Sobre el particular, considera pertinente traer a colación menciones hechas sobre la patentabilidad de las formulaciones, las cuales podrán ilustrar más a ese Despacho:

“Como regla general, las técnicas de formulación y el conjunto de compuestos que se pueden utilizar para desarrollar productos farmacéuticos viables en sus diferentes formas, son elementos bien conocidos para una persona capacitada en la técnica... Finalmente, se debe destacar que, en términos generales, los procesos para preparar formulaciones son bien conocidos como tales y de aplicación habitual. Por lo tanto, las reivindicaciones de dichos procesos rara vez son inventivas...”¹.

Y en caso que ese Despacho decidiera insistir en el cabal cumplimiento de los requisitos exigidos para acceder al beneficio de patente, me permito allegar copia del International Search Report y el respectivo Written Opinion Of The International Searching Authority, documentos en los cuales se resalta que la presente invención no cumple con los requisitos de novedad y nivel inventivo por cuanto existen documentos citados del estado del arte que afectan de manera definitiva tales exigencias. Lo anterior deja entrever, sin lugar a equívocos, que la presente solicitud no debió ser concedida, por lo cual es procedente la revocatoria de la Resolución objeto de este escrito.

En este sentido, reitero con el debido respeto la necesidad de analizar a profundidad los requisitos de novedad y nivel inventivo para así determinar si la presente solicitud es merecedora de concesión de privilegio de patente.

ANEXOS

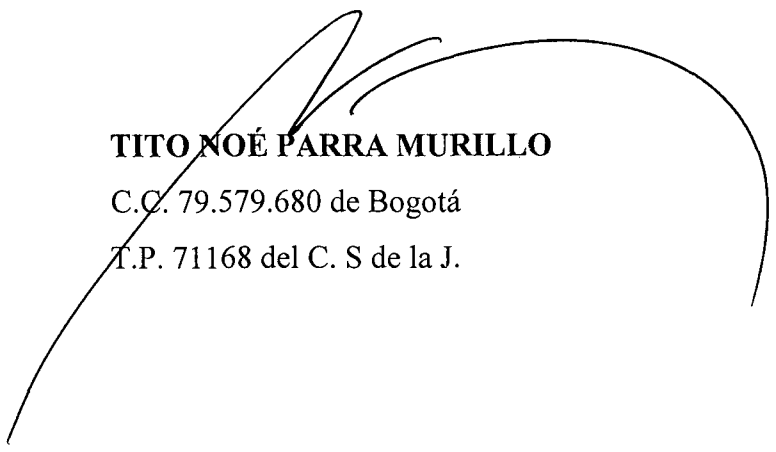
1- International Search Report y el Written Opinion Of The International Searching

¹ Correa, Carlos. *Pautas para el examen de patentes farmacéuticas. Una perspectiva desde la Salud Pública*. Universidad de Buenos Aires. 2008. Páginas 6-7.

Authority de la equivalente internacional WO 2009/064975.

En subsidio apelo.

Señor Superintendente,



TITO NOÉ PARRA MURILLO

C.C. 79.579.680 de Bogotá

T.P. 71168 del C. S de la J.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/60; A61K 31/495 (2009.01) USPC - 514/234.8, 248-249 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) USPC - 514/234.8, 248-249 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 514/228.2, 252.1, 255.05-255.06, 311; 528/332; 540/552; 544/353 (text search - see search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST (USPT, PGPB, EPAB, JPAB) and Google Web/Patent/Scholar Search terms: quinoxaline, benzopyrazine, hepatitis, HCV, ritonavir, cytochrome, p450, pegylated, interferon, macrocycle, tethered		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0106559 A1 (Wang et al.) 3 June 2004 (03.06.2004) para [0004], [0009]-[0018], [0020]-[0022], [0025]-[0026], [0042], [0193]	1-30
Y	US 2007/0060510 A1 (Nakajima et al.) 15 March 2007 (15.03.2007) para [0011]-[0012]	1-30
Y	US 2007/0054842 A1 (Blatt et al.) 8 March 2007 (08.03.2007) para [0616]	28-30
☐ 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 28 January 2009 (28.01.2009)		Date of mailing of the international search report 03 MAR 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

PCT/US2008/083541 03.03.2009

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
EDGAR W. HARLAN
ELMORE PATENT LAW GROUP, PC
515 GROTON ROAD, UNIT 1R
WESTFORD, MA 01886

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) 03 MAR 2009

Applicant's or agent's file reference
4056.4146 WO

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US 08/83541

International filing date (day/month/year)
14 November 2008 (14.11.2008)

Priority date (day/month/year)
14 November 2007 (14.11.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 43/60; A61K 31/495 (2009.01)
USPC - 514/234.8, 248-249

Applicant ENANTA PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Date of completion of this opinion 28 January 2009 (28.01.2009)	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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Form PCT/ISA/237 (cover sheet) (April 2007)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 08/83541

Box No. 1	Basis of this opinion
1.	With regard to the language, this opinion has been established on the basis of: ☒ the international application in the language in which it was filed. ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2.	☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3.	With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of: a. type of material ☐ a sequence listing ☐ table(s) related to the sequence listing b. format of material ☐ on paper ☐ in electronic form c. time of filing/furnishing ☐ contained in the international application as filed ☐ filed together with the international application in electronic form ☐ furnished subsequently to this Authority for the purposes of search
4.	☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5.	Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.:

PCT/US 08/83541

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-30	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-30	NO
Industrial applicability (IA)	Claims	1-30	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-27 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0106559 A1 to Wang et al. (hereinafter 'Wang') in view of US 2007/0060510 A1 to Nakajima et al. (hereinafter 'Nakajima').

As for claims 1-13, Wang discloses a quinoxaline containing compound: wherein A is absent or selected from -(C=O)-, -S(O)2-, -C=N-OR1 or -C(=N-CN); L201 is absent or selected from -C1-C8 alkylene, -C2-C8 alkenylene, or -C2-C8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C1-C8 alkylene, substituted -C2-C8 alkenylene, or substituted -C2-C8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkylene, or substituted -C3-C12 cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkenylene, or substituted -C3-C12 cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; M is absent or selected from O, S, SO, S(O)2 or NR1; wherein R1 is selected at each occurrence from the group consisting of: hydrogen; aryl; substituted aryl; heteroaryl; substituted heteroaryl; (iii) heterocycloalkyl or substituted heterocycloalkyl; (iv) -C1-C8 alkyl, -C2-C8 alkenyl, or -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C1-C8 alkyl, substituted -C2-C8 alkenyl, or substituted -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkyl, or substituted -C3-C12 cycloalkyl; -C3-C12 cycloalkenyl, or substituted -C3-C12 cycloalkenyl; L101 is absent or selected from -C1-C8 alkylene, -C2-C8 alkenylene, or -C2-C8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C1-C8 alkylene, substituted -C2-C8 alkenylene, or substituted -C2-C8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkylene, or substituted -C3-C12 cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkenylene, or substituted -C3-C12 cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; Z101 is absent or selected from aryl, substituted aryl, heteroaryl, or substituted heteroaryl; W101 is absent or selected from -O-, -S-, -NR1-, -C(O)- or -C(O)NR1-; X and Y taken together with the carbon atoms to which they are attached to form a carbocyclic moiety or a heterocyclic moiety selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, or substituted heterocyclic; or X and Y together form a C2-C8-alkylene group or a C2-C8-heteroalkylene group; R101 and R102 are independently selected from the group consisting of: (i) hydrogen, halogen, CN, CF3, N3, NO2, OR1, SRI, S(O)2R2, -NHS(O)2-R2, -NH(SO2)NR3R4, NR3R4, CO2R1, COR1, CONR1R2, N(R1)COR2; (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl; (iii) heterocycloalkyl or substituted heterocycloalkyl; (iv) -C1-C8 alkyl, -C2-C8 alkenyl, or -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C1-C8 alkyl, substituted -C2-C8 alkenyl, or substituted -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkyl, or substituted -C3-C12 cycloalkyl; -C3-C12 cycloalkenyl, or substituted -C3-C12 cycloalkenyl; Rand R' are each independently selected from the group consisting of: (i) -C1-C8 alkyl, -C2-C8 alkenyl, or -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C1-C8 alkyl, substituted -C2-C8 alkenyl, or substituted -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkyl, or substituted -C3-C12 cycloalkyl; -C4-C12 alkylcycloalkyl, or substituted -C4-C12 alkylcycloalkyl; -C3-C12 cycloalkenyl, or substituted -C3-C12 cycloalkenyl; C4-C12 alkylcycloalkenyl, or substituted -C4-C12 alkylcycloalkenyl; (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl; (iii) heterocycloalkyl or substituted heterocycloalkyl; (iv) hydrogen; deuterium; G is selected from -OH, -NHS(O)2-R2, -NH(SO2)NR3R4, and NR3R4; R2 is selected from: (i) aryl; substituted aryl; heteroaryl; substituted heteroaryl; (ii) heterocycloalkyl; substituted heterocycloalkyl; (iii) -C1-C8 alkyl, -C2-C8 alkenyl, or -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N, substituted -C1-C8 alkyl, substituted -C2-C8 alkenyl, or substituted -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkyl, or substituted -C3-C12 cycloalkyl; -C3-C12 cycloalkenyl, or substituted -C3-C12 cycloalkenyl; heterocyclic; substituted heterocyclic; R3 and R4 are independently selected from: (i) hydrogen; (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl; (iii) heterocycloalkyl or substituted heterocycloalkyl; (iv) -C1-C8 alkyl, -C2-C8 alkenyl, or -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C1-C8 alkyl, substituted -C2-C8 alkenyl, or substituted -C2-C8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C3-C12 cycloalkyl, or substituted -C3-C12 cycloalkyl; -C3-C12 cycloalkenyl, or substituted -C3-C12 cycloalkenyl; heterocyclic, or substituted heterocyclic;

-----continued in Supplemental Box-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/83541

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V 2. Citations and explanations:

(claims 1-13 cont'd) alternatively, R3 and R4 are taken together with the nitrogen they are attached to form a heterocyclic or substituted heterocyclic; Z is selected from the groups consisting of: (i) hydrogen; (ii) CN; (iii) N3; (iv) halogen; (v) -NH-N=CHR1; (vi) aryl, substituted aryl; (vii) heteroaryl, substituted heteroaryl; (viii) -Cr Cl2 cycloalkyl, substituted -Cr Cl2 cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl; (ix) -C1-C6 alkyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; (x) -C2-C6 alkenyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; (xi) -C2-C6 alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; W is absent, or selected from alkylene, alkenylene, alkynylene, -O-, -S-, -NR1-, C(O)NR1-, or -C(O)-; m is 0, 1, 2 or 3; m' is 0, 1, 2 or 3; and s is 1, 2, 3, or 4 (para [0009], Formula I, para [0011], 'R1 is...C3-7 cycloalkyl,' para [0012], 'm is 2,' para [0013], 'n is 1,' para [0014], 'R2 is...C1-6 alkyl...C2-6 alkenyl...optionally substituted with halogen,' para [0015], 'R3 is C1-8 alkyl,' para [0016], 'Y is H,' para [0017], 'B is...R4O(C=O)-,' para [0018], 'R4 is...C-1-10 alkyl optionally substituted...C2-6 alkenyl,' para [0020], 'X is O,' para [0021], 'R' is Het...optionally substituted with Ra,' para [0022], 'Ra is C1-6 alkyl...C6-10 aryl, C7-14 alkylaryl,' para [0059], 'Examples of bicyclic heterocycles include...(structure of quinoxaline)'). Wang does not expressly teach that the carbamoyl and heterocyclic moieties are joined in a macrocyclic ring as a tether. However, Nakajima does further teach of a quinoxaline-containing macrocyclic HCV protease inhibiting compound by an alkyl or alkenyl tether (para [0011], 'treating a hepatitis C infection...with said macrocyclic compounds,' para [0012], Formulas I and II). It would have been obvious to one of ordinary skill in the art that the macrocyclic ring could be formed from Wang's compound by joining the carbamate and heteroaromatic moieties as Nakajima's tethered compounds are used for the treatment of HCV infection and tethered analogs were well known in the art.

As for claims 14-16, Wang, in view of Nakajima, teaches a compound according to claim 1 (as described for claim 1 above). Neither Wang nor Nakajima expressly teach the specific compounds as set forth in Tables 1-3. However, Wang in view of Nakajima discloses each of the elements of the compounds in Tables 1-3 (as described in claim 1 above). It would have been obvious to one of ordinary skill in the art to apply Nakajima's teachings regarding macrocyclic protease inhibitors to Wang's compounds to arrive at the compounds of Tables 1-3.

As for claim 17, Wang further teaches a pharmaceutical composition comprising an inhibitory amount of a compound according to claim 1 (see discussion of claim 1 above) or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient (para [0025], 'compositions comprising the compounds or pharmaceutically acceptable salts, solvate or prodrugs thereof and a pharmaceutically acceptable carrier').

As for claims 18-19, Wang further teaches a method of treating a viral infection in a subject, comprising administering to the subject an inhibitory amount of a pharmaceutical composition according to claim 17 (para [0026], 'methods for treating patients infected with HCV, comprising administering to the patient a therapeutically effective amount of a compound of the present invention').

As for claim 20, Wang further teaches a method of inhibiting the replication of hepatitis C virus, the method comprising supplying a hepatitis C viral NS3 protease inhibitory amount of the pharmaceutical composition of claim 17 (para [0026], 'methods of inhibiting HCV NS3 protease by administering to a patient an effective amount of a compound of the present invention').

As for claims 21-25, Wang teaches the method of claim 18, further comprising administering concurrently an additional anti-hepatitis C virus agent (para [0193], 'treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS3 protease; inhibitors of other targets in the HCV life cycle such as helicase, polymerase, metalloprotease, or internal ribosome entry site; or combinations thereof').

As for claim 26, Wang teaches the pharmaceutical composition of claim 17, further comprising pegylated interferon (para [0004], 'combinations of pegylated alpha-interferon').

As for claim 27, Wang teaches the pharmaceutical composition of claim 17, further comprising another anti-viral, antibacterial, anti-fungal or anti-cancer agent, or an immune modulator (para [0042], 'antibacterial agents, antifungal agents').

Claims 28-30 lack an inventive step under PCT Article 33(3) as being obvious over Wang in view of Nakajima and further in view of US 2007/0054842 A1 to Blatt et al. (hereinafter 'Blatt').

As for claims 28-30, Wang, in view of Nakajima, teaches the composition of claim 17 (see discussion of claim 17 above). Neither Wang nor Nakajima teach the composition further comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof. However, Blatt does further teach of a composition for the inhibition of hepatitis C virus replication comprising Ritonavir in addition to macrocyclic compounds (title, 'Novel macrocyclic inhibitors of hepatitis C virus replication,' para [0616], 'method further includes administration of ritonavir'). It would have been obvious to one of ordinary skill in the art to include further include Ritonavir 'Because of its strong inhibitory effect on cytochrome P450 3A and the inhibitory effect on cytochrome P450 2D6, ritonavir at doses below the normal therapeutic dosage may be combined with other protease inhibitors to achieve therapeutic levels of the second protease inhibitor while reducing the number of dosage units required, the dosing frequency, or both' (para [0616]).

Claims 1-30 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.