

CASTELLANOS & Co.
Calle 94 A No.7ª-09
Bogotá-Colombia

145
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-080058- -00001-0000

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Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 329 CTOINFORMACION Folios: 94

Señora

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo Industria y Turismo

E. S. D.

Ref.: Expediente **No. 07.080.058**

Solicitud de Patente PCT entrada Fase Nacional para:

**"TETRAZOLILOS MACROCÍCLICOS COMO INHIBIDORES DE SERINA
PROTEASA DE HEPATITIS C"**

Solicitante: **ENANTA PHARMACEUTICALS, INC.**

PRESENTACION DE DOCUMENTOS

MARGARITA CASTELLANOS ABONDANO, mayor de edad,
identificada y domiciliada como aparece al pie de mi firma, atentamente me
permito presentar los siguientes documentos:

- Sustitución de poder a nombre de **MARGARITA CASTELLANOS**.
- Copia auténtica del documento de poder otorgado por la sociedad
solicitante **ENANTA PHARMACEUTICALS, INC.** con la certificación
notarial en que consta la existencia y representación de la sociedad
legalizado por Apostilla.
- Copia certificada del documento de prioridad No. 11/499,245 del 4 de
agosto de 2006, junto con la traducción de la carátula al español.

Solicito que el documento No. 11/499,245 del 4 de agosto de 2006 se tenga
como única prioridad reivindicada toda vez que el solicitante desiste de las
prioridades posteriores indicadas en el petitorio.

De esta manera se han completado los requisitos formales de la solicitud de la referencia y, en consecuencia, atentamente solicito a Ud. se continúe con el trámite correspondiente a esta solicitud de Patente de Invención.

De la Señora Jefe,


Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** de **C.S.J.**
Calle 94 A No. 7 A-09 – Bogotá, D.C.
Tel.: 610 7420 – 610 7480

Bogotá, D.C., 24 SET. 2007

Patentes/15/P1520-FNPCT/MEMORIAL PRESENTACION DE DOCUMENTOS

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Ref.: **PODER** conferido por **ENANTA PHARMACEUTICALS, INC.**

Yo, **XIMENA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra. **MARGARITA CASTELLANOS ABONDANO**, el poder que me confirió el **ENANTA PHARMACEUTICALS, INC.**, con domicilio en **500 Arsenal Street, Watertown, MA 02472, ESTADOS UNIDOS DE AMERICA**, debidamente legalizado por Apostilla el día **24 de agosto de 2007**, bajo el número **1251520**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT Entrada en Fase Nacional en Colombia, para: **TETRAZOLILOS MACROCÍCLICOS COMO INHIBIDORES DE SERINA PROTEASA DE HEPATITIS C**, Expediente No. **07 080058.-**

De la Señora Jefe,

Acepto


Ximena Castellanos Abondano
C.C. No. **39.773.330** de Usaquén
T.P.A. No. **58.236** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá
PBX: 610 74 20

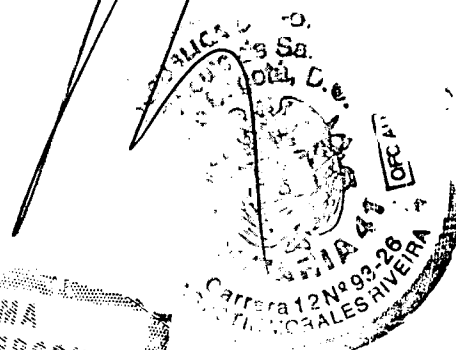

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá
PBX: 610 74 20

Bogotá, D.C.
XCA/MCA/gcb/ P1520

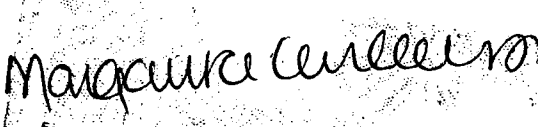
AD/ENTIFICACION DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
 (Art. 84 C.R.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
 Ante el Notario Cuarenta y Uno (41) del circulo
 de esta ciudad compareció personalmente:
Ximena Castellon
 identificado con C.C. **39773350**
 expedida en: **USC** y tarjeta profesio-
 nal de abogado(a) No. **58236** del Consejo
 Superior de la Judicatura, con documento di-
 y declaró que la firma puesta en este escrito es
 suya.


 Firma del declarante

En Bogotá D.C. a **21 SET. 2007**
 AUTORIZO ESTA DILIGENCIA EL SUSCRITO



AD/ENTIFICACION DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
 (Art. 84 C.R.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
 Ante el Notario Cuarenta y Uno (41) del circulo
 de esta ciudad compareció personalmente:
Margarita Castellon
 identificado con C.C. **39779854**
 expedida en: **USC** y tarjeta profesio-
 nal de abogado(a) No. **70119** del Consejo
 Superior de la Judicatura, con documento di-
 y declaró que la firma puesta en este escrito es
 suya.


 Firma del declarante

En Bogotá D.C. a **21 SET. 2007**
 AUTORIZO ESTA DILIGENCIA EL SUSCRITO



COLOMBIA

PODER

El (los) **ENANTA PHARMACEUTICALS, INC.**

Domiciliados en
500 Arsenal Street, Watertown, MA 02472, Estados Unidos de América

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá-Colombia para

y para obtener la protección de mi (nuestra) propiedad Industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso -administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

- Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;
- Para la obtención de registros sanitarios;
- Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy 16 de Agosto de 2007

en Watertown, MA

por **ENANTA PHARMACEUTICALS, INC.**
Paul J. Mellett, Jefe de la Oficina Financiera
(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular o mediante apostilla)

POWER OF ATTORNEY

I (we) the undersigned **ENANTA PHARMACEUTICALS, INC.**

Of
500 Arsenal Street, Watertown, MA 02472, United States of America

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS A.** attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to

and to obtain the protection of my (our) Industrial Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

- Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
- For the obtainment of Sanitary registrations;
- Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters they may substitute this power of attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this

in

by

Paul J. Mellett
Paul J. Mellett, Chief Financial Officer
Enanta Pharmaceuticals, Inc.

(Notary shall execute on the other side)

(Consular legalization or apostille is required)

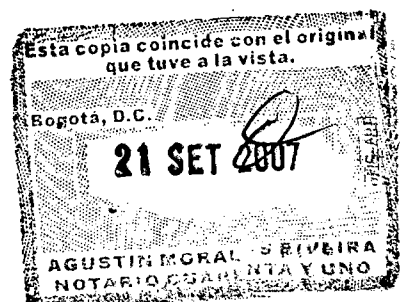
CASTELLANOS & CO

ABOGADOS COLOMBIA

Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia

Tels.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

4056.1106 CO



COLOMBIA

CERTIFICADO NOTARIAL (Sociedad)

Hoy 16 de 8 del año 2007
compareció (eron) personalmente

PAUL J. MELLETT

a quienes conozco como la(s) personas que firma(n) en
representación de la Sociedad (Compañía) denominada

Certifico :

a) Que

ENANTA PHARMACEUTICALS, INC.

es una sociedad/Compañía legalmente constituida y
existente de acuerdo con las leyes del estado de
Delaware

b) Que el domicilio de dicha Sociedad/Compañía es
500 Arsenal Street, Watertown, MA 02472, Estados Unidos de
América

c) Que el objeto u objetos para los cuales se otorga el
presente poder están comprendidos dentro del objeto
social de la mencionada Sociedad /Compañía.

d) Que el Sr.
esta autorizado para otorgar el presente poder. Lo anterior
esta probado por medio de los siguientes documentos, que
certifico he visto*

(Ciudad) WATERTOWN

(Estado) Massachusetts

Hoy del 16 de Agosto de 2007

(Notario Público)

*Los documentos debe identificarse con fecha y origen.

NOTARIAL CERTIFICATION (Corporation)

On this 16 day of August of 2007
personally appeared

PAUL J. MELLETT

whom I know to be the person(s) who signed this document as
representative(s) of the Corporation /Company named

I certify:

a) That

ENANTA PHARMACEUTICALS, INC.

is a corporation (Company legally constituted and in
existence in accordance with the laws of Delaware

b) That the domicile of said Corporation/Company is
500 Arsenal Street, Watertown, MA 02472, United States of
America.

c) That the purpose or purposes for which the present
Power of Attorney is granted are comprised within the object
set forth in the charter of the mentioned
Corporation/Company.

d) That Mr.

is (are) authorized to grant the present Power of Attorney. The
aforementioned was duly proven through the following
documents and I duly certify having seen them*:

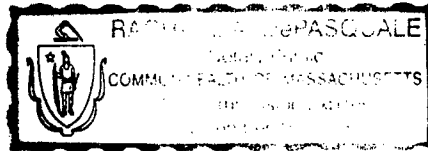
(City) Watertown

(State) Massachusetts

this 16 day of Aug of the year 2007

(Notary Public)

*Documents must be identified with date and origin



Rachael A. DePasquale

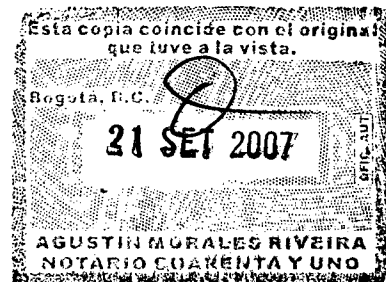
CASTELLANOS & CO

ABOGADOS COLOMBIA

Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia

Tels.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

4056.1106 CO



The Commonwealth of Massachusetts

William Francis Galvin
Secretary of the Commonwealth

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: United States of America
This public document
2. has been signed by: Rachael DePasquale
3. acting in the capacity of: Notary Public
4. bears the seal/stamp of: the State of Massachusetts
whose commission expires on: November 15, 2013

Certified

5. at: Boston, Massachusetts
6. the: 24 August, 2007
7. by: the Secretary of the Commonwealth
8. No.: 1251520
9. Seal/stamp:

Great Seal of the Commonwealth

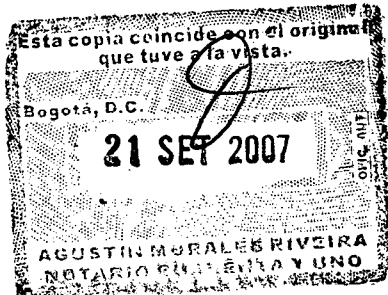
10. Signature:

William Francis Galvin

William Francis Galvin
Secretary of the Commonwealth



prepared by TCoughlin



TRADUCCIÓN OFICIAL No. 201-07, DE UN DOCUMENTO ESCRITO EN INGLÉS, SELLADO CON EL SELLO DEL SUSCRITO TRADUCTOR OFICIAL, HOY SEPTIEMBRE 19 DEL 2007, EN LA CIUDAD DE BOGOTÁ D.C., REPÚBLICA DE COLOMBIA

(PODER... SELLO NOTARIAL .../...)

Firma y sello de

RACHAEL A. DePASQUALE

Notario público Mancomunidad de Massachussets

Comisión vence: Noviembre 15, 2013.

ADJUNTO AL DOCUMENTO SE ENCUENTRA LO SIGUIENTE:

LA MANCOMUNIDAD DE MASSACHUSSETS

William Francis Galvin

Secretario de la Mancomunidad

APOSTILLE

(CONVENCION DE LA HAYE DE 5 OCTOBRE 1961)

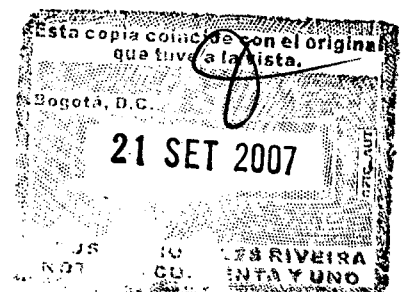
1. PAIS: ESTADOS UNIDOS DE AMERICA
ESTE DOCUMENTO PUBLICO
2. HA SIDO FIRMADO POR: RACHAEL DEPASQUALE
3. ACTUANDO EN CAPACIDAD DE: NOTARIO PUBLICO
4. LLEVA EL SELLO DEL ESTADO DE MASSACHUSSETS
Cuya comisión vence en: NOVIEMBRE 15, 2013.

CERTIFICADO

5. EN: BOSTON, MASSACHUSSETS
6. EL DIA: 24 DE AGOSTO DEL 2007
7. POR: EL SECRETARIO DE LA MANCOMUNIDAD
8. No.1251520
9. SELLO/ESTAMPILLA GRAN SELLO DE LA MANCOMUNIDAD
10. FIRMA

FIRMADO POR: WILLIAM FRANCIS GALVIN
SECRETARIO DE LA MANCOMUNIDAD.

Sergio Eleuterio Latorre Mendoza
Traductor e Interpreté Oficial
Resol. No. 2899 Minjusticia 1991



TRADUCCIÓN

ESTADOS UNIDOS DE AMÉRICA

A quien corresponda:

DEPARTAMENTO DE COMERCIO - OFICINA DE PATENTES Y MARCAS

13 de agosto de 2007

CERTIFICO QUE ADJUNTA A LA PRESENTE SE ENCUENTRA UNA COPIA FIEL DE LOS REGISTROS EN LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE REUNÍAN LOS REQUISITOS PARA LA ASIGNACIÓN DE UNA FECHA DE PRESENTACIÓN EN VIRTUD DE 35 USC 111.

SOLICITUD NUMERO: **11/499.245**

FECHA DE PRESENTACIÓN: 4 de agosto de 2006

El código de país y número de su solicitud de prioridad a ser utilizado para presentaciones en el exterior de acuerdo con el Convenio de París es: US **11/499.245.**

En nombre del Funcionario a cargo de la Subsecretaria de Comercio, Propiedad Industrial e Intelectual y a cargo de la Oficina de Patentes y Marcas.

(Firmado) N. Williams, Certificaciones.

(La presente certificación se encuentra unida en forma inviolable a sus adjuntos y lleva una oblea dorada que dice): OFICINA DE PATENTES Y MARCAS - ESTADOS UNIDOS DE AMÉRICA.

(Adjuntos)



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 13, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 11/499,245

FILING DATE: August 04, 2006

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS US11/499,245

**By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office**



N. Williams
N. WILLIAMS

Certifying Officer

0007081956/1



USPTO

Document

Date: 08/09/07

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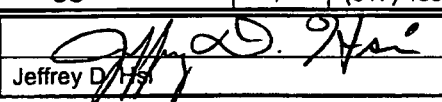
Doc 1 of 1

Patent Application as Filed
11499245

16179 U.S. PTO
080406

PTO/SB/05 (05-05)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

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UTILITY PATENT APPLICATION TRANSMITTAL		Attorney Docket No. 66055(50530)	
(ONLY FOR NEW NONPROVISIONAL APPLICATIONS UNDER 37 CFR 1.53(B))		First Inventor Ying Sun	
		Title TETRAZOLYL MACROCYCLIC HEPATITIS C SERINE PROTEASE INHIBITORS	
		Express Mail Label No. EV755075501US	
APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents.		ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	
1. ☐ Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing)		9. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee: 	
2. ☒ Applicant claims small entity status. See 37 CFR 1.27.		10. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney	
3. ☒ Specification [Total Pages 79] Both the claims and abstract must start on a new page (For information on the preferred arrangement, see MPEP 608.01(e))		11. ☐ English Translation Document (if applicable)	
4. ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets]		12. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1448) ☐ Copies of foreign patent documents, publications, & other information	
5. Oath or Declaration [Total Sheets] a. ☐ Newly executed (original or copy) b. ☐ A copy from a prior application (37 CFR 1.83(d)) (for continuation/divisional with Box 18 completed) i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).		13. ☐ Preliminary Amendment	
6. ☒ Application Data Sheet. See 37 CFR 1.76		14. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)	
7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix) ☐ Landscape Table on CD		15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)	
8. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. - c. are required) a. Computer Readable Form (CRF) i. ☐ Computer Readable Form (CRF) ii. ☐ Transfer Request (37 CFR 1.821(e)) b. Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies		16. ☐ Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.	
18. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76: ☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: Prior application information: Examiner Art Unit:		17. ☐ Other: 	
19. CORRESPONDENCE ADDRESS			
☒ The address associated with Customer Number: 21874 OR ☐ Correspondence address below			
Name Jeffrey D. Hsi EDWARDS ANGELL PALMER & DODGE LLP			
Address P.O. Box 55874			
City Boston		State MA	Zip Code 02205
Country US		Telephone (617) 439-4444	Email Address
Signature 		Date August 4, 2006	Registration No. (Attorney/Agent) 40,024
Name (Print/Type) Jeffrey D. Hsi			

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service as Express Mail, Label No. EV755075501US, on the date shown below in an envelope addressed to:
Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: August 4, 2006

Signature: Susan M. Dillon (Susan Dillon)

113264 U.S. PTO
11/499245

080406

Application No. (if known):

Attorney Docket No.: 66055(50530)

Certificate of Express Mailing Under 37 CFR 1.10

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on August 4, 2006
Date

Susan M Dillon

Signature

Susan Dillon

Typed or printed name of person signing Certificate

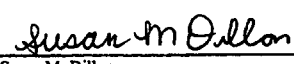
Registration Number, if applicable

(617) 439-4444

Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Application Data Sheet (3 pages)

CERTIFICATION OF MAILING UNDER 37 CFR §1.10 EXPRESS MAIL MAILING LABEL NUMBER: EV755075501US DATE OF DEPOSIT: August 4, 2006 I hereby certify that this Patent Application is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10 on the date indicated above and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.  _____ Susan M. Dillon

TETRAZOLYL MACROCYCLIC HEPATITIS C SERINE PROTEASE INHIBITORS

TECHNICAL FIELD

The present invention relates to novel macrocycles having activity against the hepatitis C virus (HCV) and useful in the treatment of HCV infections. More particularly, the invention relates to macrocyclic compounds, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

HCV is the principal cause of non-A, non-B hepatitis and is an increasingly severe public health problem both in the developed and developing world. It is estimated that the virus infects over 200 million people worldwide, surpassing the number of individuals infected with the human immunodeficiency virus (HIV) by nearly five fold. HCV infected patients, due to the high percentage of individuals inflicted with chronic infections, are at an elevated risk of developing cirrhosis of the liver, subsequent hepatocellular carcinoma and terminal liver disease. HCV is the most prevalent cause of hepatocellular cancer and cause of patients requiring liver transplantations in the western world.

There are considerable barriers to the development of anti-HCV therapeutics, which include, but are not limited to, the persistence of the virus, the genetic diversity of the virus during replication in the host, the high incident rate of the virus developing drug-resistant

mutants, and the lack of reproducible infectious culture systems and small-animal models for HCV replication and pathogenesis. In a majority of cases, given the mild course of the infection and the complex biology of the liver, careful consideration must be given to antiviral drugs, which are likely to have significant side effects.

5 Only two approved therapies for HCV infection are currently available. The original treatment regimen generally involves a 3-12 month course of intravenous interferon- α (IFN- α), while a new approved second-generation treatment involves co-treatment with IFN- α and the general antiviral nucleoside mimics like ribavirin. Both of these treatments suffer from interferon related side effects as well as low efficacy against HCV infections. There exists a need
10 for the development of effective antiviral agents for treatment of HCV infection due to the poor tolerability and disappointing efficacy of existing therapies.

 In a patient population where the majority of individuals are chronically infected and asymptomatic and the prognoses are unknown, an effective drug would desirably possess significantly fewer side effects than the currently available treatments. The hepatitis C non-
15 structural protein-3 (NS3) is a proteolytic enzyme required for processing of the viral polyprotein and consequently viral replication. Despite the huge number of viral variants associated with HCV infection, the active site of the NS3 protease remains highly conserved thus making its inhibition an attractive mode of intervention. Recent success in the treatment of HIV with protease inhibitors supports the concept that the inhibition of NS3 is a key target in the battle
20 against HCV.

 HCV is a flaviridae type RNA virus. The HCV genome is enveloped and contains a single strand RNA molecule composed of circa 9600 base pairs. It encodes a polypeptide comprised of approximately 3010 amino acids.

 The HCV polyprotein is processed by viral and host peptidase into 10 discreet peptides
25 which serve a variety of functions. There are three structural proteins, C, E1 and E2. The P7 protein is of unknown function and is comprised of a highly variable sequence. There are six non-structural proteins. NS2 is a zinc-dependent metalloproteinase that functions in conjunction with a portion of the NS3 protein. NS3 incorporates two catalytic functions (separate from its association with NS2): a serine protease at the N-terminal end, which requires NS4A as a

cofactor, and an ATP-ase-dependent helicase function at the carboxyl terminus. NS4A is a tightly associated but non-covalent cofactor of the serine protease.

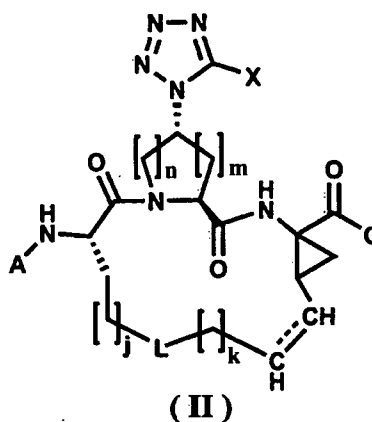
The NS3.4A protease is responsible for cleaving four sites on the viral polyprotein. The NS3-NS4A cleavage is autocatalytic, occurring in cis. The remaining three hydrolyses, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B all occur in trans. NS3 is a serine protease which is structurally classified as a chymotrypsin-like protease. While the NS serine protease possesses proteolytic activity by itself, the HCV protease enzyme is not an efficient enzyme in terms of catalyzing polyprotein cleavage. It has been shown that a central hydrophobic region of the NS4A protein is required for this enhancement. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficacy at all of the sites.

A general strategy for the development of antiviral agents is to inactivate virally encoded enzymes, including NS3, that are essential for the replication of the virus. Current efforts directed toward the discovery of NS3 protease inhibitors were reviewed by S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies, *Nature Rev. Drug Discov.*, 1, 867-881 (2002). Other patent disclosures describing the synthesis of HCV protease inhibitors are: WO 00/59929 (2000); WO 99/07733 (1999); WO 00/09543 (2000); WO 99/50230 (1999); US5861297 (1999); and US2002/0037998 (2002).

SUMMARY OF THE INVENTION

The present invention relates to novel macrocyclic compounds and methods of treating a hepatitis C infection in a subject in need of such therapy with said macrocyclic compounds. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters, or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In one embodiment of the present invention there are disclosed compounds represented by Formulas I and II, or pharmaceutically acceptable salts, esters, or prodrugs thereof:



A is selected from R_1 , $-(C=O)-O-R_1$, $-(C=O)-R_2$, $-C(=O)-NH-R_2$, or $-S(O)_2-R_1$, NHR_2 ;

(i) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(ii) heterocycloalkyl or substituted heterocycloalkyl;

(iii) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

- (i) hydrogen;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-$

C₈ alkenyl, or substituted –C₂-C₈ alkynyl 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;

5 G is selected from –OH, –NHS(O)₂–R₃, –NH(SO₂)NR₄R₅;

R₃ is selected from:

- 10 (i) aryl; substituted aryl; heteroaryl; substituted heteroaryl
(ii) heterocycloalkyl or substituted heterocycloalkyl;
(iii) –C₁-C₈ alkyl, –C₂-C₈ alkenyl, or –C₂-C₈ alkynyl 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 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;

15

R₄ and R₅ are independently selected from:

- 20 (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 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 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;

25

L is selected from –CH₂–, –O–, –S–, or –S(O)₂–;

X is selected from:

- (i) hydrogen;

- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;
- (v) $-W-R_6$, where W is absent, or selected from $-O-$, $-S-$, $-NH-$, $-N(Me)-$, $-C(O)NH-$, or $-C(O)N(Me)-$; R_6 is selected from the group consisting of:
 - (a) Hydrogen;
 - (b) aryl; substituted aryl; heteroaryl; substituted heteroaryl
 - (c) heterocyclic or substituted heterocyclic;
 - (d) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

$\equiv$ denotes a carbon-carbon single or double bond.

$j = 0, 1, 2, 3, \text{ or } 4$;

$k = 1, 2, \text{ or } 3$;

$m = 0, 1, \text{ or } 2$;

$n = 1, 2 \text{ or } 3$.

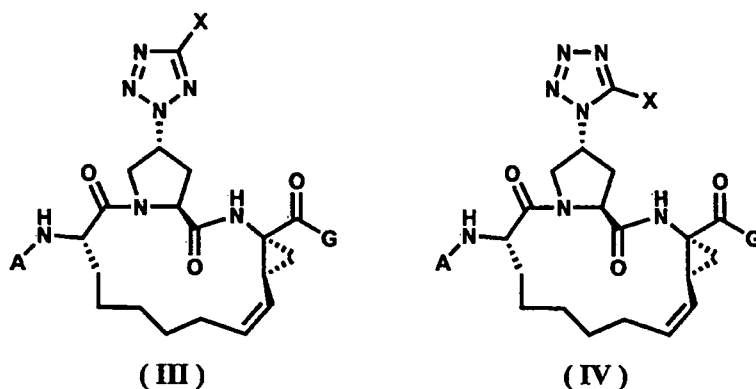
Detailed Description of the Invention

A first embodiment of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient.

- 5 A second embodiment of the invention is a compound represented by Formula II as described above, or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient.

Representative subgenera of the invention include, but are not limited to:

- 10 A compound of Formula III and IV:



where A, G and X are as previously defined.

- 15 Representative compounds of the invention include, but are not limited to, the following compounds (Table 1) according to Formula V:

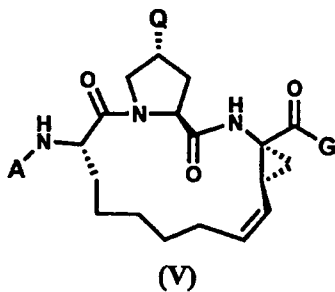
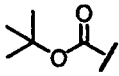
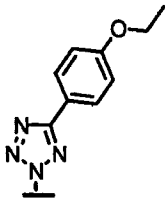
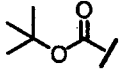
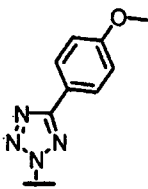
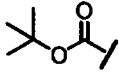
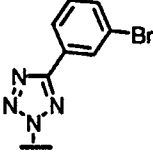
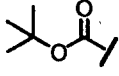
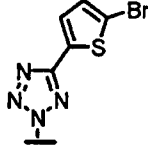
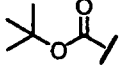
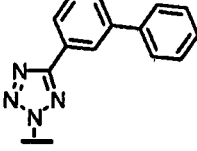
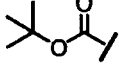
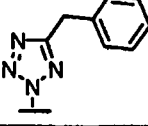
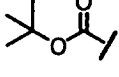
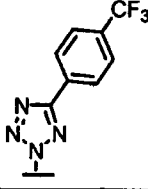
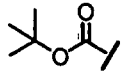
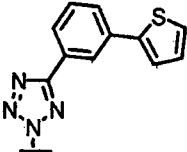
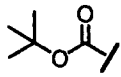
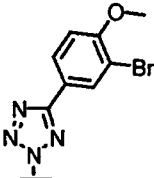
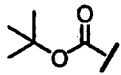
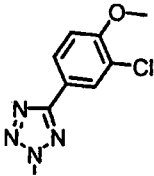
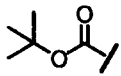
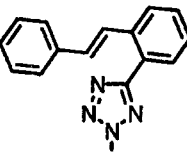
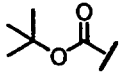
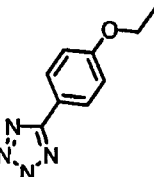
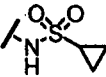
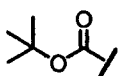
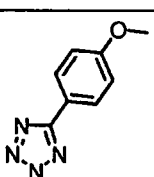
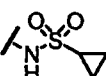
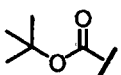
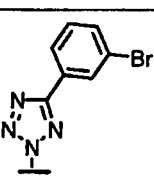
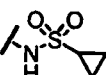
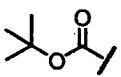
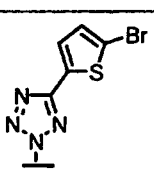
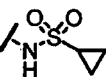
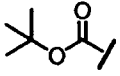
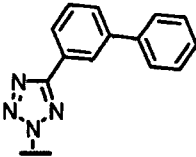
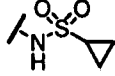
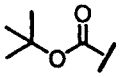
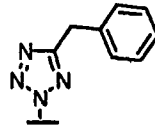
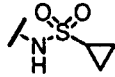
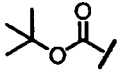
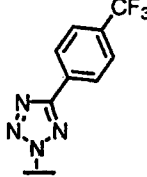
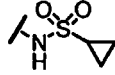
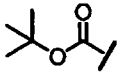
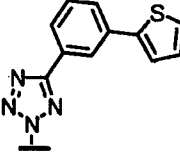
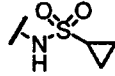
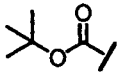
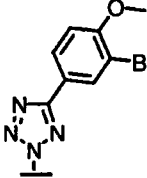
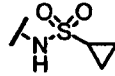
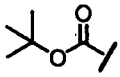
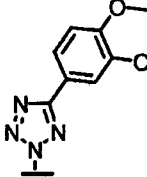
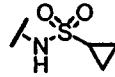
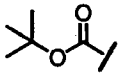
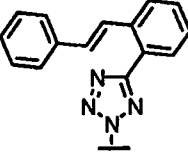
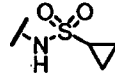
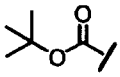
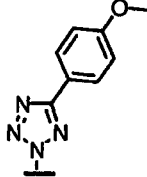
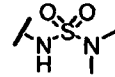
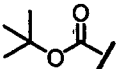
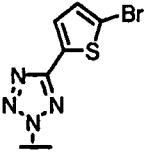
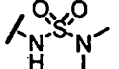
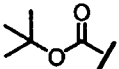
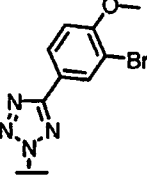
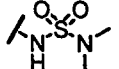
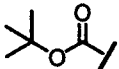
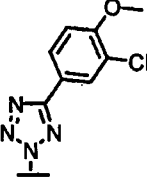
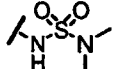
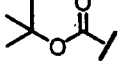
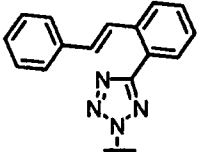
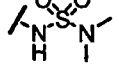
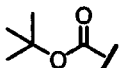
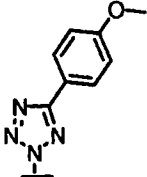
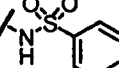
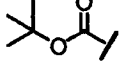
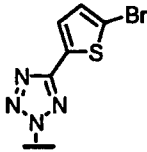
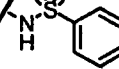
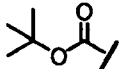
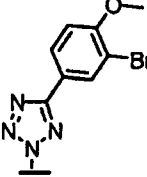
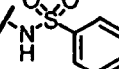
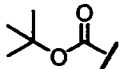
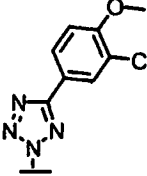
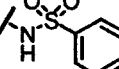


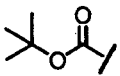
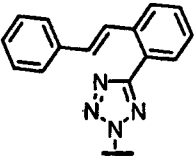
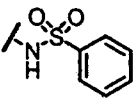
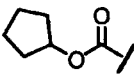
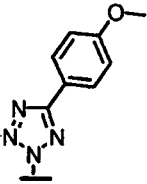
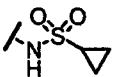
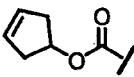
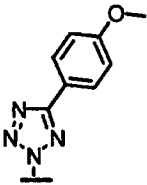
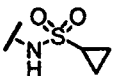
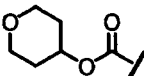
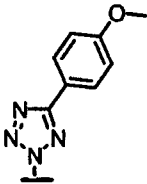
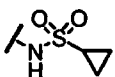
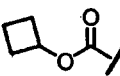
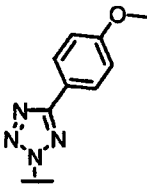
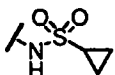
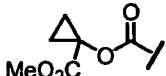
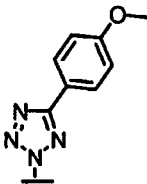
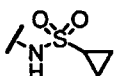
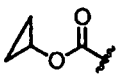
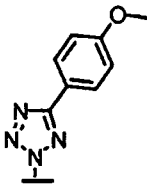
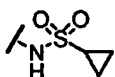
TABLE 1

Example#	A	Q	G
4			-OH
5			-OH
6			-OH
7			-OH
8			-OH
9			-OH
10			-OH

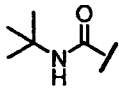
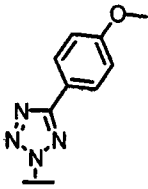
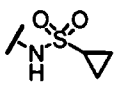
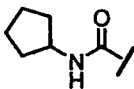
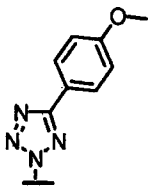
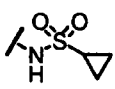
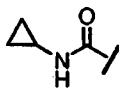
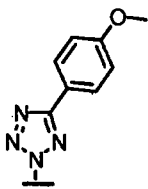
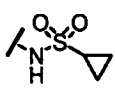
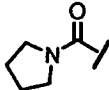
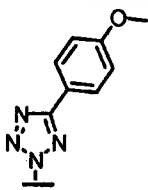
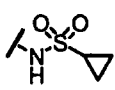
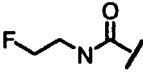
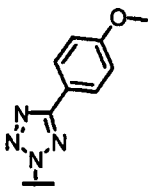
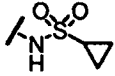
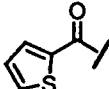
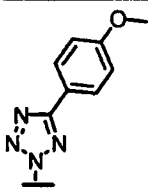
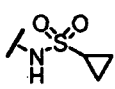
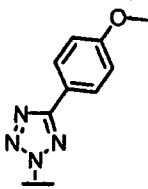
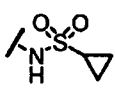
11			-OH
12			-OH
13			-OH
14			-OH
15			
16			
17			
18			

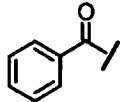
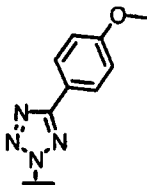
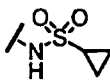
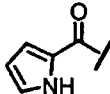
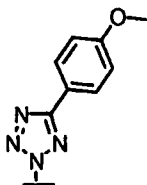
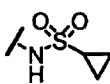
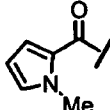
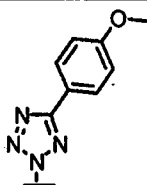
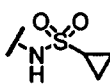
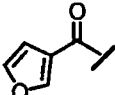
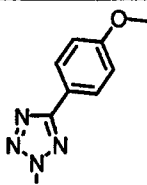
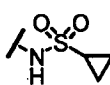
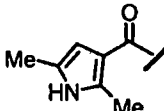
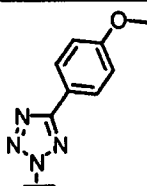
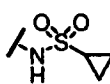
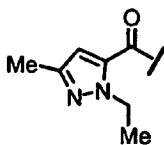
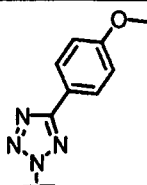
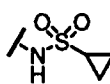
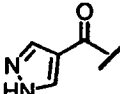
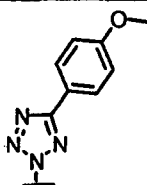
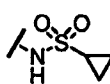
19			
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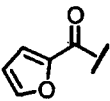
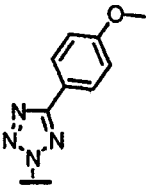
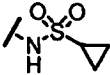
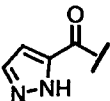
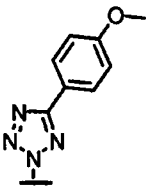
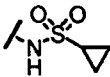
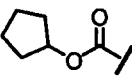
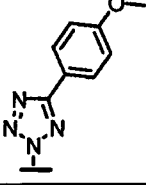
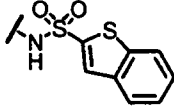
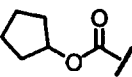
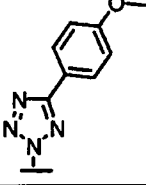
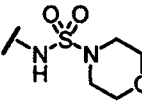
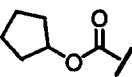
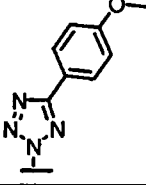
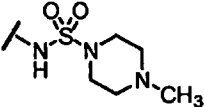
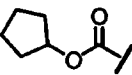
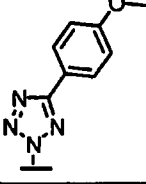
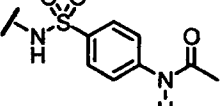
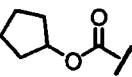
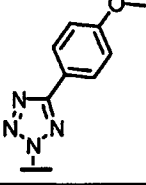
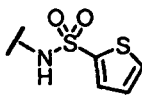
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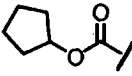
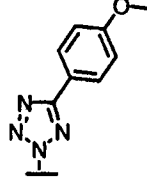
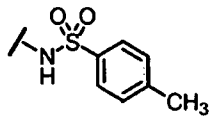
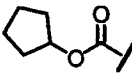
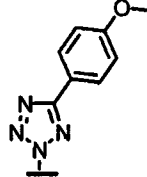
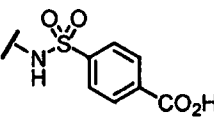
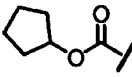
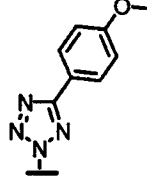
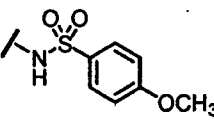
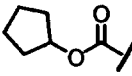
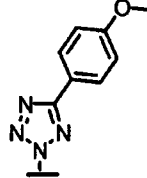
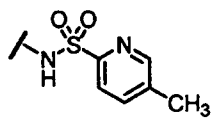
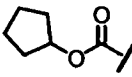
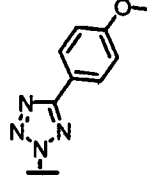
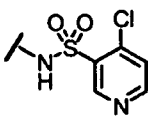
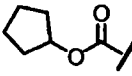
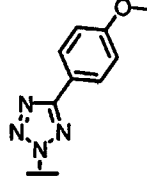
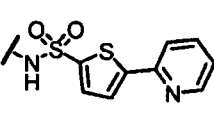
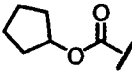
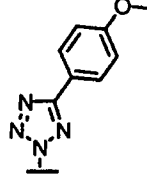
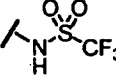
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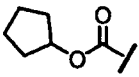
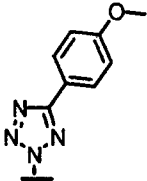
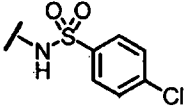
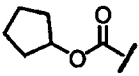
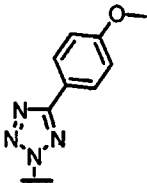
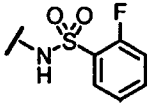
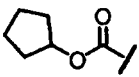
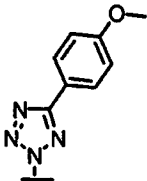
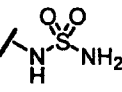
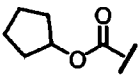
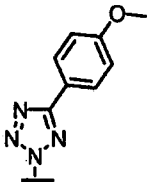
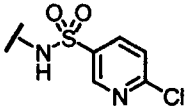
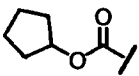
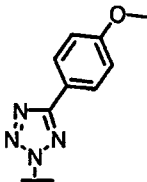
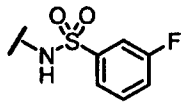
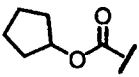
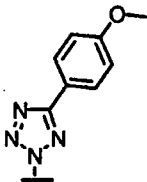
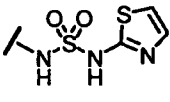
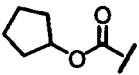
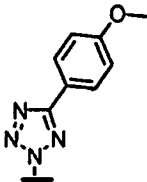
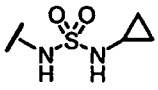
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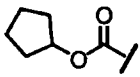
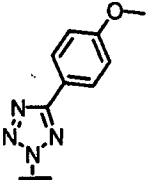
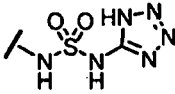
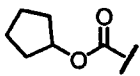
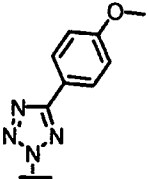
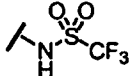
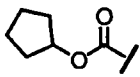
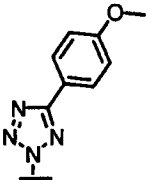
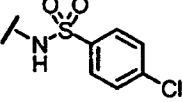
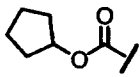
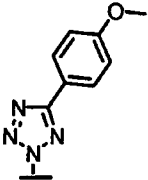
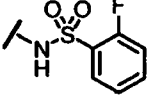
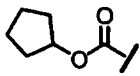
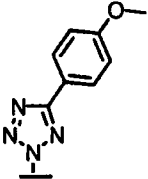
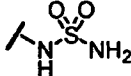
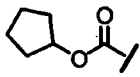
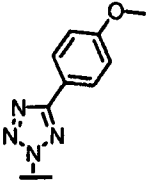
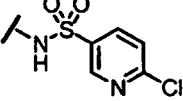
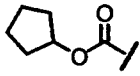
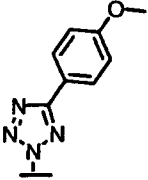
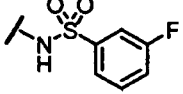
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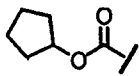
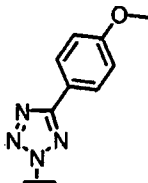
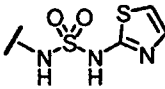
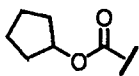
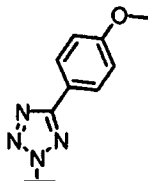
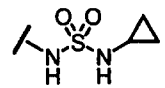
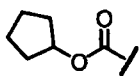
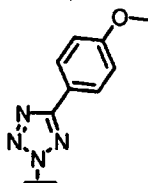
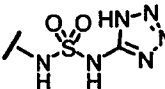
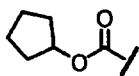
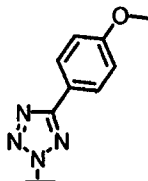
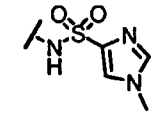
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According to an alternate embodiment, the pharmaceutical compositions of the present invention may further contain other anti-HCV agents. Examples of anti-HCV agents include, but are not limited to, α -interferon, β -interferon, ribavirin, and amantadine. For further details see S.

- 5 Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies, *Nature Rev. Drug Discov.*, 1, 867-881 (2002); WO 00/59929 (2000); WO 99/07733 (1999); WO 00/09543 (2000); WO 99/50230 (1999); US5861297 (1999); and US2002/0037998 (2002) which are herein incorporated by reference in their entirety.

- 10 According to an additional embodiment, the pharmaceutical compositions of the present invention may further contain other HCV protease inhibitors.

According to yet another embodiment, the pharmaceutical compositions of the present invention may further comprise inhibitor(s) of other targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, and internal ribosome entry site (IRES).

5 According to a further embodiment, the present invention includes methods of treating hepatitis C infections in a subject in need of such treatment by administering to said subject an anti-HCV virally effective amount or an inhibitory amount of the pharmaceutical compositions of the present invention.

10 An additional embodiment of the present invention includes methods of treating biological samples by contacting the biological samples with the compounds of the present invention.

15 Yet a further aspect of the present invention is a process of making any of the compounds delineated herein employing any of the synthetic means delineated herein.

Definitions

20 Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

25 The term "C₁-C₆ alkyl," or "C₁-C₈ alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and six, or one and eight carbon atoms, respectively. Examples of C₁-C₆ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl radicals; and examples of C₁-C₈ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl, heptyl, octyl radicals.

 The term "C₂-C₆ alkenyl," or "C₂-C₈ alkenyl," as used herein, denote a monovalent group derived from a hydrocarbon moiety containing from two to six, or two to eight carbon atoms

having at least one carbon-carbon double bond by the removal of a single hydrogen atom.

Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

5 The term "C₂-C₆ alkynyl," or "C₂-C₈ alkynyl," as used herein, denote a monovalent group derived from a hydrocarbon moiety containing from two to six, or two to eight carbon atoms having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butylnyl, heptynyl, octynyl and the like.

10 The term "C₃-C₈-cycloalkyl", or "C₃-C₁₂-cycloalkyl," as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom, respectively. Examples of C₃-C₈-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C₃-C₁₂-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

15 The term "C₃-C₈-cycloalkenyl", or "C₃-C₁₂-cycloalkenyl" as used herein, denote a monovalent group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Examples of C₃-C₈-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C₃-C₁₂-cycloalkenyl
20 include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl,
25 tetrahydronaphthyl, indanyl, idenyl and the like.

The term "arylalkyl," as used herein, refers to a C₁-C₃ alkyl or C₁-C₆ alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "heteroaryl," as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxaliny, and the like.

The term "heteroarylalkyl," as used herein, refers to a C₁–C₃ alkyl or C₁–C₆ alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused system, where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, and (v) any of the above rings may be fused to a benzene ring. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

The terms "substituted", "substituted C₁–C₆ alkyl," "substituted C₁–C₈ alkyl," "substituted C₂–C₆ alkenyl," "substituted C₂–C₈ alkenyl," "substituted C₂–C₆ alkynyl," "substituted C₂–C₈ alkynyl," "substituted C₃–C₁₂ cycloalkyl," "substituted C₃–C₈ cycloalkenyl," "substituted C₃–C₁₂ cycloalkenyl," "substituted aryl", "substituted heteroaryl," "substituted arylalkyl", "substituted heteroarylalkyl," "substituted heterocycloalkyl," as used herein, refer to CH, NH, C₁–C₆ alkyl, C₁–C₈ alkyl, C₂–C₆ alkenyl, C₂–C₈ alkenyl, C₂–C₆ alkynyl, C₂–C₈ alkynyl, C₃–C₁₂ cycloalkyl, C₃–C₈ cycloalkenyl, C₃–C₁₂ cycloalkenyl, aryl, heteroaryl, arylalkyl,

heteroarylalkyl, heterocycloalkyl groups as previously defined, substituted by independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -NH₂, protected amino, -NH -C₁-C₁₂-alkyl, -NH -C₂-C₁₂-alkenyl, -NH -C₂-C₁₂-alkenyl, -NH -C₃-C₁₂-
5 cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)- C₁-C₁₂-alkyl, -C(O)- C₂-C₁₂-alkenyl, -C(O)- C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH- C₁-C₁₂-alkyl, -CONH- C₂-C₁₂-alkenyl, -CONH- C₂-C₁₂-
10 alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂- C₁-C₁₂-alkyl, -OCO₂- C₂-C₁₂-alkenyl, -OCO₂- C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH- C₁-C₁₂-alkyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₃-C₁₂-cycloalkyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)- C₁-C₁₂-alkyl, -
15 NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂- C₁-C₁₂-alkyl, -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₃-C₁₂-cycloalkyl, -NHCO₂- aryl, -NHCO₂-heteroaryl, -NHCO₂- heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH- C₁-C₁₂-alkyl, -NHC(O)NH- C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-
20 aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, -NHC(S)NH- C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH- C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH- C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-
25 heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, - S(O)-C₂-C₁₂-alkenyl, -

S(O)-C₂-C₁₂-alkenyl, - S(O)-C₃-C₁₂-cycloalkyl, - S(O)-aryl, - S(O)-heteroaryl, - S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted.

In accordance with the invention, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group, an alicyclic group or a heterocyclic group. An “aliphatic group” is non-aromatic moiety that may contain any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted. It is understood that aliphatic groups may be used in place of the alkyl, alkenyl, alkynyl, alkylene, alkenylene, and alkynylene groups described herein.

The term “alicyclic,” as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Such alicyclic groups may be further substituted.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

5 The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by
10 the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic
15 double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily
20 herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be referred to herein as a patient.

25

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a

reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J.

Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free

5 base function with a suitable organic acid. Examples of pharmaceutically acceptable include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other
10 pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate,
15 malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts
20 include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the
25 compounds formed by the process of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms.

Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

5 The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs
of the compounds formed by the process of the present invention which are, within the scope of
sound medical judgment, suitable for use in contact with the tissues of humans and lower
animals with undue toxicity, irritation, allergic response, and the like, commensurate with a
reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic
forms, where possible, of the compounds of the present invention. "Prodrug", as used herein
10 means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to
afford any compound delineated by the formulae of the instant invention. Various forms of
prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of
Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press
(1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug
15 Design and Development, Chapter 5, 113-191 (1991); Bundgaard, et al., Journal of Drug Deliver
Reviews, 8:1-38(1992); Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988);
Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society
(1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism:
Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

20

Combinations of substituents and variables envisioned by this invention are only those
that result in the formation of stable compounds. The term "stable", as used herein, refers to
compounds which possess stability sufficient to allow manufacture and which maintains the
integrity of the compound for a sufficient period of time to be useful for the purposes detailed
25 herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further
purified by a method such as column chromatography, high pressure liquid chromatography, or
recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing

the compounds of the formulae herein will be evident to those of ordinary skill in the art.

Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and one of ordinary skill in the art will

5 recognize that variation of the reaction conditions can produce the desired bridged macrocyclic products of the present invention. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

15 The compounds of this invention may be modified by appending various functionalities via any synthetic means delineated herein to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter
20 rate of excretion.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more
25 pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl

cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide
5 and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.
10 The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable
15 emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed,
20 groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

25 Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed

are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

5

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

10

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

25 Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

5 The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as
10 sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only,
15 or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

 Dosage forms for topical or transdermal administration of a compound of this invention
20 include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

25 The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary
5 propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of
10 the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Antiviral Activity

An inhibitory amount or dose of the compounds of the present invention may range from
15 about 0.1 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

20 According to the methods of treatment of the present invention, viral infections are treated or prevented in a subject such as a human or lower mammal by administering to the subject an anti-hepatitis C virally effective amount or an inhibitory amount of a compound of the present invention, in such amounts and for such time as is necessary to achieve the desired result. An additional method of the present invention is the treatment of biological samples with an
25 inhibitory amount of a compound of composition of the present invention in such amounts and for such time as is necessary to achieve the desired result.

The term "anti-hepatitis C virally effective amount" of a compound of the invention, as used herein, mean a sufficient amount of the compound so as to decrease the viral load in a

biological sample or in a subject. As well understood in the medical arts, an anti-hepatitis C virally effective amount of a compound of this invention will be at a reasonable benefit/risk ratio applicable to any medical treatment.

5 The term “inhibitory amount” of a compound of the present invention means a sufficient amount to decrease the hepatitis C viral load in a biological sample or a subject. It is understood that when said inhibitory amount of a compound of the present invention is administered to a subject it will be at a reasonable benefit/risk ratio applicable to any medical treatment as determined by a physician. The term “biological sample(s),” as used herein, means a substance
10 of biological origin intended for administration to a subject. Examples of biological samples include, but are not limited to, blood and components thereof such as plasma, platelets, subpopulations of blood cells and the like; organs such as kidney, liver, heart, lung, and the like; sperm and ova; bone marrow and components thereof; or stem cells. Thus, another embodiment of the present invention is a method of treating a biological sample by contacting said biological
15 sample with an inhibitory amount of a compound or pharmaceutical composition of the present invention.

 Upon improvement of a subject’s condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently,
20 the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

25 It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed;

the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

5

The total daily inhibitory dose of the compounds of this invention administered to a subject in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment
10 regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

Unless otherwise defined, all technical and scientific terms used herein are accorded the
15 meaning commonly known to one with ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

Abbreviations

20 Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

ACN for acetonitrile;

BME for 2-mercaptoethanol;

BOP for benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate;

25 COD for cyclooctadiene;

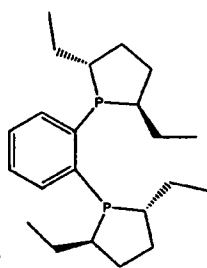
DAST for diethylaminosulfur trifluoride;

DABCYL for 6-(N-4'-carboxy-4-(dimethylamino)azobenzene)- aminohexyl-

1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite;

DCM for dichloromethane;

DIAD for diisopropyl azodicarboxylate;
DIBAL-H for diisobutylaluminum hydride;
DIEA for diisopropyl ethylamine;
DMAP for N,N-dimethylaminopyridine;
5 DME for ethylene glycol dimethyl ether;
DMEM for Dulbecco's Modified Eagles Media;
DMF for N,N-dimethyl formamide;
DMSO for dimethylsulfoxide;



DUPHOS for ;

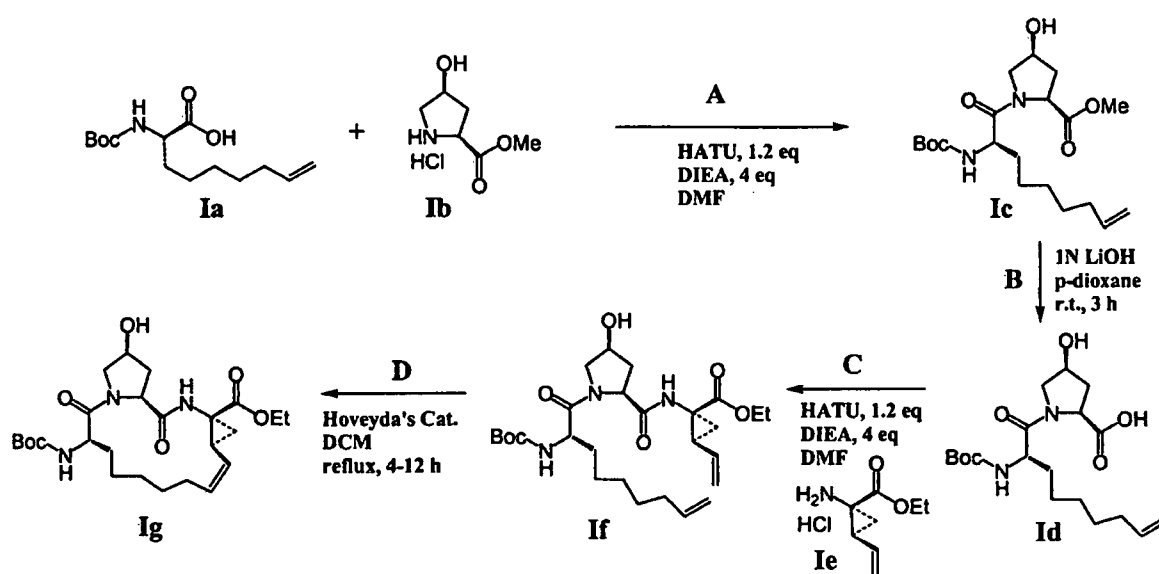
- 10 EDANS for 5-(2-Amino-ethylamino)-naphthalene-1-sulfonic acid;
EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
EtOAc for ethyl acetate;
HATU for O (7-Azabenzotriazole-1-yl)-N,N,N',N' – tetramethyluronium
hexafluorophosphate;
15 Hoveyda's Cat. for Dichloro(*o*-isopropoxyphenylmethylene)
(tricyclohexylphosphine)ruthenium(II);
KHMDs is potassium bis(trimethylsilyl) amide;
Ms for mesyl;
NMM for N-4-methylmorpholine
20 PyBrOP for Bromo-tri-pyrolidino-phosphonium hexafluorophosphate;
Ph for phenyl;
RCM for ring-closing metathesis;
RT for reverse transcription;
RT-PCR for reverse transcription-polymerase chain reaction;
25 TEA for triethyl amine;

TFA for trifluoroacetic acid;
THF for tetrahydrofuran;
TLC for thin layer chromatography;
TPP or PPh₃ for triphenylphosphine;
5 tBOC or Boc for tert-butyloxy carbonyl; and
Xantphos for 4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene.

Synthetic Methods

10 The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared.

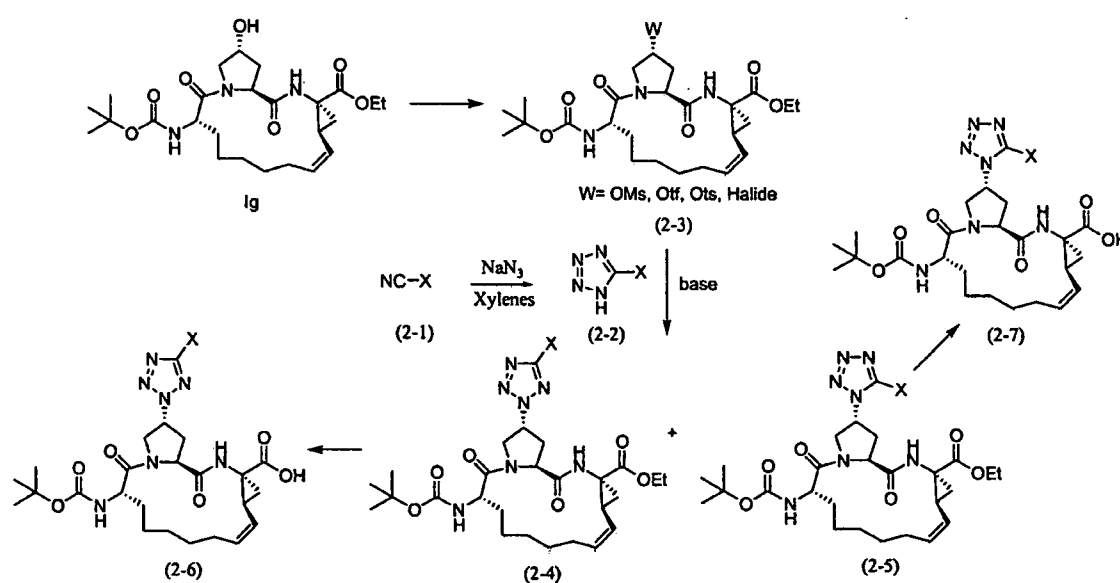
Scheme 1



15 Scheme 1 describes the synthesis of intermediate Ig. The cyclic peptide precursor Ig was synthesized from Boc-L-2-amino-8-nonenoic acid Ia and cis-L-hydroxyproline methyl ester Ib via steps A-D set forth generally in Scheme 1. For further details of the synthetic methods employed to produce the cyclic peptide precursor Ig, see U.S. Pat. No. 6,608,027, which is herein incorporated by reference in its entirety. Other amino acid derivatives containing a

terminal alkene may be used in place of Ia in order to create varied macrocyclic structures (for further details see WO/0059929). Ring closure metathesis with a Ruthenium-based catalyst gave the desired key intermediate Ig (for further details on ring closing metathesis see recent reviews: Grubbs et al., *Acc. Chem. Res.*, 1995, 28, 446; Shrock et al., *Tetrahedron* 1999, 55, 8141; Furstner, A. *Angew. Chem. Int. Ed.* 2000, 39, 3012; Tmka et al., *Acc. Chem. Res.* 2001, 34, 18; and Hoveyda et al., *Chem. Eur. J.* 2001, 7, 945).

Scheme 2

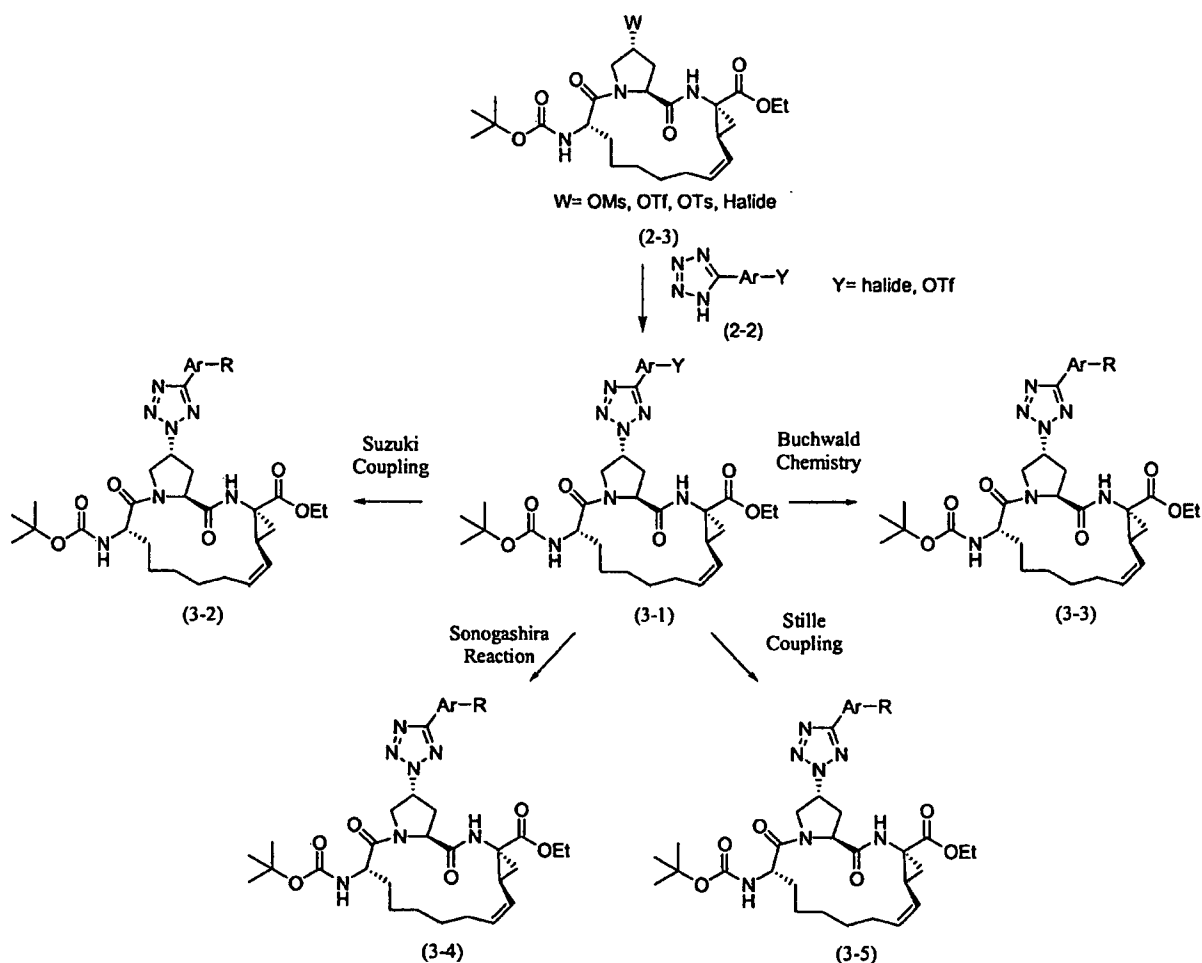


10

Scheme 2 illustrates the general synthetic method of tetrazole analogs. 5-substituted tetrazoles (2-2) were synthesized from nitrile compounds (2-1) with azide, but not limited to sodium azide. Intermediate (2-4) and (2-5) can be made through SN2 replacement of activated hydroxyl group by converting hydroxy intermediate Ig to a suitable leaving group such as, but not limited to OMs, OTs, OTf, bromide, or iodide. Subsequent hydrolysis of the ester gives compounds of formula (2-6) or (2-7).

15

Scheme 3

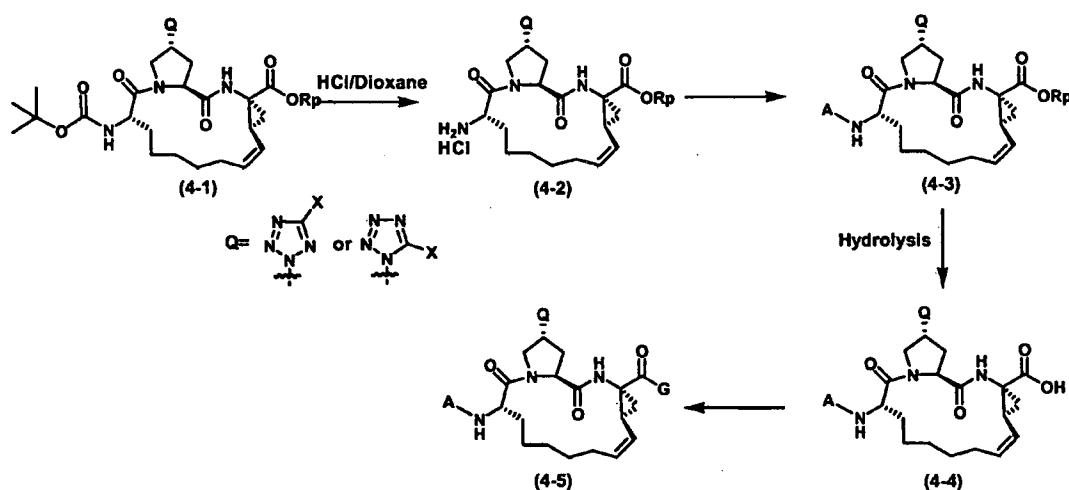


- Intermediate (3-1) was synthesized under the conditions with macrocyclic mesylate (2-3) and 5-substituted tetrazoles as described in Scheme 2. Intermediate (3-1) may then undergo Suzuki coupling reactions, Sonogashira reactions, or Stille couplings at the position occupied by the halide or OTf. For further details concerning the Suzuki coupling reaction see: A. Suzuki, *Pure Appl. Chem.* 1991, 63, 419-422 and A. R. Martin, Y. Yang, *Acta Chem. Scand.* 1993, 47, 221-230. For further details of the Sonogashira reaction see: Sonogashira, Comprehensive Organic Synthesis, Volume 3, Chapters 2,4 and Sonogashira, *Synthesis* 1977, 777. For further details of the Stille coupling reaction see: J. K. Stille, *Angew. Chem. Int. Ed.* 1986, 25, 508-524, M. Pereyre *et al.*, Tin in Organic Synthesis (Butterworths, Boston, 1987) pp 185-207 *passim*, and

a review of synthetic applications in T. N. Mitchell, *Synthesis* 1992, 803-815. The Buchwald reaction allows for the substitution of amines, both primary and secondary, as well as 1H-nitrogen heterocycles at the aryl bromide. For further details of the Buchwald reaction see J. F. Hartwig, *Angew. Chem. Int. Ed.* 1998, 37, 2046-2067.

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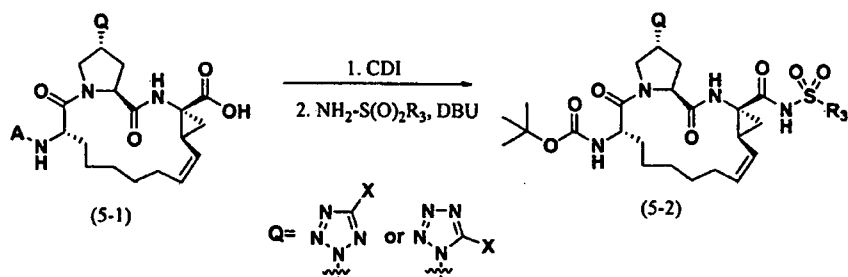
Scheme 4



Scheme 4 illustrates the modification of the N-terminal and C-terminal of the macrocycle.

- 10 Deprotection of the Boc moiety with an acid, such as, but not limited to hydrochloric acid yields compounds of formula (4-2). The amino moiety of formula (4-2) can be alkylated or acylated with appropriate alkyl halide or acyl groups to give compounds of formula (4-3). Compounds of formula (4-3) can be hydrolyzed with base such as lithium hydroxide to free up the acid moiety of formula (4-4). Subsequent activation of the acid moiety followed by treatment with
- 15 appropriate acyl or sulfonyl groups to provide compounds of formula (4-5).

Scheme 5



The sulfonamides (5-2) were prepared from the corresponding acids (5-1) by subjecting the acid to a coupling reagent (i.e. CDI, HATU, DCC, EDC and the like) at RT or at elevated temperature, with the subsequent addition of the corresponding sulfonamide $\text{R}_3\text{-S(O)}_2\text{-NH}_2$ in the presence of base wherein R_3 is as previously defined.

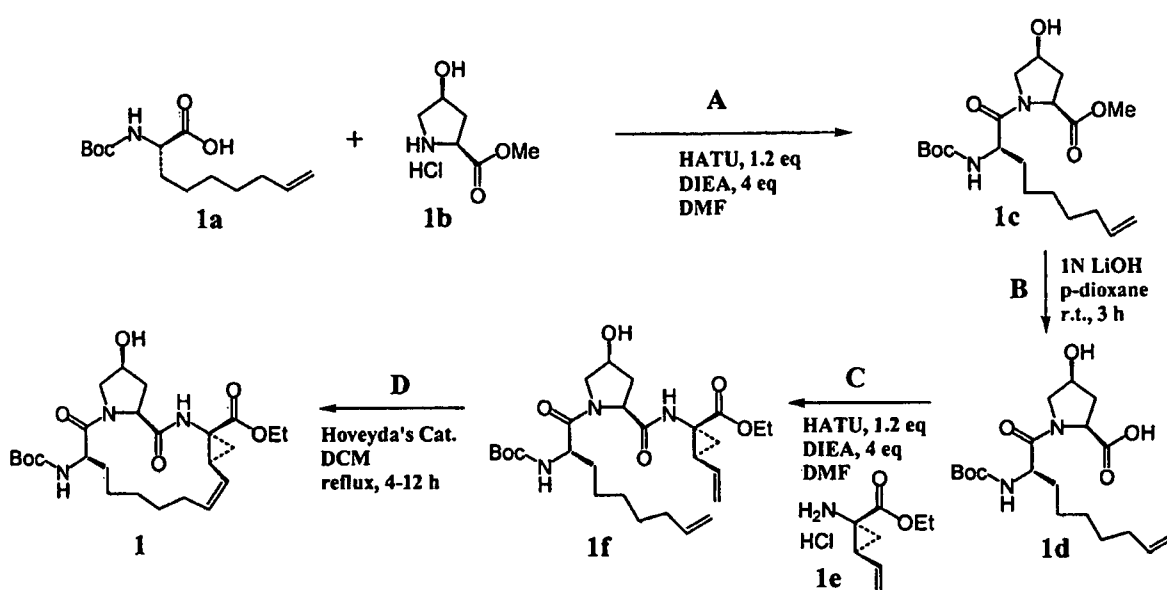
Examples

10

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

15

Example 1. Synthesis of the cyclic peptide precursor



1A. To a solution of Boc-L-2-amino-8-nonenic acid **1a** (1.36g, 5 mmol) and the commercially available cis-L-hydroxyproline methyl ester **1b** (1.09g, 6 mmol) in 15 ml DMF, was added DIEA (4 ml, 4eq.) and HATU (4g, 2eq). The coupling was carried out at 0 °C over a period of 1 hour. The reaction mixture was diluted with 100 mL EtOAc, and followed by washing with 5% citric acid 2x 20 ml, water 2x20 ml, 1M NaHCO₃ 4x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na₂SO₄ and then was evaporated, affording the dipeptide **1c** (1.91g, 95.8%) that was identified by HPLC (Retention time = 8.9 min, 30-70%, 90%B), and MS (found 421.37, M+Na⁺).

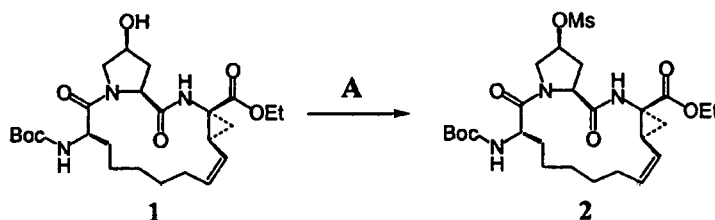
1B. The dipeptide **1c** (1.91g) was dissolved in 15 mL of dioxane and 15 mL of 1 N LiOH aqueous solution and the hydrolysis reaction was carried out at RT for 4 hours. The reaction mixture was acidified by 5% citric acid and extracted with 100 mL EtOAc, and followed by washing with water 2x20 ml, and brine 2x20 ml, respectively. The organic phase was dried over anhydrous Na₂SO₄ and then removed in vacuum, yielding the free carboxylic acid compound **1d** (1.79g, 97%), which was used for next step synthesis without need for further purification.

1C. To a solution of the free acid obtained above (1.77, 4.64 mmol) in 5 ml DMF, D-β-vinyl cyclopropane amino acid ethyl ester **1e** (0.95g, 5 mmol), DIEA (4 ml, 4eq.) and HATU (4g, 2eq) were added. The coupling was carried out at 0 °C over a period of 5 hours. The

reaction mixture was diluted with 80 mL EtOAc, and followed by washing with 5% citric acid 2x 20 ml, water 2x20 ml, 1M NaHCO₃ 4x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na₂SO₄ and then evaporated. The residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (5:1→3:1→1:1→1:2→1:5). The linear tripeptide **1f** was isolated as an oil after removal of the elution solvents (1.59g, 65.4%), identified by HPLC (Retention time = 11.43 min) and MS (found 544.84, M+Na⁺).

1D. Ring Closing Metathesis (RCM). A solution of the linear tripeptide **1f** (1.51g, 2.89 mmol) in 200 ml dry DCM was deoxygenated by bubbling N₂. Hoveyda's 1st generation catalyst (5 mol% eq.) was then added as solid. The reaction was refluxed under N₂ atmosphere 12 hours. The solvent was evaporated and the residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1→1:2→1:5). The cyclic peptide precursor **1** was isolated as a white powder after removal of the elution solvents (1.24g, 87%), identified by HPLC (Retention time = 7.84 min, 30-70%, 90%B), and MS (found 516.28, M+Na⁺). For further details of the synthetic methods employed to produce the cyclic peptide precursor **1**, see U.S. Patent No. 6,608,027, which is herein incorporated by reference in its entirety.

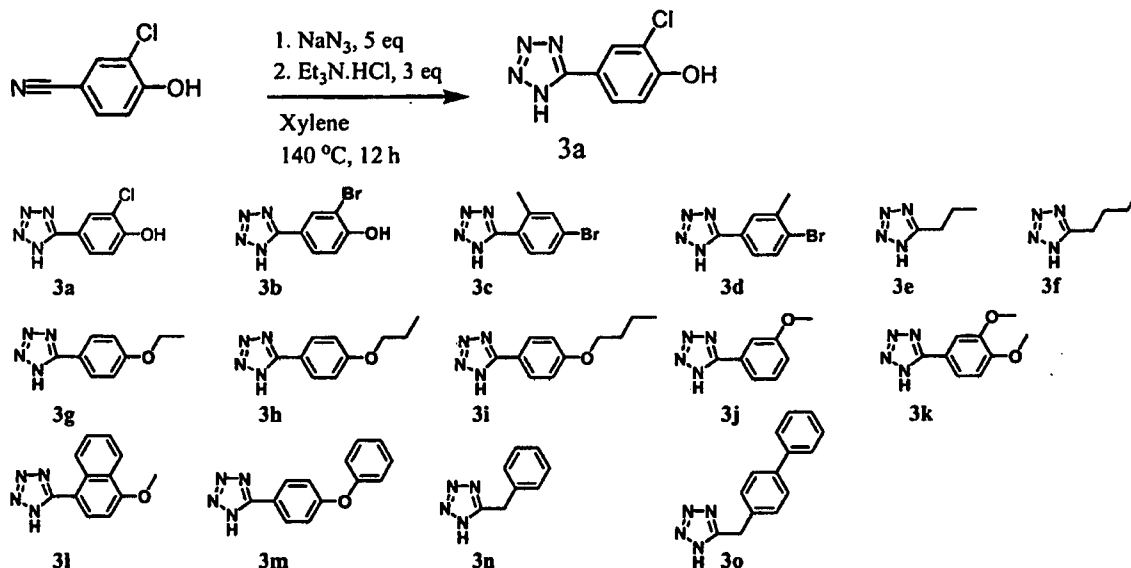
Example 2. Synthesis of the cyclic peptide precursor mesylate



2A. To a solution of the macrocyclic peptide precursor **1** (500mg, 1.01 mmol) and DIEA (0.4 ml, 2 mmol) in 2.0 ml DCM, mesylate chloride (0.1 ml) was added slowly at 0 °C where the reaction was kept for 3 hours. 30 mL EtOAc was then added and followed by washing with 5% citric acid 2x10 ml, water 2x10 ml, 1M NaHCO₃ 2x10 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na₂SO₄ and evaporated, yielding the title compound mesylate that was used for next step synthesis without need for further purification.

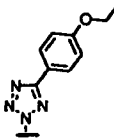
Example 3. Tetrazole Synthesis

Structurally diverse tetrazoles IIIa-IIIq, for use in preparing tetrazolyl macrocycles of the invention were synthesized from commercially available nitrile compounds as described below:



To a sealed tube containing 5 ml xylene, was added 3-chloro-4-hydroxybenzoacetonitrile (0.31g, 5 mol), NaN_3 (0.65g, 10 mmol) and the triethylamine hydrochloride (0.52g, 3 mmol).

- 10 The mixture was stirred vigorously at 140 °C over a period of 20-30 hours. The reaction mixture was then cooled and poured to a mixture of EtOAc (30 ml) and aqueous citric acid solution (20 mL). After washing with water 2x10 ml and brine 2x10 ml, the organic phase was dried over anhydrous Na_2SO_4 and was evaporated to a yellowish solid. After re-crystallization with EtOAc-hexanes, the tetrazole compound 3a was obtained in good yield (0.4g, 86%), high
- 15 purity (>90%, by HPLC), and identified by NMR and MS (found 197.35 and 199.38, $\text{M} + \text{H}^+$).

Example 4. Compound of formula V, wherein A = Boc, Q=  and G = OH.

Step 4a: Replacement Method

The title compound was prepared via the replacement of the mesylate from Example 2 and tetrazole 3g. The replacement method is performed by dissolving 0.041mmol of the macrocyclic peptide precursor mesylate 2 and 0.123mmol of tetrazole 3g in 3ml of DMF and adding 0.246mmol of sodium carbonate (60mg). The resulting reaction mixture is stirred at 60°C for 4-10 hours and subsequently cooled and extracted with ethyl acetate. The organic extract was washed with water (2x30ml), and the organic solution is concentrated *in vacuo* to be used in crude form for hydrolysis of the ethyl ester.

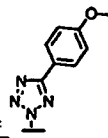
MS (ESI): $m/z = 688.29$ [M+Na].

Step 4b

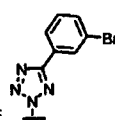
The title compound was prepared by dissolving the title compound of Example 4 (20mg) in 2 mL of dioxane and 1 mL of 1 N LiOH aqueous solution. The resulting reaction mixture was stirred at RT for 4-8 hours. The reaction mixture was acidified with 5% citric acid, extracted with 10 mL EtOAc, and washed with water 2x20 mL. The solvent was evaporated and the residue was purified by HPLC on a YMC AQ12S11-0520WT column with a 30-80% (100% acetonitrile) gradient over a 20 min period. After lyophilization, title compound was obtained as a white amorphous solid.

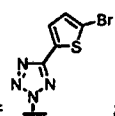
MS (ESI): $m/z = 660.92$ [M+Na].

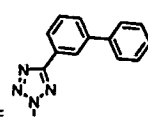
Example 5 to Example 14 were made with different 5-substituted tetrazoles following the similar procedures described in Example 4.

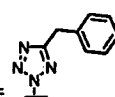
Example 5. Compound of formula V, wherein A = Boc, Q=  and G = OH.

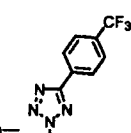
MS (ESI): $m/z = 612.31$ [M+H].

Example 6. Compound of formula V, wherein A = Boc, Q=  and G = OH.
MS (ESI): $m/z = 672.32, 674.31[M+H]$.

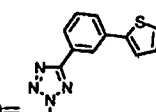
Example 7. Compound of formula V, wherein A = Boc, Q=  and G = OH.
5 MS (ESI): $m/z = 678.27, 680.27[M+H]$.

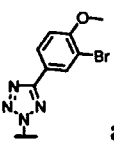
Example 8. Compound of formula V, wherein A = Boc, Q=  and G = OH.
MS (ESI): $m/z = 692.38 [M+Na]$.

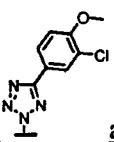
10 Example 9. Compound of formula V, wherein A = Boc, Q=  and G = OH.
MS (ESI): $m/z = 630.35 [M+Na]$.

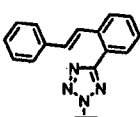
Example 10. Compound of formula V, wherein A = Boc, Q=  and G = OH.
MS (ESI): $m/z = 684.32 [M+Na]$.

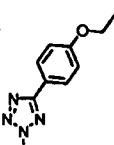
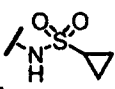
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Example 11. Compound of formula V, wherein A = Boc, Q=  and G = OH.
MS (ESI): $m/z = 698.32 [M+Na]$.

Example 12. Compound of formula V, wherein A = Boc, Q=  and G = OH.
MS (ESI): m/z = 702.33, 704.33[M+H].

Example 13. Compound of formula V, wherein A = Boc, Q=  and G = OH.
5 MS (ESI): m/z = 658.37, 660.37[M+H].

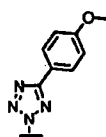
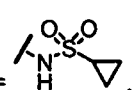
Example 14. Compound of formula V, wherein A = Boc, Q=  and G = OH.
MS (ESI): m/z = 696.44 [M+H].

10 Example 15. Compound of formula V, wherein A = Boc, Q=  and G = .

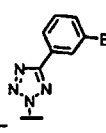
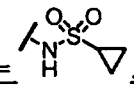
To a solution of the compound (33mg) of Example 4 in DMF was added CDI (12mg). The reaction mixture was stirred at 40°C for 1h and then added cyclopropylsulfonamide (12mg) and DBU (15μl). The reaction mixture was stirred overnight at 40°C. The reaction mixture was
15 extracted with EtOAc. The organic extracts were washed with 1M NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatograph to give desired product (22mg).

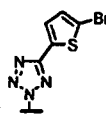
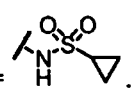
MS (ESI): m/z = 741.40 [M+H].
13C(CD₃OD): 177.5, 173.7, 169.4, 165.0, 161.1, 155.9, 135.4, 128.2, 125.1, 119.7, 114.6, 79.0,
20 63.5, 63.4, 60.1, 53.6, 52.3, 43.8, 33.6, 32.0, 30.7, 30.3, 27.3, 27.0, 26.3, 22.2, 21.5, 13.9.

Example 16 to Example 35 were made with different sulfonamides following the similar procedures described in Example 15.

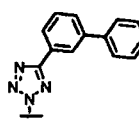
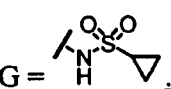
Example 16. Compound of formula V, wherein A = Boc, Q=  and G = 
MS (ESI): $m/z = 727.27$ [M+H].

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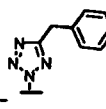
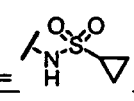
Example 17. Compound of formula V, wherein A = Boc, Q=  and G = 
MS (ESI): $m/z = 775.41, 777.39$ [M+H].

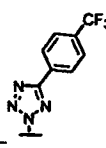
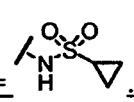
Example 18. Compound of formula V, wherein A = Boc, Q=  and G = 
MS (ESI): $m/z = 781.31, 783.38$ [M+H].

10

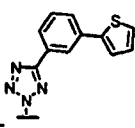
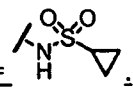
Example 19. Compound of formula V, wherein A = Boc, Q=  and G = 
MS (ESI): $m/z = 773.53$ [M+H].

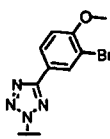
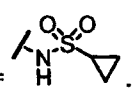
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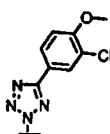
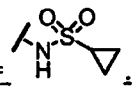
Example 20. Compound of formula V, wherein A = Boc, Q=  and G = 
MS (ESI): $m/z = 711.50$ [M+H].

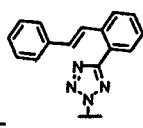
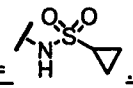
Example 21. Compound of formula V, wherein A = Boc, Q=  and G = 
MS (ESI): $m/z = 765.49$ [M+H].

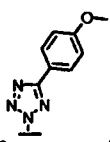
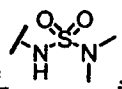
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Example 22. Compound of formula V, wherein A = Boc, Q=  and G= .
MS (ESI): $m/z = 779.45$ [M+H].

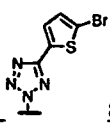
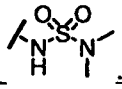
5 Example 23. Compound of formula V, wherein A = Boc, Q=  and G= .
MS (ESI): $m/z = 805.37, 807.38$ [M+H].

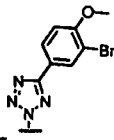
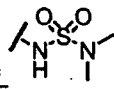
Example 24. Compound of formula V, wherein A = Boc, Q=  and G= .
MS (ESI): $m/z = 761.47, 763.47$ [M+H].

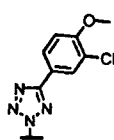
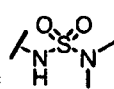
10 Example 25. Compound of formula V, wherein A = Boc, Q=  and G= .
MS (ESI): $m/z = 799.45$ [M+H].

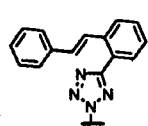
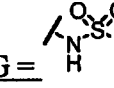
Example 26. Compound of formula V, wherein A = Boc, Q=  and G= .
MS (ESI): $m/z = 730.33$ [M+H].

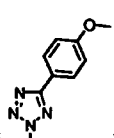
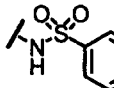
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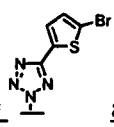
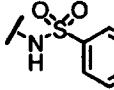
Example 27. Compound of formula V, wherein A = Boc, Q=  and G= .
MS (ESI): $m/z = 7784.21, 786.19$ [M+H].

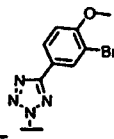
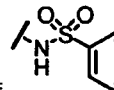
Example 28. Compound of formula V, wherein A = Boc, Q=  and G = .
MS (ESI): $m/z = 808.25, 810.26[M+H]$.

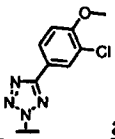
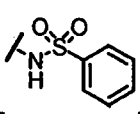
Example 29. Compound of formula V, wherein A = Boc, Q=  and G = .
5 MS (ESI): $m/z = 764.31, 766.32[M+H]$.

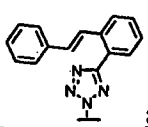
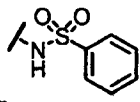
Example 30. Compound of formula V, wherein A = Boc, Q=  and G = .
MS (ESI): $m/z = 802.38 [M+H]$.

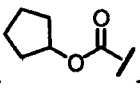
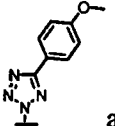
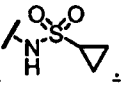
10 Example 31. Compound of formula V, wherein A = Boc, Q=  and G = .
MS (ESI): $m/z = 763.33[M+H]$.

Example 32. Compound of formula V, wherein A = Boc, Q=  and G = .
MS (ESI): $m/z = 817.19, 819.21[M+H]$.

15 Example 33. Compound of formula V, wherein A = Boc, Q=  and G = .
MS (ESI): $m/z = 841.25, 843.25[M+H]$.

Example 34. Compound of formula V, wherein A = Boc, Q=  and G = 
MS (ESI): $m/z = 797.30, 799.30[M+H]$.

Example 35. Compound of formula V, wherein A = Boc, Q=  and G = 
5 MS (ESI): $m/z = 835.37[M+H]$.

Example 36. Compound of formula V, wherein A =  , Q=  and G = .

Step 36a

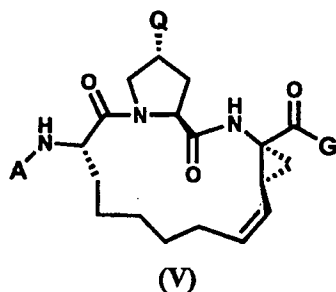
- 10 The solution of the compound from Example 16 in 5ml 4NHCl/Dioxne was stirred at RT for 1h. The reaction mixture was concentrated in vacuum. The residue was evaporated twice with DCM. The desired product was carried out directly to the next step.
MS (ESI): $m/z = 627.33 [M+H]$.

15 Step 36b

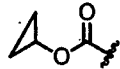
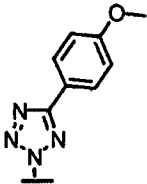
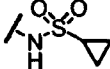
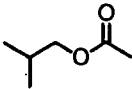
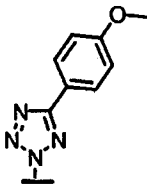
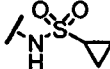
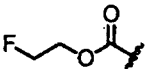
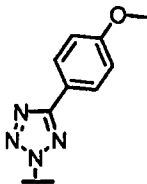
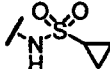
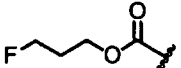
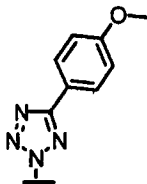
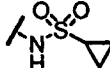
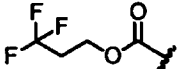
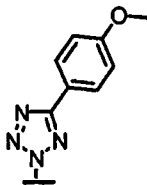
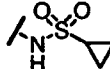
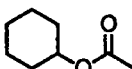
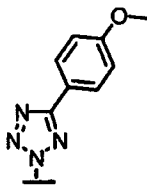
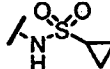
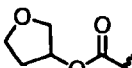
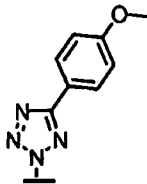
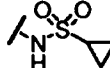
- To the solution of the compound from step 36a in 2ml DCM was added DIEA (143μl) and cyclopentylchloroformate (0.246mmol). The reaction mixture was stirred at RT for 1h. The reaction mixture was extracted with EtOAc. The organic layer was washed with 1M NaHCO₃, water, brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by HPLC to
20 give 42mg of desired product.
MS (ESI): $m/z = 739.32 [M+H]$.
13C(CD₃OD): 177.5, 173.4, 169.4, 165.1, 161.8, 156.6, 135.4, 128.2, 125.1, 119.9, 114.1, 77.5, 63.3, 60.2, 54.7, 53.4, 52.5, 43.9, 43.8, 33.7, 32.3, 32.2, 32.0, 30.7, 30.3, 27.3, 27.0, 26.3, 23.2, 22.2, 21.5.

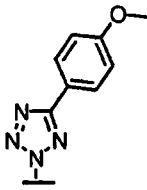
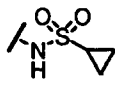
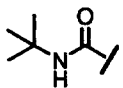
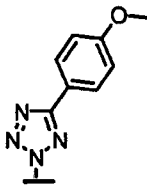
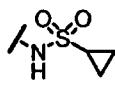
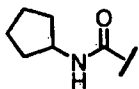
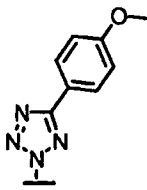
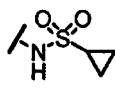
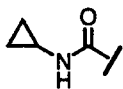
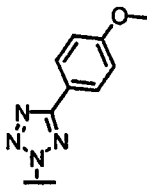
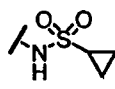
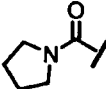
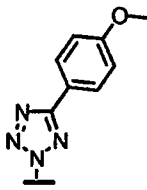
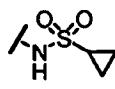
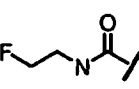
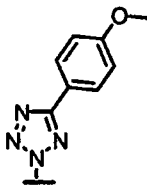
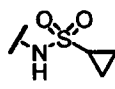
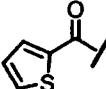
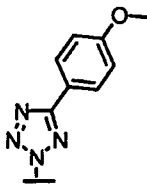
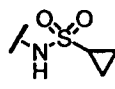
Example 37 to Example 94 (Formula V) are made following the procedures described in Examples 15 or 36.

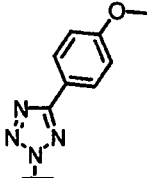
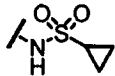
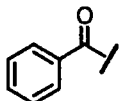
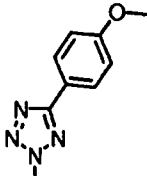
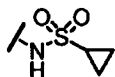
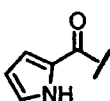
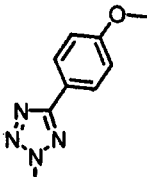
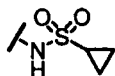
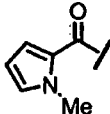
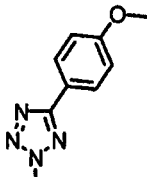
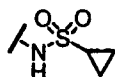
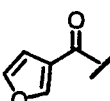
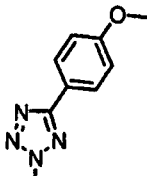
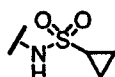
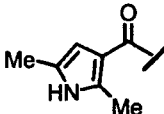
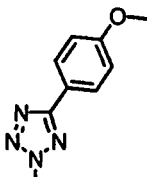
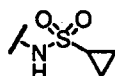
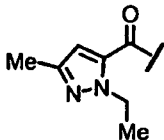
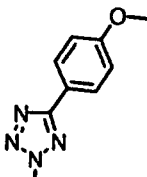
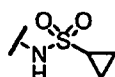
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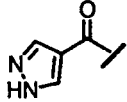
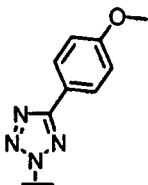
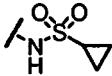
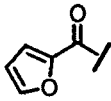
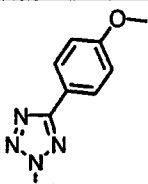
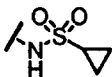
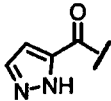
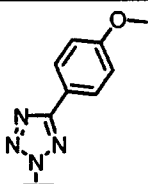
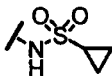
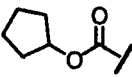
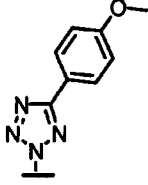
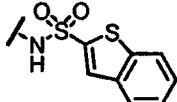
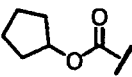
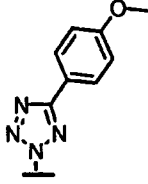
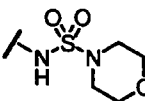
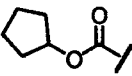
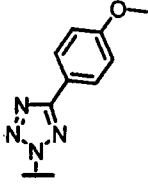
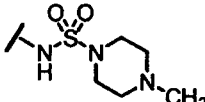
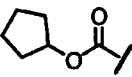
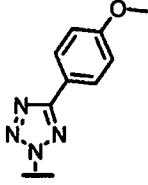
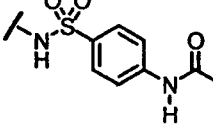


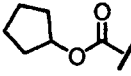
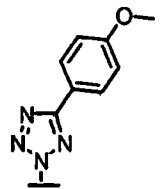
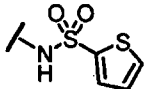
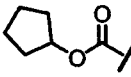
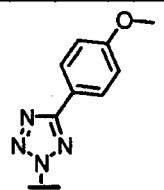
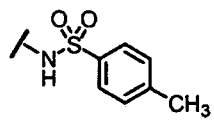
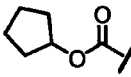
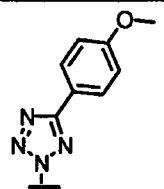
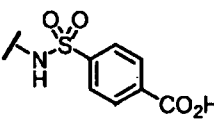
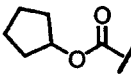
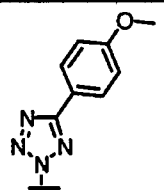
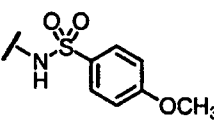
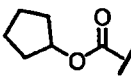
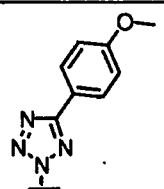
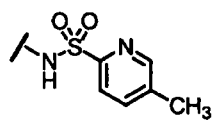
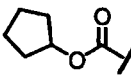
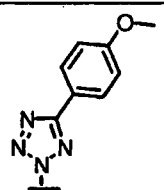
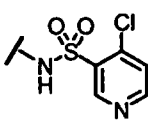
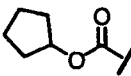
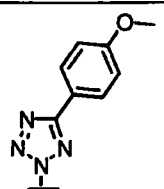
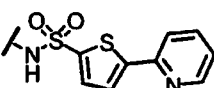
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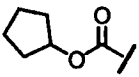
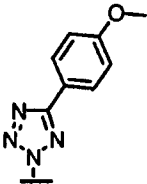
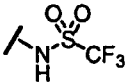
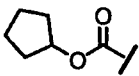
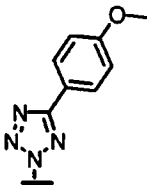
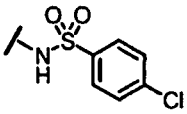
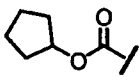
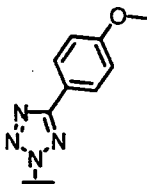
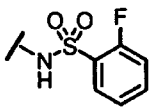
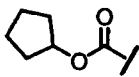
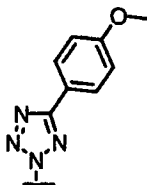
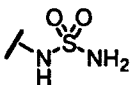
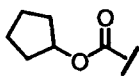
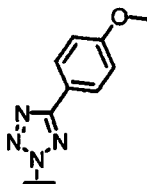
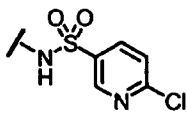
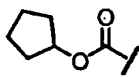
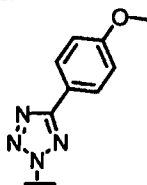
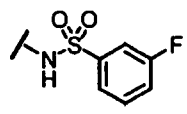
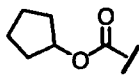
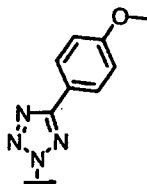
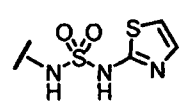
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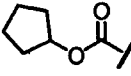
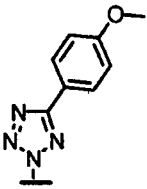
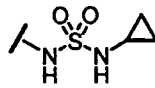
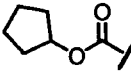
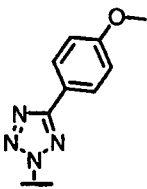
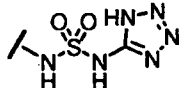
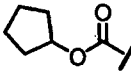
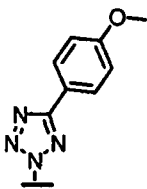
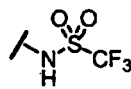
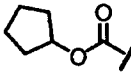
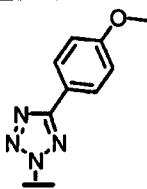
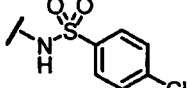
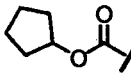
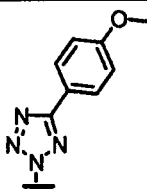
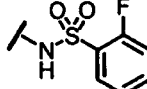
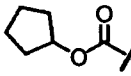
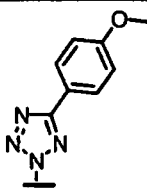
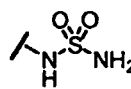
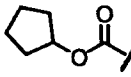
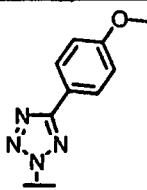
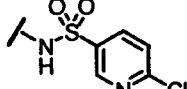
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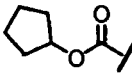
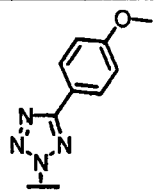
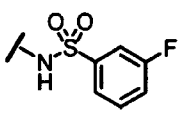
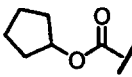
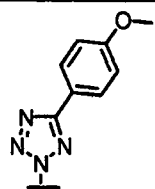
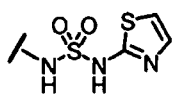
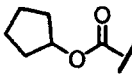
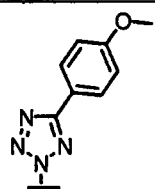
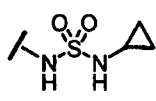
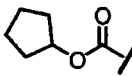
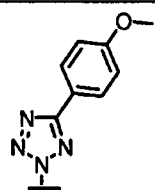
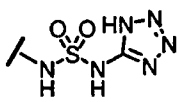
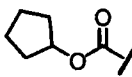
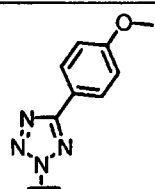
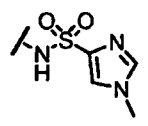
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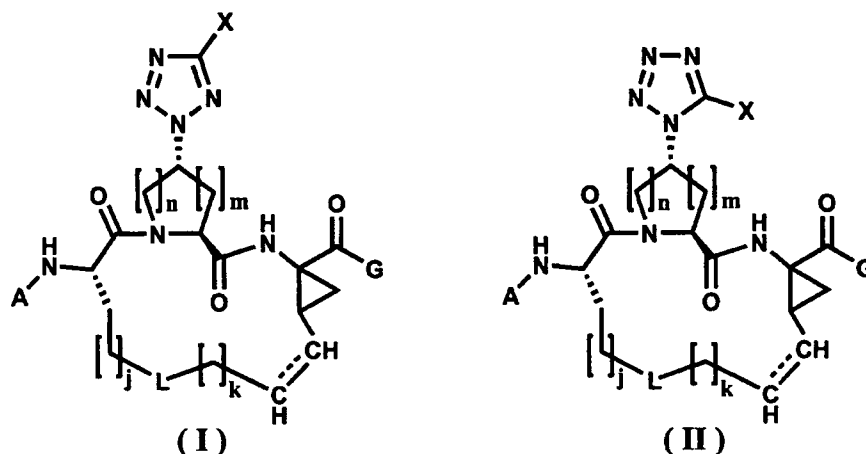
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Representative compounds of the invention show particularly advantageous biological activity in enzyme inhibition and cell-based replicon assays for HCV activity. Such assays are known in the art and include, for example, those delineated in US 2004/0180815; US 2004/0266669; US

5 2005/50192212; each incorporated by reference.

WHAT IS CLAIMED:

1. A compound of Formula I or II:



Wherein

A is selected from R_1 , $-(C=O)-O-R_1$, $-(C=O)-R_2$, $-C(=O)-NH-R_2$, or $-S(O)_2-R_1$,

$-S(O)_2NHR_2$;

R_1 is selected from the group consisting of:

- (i) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (ii) heterocycloalkyl or substituted heterocycloalkyl;
- (iii) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

R_2 is independently selected from the group consisting of:

- (i) hydrogen;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3
5 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

10 G is selected from $-OH$, $-NHS(O)_2-R_3$, $-NH(SO_2)NR_4R_5$;

R_3 is selected from:

- (i) aryl; substituted aryl; heteroaryl; substituted heteroaryl
- (ii) heterocycloalkyl or substituted heterocycloalkyl;
- (iii) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3
15 heteroatoms selected from O, S or N, substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

20 R_4 and R_5 are independently selected from:

- (i) hydrogen;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3
25 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

L is selected from -CH₂-, -O-, -S-, or -S(O)₂-;

X is selected from:

- 5 (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 containing 0, 1, 2, or 3
heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-
10 C₈ alkenyl, or substituted -C₂-C₈ alkynyl 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;
- (v) -W-R₆, where W is absent, or selected from -O-, -S-, -NH-, -N(Me)-, -
C(O)NH-, or -C(O)N(Me)-; R₆ is selected from the group consisting of:
- 15 (a) Hydrogen;
- (b) aryl; substituted aryl; heteroaryl; substituted heteroaryl
- (c) heterocyclic or substituted heterocyclic;
- (d) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl containing 0, 1, 2,
or 3 heteroatoms selected from O, S or N; substituted -C₁-C₈ alkyl,
20 substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl
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;

25 --- denotes a carbon-carbon single or double bond.

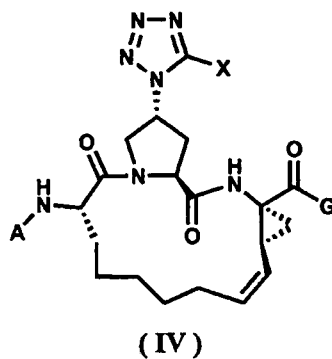
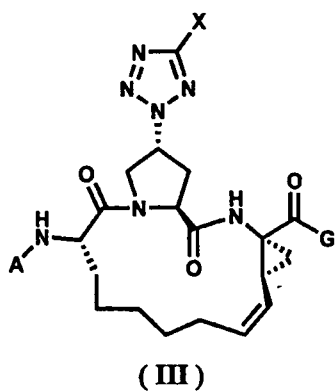
j = 0, 1, 2, 3, or 4;

k = 1, 2, or 3;

m = 0, 1, or 2;

$n = 1, 2 \text{ or } 3.$

2. The compound of claim 1, wherein the compound is of Formula III or IV:



where A, G and X are as previously defined.

3. A compound according to claim 1 which is selected from compounds of Formula V, Table 1.

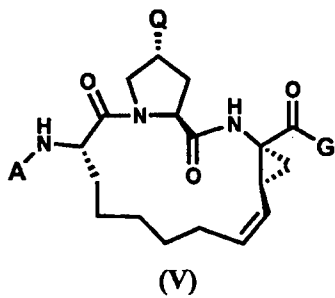
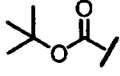
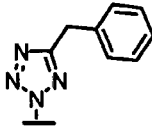
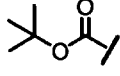
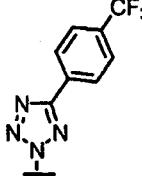
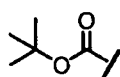
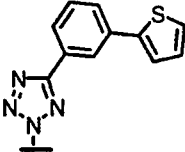
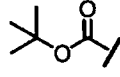
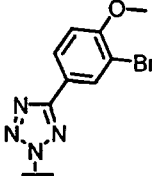
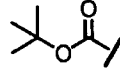
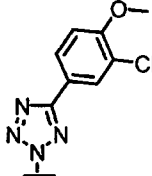
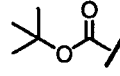
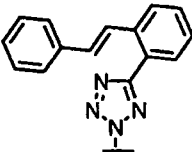
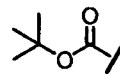
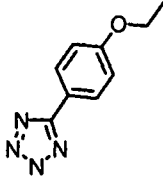
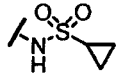
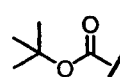
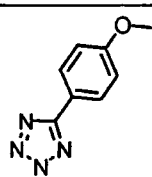
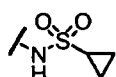
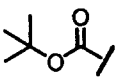
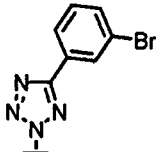
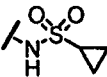
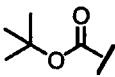
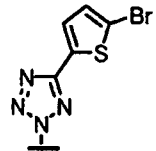
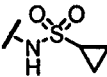
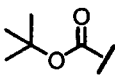
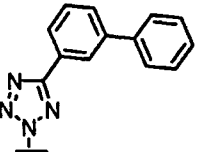
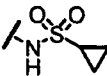
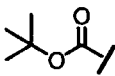
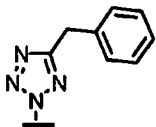
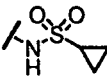
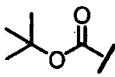
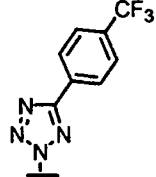
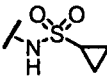
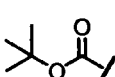
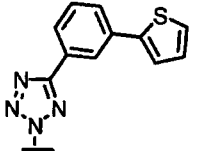
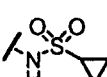
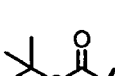
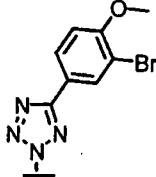
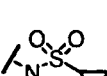
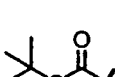
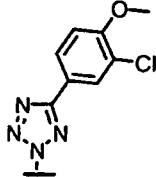
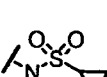


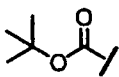
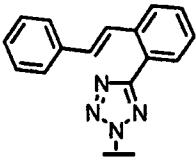
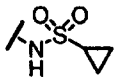
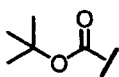
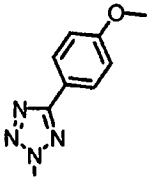
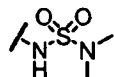
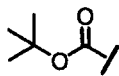
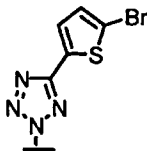
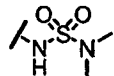
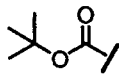
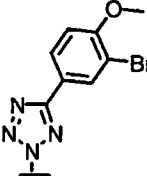
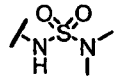
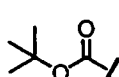
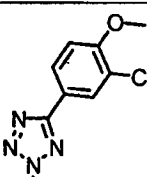
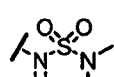
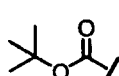
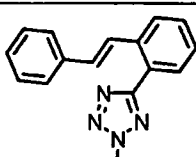
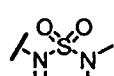
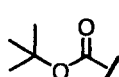
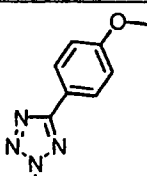
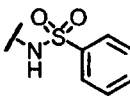
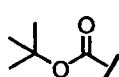
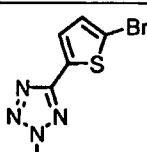
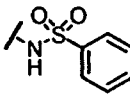
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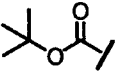
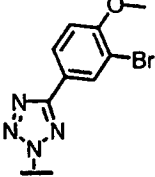
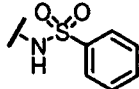
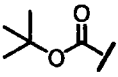
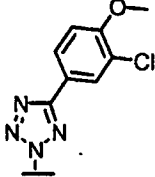
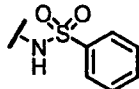
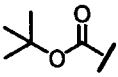
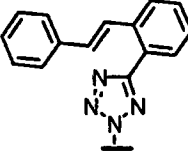
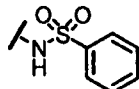
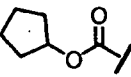
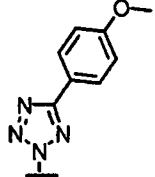
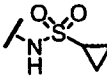
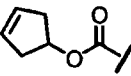
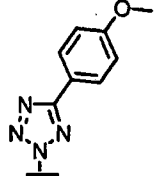
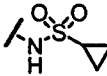
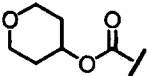
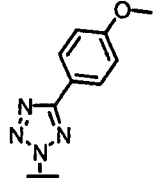
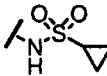
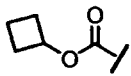
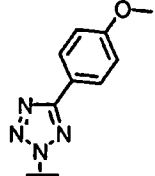
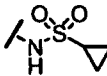
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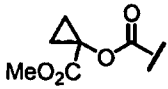
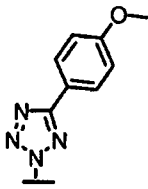
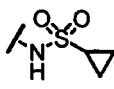
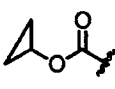
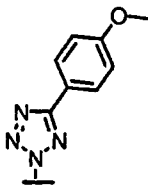
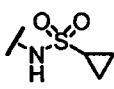
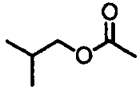
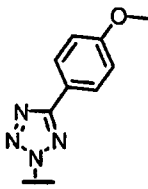
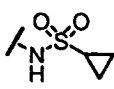
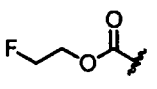
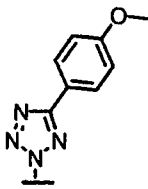
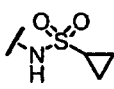
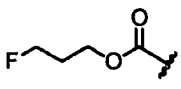
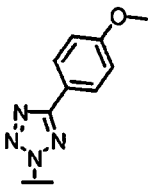
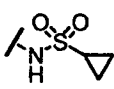
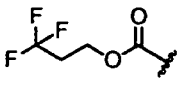
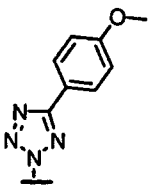
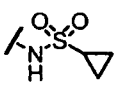
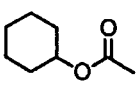
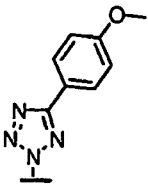
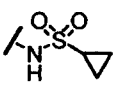
Example#	A	Q	G
4			-OH
5			-OH
6			-OH
7			-OH
8			-OH

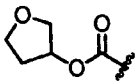
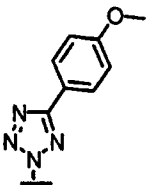
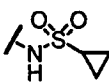
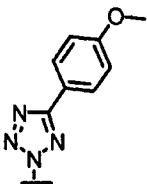
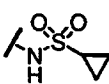
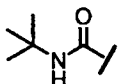
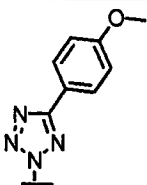
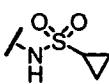
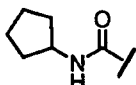
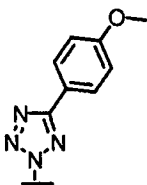
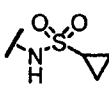
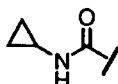
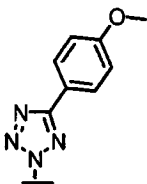
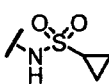
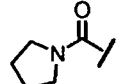
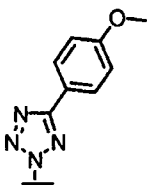
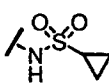
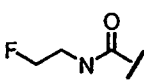
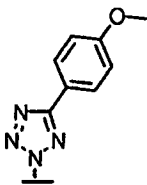
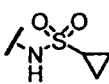
9			-OH
10			-OH
11			-OH
12			-OH
13			-OH
14			-OH
15			
16			

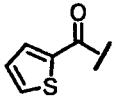
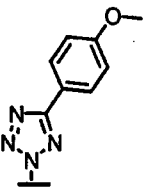
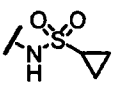
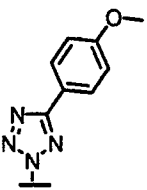
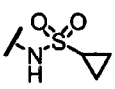
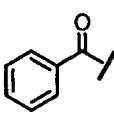
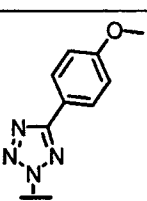
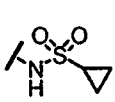
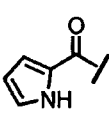
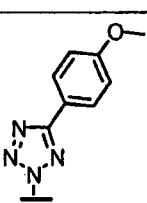
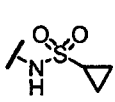
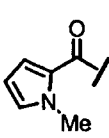
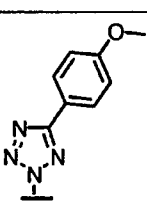
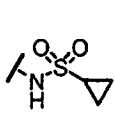
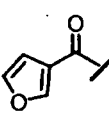
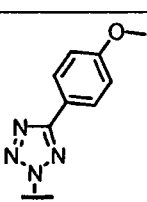
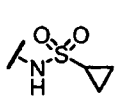
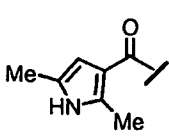
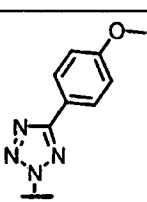
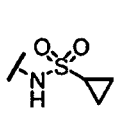
17			
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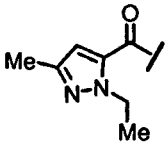
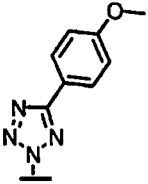
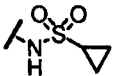
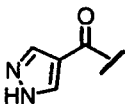
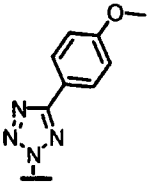
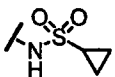
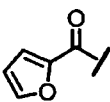
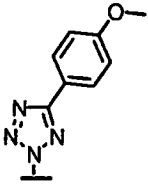
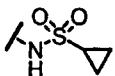
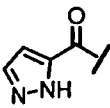
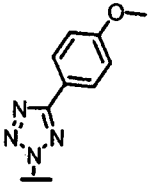
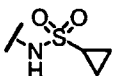
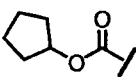
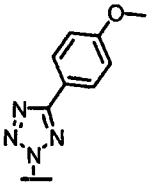
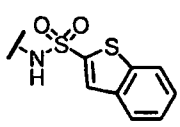
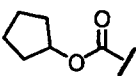
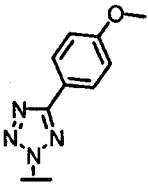
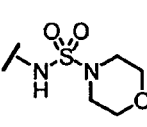
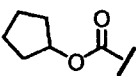
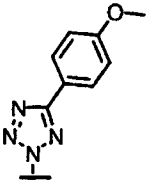
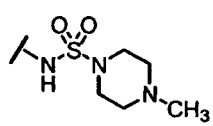
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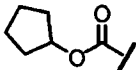
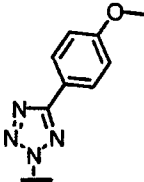
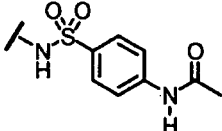
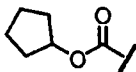
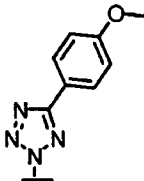
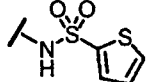
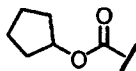
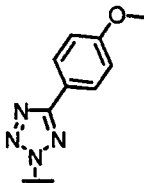
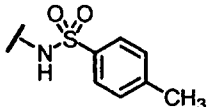
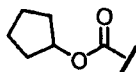
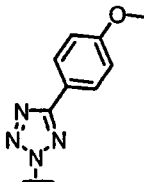
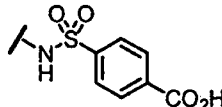
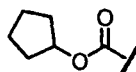
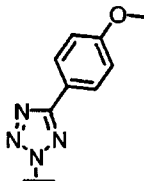
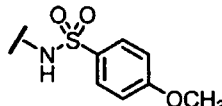
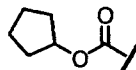
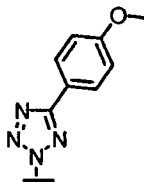
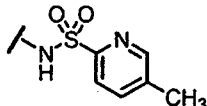
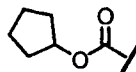
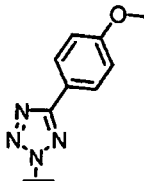
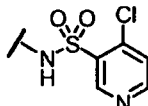
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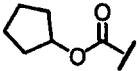
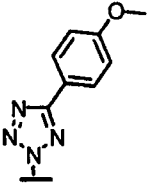
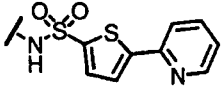
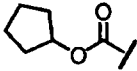
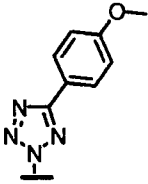
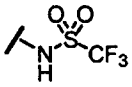
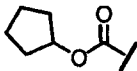
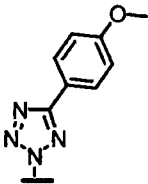
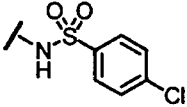
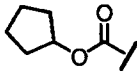
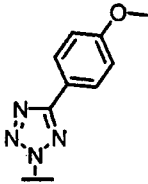
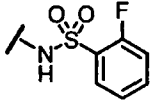
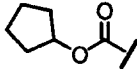
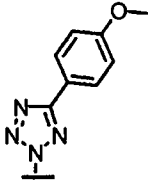
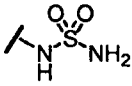
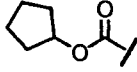
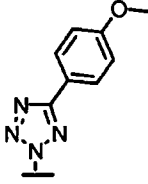
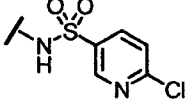
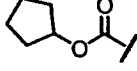
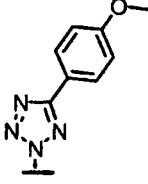
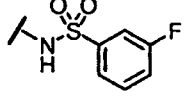
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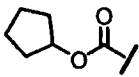
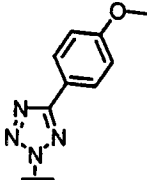
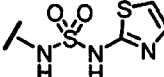
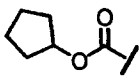
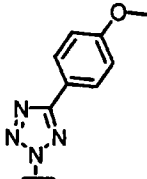
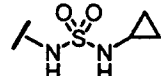
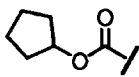
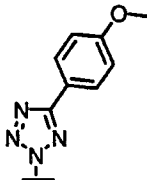
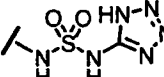
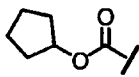
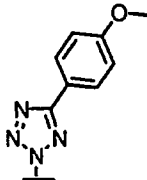
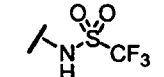
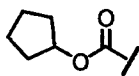
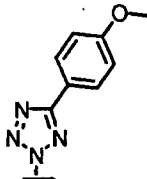
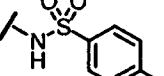
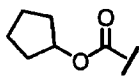
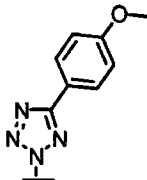
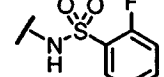
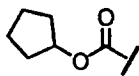
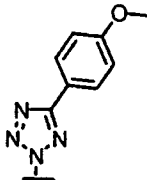
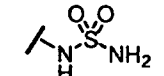
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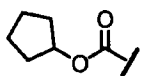
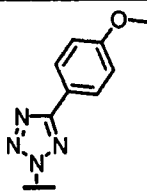
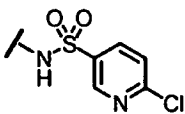
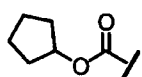
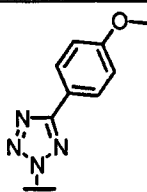
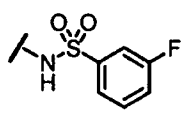
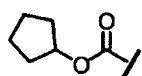
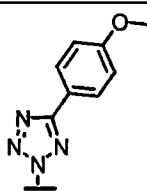
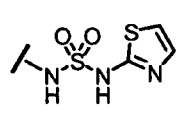
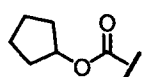
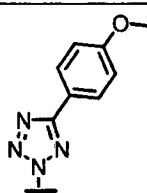
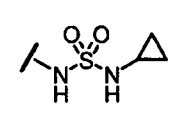
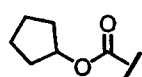
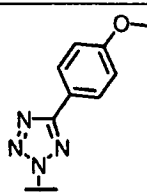
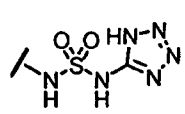
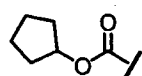
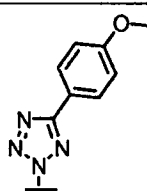
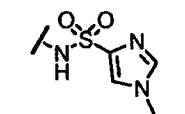
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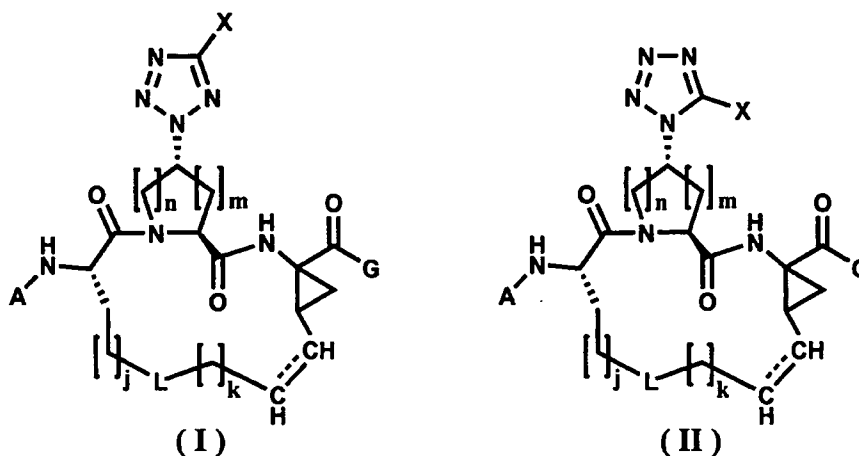
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4. A pharmaceutical composition comprising an inhibitory amount of a compound according to claim 1 or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

5. A method of treating a hepatitis C viral infection in a subject, comprising administering to the subject an inhibitory amount of a pharmaceutical composition according to claim 4.
6. A method of inhibiting the replication of hepatitis C virus, the method comprising supplying
5 a hepatitis C viral NS3 protease inhibitory amount of the pharmaceutical composition of claim 4.
7. The method of claim 5 further comprising administering concurrently an additional anti-hepatitis C virus agent.
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8. The method of claim 7, wherein said additional anti-hepatitis C virus agent is selected from the group consisting of: α -interferon, β -interferon, ribavarin, and adamantine.
9. The method of claim 7, wherein said additional anti-hepatitis C virus agent is an inhibitor of
15 hepatitis C virus helicase, polymerase, metalloprotease, or IRES.

5 The present invention relates to compounds of Formula I and II, or a pharmaceutically acceptable salt, ester, or prodrug, thereof:



which inhibit serine protease activity, particularly the activity of hepatitis C virus (HCV) NS3-NS4A protease. Consequently, the compounds of the present invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention.

Application Data Sheet

Application Information

Application Type::	Regular
Subject Matter::	Utility
Suggested Group Art Unit::	N/A
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	TETRAZOLYL MACROCYCLIC HEPATITIS C SERINE PROTEASE INHIBITORS
Attorney Docket Number::	66055(50530)
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	Yes
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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Correspondence Information

Correspondence Customer Number:: 21874

Representative Information

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Representative Customer Number:: 21874

Domestic Priority Information

Foreign Priority Information

Assignee Information

Assignee name:: Enanta Pharmaceuticals, Inc.
Street of mailing address:: 500 Arsenal Street
City of mailing address:: Watertown
State or Province of mailing address:: MA
Postal or Zip Code of mailing address:: 02472

COPIA 246

CASTELLANOS & Co.
Calle 94 A No.7ª-09
Bogotá-Colombia

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-080058- -00001-0000

Fecha: 2007-09-24 14:16:53 Dep. 2020 NUECREACIONE
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 329 CTOINFORMACION Folios: 94

Señora

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo Industria y Turismo

E. S. D.

Ref.: Expediente No. 07.080.058

Solicitud de Patente PCT entrada Fase Nacional para:

**"TETRAZOLILOS MACROCÍCLICOS COMO INHIBIDORES DE SERINA
PROTEASA DE HEPATITIS C"**

Solicitante: **ENANTA PHARMACEUTICALS, INC.**

PRESENTACION DE DOCUMENTOS

MARGARITA CASTELLANOS ABONDANO, mayor de edad,
identificada y domiciliada como aparece al pié de mi firma, atentamente me
permito presentar los siguientes documentos:

- Sustitución de poder a nombre de **MARGARITA CASTELLANOS**.
- Copia auténtica del documento de poder otorgado por la sociedad
solicitante **ENANTA PHARMACEUTICALS, INC.** con la certificación
notarial en que consta la existencia y representación de la sociedad
legalizado por Apostilla.
- Copia cerificada del documento de prioridad No. 11/499,245 del 4 de
agosto de 2006, junto con la traducción de la carátula al español.

Solicito que el documento No. 11/499,245 del 4 de agosto de 2006 se tenga
como única prioridad reivindicada toda vez que el solicitante desiste de las
prioridades posteriores indicadas en el petitorio.

De esta manera se han completado los requisitos formales de la solicitud de la referencia y, en consecuencia, atentamente solicito a Ud. se continúe con el trámite correspondiente a esta solicitud de Patente de Invención.

De la Señora Jefe,

Margarita Castellanos Abondano
Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** de C.S.J.
Calle 94 A No. 7 A-09 – Bogotá, D.C.
Tel.: 610 7420 – 610 7480

Bogotá, D.C., 24 SET. 2007

Patentes/15/P1520-FNPCT/MEMORIAL PRESENTACION DE DOCUMENTOS

248

ESTADOS UNIDOS DE AMERICA

A QUIEN CORRESPONDA

EL DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Marcas y Patentes de Los Estados Unidos

Septiembre 26 de 2007

POR LA PRESENTE CERTIFICO QUE EL ANEXO ES UNA COPIA FIEL DE LOS
REGISTROS DE ESTA OFICINA DE LA APLICACIÓN SOLICITADA COMO:

APLICACIÓN DE MARCA REGISTRADA: 77/095,999
FECHA DE PRESENTACION: Enero 31 de 2007

Por Autorización del
Sub Secretario de la Oficina de Comercio de Propiedad Intelectual y el
Director de la Oficina de Marcas y Patentes de Los Estados Unidos

Nota: Con firma en el original y sello al costado inferior izquierdo
P.R. GRANT
Funcionario Certificado

249

Formulario PTO 1478 (Rev 9/2006)

OMB No. 0651-0009 (Exp 09/03/2008)

Marca/Aplicación de Marca de Identificación de Servicios, Registro Principal

Serial No: 77095999

Fecha de Presentación: 01/31/2007

La siguiente tabla presenta los datos tal y como se ingresaron.

Entrada	Ingreso
SERIAL No.	77095999
INFORMACION DE MARCA	
* MARCA	\\TICRS2\EXPORT12\770\959\77095999 \xml1\APP0002.JPG
FORMA ESPECIAL	SI
IMAGEN GENERADA EN USPTO	NO
ELEMENTO LITERAL	Arius Eickert
MARCA DE COLOR	NO
DESCRIPCIÓN DE LA MARCA (Y ubicación del Color, si aplica)	La marca consiste de las palabras Arius Eickert con una estrella atravesando la A y la R.
NUMERO ACEPTABLE DE PÍXELES	SI
NUMERO DE PÍXELES	750 x 441
INFORMACIÓN DEL SOLICITANTE	
* PROPIETARIO DE LA MARCA	Sunbeam Products, Inc.
* DIRECCION	2381 Executive Center Drive
* CIUDAD	Boca Ratón
* ESTADO (Para solicitantes de los EE.UU.)	Florida
* PAIS	Estados Unidos
* CÓDIGO ZIP/POSTAL (Únicamente para solicitantes de EE.UU.)	33431
TELEFONO	561-912-5785
FAX	561-912-4182
INFORMACIÓN SOBRE LA PERSONA JURIDICA	

archivo://D:\p2mp\temp\html\OEMS.htm

9/24/2007

250

* TIPO	SOCIEDAD ANÓNIMA
* ESTADO/PAIS DE CONSTITUCIÓN	Delaware
SECCION DE BIENES Y/O SERVICIOS	
CLASE INTERNACIONAL	
DESCRIPCIÓN	Tijeras, tijeras para podar, navajas (no quirúrgicas), cuchillas, maquinas para cortar pelo, pinzas, limas para uñas, removedores y moldeadores de cutícula, juegos de manicura que comprenden la combinación de dos o más de los siguientes: pinzas, tijeras, limas, pulidores, cortadores, limpiadores de uñas, escalpelos para cutícula y moldeadores de uñas.
BASE PARA LA APLICACIÓN	SECCION 1(b)
INFORMACIÓN DEL ABOGADO	
NOMBRE	Lawrence J. Shurupoff
EXPEDIENTE DEL APODERADO	Sunhpro-49862
NOMBRE DE LA COMPAÑÍA	Sunbeam Products, Inc.
DIRECCIÓN	2381 Executive Center Drive
CIUDAD	Boca Ratón
ESTADO	Florida
PAIS	Estados Unidos
CÓDIGO ZIP/POSTAL	33431
TELEFONO	561-912-5185
FAX	561-912-4182
INFORMACION DE CORRESPONDENCIA	
NOMBRE	Lawrence J. Shurupoff
NOMBRE DE LA COMPAÑÍA	Sunbeam Products, Inc.
DIRECCIÓN	2381 Executive Center Drive
CIUDAD	Boca Ratón
ESTADO	Florida
PAIS	Estados Unidos
CÓDIGO ZIP/POSTAL	33431
TELEFONO	561-912-5185

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9/24/2007

22
251

FAX	561-912-4182
INFORMACIÓN DE HONORARIOS	
NÚMERO DE CLASES	1
HONORARIOS POR CLASE	325
TOTAL DE HONORARIOS DEBIDO	325
INFORMACION DE LA FIRMA	
FIRMA	/Lawrence J. Shurupoff/
NOMBRE DEL FIRMANTE	Lawrence J. Shurupoff
CARGO DEL FIRMANTE	Asistente del Secretario
FECHA DE FIRMA	01/31/2007
SECCION DE APLICACIÓN DE LA INFORMACIÓN	
FECHA DE PRESENTACIÓN	Miércoles Enero 31 16:55 EST 2007
SELLO TEAS	USPTO/BAS-12.45.76.148-20 070131165545584358-770959 99-36094de20945028e7d9ed1 935a229505ea1-DA-574-2007 0131163851625518

archivo://D:\p2mp\temp\html\OEMS.htm

9/24/2007

Formulario PTO 1478 (Rev 9/2006)

OMB No. 0651-0009 (Exp 09/03/2008)

Marca/Aplicación de Marca de Identificación de Servicios, Registro Principal

Serial No: 77095999

Fecha de Presentación: 01/31/2007

Al Delegado de Marcas:

MARCA: Arius Eickert (estilizada y/o con diseño, ver marca)

El elemento literal de la marca consiste de las palabras Arius Eickert. El solicitante no declara un color como una característica de la marca. La marca consiste de las palabras Arius Eickert con una estrella atravesando la A y la R.

El solicitante, Sunbeam Products, Inc., compañía constituida en Delaware, con domicilio en 2381 Executive Center Drive, Boca Ratón, Florida, Estados Unidos, 33431, solicita registro de la marca/marca de Identificación de Servicios identificada anteriormente en la Oficina de Marcas y Patentes de Estados Unidos con el Registro Principal establecido por Acta de Julio 5, 1946 (15 U.S.C. Sección 1051 et seq.), tal como ha sido modificado.

Clase Internacional ____: Tijeras, tijeras para podar, navajas (no quirúrgicas), cuchillas, maquinas para cortar pelo, pinzas, limas para uñas, removedores y moldeadores de cutícula, juegos de manicura que comprenden la combinación de dos o más de los siguientes: pinzas, tijeras, limas, pulidores, cortadores, limpiadores de uñas, escalpelos para cutícula y moldeadores de uñas.

Intención de Uso: El solicitante tiene buena fe en su Intention to Use o de uso a través de la compañía o titular de la licencia relacionada con el mismo, de comercializar con o en conexión con los bienes y/o servicios identificados. (15 U.S.C. Sección 1051 (b)).

El solicitante nombra por la presente al señor Lawrence J. Shurupoff, de Sunbeam Products, Inc., con domicilio en 2381 Executive Center Drive, Boca Ratón, Florida, Estados Unidos, 33431 para presentar esta aplicación en nombre del solicitante. El número de expediente/referencia del apoderado es Sunhpro-49862.

Información de correspondencia: Lawrence J. Shurupoff
2381 Executive Center Drive
Boca Ratón, Florida, 33431
561-912-5185 (teléfono)
561-912-4182 (fax)

archivo://D:\p2mp\temp\html\OEMS.htm

9/24/2007

Se debe presentar un pago por honorarios por la suma de US \$325 junto con la aplicación, el cual equivale al pago por 1 clase(es).

Declaración

El firmante, advertido por la presente que los falsos testimonios y similares son punibles con multas o cárcel, o ambos, bajo artículo 18 U.S.C. Sección 1001, y que tales falsos testimonios o similares, pueden poner en peligro la validez de la aplicación o de cualquier registro que resulte de la misma, declara que el/ella está debidamente autorizado para firmar la presente aplicación en nombre del solicitante; el/ella cree que el solicitante es el dueño de la marca/marca de identificación de servicios que se busca registrar, o, si la aplicación se hace bajo el artículo 15 U.S.C. Sección 1051 (b), el/ella cree que el solicitante tiene derecho de usar tal marca de manera comercial, ya sea de manera idéntica a la misma o con tal parecido a la misma que pueda causar confusión, error o engaño cuando se use con o en conexión a los bienes/servicios por otra persona semejante; y que todas las declaraciones en su conocimiento son verdaderas; y que todas las declaraciones hechas sobre la información y la evidencia son consideradas como verdaderas.

Firma: /Lawrence J. Shurupoff/ Fecha de firma: 01/31/2007

Nombre del firmante: Lawrence J. Shurupoff

Cargo del firmante: Asistente del Secretario

Número RAM de venta: 574

Fecha de contabilidad RAM: 02/01/2007

No. Serial: 77095999

Fecha de Transmisión por Internet: Mie, Enero 31 16:55:45 EST 2007

Sello TEAS: USPTO/BAS-12.45.76.148-20070131165545584

358-77095999-36094de20945028e7d9ed1935a2

29505ea1-DA-574-20070131163851625518

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 254

2020
Bogotá D.C.,

Doctor(a)
CASTELLANOS ABONDANO MARGARITA
Apoderado(a) y/o Representante de
ENANTA PHARMACEUTICALS INC

REFERENCIA	Radicación No. 07 80058
	Trámite 2
	Evento 1
	Actuación 416
	Oficio No. 5012
	Folios 1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

De acuerdo con lo previsto por el artículo 40 de la Decisión 486/00, la publicación en este caso se hará a partir del día 06 del mes de febrero de 2009.

Cúmplase
Dado en Bogotá DC,

18 DIC. 2007

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa10

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No.07-080058

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **602** DE
FECHA **31 DE MARZO DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY
EXPIRA EL **02 DE JULIO DEL 2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☐ NO ☒ X ☐