(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 February 2013 (28.02.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/028953 A1

(51) International Patent Classification:
A01N 43/38 (2006.01) *A61K 31/40* (2006.01)
A01N 37/18 (2006.01) *A61P 1/16* (2006.01)

(21) International Application Number:
PCT/US2012/052216

(22) International Filing Date:
24 August 2012 (24.08.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/526,798	24 August 2011 (24.08.2011)	US
61/529,358	31 August 2011 (31.08.2011)	US
61/617,813	30 March 2012 (30.03.2012)	US

(71) Applicant *(for all designated States except US)*: **GLAXOSMITHKLINE LLC** [US/US]; One Franklin Plaza, 200 North 16th Street, Philadelpha, Pennsylvania 19102 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WALKER, Jill** [US/US]; c/o GlaxoSmithKline, Global Patents, Five Moore Drive, PO Box 13398, Research Triangle Park, North Carolina 27709 (US). **VOITENLEITNER, Christian** [DE/US]; c/o GlaxoSmithKline, Global Patents, Five Moore Drive, PO Box 13398, Research Triangle Park, North Carolina 27709 (US).

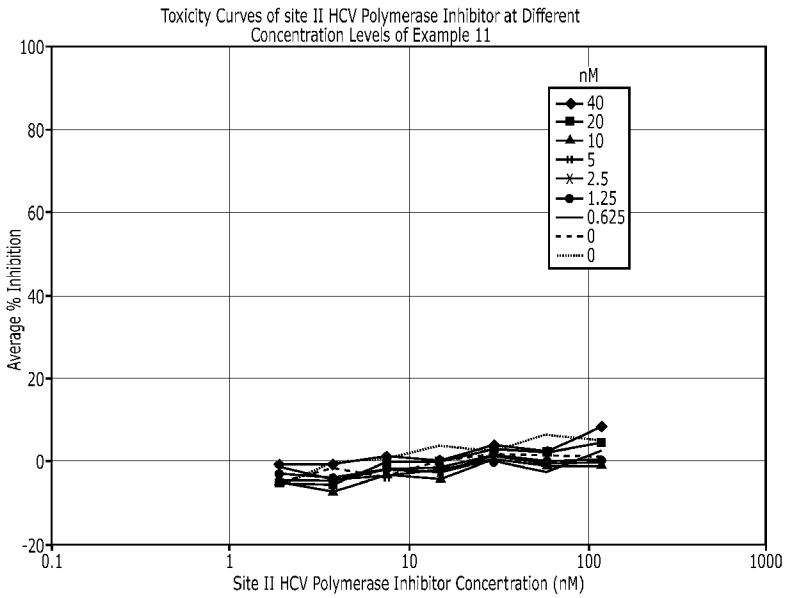
(74) Agents: **THOMAS, Robert (Steve)** et al.; GlaxoSmithKline, Global Patents, Five Moore Drive, PO Box 13398, Research Triangle Park, North Carolina 27709 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: COMBINATION TREATMENTS FOR HEPATITIS C



(57) Abstract: The present invention features methods and pharmaceutical compositions for the treatment of Hepatitis C in a human in need thereof comprising administering a compound of Formula (I), (II), (III), (IV), (V), or (VI) described herein or a pharmaceutically acceptable salt thereof in combination with one or more additional Hepatitis C therapeutic agents.

WO 2013/028953 A1

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

COMBINATION TREATMENTS FOR HEPATITIS C

CROSS-REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

This is a Patent Cooperation Treaty application and claims the benefit of US Provisional Application No. 61/526,798, filed August 24, 2011, US Provisional Application No. 61/529,358, filed August 31, 2011, and US Provisional Application No. 61/617,813, filed March 30, 2012, all of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to methods for the treatment of viral infections mediated by a member of the *Flaviviridae* family of viruses such as Hepatitis C virus (HCV), and to compositions for such treatment, and more particularly to methods for the treatment of Hepatitis C in subjects needing such treatment comprising administering a NS5A inhibitor described herein in combination with one or more Hepatitis C therapeutic agents and to compositions and pharmaceutical compositions comprising a NS5A inhibitor described herein in combination with one or more alternative Hepatitis C therapeutic agents.

BACKGROUND OF THE INVENTION

Chronic infection with HCV is a major health problem associated with increased risk for chronic liver disease, cirrhosis, hepatocellular carcinoma, and liver failure. HCV is a *hepacivirus* member of the *Flaviviridae* family of RNA viruses that affect animals and humans. The genome is a single ~9.6-kilobase strand of RNA, and consists of one open reading frame that encodes for a polyprotein of ~3000 amino acids flanked by untranslated regions at both 5' and 3' ends (5'- and 3'-UTR). The polyprotein serves as the precursor to at least 10 separate viral proteins critical for replication and assembly of progeny viral particles. The organization of structural and non-structural proteins in the HCV polyprotein is as follows: C-E1-E2-p7-NS2-NS3-NS4a-NS4b-NS5a-NS5b. Because the replicative cycle of HCV does not involve any DNA intermediate and the virus is not integrated into the host genome, HCV infection can theoretically be cured. While the pathology of HCV infection affects mainly the liver, the virus is found in other cell types in the body including peripheral blood lymphocytes.

HCV is the major causative agent for post-transfusion and for sporadic hepatitis. Infection by HCV is insidious in a high proportion of chronically infected (and infectious) carriers who may not experience clinical symptoms for many years. An estimated 170 million chronic carriers worldwide are at risk of developing liver disease. See, for

example, Szabo, *et al.*, *Pathol.Oncol.Res.* 2003, 9:215-221, and Hoofnagle JH, *Hepatology* 1997, 26:15S-20S. In the United States alone 2.7 million are chronically infected with HCV, and the number of HCV-related deaths in 2000 was estimated between 8,000 and 10,000, a number that is expected to increase significantly over the next years.

Historically, the standard treatment for chronic HCV was interferon alpha (IFN-alpha), particularly, pegylated interferon (PEG-IFN) alpha, in combination with ribavirin, which required six to twelve months of treatment. This combination regimen included 48 weekly injections of interferon and daily doses of oral ribavirin HCV patients infected with the genotype 1 virus.

IFN-alpha belongs to a family of naturally occurring small proteins with characteristic biological effects such as antiviral, immunoregulatory, and antitumoral activities. Interferons are produced and secreted by most animal nucleated cells in response to several diseases, in particular viral infections. IFN-alpha is an important regulator of growth and differentiation affecting cellular communication and immunological control. Treatment of HCV with interferon has frequently been associated with adverse side effects such as fatigue, fever, chills, headache, myalgias, arthralgias, mild alopecia, psychiatric effects and associated disorders, autoimmune phenomena and associated disorders and thyroid dysfunction.

Ribavirin, an inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH), enhances the efficacy of IFN-alpha in the treatment of HCV. Despite the introduction of ribavirin, more than 50% of the patients do not eliminate the virus with the current standard therapy of interferon-alpha (IFN) and ribavirin. Also, a number of patients still have significant side effects related to ribavirin. Ribavirin causes significant hemolysis in 10-20% of patients treated at currently recommended doses, and the drug is both teratogenic and embryotoxic.

A number of additional approaches are being pursued to combat the virus. These include, for example, application of antisense oligonucleotides or ribozymes for inhibiting HCV replication. Furthermore, low-molecular weight compounds that directly inhibit HCV proteins and interfere with viral replication are considered as attractive strategies to control HCV infection. Among the viral targets, the NS3/4A protease/helicase, the NS5B RNA-dependent RNA polymerase, and the non-structural NS5A protein, are considered the most promising HCV viral targets for new drugs. Indeed, compounds said to be useful for treating HCV infections are disclosed, for example, in WO2005/051318 (Chunduru, *et al.*) and WO2009/023179 (Schmitz, *et al.*). These references disclose methods for preparing the compounds, compositions comprising the compounds, compositions comprising the compounds and additional compounds, and methods of treating HCV.

Recently, two HCV therapeutic drugs have been approved in the US; each used as 3-way combination therapies in conjunction with pegylated interferon and ribavirin. These are Vertex's and Johnson and Johnson's NS3/4A protease inhibitor, Incivek® (telaprevir) and Merck's NS3/4A protease inhibitor, Victrelis® (boceprevir). The older 2-way pegylated interferon and ribavirin treatment regimen for HCV only cured about 40% of genotype 1 infected patients. Adding Victrelis® to that regimen shortens treatment duration for some and improves cure rates to more than 60%. Likewise, adding Incivek® to that regimen shortens treatment and boosts cure rates to as high as 80%. Unfortunately, neither Victrelis® nor Incivek® can be used alone without also including the pegylated interferon and ribavirin regimen, which brings along their concomitant unfavorable side effect profiles. These protease inhibitors also are associated with additional side effects such as rash and increased neutropenia. Such single active agent drugs also increase the risk of selecting for particular HCV mutations within the patient's body, which are resistant to these protease inhibitors.

Even with these recent improvements, a substantial fraction of patients do not respond with a sustained reduction in viral load and there is a clearly a need for more effective antiviral therapy of HCV infection. Therefore, what is needed is a combination therapy strategy to combat the HCV virus without having to include the problematic pegylated interferon and ribavirin therapeutics. Multiple combination therapies that include Direct-acting antivirals (DAA) targeted to more than one particular type of HCV protein could reduce the incidence of side effects. Just as importantly, DAAs could reduce the virus's ability to mutate within the patient's body, which can lead to a resurgence of HCV viral titer.

In view of the worldwide epidemic level of HCV,the limited treatment options available, and the need to expand access to all oral DAA regimens, there is a an ever growing need for new effective drugs for treating chronic HCV infections.

SUMMARY OF THE INVENTION

In accordance with one embodiment of the present invention, there is provided a method for the treatment of Hepatitis C in a human in need thereof comprising administering a compound of Formula (I), (II), or (III) described herein or a pharmaceutically acceptable salt thereof in combination with one or more additional Hepatitis C therapeutic agents. In accordance with another embodiment of the present invention, there is provided a pharmaceutical composition for the treatment of Hepatitis C comprising a compound of Formula (I), (II), or (III) described herein or a pharmaceutically

acceptable salt thereof in combination with one or more additional Hepatitis C therapeutic agents and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a line graph showing toxicity of Example 11 with a site II HCV polymerase inhibitor.

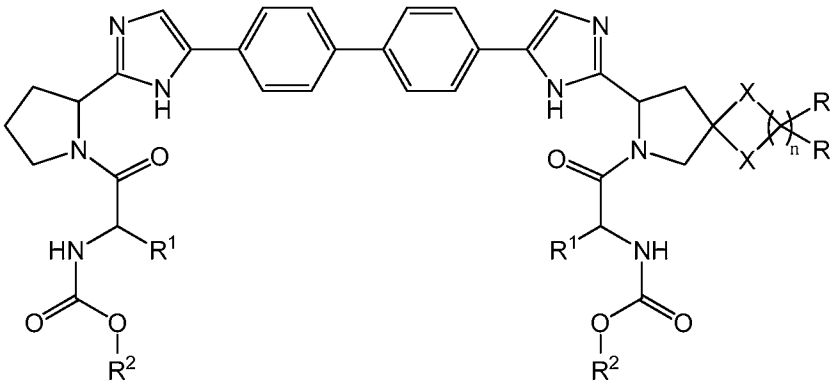
Figure 2 are line graphs showing toxicity of Example 11 with a site II HCV polymerase inhibitor.

Figure 3 are line graphs showing toxicity of Example 11 with an HCV cyclophilin inhibitor.

Figure 4 are line graphs showing toxicity of Example 11 with an HCV cyclophilin inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of preventing or treating Hepatitis C in a human in need thereof comprising administering to the human a compound of Formula (I):



(I)

wherein:

n is 2 or 3;

each R^1 is independently H or $C_{1\text{-}3}$alkyl;

each R^2 is independently $C_{1\text{-}3}$alkyl;

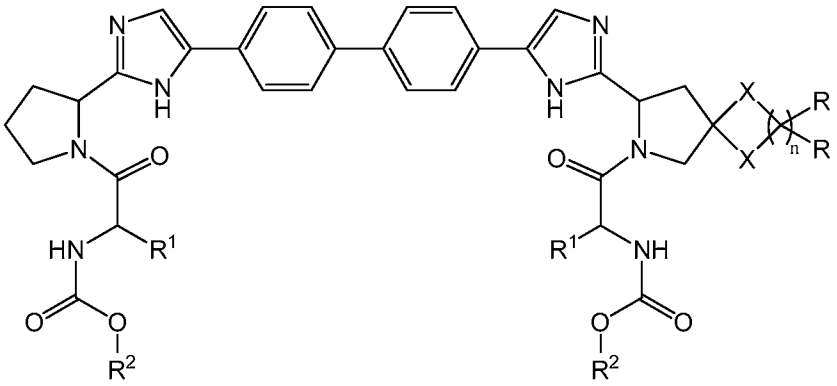
each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride

transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a composition comprising a compound of Formula (I):



(I)

wherein:

n is 2 or 3;

each R^1 is independently H or C_{1-3}alkyl;

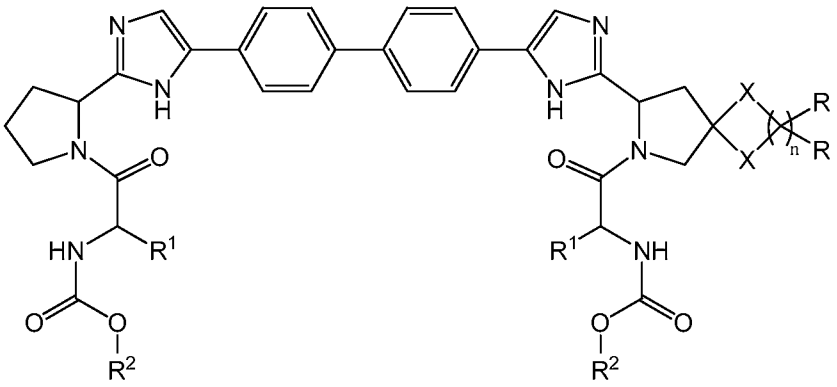
each R^2 is independently C_{1-3}alkyl;

each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a pharmaceutical composition comprising a compound of Formula (I):



(I)

wherein:

n is 2 or 3;

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

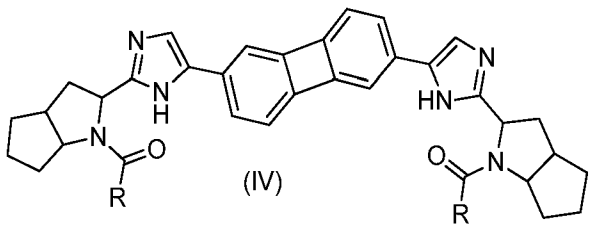
each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue,

and a pharmaceutically acceptable carrier.

The present invention also provides a composition comprising a compound of Formula (IV):



(IV)

wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

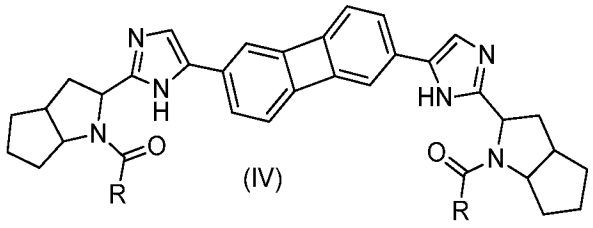
wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV

NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a method of preventing or treating Hepatitis C in a human in need thereof comprising administering to the human a compound of Formula (IV):



(IV)

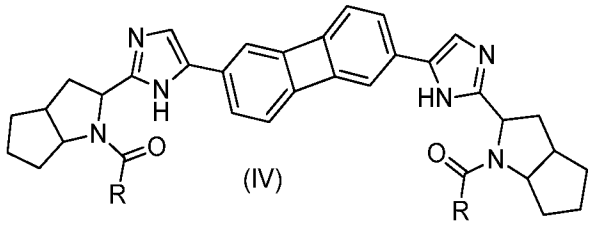
wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a composition comprising a compound of Formula (IV):



(IV)

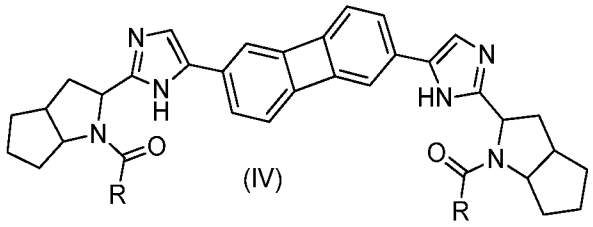
wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a method of preventing or treating Hepatitis C in a human in need thereof comprising administering to the human a compound of Formula (IV):



(IV)

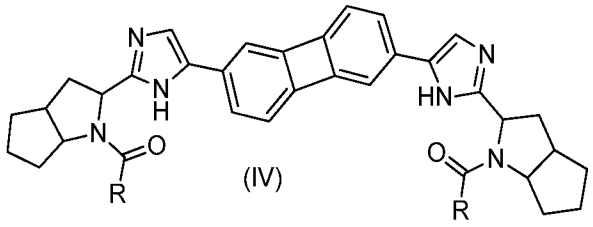
wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a pharmaceutical composition comprising a compound of Formula (IV):



(IV)

wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue,

and a pharmaceutically acceptable carrier.

Throughout this application, references are made to various embodiments relating to compounds, compositions, and methods. The various embodiments described are meant to provide a variety of illustrative examples and should not be construed as descriptions of alternative species. Rather it should be noted that the descriptions of various embodiments provided herein may be of overlapping scope. The embodiments discussed herein are merely illustrative and are not meant to limit the scope of the present invention.

It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to limit the scope of the present invention. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings.

The term “alkyl” refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms. For example, C_{1-4}alkyl means a straight or branched alkyl containing at least 1, and at most 4, carbon atoms. Examples of “alkyl” as used herein include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, and *t*-butyl.

The term “cycloalkyl” refers to a saturated cyclic group containing 3 to 6 carbon ring-atoms (unless otherwise specified). Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The present invention provides a method for the treatment of Hepatitis C in a human in need thereof comprising administering to the human a compound of Formula (I) or Formula IV, or a pharmaceutically acceptable salt thereof, in combination with one or more of the following therapeutic agents: an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal

ribosome entry site (IRES) inhibitor, a microsomal triglyceride transfer protein (MTP) inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue, which are administered in effective amounts as is known in the art.

Examples of suitable HCV NS3/4A protease inhibitors include boceprevir (such as Victrelis™), telaprevir (such as Incivek™), simeprevir (also known as TMC-435350), danoprevir (also known as RG7227 or ITMN-191), BI-201335, narlaprevir (also known as SCH 900518), vaniprevir (also known as MK-7009), asunaprevir (also known as BMS-650032), GS 9256, GS 9451, ACH-0141625, VX-985, ABT-450, PHX1766, IDX320, MK-5172, GNS-227, AVL-192, ACH-2684, and ACH-1095.

Examples of suitable HCV NS4B replication factor inhibitors include clemizole.

Examples of suitable HCV NS5B polymerase inhibitors include silibinin sodium hemisuccinate, tegobuvir (also known as GS-9190), filibuvir (also known as PF-00868554), VX-222, VX-759, ANA598, BMS-791325, ABT-333, ABT-072, BI 207127, IDX375, mericitabine (also known as RG7128), RG7348 (also known as MB-11362), RG7432, PSI-7977, PSI-7851, PSI-352938, PSI-661, TMC 649128, IDX184, INX-08189, JTK-853, VCH-916, BILB 1941, GS-6620, and GS-9669.

Examples of suitable HCV entry inhibitors include PRO-206, ITX-5061, ITX4520, REP 9C, SP-30, and JTK-652.

Examples of suitable microsomal triglyceride transfer protein (MTP) inhibitors include BMS-201038 and CP-346086.

Examples of suitable α-glucosidase inhibitors include celgosovir (also known as MX-3253 or MBI-3253) and castanospermine.

Examples of suitable caspase inhibitors include IDN-6556.

Examples of suitable cyclophilin inhibitors include alisporivir (also known as DEBIO-025), NIM811 (also known as *N*-methyl-4-isoleucine cyclosporine), and SCY-635 (also known as [(*R*)-2-(*N*,*N*-dimethylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A).

Examples of suitable immunomodulators include Alloferon, IMN-6001, NOV-205, ME-3738, interleukin-7 (such as CYT 107), ANA-773, IMO-2125, and GS 9620.

Examples of suitable metabolic pathway inhibitors include ritonavir (such as Norvir®).

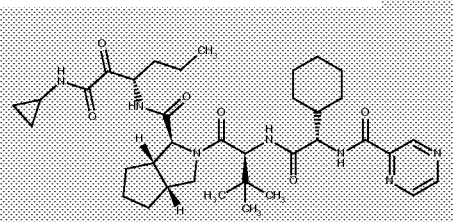
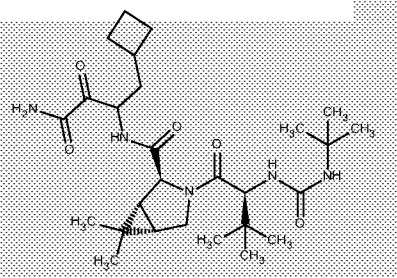
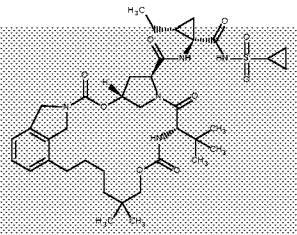
Examples of suitable interferons include interferon alfa-2a (such as Roferon-A®, Veldona®, or LBSI5535), peginterferon alfa-2a (such as Pegasys®), interferon alfa-2b (such as Intron A® or Locteron®), peginterferon alfa-2b (such as PEG Intron® or P1101), interferon alfa-2b analogues (such as Hanferon™), interferon alpha-2b XL, interferon

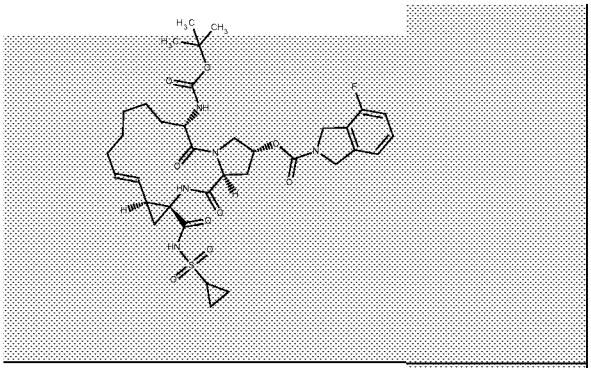
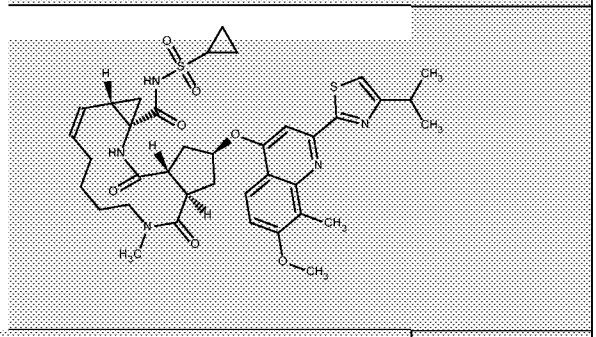
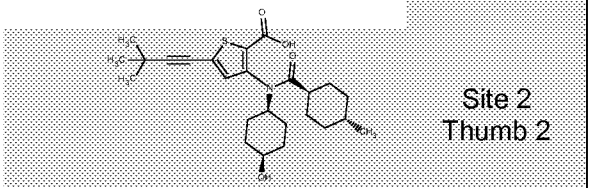
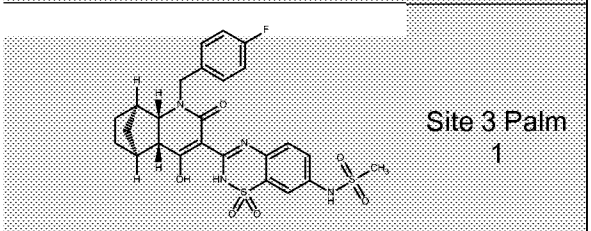
alfacon-1 (such as Infergen®), interferon alfa-n1 (such as Wellferon®), interferon omega (such as Biomed 510), HDV-interferon, peginterferon beta (such as TRK-560), peginterferon lambda (such as BMS-914143), and interferon-alpha5.

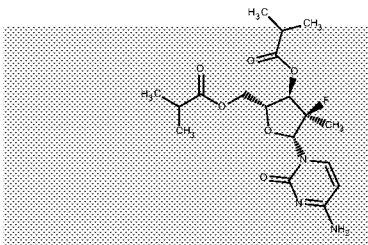
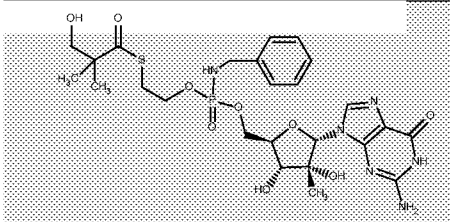
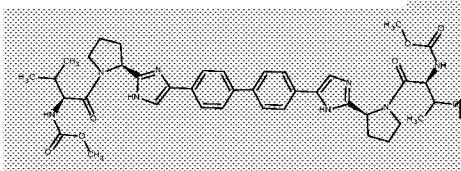
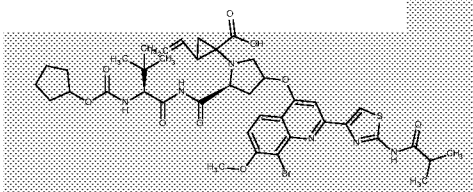
Examples of suitable nucleoside analogues include ribavirin (such as Copegus®, Ravanex®, Rebetol®, RibaPak™, Ribasphere®, Vilona®, and Virazole®), taribavirin (also known as viramidine), and isatoribine (also known as ANA245) and its prodrugs ANA971 and ANA975.

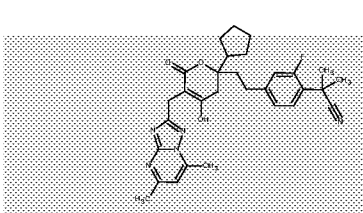
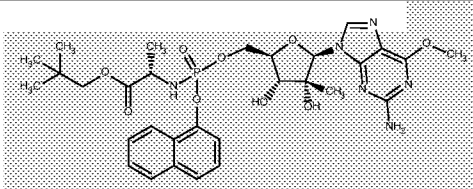
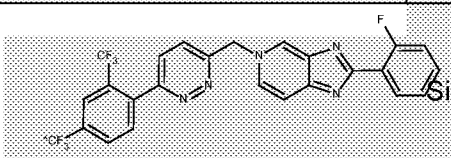
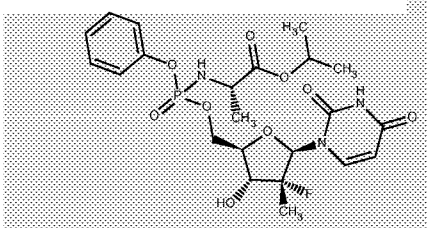
Table 1 belows lists additional suitable Hepatitis C therapeutic agents that may be used in combination with a compound of Formula I or IV in the present invention.

Table 1

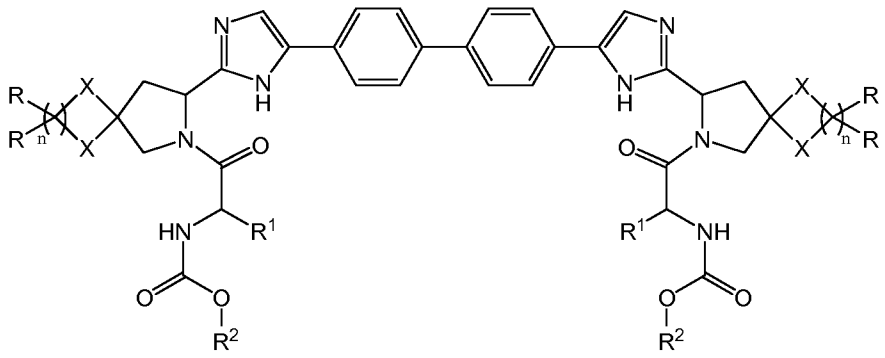
Name	Company	Class	Phase	Structure	Notes
Telaprevir	Vertex	PI	M		
Boceprevir	Merck	PI	M		
Vaniprevir MK-7009	Merck	PI	III		
MK-5172	Merck	PI	II	n/a	

Danoprevir RG7227 ITMN-191	Roche	PI	II		
Simeprevir TMC-435	JNJ Tibotec	PI	III		
IDX-077	Idenix	PI	PC	n/a	
IDX-791	Idenix	PI	PC	n/a	
ACH-1625	Achillion	PI	II	n/a	
ACH-2684	Achillion	PI	I	n/a	
ABT-450	Abbott	PI	II	n/a	rtv boosted
VX-222	Vertex	NNI	II b		Site 2 Thumb 2
Setrobuvir RG-7790 ANA-598	Roche	NNI	II		Site 3 Palm 1
TMC-647055	J&J	NNI	I	n/a	Indole site 1
IDX-375	Idenix	NNI	II	n/a	Palm site
ALS-2200	Vertex	NI	I	n/a	
ALS-2158	Vertex	NI	I	n/a	

Mericitabine RG-7128	Roche	NI	II		
IDX-184	Idenix	NI	II		
MK-4882	Merck	NS5A	PC	n/a	
IDX-719	Idenix	NS5A	II	n/a	1st gen?
IDX-19370	Idenix	NS5A	PC	n/a	
IDX-19368	Idenix	NS5A	PC	n/a	
ACH-2928	Achillion	NS5A	I	n/a	1st gen
ACH-3102	Achillion	NS5A	PC	n/a	2nd gen
PPI-461	Presidio	NS5A	Ib	n/a	1st gen
PPI-668	Presidio	NS5A	Ib	n/a	
PPI-437	Presidio	NS5A	Ib	n/a	
EDP-239	Novartis	NS5A	PC	n/a	from Enanta
MK-4882	Merck	NS5A	PhI	n/a	
GS-5885	Gilead	NS5A	II	n/a	1st gen
Daclatasvir BMS-790052	BMS	NS5A	III		1st gen
BMS-824393	BMS	NS5A	I	n/a	
ABT-267	Abbott	NS5A	II	n/a	1st gen
BI-201335	BI	PI	III		
BI-207127	BI	NNI	II b	n/a	Thumb- site 1

Filibuvir PF-868554	Pfizer	NNI	II		Site 2 Thumb 2
BMS-791325	BMS	NNI	II a	n/a	
INX-189	BMS	NI	II		
ABT-333	Abbott	NNI	II	n/a	Site 4 Palm 2
ABT-072	Abbott	NNI	II	n/a	
Debio-025	Novartis	Cyclophillin Analogue	III	n/a	
SCY-635	Scynexis	Cyclophillin Analogue	II	n/a	
Tegobuvir GS-9190	Gilead	NNI	II		Site 4 Palm 2
GS-9669	Gilead	NNI	I	n/a	Thumb site 2
GS-7977	Gilead	NI	III		

The present invention further provides a method of preventing or treating Hepatitis C Virus in a human in need thereof comprising administering to the human a compound of Formula (II):



(II)

wherein:

n is 2 or 3;

each R^1 is independently H or C_{1-3}alkyl;

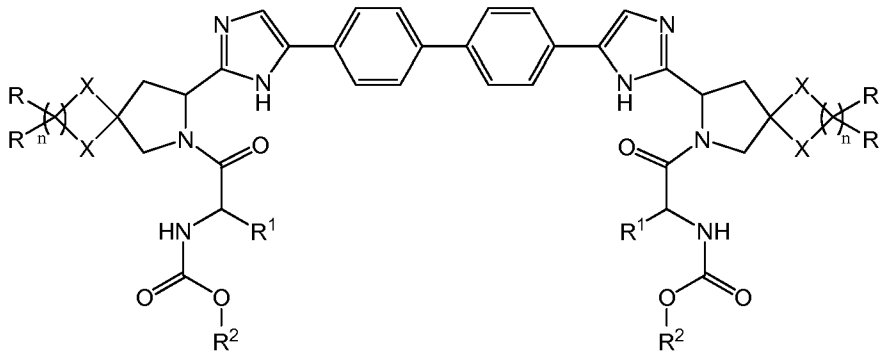
each R^2 is independently C_{1-3}alkyl;

each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a pharmaceutical composition comprising a compound of Formula (II):



(II)

wherein:

n is 2 or 3;

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

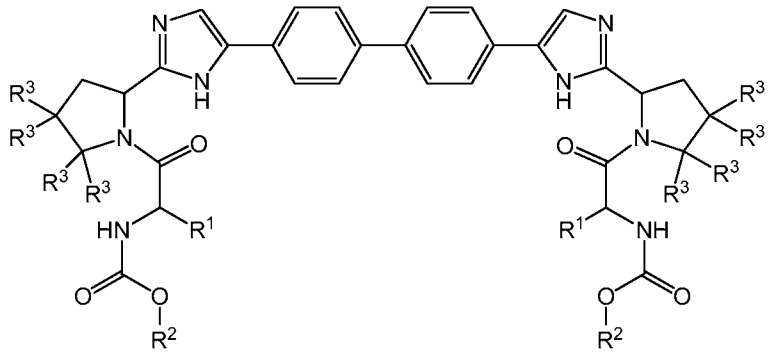
each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, and one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue;

and a pharmaceutically acceptable excipient.

The present invention further provides a method of preventing or treating Hepatitis C in a human in need thereof comprising administering to the human a compound of Formula (III):



(III)

wherein:

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

on each carbon to which there are R^3 groups attached, either both R^3s are H or the R^3 groups together with the carbon to which they are bonded form a 4-, 5-, or 6-membered saturated spiro ring with the proviso that there is no more than 1 spiro ring on each saturated nitrogen-containing ring;

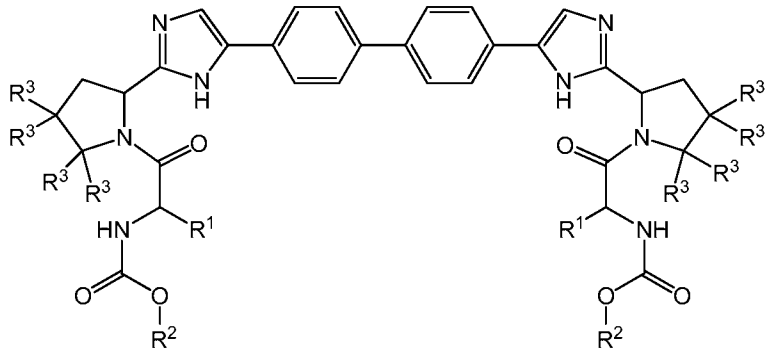
each saturated spiro formed from R^3 groups is independently cycloalkyl, or may contain 1 or 2 oxygen atoms, or 1 or 2 sulfur atoms, or 1 SO_2, or 1 NR^4;

each R^4 is independently H, $C(O)OC_{1-4}$alkyl, $C(O)C_{1-4}$alkyl, $C(O)NC_{1-4}$alkyl, or SO_2C_{1-4}alkyl; and

each spiro ring may optionally be substituted with deuterium, fluorine, or 1 or 2 methyl groups;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a pharmaceutical composition comprising a compound of Formula (III):



(III)

wherein:

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

on each carbon to which there are R^3 groups attached, either both R^3s are H or the R^3 groups together with the carbon to which they are bonded form a 4-, 5-, or 6-membered saturated spiro ring with the proviso that there is no more than 1 spiro ring on each saturated nitrogen-containing ring;

each saturated spiro formed from R^3 groups is independently cycloalkyl, or may contain 1 or 2 oxygen atoms, or 1 or 2 sulfur atoms, or 1 SO_2, or 1 NR^4;

each R^4 is independently H, $C(O)OC_{1-4}$alkyl, $C(O)C_{1-4}$alkyl, $C(O)NC_{1-4}$alkyl, or SO_2C_{1-4}alkyl; and

each spiro ring may optionally be substituted with deuterium, fluorine, or 1 or 2 methyl groups;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue;

and a pharmaceutically acceptable excipient.

One embodiment of the present invention features a compound of Formula (I) or (II) wherein each X is identical.

Another embodiment of the present invention features a compound of Formula (I) or (II) wherein either all Rs are H or all Rs are deuterium (D). In other words, one embodiment of the present invention features a compound of Formula (I) or (II) wherein, either every CRR group in the spiro is CH_2 or every CRR group in the spiro is CD_2. Deuterium is naturally present in very small amounts in hydrogen compounds. By designating a substituent as deuterium or D, applicants mean that the natural isotopic amount of deuterium has been increased so that more that half of that particular substituent is D as compared to H.

Another embodiment of the present invention features a compound of Formula (I) or (II) wherein no more than 2 Rs are methyl.

In another embodiment of the invention, in compounds of Formula (III), when R^3 groups form a spiro ring on each saturated nitrogen-containing ring, each of said spiro groups is bonded to the same relative carbon atom in each saturated nitrogen containing ring.

The present invention also features a compound of Formula (I), (II), or (III) selected from the group consisting of:

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(3*S*,7*S*,9*S*)-7,9-dimethyl-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

dimethyl (4,4'-biphenyldiylbis{1*H*-imidazole-4,2-diyl[(3*S*,7*S*,9*S*)-7,9-dimethyl-6,10-dioxa-2-azaspiro[4.5]decane-3,2-diyl][(2*S*)-3-methyl-1-oxo-1,2-butanediyl]})biscarbamate;

dimethyl (4,4'-biphenyldiylbis{1*H*-imidazole-4,2-diyl(8*S*)-1,4-dioxa-7-azaspiro[4.4]nonane-8,7-diyl[(2*S*)-3-methyl-1-oxo-1,2-butanediyl]})biscarbamate;

methyl ((1*S*)-1-methyl-2-{(3*S*)-3-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-6,10-dioxa-2-azaspiro[4.5]dec-2-yl}-2-oxoethyl)carbamate;

methyl [(1S)-2-methyl-1-({(2S)-2-[4-(4'-{2-[(3S)-2-((2S)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(3*S*)-8,8-dimethyl-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(3*S*)-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate-d_6;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate-d_4;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(2*R*,3*R*,8*S*)-2,3-dimethyl-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-5-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(2*S*,3*S*,8*S*)-2,3-dimethyl-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-5-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dithia-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl[(1S)-2-methyl-1-({(2S)-2-[4-(4'-{2-[(8S)-7-((2S)-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dithia-7-azaspiro[4.4]non-8-yl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-({[(methyloxy)carbonyl]amino}acetyl)-1,4-dithia-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-8-oxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-8,8-dioxido-8-thia-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[8,8-difluoro-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

dimethyl (4,4'-biphenyldiylbis{1*H*-imidazole-4,2-diyl(3*S*)-8-oxa-2-azaspiro[4.5]decane-3,2-diyl[(2*S*)-3-methyl-1-oxo-1,2-butanediyl]})biscarbamate;

1,1-dimethylethyl 2-{*N*-[(methyloxy)carbonyl]-L-valyl}-3-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,8-diazaspiro[4.5]decane-8-carboxylate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,8-diazaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate.;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[8-acetyl-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,8-diazaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl 2-{*N*-[(methyloxy)carbonyl]-L-valyl}-3-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,8-diazaspiro[4.5]decane-8-carboxylate;

1,1-dimethylethyl 6-{*N*-[(methyloxy)carbonyl]-L-valyl}-7-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[2-acetyl-6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl 6-{*N*-[(methyloxy)carbonyl]-L-valyl}-7-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-[(methylamino)carbonyl]-6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-(methylsulfonyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(7*S*)-2,2-difluoro-6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6-azaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-8-oxa-1-azaspiro[4.5]dec-2-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl ((1*S*)-1-{[(2*S*)-2-(4-{4'-[2-(1-acetyl-8-oxa-1-azaspiro[4.5]dec-2-yl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-1-pyrrolidinyl]carbonyl}-2-methylpropyl)carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[8,8-difluoro-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1-azaspiro[4.5]dec-2-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-1-({8,8-difluoro-2-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-azaspiro[4.5]dec-1-yl}carbonyl)propyl]carbamate;

methyl ((1*S*)-2-{8,8-difluoro-2-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-azaspiro[4.5]dec-1-yl}-1-methyl-2-oxoethyl)carbamate;

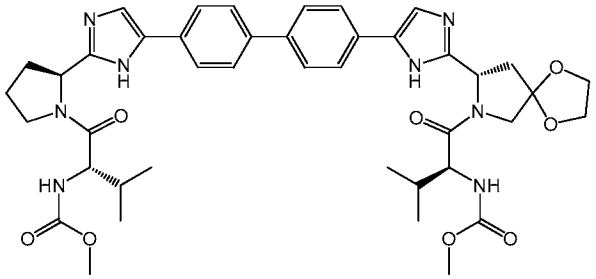
methyl [(1*S*)-1-({8,8-difluoro-2-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-azaspiro[4.5]dec-1-yl}carbonyl)-3-methylbutyl]carbamate;

methyl ((1*S*)-1-{[(2*S*)-2-(4-{4'-[2-(1-acetyl-8,8-difluoro-1-azaspiro[4.5]dec-2-yl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-1-pyrrolidinyl]carbonyl}-2-methylpropyl)carbamate; and

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-8,8-dioxido-8-thia-1-azaspiro[4.5]dec-2-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

and pharmaceutically acceptable salts thereof.

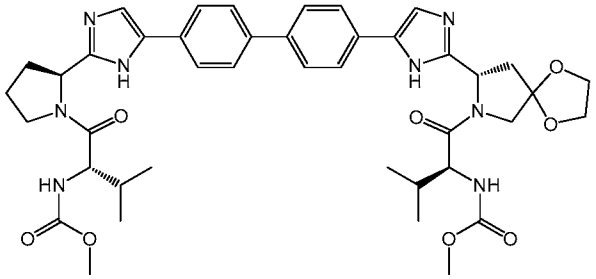
The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:



or a pharmaceutically acceptable salt thereof,

in combination with a one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:

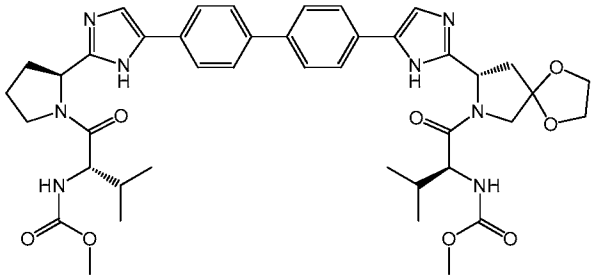


or a pharmaceutically acceptable salt thereof,

in combination with a one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue;

and a pharmaceutically acceptable excipient.

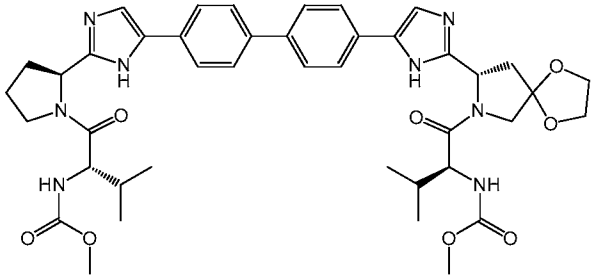
The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:



or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds listed in Table 1.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:

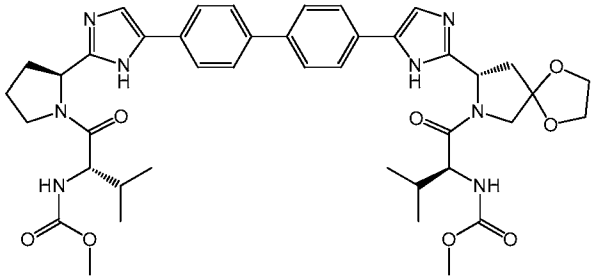


or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds listed in Table 1;

and a pharmaceutically acceptable excipient.

The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:



or a pharmaceutically acceptable salt thereof,

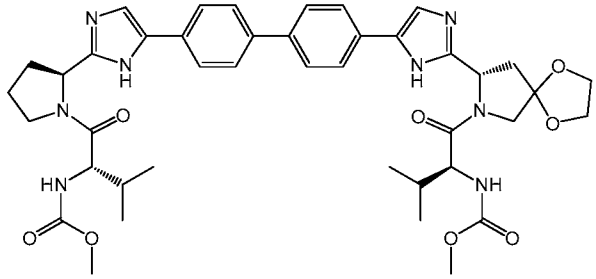
in combination with one or more compounds selected from the group of:

Telaprevir	Vertex
Boceprevir	Merck

Vaniprevir (MK-7009)	Merck
MK-5172	Merck
Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
IDX-077	Idenix
IDX-791	Idenix
ACH-1625	Achillion
ACH-2684	Achillion
ABT-450	Abbott
VX-222	Vertex
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
IDX-375	Idenix
ALS-2200	Vertex
ALS-2158	Vertex
Mericitabine (RG-7128)	Roche
IDX-184	Idenix
MK-4882	Merck
IDX-719	Idenix
IDX-19370	Idenix
IDX-19368	Idenix
ACH-2928	Achillion
ACH-3102	Achillion
PPI-461	Presidio
PPI-668	Presidio
PPI-437	Presidio
EDP-239	Novartis
MK-4882	Merck
GS-5885	Gilead
Daclatasvir (BMS-790052)	BMS
BMS-824393	BMS
ABT-267	Abbott
BI-201335	BI
BI-207127	BI
Filibuvir (PF-868554)	Pfizer
BMS-791325	BMS

INX-189	BMS
ABT-333	Abbott
ABT-072	Abbott
Debio-025	Novartis
SCY-635	Scynexis
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:



or a pharmaceutically acceptable salt thereof,

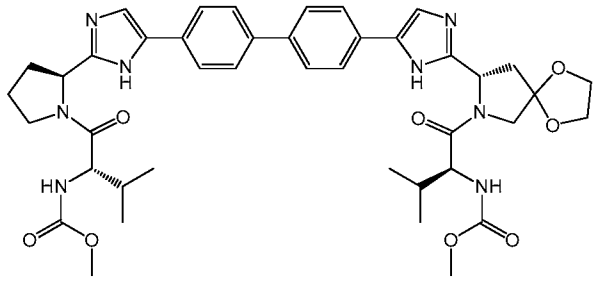
in combination with one or more compounds selected from the group of:

Telaprevir	Vertex
Boceprevir	Merck
Vaniprevir (MK-7009)	Merck
MK-5172	Merck
Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
IDX-077	Idenix
IDX-791	Idenix
ACH-1625	Achillion
ACH-2684	Achillion
ABT-450	Abbott
VX-222	Vertex
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
IDX-375	Idenix
ALS-2200	Vertex
ALS-2158	Vertex
Mericitabine (RG-7128)	Roche

IDX-184	Idenix
MK-4882	Merck
IDX-719	Idenix
IDX-19370	Idenix
IDX-19368	Idenix
ACH-2928	Achillion
ACH-3102	Achillion
PPI-461	Presidio
PPI-668	Presidio
PPI-437	Presidio
EDP-239	Novartis
MK-4882	Merck
GS-5885	Gilead
Daclatasvir (BMS-790052)	BMS
BMS-824393	BMS
ABT-267	Abbott
BI-201335	BI
BI-207127	BI
Filibuvir (PF-868554)	Pfizer
BMS-791325	BMS
INX-189	BMS
ABT-333	Abbott
ABT-072	Abbott
Debio-025	Novartis
SCY-635	Scynexis
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead;

and a pharmaceutically acceptable excipient.

The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:

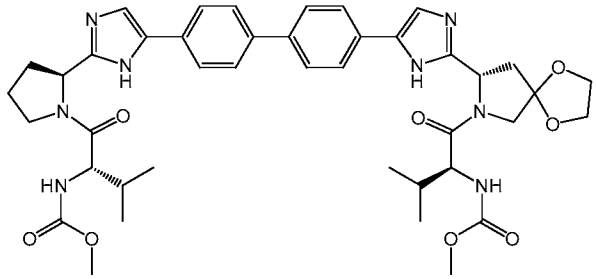


or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
Mericitabine (RG-7128)	Roche
GS-5885	Gilead
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:



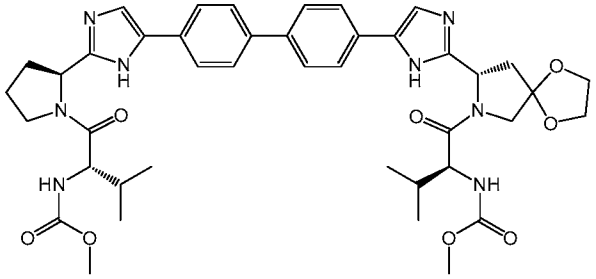
or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
Mericitabine (RG-7128)	Roche
GS-5885	Gilead
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead;

and a pharmaceutically acceptable excipient.

The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:

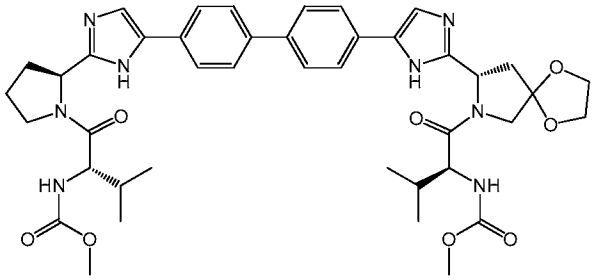


or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055, and	J&J
Mericitabine (RG-7128)	Roche.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:



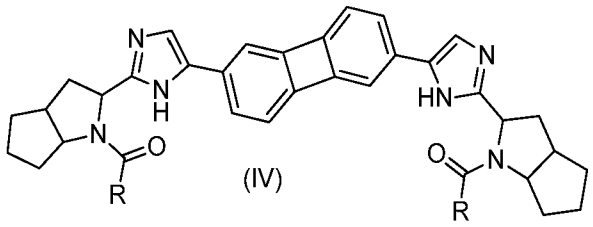
or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055, and	J&J
Mericitabine (RG-7128)	Roche;

and a pharmaceutically acceptable excipient.

The present invention also provides a composition comprising a compound of Formula (IV):



(IV)

wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

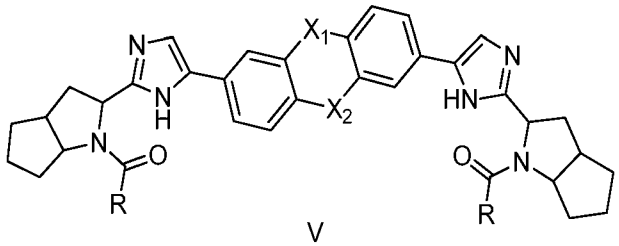
or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

In certain embodiments, each R group of Formula (IV) above is enantiomerically enriched with the enantiomer where the chiral carbon to which R^1 is bonded has an absolute configuration of S.

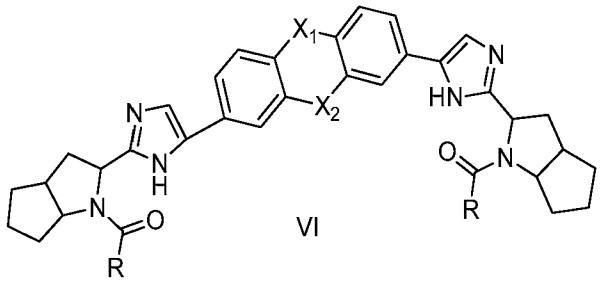
In other embodiments, each R^1 group of Formula (IV) is enantiomerically enriched with the enantiomer where the chiral carbon in each R^1 group has an absolute configuration of R.

In other embodiments, each R^2 of Formula (IV) is methyl.

In still other embodiments, the present invention also provides a composition comprising a compound of Formula (V or VI):



V



VI

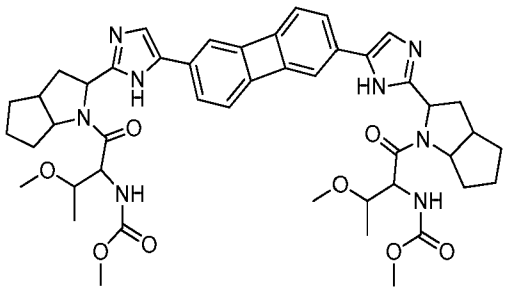
,

wherein X^1 and X^2 are independently O, SO_2, NCH_3, CF_2, CH_2, CH_2CH_2, or a bond (i.e. absent); and each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

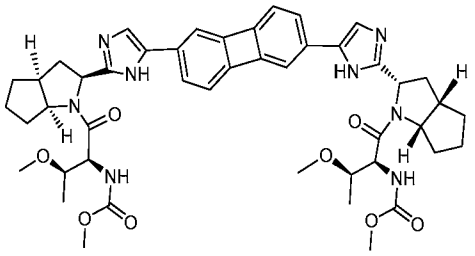
each R^2 is independently C_{1-3}alkyl, or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

In some embodiments, the compound of any of Formulas IV, V, or VI is a compound having the structure:



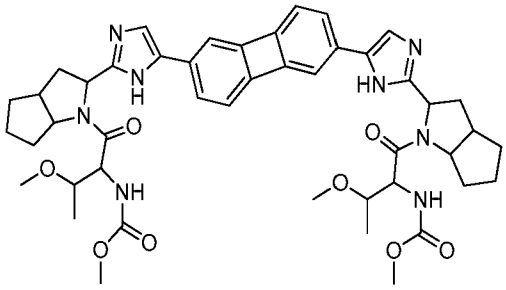
, or a pharmaceutically acceptable salt thereof.

In other embodiments, the compound of any of Formulas IV, V, or VI is a compound having the structure:



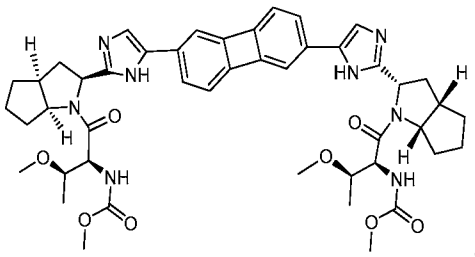
,or a pharmaceutically acceptable salt thereof.

In still other embodiments, the present invention also provides a composition comprising a compound having the structure:



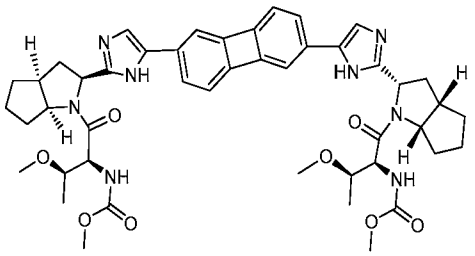
, or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

In still other embodiments, the present invention also provides a composition comprising a compound having the structure:



, or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

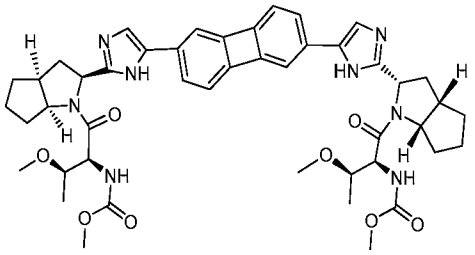
The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:



or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds listed in Table 1.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:

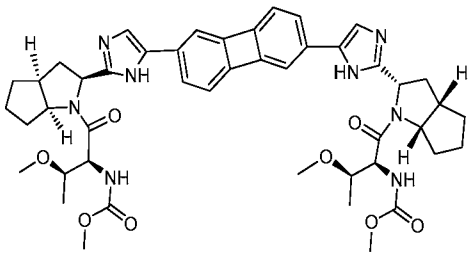


or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds listed in Table 1;

and a pharmaceutically acceptable excipient.

The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:



or a pharmaceutically acceptable salt thereof,

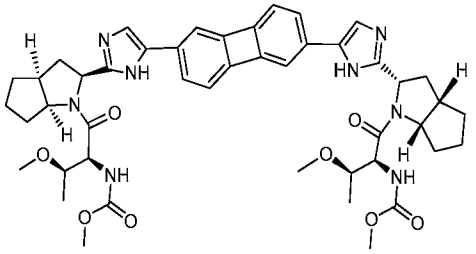
in combination with one or more compounds selected from the group of:

Telaprevir	Vertex
Boceprevir	Merck
Vaniprevir (MK-7009)	Merck
MK-5172	Merck
Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec

IDX-077	Idenix
IDX-791	Idenix
ACH-1625	Achillion
ACH-2684	Achillion
ABT-450	Abbott
VX-222	Vertex
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
IDX-375	Idenix
ALS-2200	Vertex
ALS-2158	Vertex
Mericitabine (RG-7128)	Roche
IDX-184	Idenix
MK-4882	Merck
IDX-719	Idenix
IDX-19370	Idenix
IDX-19368	Idenix
ACH-2928	Achillion
ACH-3102	Achillion
PPI-461	Presidio
PPI-668	Presidio
PPI-437	Presidio
EDP-239	Novartis
MK-4882	Merck
GS-5885	Gilead
Daclatasvir (BMS-790052)	BMS
BMS-824393	BMS
ABT-267	Abbott
BI-201335	BI
BI-207127	BI
Filibuvir (PF-868554)	Pfizer
BMS-791325	BMS
INX-189	BMS
ABT-333	Abbott
ABT-072	Abbott
Debio-025	Novartis

SCY-635	Scynexis
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:



or a pharmaceutically acceptable salt thereof,

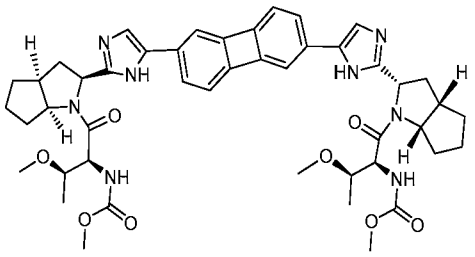
in combination with one or more compounds selected from the group of:

Telaprevir	Vertex
Boceprevir	Merck
Vaniprevir (MK-7009)	Merck
MK-5172	Merck
Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
IDX-077	Idenix
IDX-791	Idenix
ACH-1625	Achillion
ACH-2684	Achillion
ABT-450	Abbott
VX-222	Vertex
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
IDX-375	Idenix
ALS-2200	Vertex
ALS-2158	Vertex
Mericitabine (RG-7128)	Roche
IDX-184	Idenix
MK-4882	Merck
IDX-719	Idenix
IDX-19370	Idenix
IDX-19368	Idenix

ACH-2928	Achillion
ACH-3102	Achillion
PPI-461	Presidio
PPI-668	Presidio
PPI-437	Presidio
EDP-239	Novartis
MK-4882	Merck
GS-5885	Gilead
Daclatasvir (BMS-790052)	BMS
BMS-824393	BMS
ABT-267	Abbott
BI-201335	BI
BI-207127	BI
Filibuvir (PF-868554)	Pfizer
BMS-791325	BMS
INX-189	BMS
ABT-333	Abbott
ABT-072	Abbott
Debio-025	Novartis
SCY-635	Scynexis
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead;

and a pharmaceutically acceptable excipient.

The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:



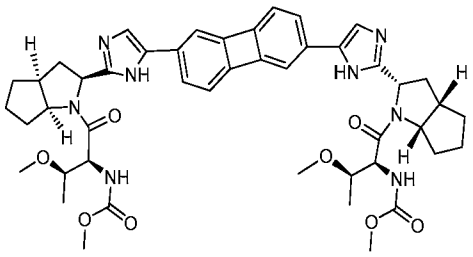
or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche

Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
Mericitabine (RG-7128)	Roche
GS-5885	Gilead
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:



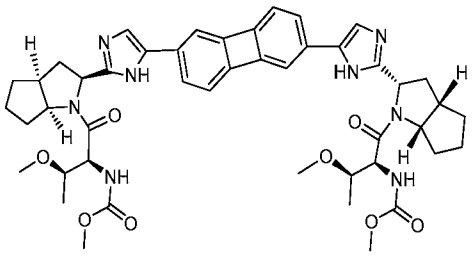
or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
Mericitabine (RG-7128)	Roche
GS-5885	Gilead
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead;

and a pharmaceutically acceptable excipient.

The present invention further provides a method of treatment of Hepatitis C Virus (HCV) in a human in need thereof comprising administering a compound having the structure:

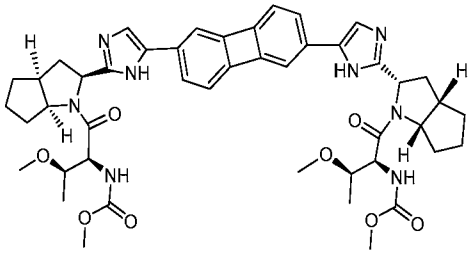


or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055, and	J&J
Mericitabine (RG-7128)	Roche.

The present invention also provides a pharmaceutical composition comprising a compound having the structure:



or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055, and	J&J
Mericitabine (RG-7128)	Roche;

and a pharmaceutically acceptable excipient.

When a compound of Formula (I), (II), (III), (IV), (V), or (VI), or pharmaceutically acceptable salt thereof is used in combination with a one ore more therapeutic agents the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions by any convenient route. When administration is sequential, either the compound of Formula (I), (II), (III), (IV), (V), or (VI), or the one or more therapeutic agents may be administered first. When administration is simultaneous, the combination(s) may be administered either in the same or different pharmaceutical composition.

The present invention further provides a pharmaceutical composition comprising a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents as described above. When combined in the same formulation it will be appreciated that the compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

Certain compounds of Formulas (I), (II), (III), (IV), (V), or (VI), may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms

It is understood that compounds of Formulas (I), (II), (III), (IV), (V), or (VI),may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

It will also be appreciated that compounds of the invention which exist as polymorphs, and mixtures thereof, are within the scope of the present invention.

The present invention also features a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof. As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. For a review on suitable salts see Berge et al, J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

In certain embodiments, compounds of Formula (I), (II), (III), (IV), (V), or (VI), may contain an acidic functional group and may therefore be capable of forming

pharmaceutically acceptable base addition salts by treatment with a suitable base. Pharmaceutically acceptable base salts include ammonium salts (for example ammonium or tetraalkylammonium), metal salts, for example alkali-metal or alkaline-earth-metal salts (such as hydroxides, sodium, potassium, calcium or magnesium), organic amines (such as tris [also known as tromethamine or tris(hydroxymethyl)aminomethane], ethanolamine, diethylamine, triethanolamine, choline, isopropylamine, dicyclohexylamine or *N*-methyl-D-glucamine), cationic amino acids (such as arginine, lysine or histidine) or bases for insoluble salts (such as procaine or benzathine).

In certain embodiments, compounds according to Formula (I), (II), (III), (IV), (V), or (VI), may contain a basic functional group and may therefore be capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. A pharmaceutically acceptable acid addition salt may be formed by reaction of a compound of Formula (I), (II), (III), (IV), (V), or (VI), with a suitable strong inorganic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric or perchloric) or a suitable strong organic acid, for example, sulfonic acids [such as p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, naphthalenesulfonic (e.g. 2-naphthalenesulfonic)], carboxylic acids (such as acetic, propionic, fumaric, maleic, benzoic, salicylic or succinic), anionic amino acids (such as glutamaic or aspartic), hydroxyl acids (such as citric, lactic, tartaric or glycolic), fatty acids (such as caproic, caprylic, decanoic, oleic or stearic) or acids for insoluble salts (such as pamoic or resinic [e.g. polystyrene sulfonate]), optionally in a suitable solvent such as an organic solvent, to give salt which is usually isolated for example by crystallisation and filtration. In one embodiment, a pharmaceutically acceptable acid addition salt of a compound of Formula (I), (II), (III), (IV), (V), or (VI), is a salt of a strong acid, for example a hydrobromide, hydrochloride, hydroiodide, sulfate, nitrate, perchlorate, phosphate p-toluenesulfonic, benzenesulfonic or methanesulfonic salt.

It will be appreciated by those skilled in the art that organoboronic acids and/or their organoboronate esters may form "ate" complex addition salts, such as organoborate complex addition salts, in the presence of suitable nucleophilic complexing reagents. Suitable nucleophilic complexing reagents include, but are not limited to alkali metal hydroxides, for example lithium hydroxide, sodium hydroxide or potassium hydroxide, or fluoride. Examples of organoborate complex addition salts and methods for their preparation will be readily apparent. For example, one such suitable organoborate complex addition salt is an alkali metal trihydroxyorganoborate salt, such as a sodium trihydroxyorganoborate salt. By way of illustration, sodium trihydroxyarylborate and sodium trihydroxyalkylborate complex addition salts and methods for their preparation are

described in Cammidge, A.N. et al, *Org. Lett.*, **2006**, *8*, 4071-4074. Pharmaceutically acceptable "ate" complex addition salts as described herein are also considered to be within the scope of this invention.

The present invention features suitable pharmaceutically acceptable salts of the compounds of Formulas (I), (II), (III), (IV), (V), or (VI), including acid salts, for example sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium and tris (tromethamine - tris(hydroxymethyl)aminomethane) salts and the like, or mono- or di-basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like.

The present invention features pharmaceutically acceptable base addition salts of a compound of Formula (I), (II), (III), (IV), (V), or (VI), which are salts of a strong base, for example, sodium, lysine, ammonium, *N*-methyl-D-glucamine, potassium, choline, arginine (for example L-arginine) or magnesium. In a further aspect the salt is sodium, lysine, ammonium, *N*-methyl-D-glucamine, potassium, choline or arginine (for example L-arginine).

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of Formulas (I), (II), (III), (IV), (V), or (VI).

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates”. For example, a complex with water is known as a “hydrate”. Solvates of the compounds of Formulas (I), (II), and (III) and solvates of the salts of the compounds of Formulas (I), (II), (III), (IV), (V), or (VI), are included within the scope of the present invention.

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of Formula (I), (II), (III), (IV), (V), or (VI), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds defined in the first aspect which are pharmacologically active. Such derivatives may therefore be described as “prodrugs”. All protected derivatives and prodrugs of compounds defined in the first aspect are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 - 538 and in Topics in Chemistry, Chapter 31, pp 306 - 316 and in “Design of Prodrugs” by H. Bundgaard, Elsevier, 1985,

Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within the compounds of Formula (I), (II), (III), (IV), (V), or (VI). Suitable prodrugs for compounds of the invention include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals ketals, boronic esters and boronic acid anhydrides.

As described in International Patent Application Publication No. WO 2011/028596 and in International Patent Application Serial No. PCT/US2012/049681, both of which are hereby incorporated into the present application in their entireties, the compounds of Formulas (I), (II), (III), (IV), (V), or (VI), have been found to exhibit antiviral activity, specifically HCV inhibitory activity, and may therefore useful in treating or preventing viral infections, such as HCV infections, or diseases associated with such infections. In vitro studies have been performed which demonstrate the usefulness of compounds described herein as antiviral agents when administered in combination with a second therapeutic agent.

The present invention provides a method for treating and/or preventing viral infections, such as HCV infections, or diseases associated with such infections which method comprises administering to a subject, for example a human, in need thereof, a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue. Another embodiment of the present invention provides the above method further comprising administering a third therapeutic agent independently selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an

interferon, and a nucleoside analogue. Another embodiment of the present invention provides the above method further comprising administering a fourth therapeutic agent independently selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue. Another embodiment of the present invention provides the above method further comprising administering a fifth therapeutic agent independently selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

One embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), and an interferon. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI),, an interferon, and a nucleoside analogue. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), and a metabolic pathway inhibitor. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI),, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), and an HCV NS3/4A protease inhibitor. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), and an HCV NS5B polymerase inhibitor. Another embodiment of the

present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), an HCV NS3/4A protease inhibitor, and an HCV NS5B polymerase inhibitor. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), an HCV NS3/4A protease inhibitor, an interferon, and a nucleoside analogue. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula ((I), (II), (III), (IV), (V), or (VI)), a metabolic pathway inhibitor, an HCV NS3/4A protease inhibitor, an interferon, and a nucleoside analogue. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula ((I), (II), (III), (IV), (V), or (VI), an HCV NS5B polymerase inhibitor, an interferon, and a nucleoside analogue. Another embodiment of the present invention provides a method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula ((I), (II), (III), (IV), (V), or (VI), an HCV NS3/4A protease inhibitor, an HCV NS5B polymerase inhibitor, an interferon, and a nucleoside analogue.

In a specific embodiment of the present invention, the interferon is selected from the group consisting of interferon alfa-2a, peginterferon alfa-2a, interferon alfa-2b, peginterferon alfa-2b, an interferon alfa-2b analogue, interferon alpha-2b XL, interferon alfacon-1, interferon alfa-n1, interferon omega, HDV-interferon, peginterferon beta, peginterferon lambda, and interferon-alpha5. In another specific embodiment of the present invention, the interferon is selected from the group consisting of interferon alfa-2a, peginterferon alfa-2a, interferon alfa-2b, peginterferon alfa-2b, an interferon alfa-2b analogue, interferon alfacon-1, and interferon alfa n1.

In another specific embodiment of the present invention, the metabolic pathway inhibitor is ritonavir. In another specific embodiment of the present invention, the metabolic pathway inhibitor is ritonavir, which is administered at a daily dose of 100 mg. In another specific embodiment of the present invention, the metabolic pathway inhibitor is ritonavir, which is administered at a daily dose of 200 mg.

In another specific embodiment of the present invention, the nucleoside analogue is ribavirin. In another specific embodiment of the present invention, the nucleoside analogue is ribavirin, which is administered at a daily dose of 800 mg. In another specific embodiment of the present invention, the nucleoside analogue is ribavirin, which is

administered at a daily dose of 1000 mg. In another specific embodiment of the present invention, the nucleoside analogue is ribavirin, which is administered at a daily dose of 1200 mg.

In another specific embodiment of the present invention, HCV NS3/4A protease inhibitor is selected from the group consisting of boceprevir, telaprevir, simeprevir, danoprevir, narlaprevir, vaniprevir, and asunaprevir. In another specific embodiment of the present invention, HCV NS3/4A protease inhibitor is selected from the group consisting of boceprevir and telaprevir.

In another specific embodiment of the present invention, the compound of Formula (I) is methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate or a pharmaceutically acceptable salt thereof.

In another specific embodiment of the present invention, the compound of Formula (IV) is dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(biphenylene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate, or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference herein to therapy or treatment may include, but is not limited to prevention, retardation, prophylaxis, and cure of the disease. The present invention provides compounds and pharmaceutical compositions for the treatment and prevention of viral infections, such as HCV infections, as well as diseases associated with viral infections in living hosts. It will further be appreciated that references herein to treatment or prophylaxis of HCV infection include treatment or prophylaxis of HCV-associated disease such as liver fibrosis, cirrhosis and hepatocellular carcinoma.

Within the context of the present invention, the terms describing the indications used herein are classified in the Merck Manual of Diagnosis and Therapy, 17th Edition and/or the International Classification of Diseases 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention.

The compounds of Formulas (I), (II), (III), (IV), (V), or (VI), may be made by the processes described herein or by any method known to those skilled in the art.

The invention further provides pharmaceutical compositions comprising a compound of Formula (I), (II), (III), (IV), (V), or (VI), (hereinafter compound A) and one or more additional therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an

HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue (hereinafter compound B), and one or more pharmaceutically acceptable carriers, diluents, or excipients. Optionally, such pharmaceutical compositions may further comprise one or more additional therapeutic agent(s) independently selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue (hereinafter compound C, compound D, etc.). The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation, capable of pharmaceutical formulation, and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition comprising admixing a Compound A and Compound B, with one or more pharmaceutically acceptable carriers, diluents, or excipients. Such elements of the pharmaceutical compositions utilized may be presented in separate pharmaceutical combinations or formulated together in one pharmaceutical composition. Accordingly, the invention further provides a combination of pharmaceutical compositions one of which includes Compound A and one or more pharmaceutically acceptable carriers, diluents, or excipients and a pharmaceutical composition containing Compound B and one or more pharmaceutically acceptable carriers, diluents, or excipients. Optionally, the combination of pharmaceutical compositions may further comprise one or more additional pharmaceutical compositions, one of which includes Compound C and one or more pharmaceutically acceptable carriers, diluents, or excipients and optionally another which includes Compound D and one or more pharmaceutically acceptable carriers, diluents, or excipients.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. As is known to those skilled in the art, the amount of active ingredient per dose will depend on the condition being treated, the route of administration and the age, weight and condition of the patient. Preferred unit dosage compositions are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Compounds A, B, C, D, etc. may be administered by any appropriate route. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intraveneous, intradermal, intrathecal, and epidural). It will be appreciated that the preferred route may vary with, for example, the condition of the recipient of the combination. It will also be appreciated that each of the agents administered may be administered by the same or different routes and that any combination of compounds (e.g. Compounds A and B; Compounds A and C; Compounds A, B, and C) may be compounded together in a pharmaceutical composition.

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. Optional ingredients include other binders such as starch, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, polyethylene glycol, waxes

and the like. The powder mixture can be wet-granulated with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials, and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet-forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, compositions for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The agents for use according to the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds A and B may be employed in combination in accordance with the invention by administration simultaneously in a unitary pharmaceutical composition including both compounds. Alternatively, the combination may be administered separately in separate pharmaceutical compositions, each including one of the compounds A and B in a sequential manner wherein, for example, Compound A or Compound B is administered first and the other second. Such sequential administration may be close in time (e.g. simultaneously) or remote in time. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered parenterally and the other compound may be administered orally. Suitably, both compounds are administered orally. Optionally, Compound C may be administered in combination with either or both of Compounds A and B or may be administered separately in separate pharmaceutical composition. Compound C may be administered simultaneously with either or both of Compounds A and B or may be administered in a sequential manner relative to either or both of Compounds A and B. Optionally, Compound D may be administered in combination with any or all of Compounds A, B, and C or may be administered separately in separate pharmaceutical composition. Compound D may be administered simultaneously with any or all of Compounds A, B, and C or may be administered in a sequential manner relative to any or all of Compounds A, B, and C.

Thus, in one embodiment, one or more doses of Compound A are administered simultaneously or separately with one or more doses of Compound B. Unless otherwise defined, in all dosing protocols described herein, the regimen of compounds administered does not have to commence with the start of treatment and terminate with the end of

treatment, it is only required that the number of consecutive days in which both compounds are administered and the optional number of consecutive days in which only one of the component compounds is administered, or the indicated dosing protocol - including the amount of compound administered, occur at some point during the course of treatment.

In one embodiment, multiple doses of Compound A are administered simultaneously or separately with multiple doses of Compound B.

In another embodiment, multiple doses of Compound A are administered simultaneously or separately with one dose of Compound B.

In another embodiment, one dose of Compound A is administered simultaneously or separately with multiple doses of Compound B.

In another embodiment one dose of Compound A is administered simultaneously or separately with one dose of Compound B.

In all the above embodiments Compound A may be administered first or Compound B may be administered first.

The combinations may be presented as a combination kit. By the term "combination kit" or "kit of parts" as used herein is meant the pharmaceutical composition or compositions that are used to administer Compound A and Compound B according to the invention. Optionally, the kit may further comprise pharmaceutical composition or compositions that are used to administer Compound C and optionally Compound D. When Compound A and Compound B are administered simultaneously, the combination kit can contain Compound A and Compound B in a single pharmaceutical composition, such as a tablet, or in separate pharmaceutical compositions. Optionally, the kit may contain Compounds A, B, and C in a single pharmaceutical composition, such as a tablet, or any two of Compounds A, B, and C in a single pharmaceutical composition, or each of Compounds A, B, and C in a separate pharmaceutical composition. Optionally, the kit may contain Compounds A, B, C, and D in a single pharmaceutical composition, such as a tablet, or any three of Compounds A, B, C, and D in a single pharmaceutical composition, or any two of Compounds A, B, C, and D in a single pharmaceutical composition, or each of Compounds A, B, C, and D in a separate pharmaceutical composition. When Compounds A and B are not administered simultaneously, the combination kit will contain Compound A and Compound B in separate pharmaceutical compositions either in a single package or Compound A and Compound B in separate pharmaceutical compositions in separate packages. Optionally, the kit may contain Compounds A, B, and C in separate pharmaceutical compositions either in a single package or in separate packages. Optionally, the kit may contain Compounds A, B, C,

and D in separate pharmaceutical compositions either in a single package or in separate packages.

In one embodiment of the invention there is provided a kit of parts comprising components:

Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier.

In another embodiment of the invention there is provided a kit of parts comprising components:

Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier, wherein the components are provided in a form which is suitable for sequential, separate, and/or simultaneous administration.

In another embodiment of the invention there is provided a kit of parts comprising components:

a first container comprising Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

a second container comprising Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier, and a container means for containing said first and second containers.

In another embodiment of the invention there is provided a kit of parts comprising components:

Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier;

Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

Compound C in association with a pharmaceutically acceptable excipient, diluent, or carrier.

In another embodiment of the invention there is provided a kit of parts comprising components:

Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier;

Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

Compound C in association with a pharmaceutically acceptable excipient, diluent, or carrier, wherein the components are provided in a form which is suitable for sequential, separate, and/or simultaneous administration.

In another embodiment of the invention there is provided a kit of parts comprising components:

a first container comprising Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier;

a second container comprising Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

a third container comprising Compound C in association with a pharmaceutically acceptable excipient, diluent, or carrier, and a container means for containing said first, second, and third containers.

In another embodiment of the invention there is provided a kit of parts comprising components:

Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier;

Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier;

Compound C in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

Compound D in association with a pharmaceutically acceptable excipient, diluent, or carrier.

In another embodiment of the invention there is provided a kit of parts comprising components:

Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier;

Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier;

Compound C in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

Compound D in association with a pharmaceutically acceptable excipient, diluent, or carrier, wherein the components are provided in a form which is suitable for sequential, separate, and/or simultaneous administration.

In another embodiment of the invention there is provided a kit of parts comprising components:

a first container comprising Compound A in association with a pharmaceutically acceptable excipient, diluent, or carrier;

a second container comprising Compound B in association with a pharmaceutically acceptable excipient, diluent, or carrier;

a third container comprising Compound C in association with a pharmaceutically acceptable excipient, diluent, or carrier; and

a fourth container comprising Compound D in association with a pharmaceutically acceptable excipient, diluent, or carrier, and a container means for containing said first, second, third, and fourth containers.

Suitably the combinations of this invention are administered within a "specified period". By the term "specified period" as used herein is meant the interval of time between the administration of, for example, one of Compound A and Compound B and the other of Compound A and Compound B. Unless otherwise defined, the specified period can include simultaneous administration. When Compound A and Compound B are administered once a day, the specified period refers to administration of Compound A and Compound B during a single day. When one or both compounds are administered more than once a day, the specified period is calculated based on the first administration of each compound on a specific day. All administrations of a compound of the invention that are subsequent to the first during a specific day are not considered when calculating the specific period.

Suitably, if the compounds are administered within a "specified period" and not administered simultaneously, they are administered within about 24 hours of each other - in this case, the specified period will be about 24 hours; suitably they will be administered within about 12 hours of each other - in this case, the specified period will be about 12 hours; suitably they will be administered within about 11 hours of each other - in this case, the specified period will be about 11 hours; suitably they will be administered within about 10 hours of each other - in this case, the specified period will be about 10 hours; suitably

they will be administered within about 9 hours of each other - in this case, the specified period will be about 9 hours; suitably they will be administered within about 8 hours of each other - in this case, the specified period will be about 8 hours; suitably they will be administered within about 7 hours of each other - in this case, the specified period will be about 7 hours; suitably they will be administered within about 6 hours of each other - in this case, the specified period will be about 6 hours; suitably they will be administered within about 5 hours of each other - in this case, the specified period will be about 5 hours; suitably they will be administered within about 4 hours of each other - in this case, the specified period will be about 4 hours; suitably they will be administered within about 3 hours of each other - in this case, the specified period will be about 3 hours; suitably they will be administered within about 2 hours of each other - in this case, the specified period will be about 2 hours; suitably they will be administered within about 1 hour of each other - in this case, the specified period will be about 1 hour. As used herein, the administration of Compound A and Compound B in less than about 45 minutes apart is considered simultaneous administration.

Suitably, when the combination of the invention is administered for a "specified period", the compounds will be co-administered for a "duration of time". By the term "duration of time" as used herein is meant that each of the compounds of the invention are administered for an indicated number of consecutive days.

Regarding "specified period" administration: Suitably, each of the compounds will be administered within a specified period for at least one day - in this case, the duration of time will be at least one day; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 3 consecutive days - in this case, the duration of time will be at least 3 days; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 5 consecutive days - in this case, the duration of time will be at least 5 days; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 7 consecutive days - in this case, the duration of time will be at least 7 days; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 14 consecutive days - in this case, the duration of time will be at least 14 days; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 30 consecutive days - in this case, the duration of time will be at least 30 days; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 60 consecutive days - in this case, the duration of time will be at least 60 days; suitably, during the course of treatment, each of the compounds will be administered

within a specified period for at least 90 consecutive days - in this case, the duration of time will be at least 90 days; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 180 consecutive days - in this case, the duration of time will be at least 180 days; suitably, during the course of treatment, each of the compounds will be administered within a specified period for at least 365 consecutive days - in this case, the duration of time will be at least 365 days.

Further regarding "specified period" administration: Suitably, during the course of treatment, Compound A and Compound B will be administered within a specified period for from 1 to 4 days over a 7 day period, and during the other days of the 7 day period Compound A will be administered alone or optionally with Compound C and optionally Compound D. Suitably, this 7 day protocol is repeated for 2 cycles or for 14 days; suitably for 4 cycles or 28 days; suitably for 12 cycles or 84 days; suitably for continuous administration.

Suitably, during the course of treatment, Compound A and Compound B will be administered within a specified period for 1 day during a 7 day period, and during the other days of the 7 day period Compound A will be administered alone or optionally with Compound C and optionally Compound D. Suitably, this 7 day protocol is repeated for 2 cycles or for 14 days; suitably for 4 cycles or 28 days; suitably for 12 cycles or 84 days; suitably for continuous administration.

Suitably, if the compounds are not administered during a "specified period", they are administered sequentially. By the term "sequential administration", and derivates thereof, as used herein is meant that one of Compound A and Compound B is administered for two or more consecutive days and the other of Compound A and Compound B is subsequently administered for two or more consecutive days. Also, contemplated herein is a drug holiday utilized between the sequential administration of one of Compound A and Compound B and the other of Compound A and Compound B. As used herein, a drug holiday is a period of days after the sequential administration of one of Compound A and Compound B and before the administration of the other of Compound A and Compound B where neither Compound A nor Compound B is administered. Suitably the drug holiday will be a period of days selected from: 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, and 14 days.

Regarding sequential administration: Suitably, one of Compound A and Compound B is administered for from 2 to 30 consecutive days, followed by an optional drug holiday, followed by administration of the other of Compound A and Compound B for from 2 to 30 consecutive days. Suitably, one of Compound A and Compound B is administered for

from 2 to 21 consecutive days, followed by an optional drug holiday, followed by administration of the other of Compound A and Compound B for from 2 to 21 consecutive days. Suitably, one of Compound A and Compound B is administered for from 2 to 14 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of the other of Compound A and Compound B for from 2 to 14 consecutive days. Suitably, one of Compound A and Compound B is administered for from 3 to 7 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of the other of Compound A and Compound B for from 3 to 7 consecutive days.

Suitably, Compound B will be administered first in the sequence, followed by an optional drug holiday, followed by administration of Compound A. Suitably, Compound B is administered for from 2 to 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound A for from 2 to 21 consecutive days. Suitably, Compound B is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound A for from 3 to 21 consecutive days. Suitably, Compound B is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound A for from 3 to 21 consecutive days.

Suitably, Compound A will be administered first in the sequence, followed by an optional drug holiday, followed by administration of Compound B. Suitably, Compound A is administered for from 2 to 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound B for from 2 to 21 consecutive days. Suitably, Compound A is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound B for from 3 to 21 consecutive days. Suitably, Compound A is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound B for from 3 to 21 consecutive days.

It is understood that a “specified period” administration and a “sequential” administration can be followed by repeat dosing or can be followed by an alternate dosing protocol, and a drug holiday may precede the repeat dosing or alternate dosing protocol.

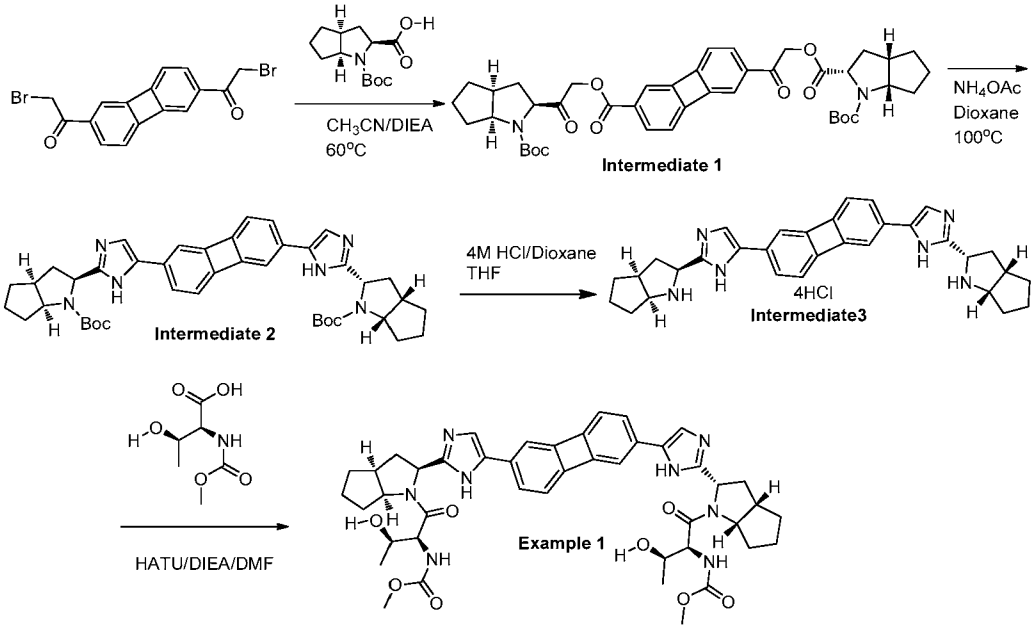
Suitably, the amount of Compound A (based on weight of unsalted/unsolvated amount) administered as part of the combination according to the present invention will be in the range of 0.01 to 100 mg per kilogram body weight of the recipient (e.g. a human) per day; suitably, the amount will be selected in the range of 0.1 to 30 mg per kilogram body weight per day; suitably, the amount will be selected in the range of 0.1 to 10 mg per kilogram body weight per day; suitably, the amount will be selected in the range of 0.5 to

10 mg per kilogram body weight per day. The desired dose may be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. In some cases the desired dose may be given on alternative days or other appropriate schedule, for example, weekly, or monthly. These sub-doses may be administered in unit dosage forms, for example, containing 0.5 to 100 mg, 5 to 1000 mg or 50 to 500 mg, or 20 to 500 mg, of active ingredient per unit dosage form.

The following non-limiting examples illustrate the present invention.

EXAMPLES

Preparation of Example I:



Intermediate 1: (2S,2'S,3aS,3a'S,6aS,6a'S)-O'2,O2-(biphenylene-2,6-diylbis(2-oxoethane-2,1-diyl)) 1-di-tert-butyl bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate)

1,1'-(2,6-Diphenylenediyl)bis(2-bromoethanone) (1.5g, 1.90 mmol) was dissolved in Acetonitrile (10 mL). (2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (1.215 g, 4.76 mmol) and DIEA (1mL, 5.71 mmol) was added and the solution was stirred at 65°C for 4h. The solid material was filtered and solvent was evaporated to provide the crude compound which was purified by isco column using 40g of silica cartridge with hexane/ethyl acetate (increasing gradient from 0% to 100% EA).

Yield : 92%; ES LC-MS *m/z* = 743 $(M+H)^+$;

1H NMR (400 MHz, *DMSO-d* 6) δ ppm 7.70 (m, 2 H), 7.40 (m, 2 H), 7.06 (m, 2 H), 5.49 (s, 4

H),4.39 (m, 2 H), 4.10 (m, 2 H), 2.67 (m, 3 H), 2.45 (m, 1 H), 2.33 (m, 1 H), 1.83 - 2.02 (m, 3 H), 1.73- 1.82 (m, 3 H), 1.68 (m, 4 H), 1.37 (m, 21 H).

Intermediate 2: (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(biphenylene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate)

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-O'2,O2-(biphenylene-2,6-diylbis(2-oxoethane-2,1-diyl)) 1-di-tert-butyl bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate) (1.3 g, 1.750 mmol, 92 % yield) in 1,4-Dioxane (10 mL) in a sealed tube was added ammonium acetate (0.147 g, 1.904 mmol). The reaction mixture was refluxed at 100°C for 10h. After cooling down, the solid at the bottom was filtered off and washed with ethyl acetate. The filtrate was evaporated and the residue was purified by flash column using 40g of silica cartridge with hexane/ethyl acetate (increasing gradient from 0% to 100% EA) to give the product as a brown solid.

Yield : 45%; ES LC-MS *m/z* = 703 $(M+H)^+$;

1H NMR (400 MHz, *DMSO-d6*) δ ppm 11.43 - 12.03 (m, 2 H), 7.40 (m, 2 H), 7.19 - 7.26 (m, 2H), 7.09 - 7.17 (m, 2 H), 6.69 - 6.87 (m, 2 H), 4.81 (m, 2 H), 4.15 (m, 2 H), 2.68 (m, 2 H), 2.30 -2.44 (m, 2 H), 1.87 - 2.02 (m, 3 H), 1.83 (m, 3 H), 1.63 (m, 4 H), 1.45 (m, 9 H), 1.28 - 1.38 (m, 4H), 1.24 (m, 9 H).

Intermediate 3: 2,6-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)biphenylene tetrahydrochloride

To the (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(biphenylene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate) (500 mg, 0.711 mmol) in Tetrahydrofuran (THF) (2ml) was slowly added HCl (3.56 ml, 14.23 mmol) in dioxane. The solution was stirred for 12h at rt and solvent was evaporated, ether (50mL) was added and the dark brown solid was filtered and dried in house vacuum (2h) which provided tetra-HCl salt of the amine which was used in the next step without further purification.

Yield : 84%; ES LC-MS *m/z* = 503 $(M+H)^+$;

1H NMR (400 MHz, *DMSO-d* 6) δppm 10.39 (m, 2 H), 9.51 (m, 2 H), 7.98 (s, 2 H), 7.43 (d, *J*=7.3 Hz, 2H), 7.31 (s, 2 H), 6.96 (d, *J*=7.3 Hz, 2 H), 4.84 (m, 2 H), 4.17 (m, 4 H), 2.99 (m, 2 H), 2.58 - 2.76 (m,2 H), 2.06 (m, 3 H), 1.87 - 2.00 (m, 1 H), 1.75 (m, 2 H), 1.65 (m, 6 H).

Example 1: dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(biphenylene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-hydroxy-1-oxobutane-2,1-diyl))dicarbamate

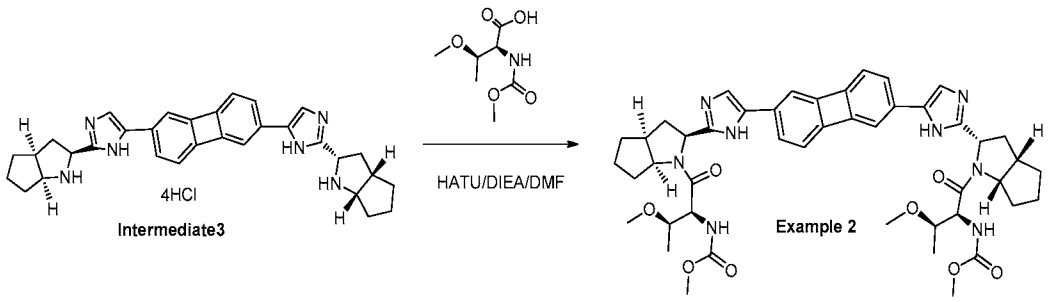
To the crude 2,6-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-

imidazol-5-yl)biphenylene (80 mg, 0.16 mmol) in N,N-Dimethylformamide (2ml) was added (2S,3R)-3-hydroxy-2-((methoxycarbonyl)amino)butanoic acid (71mg, 0.4mmol), HATU (60.5 mg, 0.16 mmol) and DIEA (0.06 ml, 0.32 mmol), the solution was stirred at rt for 4h. The reaction was partitioned between ethyl acetate (5mL) and sat. aq. $NaHCO_3$ (2mL). The organic phase was separated and dried over sodium sulphate and evaporated in vacuo to give the crude product which was purified on Gilson-HPLC, eluting with 5 to 80 % acetonitrile/ water (0.2 % $NH_3.H_2O$), to give the pure product.

Yield : 17%; ES LC-MS *m/z* = 821.3 $(M+H)^+$;

1H NMR (400 MHz, *DMSO-d6*) δ ppm 12.05 (m, 1 H), 11.65 (m, 1 H), 7.40 (s, 1 H), 7.26 (m, 2H), 7.20 (m, 2 H), 7.14 (s, 1 H), 7.09 (s, 1 H), 6.73 (m, 2 H), 5.54 (m, 1 H), 5.10 (m, 2 H), 4.80 (m, 2 H), 4.71 (m, 2 H), 4.32 (m, 1 H), 4.19 (m, 2 H), 3.74 (m, 2 H), 3.56 (s, 6 H), 2.77 (m, 2 H), 2.28 - 2.45 (m, 2 H), 2.05 (m, 4 H), 1.77 (m, 4 H),1.53 (m, 4 H), 0.99 - 1.13 (m, 7 H).

Preparation of Example 2:



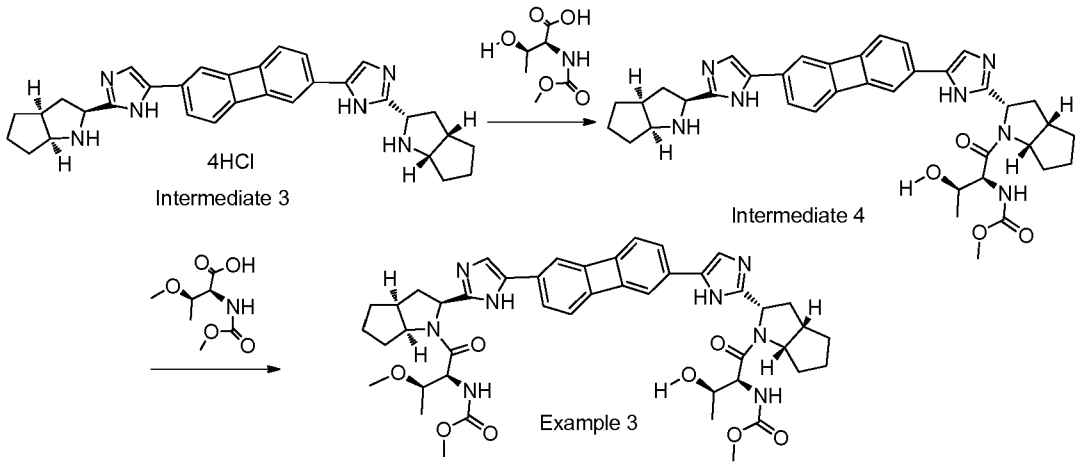
Example 2: dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(biphenylene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate

This example was made similar to the one explained for example 1 using (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid.

Yield : 12%; ES LC-MS *m/z* = 849.4 $(M+H)^+$;

1H NMR (400 MHz, *DMSO-d6*) δppm 11.60 – 12.11 (m, 2 H), 7.54 (m, 2 H), 7.39 (s, 2 H), 7.17 (m, 2 H), 7.05 – 7.13 (m, 2 H), 6.94 – 7.04 (m, 1 H), 6.72 (m, 2 H), 5.07 (m, 2 H),4.78 (m, 2 H), 4.39 (m, 1 H), 4.25 (m, 2 H), 3.49 – 3.58 (m, 7 H), 3.44 (m, 2 H), 3.17- 3.22 (m, 6 H), 2.75 (m, 2 H), 2.29 – 2.43 (m, 2 H), 2.09 (m, 3 H), 1.92 – 2.03 (m, 1 H), 1.80 – 1.89 (m, 2H), 1.68 – 1.79 (m, 2 H), 1.51 (m, 3 H), 0.95 – 1.14 (m, 6 H).

Preparation of Example 3:



Intermediate 4:Methyl ((2S,3R)-3-hydroxy-1-((2S,3aS,6aS)-2-(5-(6-(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)biphenylen-2-yl)-1H-imidazol-2-yl)hexahydrocyclopenta[b]pyrrol-1(2H)-yl)-1-oxobutan-2-yl)carbamate

This intermediate was prepared similar to the one explained for example 1 using 1eq. of (2S,3R)-3-hydroxy-2-((methoxycarbonyl)amino)butanoic acid.

Yield : 18%; ES LC-MS *m/z* = 662.3 $(M+H)^+$;

1H NMR (400 MHz, *DMSO-d6*) δppm 11.53 - 12.09 (m, 2 H), 7.41 (m, 1 H), 7.19 (m, 5 H), 6.74 (m, 2 H), 5.10 (s, 1 H), 4.71 (s, 1 H), 4.19 (s, 1 H), 3.98 (m, 1 H), 3.80 - 3.93 (m, 1 H), 3.67 - 3.78 (m, 1 H),3.60 - 3.68 (m, 1 H), 3.56 (s, 3 H), 2.69 (m, 1 H), 2.54 - 2.60 (m, 2 H), 2.35 (m, 2 H), 2.19 - 2.31 (m, 1H), 2.07 (m, 2 H), 1.78 (m, 3 H), 1.48 (m, 8 H), 1.07 (m, 4 H).

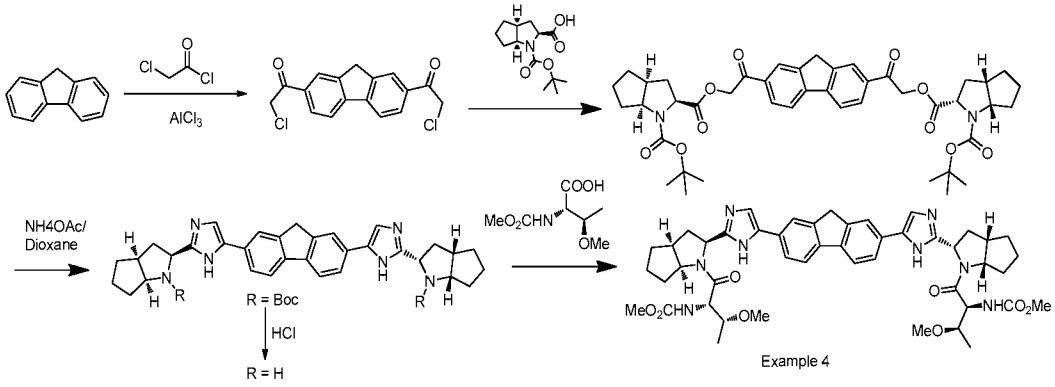
Example 3: Methyl [(1*S*,2*R*)-1-{[(2*S*,3a*S*,6a*S*)-2-[4-(6-{2-[(2*S*,3a*S*,6a*S*)-1-((2*S*,3*R*)-3-hydroxy-2-{[(methyloxy)carbonyl]amino}butanoyl)octahydrocyclopenta[*b*]pyrrol-2-yl]-1*H*-imidazol-4-yl}-2-biphenylenyl)-1*H*-imidazol-2-yl]hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]carbonyl}-2-(methyloxy)propyl]carbamate

This example was made similar to the one explained for example 1 using (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid.

Yield : 14%; ES LC-MS *m/z* = 835.4 $(M+H)^+$;

1H NMR (400 MHz, *DMSO-d6*) δppm 11.50 - 12.15 (m, 2 H), 7.55 (m, 1 H), 7.41 (s, 1 H), 7.19 - 7.35 (m, 3H), 7.09 (s, 1 H), 6.74 (m, 2 H), 5.09 (m, 1 H), 4.80 (m, 1 H), 4.65 - 4.76 (m, 1 H), 4.42 (m, 1 H),4.28 (s, 1 H), 4.13 - 4.25 (m, 1 H), 3.82 - 4.10 (m, 1 H), 3.74 (m, 1 H), 3.56 (s, 6 H), 3.40 (s, 2 H), 3.36 -3.38 (m, 2 H), 3.24 - 3.32 (m, 2 H), 3.17 - 3.24 (m, 1 H), 2.75 (s, 2 H), 2.57 (m, 1 H), 2.47 (m, 1H), 2.35 (m, 1 H), 2.09 (s, 3 H), 2.01 (s, 1 H), 1.77 (m, 4 H), 1.54 (m, 4 H), 1.21 (s, 1 H), 1.07 (m, 5 H).

Preparation of Example 4:



Example 4

1,1'-(9H-fluorene-2,7-diyl)bis(2-chloroethane)

To a stirred solution of 2-chloroacetyl chloride (1.589 mL, 19.97 mmol) and aluminum trichloride (2.66 g, 19.97 mmol) in dichloromethane (DCM) (20 mL) 9H-fluorene (0.83 g, 4.99 mmol) in dichloromethane (DCM) (20 mL) was added dropwise over 5 min at r.t. and left stirring for 2 h. The reaction mixture was then added to a mixture of methanol (50 mL) and H_2O (50 mL) chilled to -5°C. The slurry was warmed to ambient, stirred for 30-60 min and the solids collected. The solids were washed well with H_2O and dried at 50-60°C to constant weight. Yield: 1g, 54.6%; ES LC-MS *m/z* = 320.7 ($M+H^+$);
1H NMR (400 MHz, *DMSO-d6*) δppm 8.26 (s, 2H), 8.22 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 8.0 Hz, 2H), 5.27 (s, 4H), 4.14 (s, 2H)

(2S,2'S,3aS,3a'S,6aS,6a'S)-O'2,O2-((9H-fluorene-2,7-diyl)bis(2-oxoethane-2,1-diyl)) 1-di-tert-butyl bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate)

1,1'-(9H-fluorene-2,7-diyl)bis(2-chloroethanone) (1 g, 2.73 mmol), (2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (1.461 g, 5.72 mmol) in acetonitrile (45 mL), and DIPEA (2.86 mL, 16.35 mmol) were mixed and stirred for 6 h at 70 °C. The reaction mixture was then filtered to remove the insoluble solids, which were washed with additional acetonitrile (2 x 5 mL). The organic mixture was reduced to ~20 mL and added to briskly stirring H_2O (100 mL). The resulting slurry was cooled to 0-5 °C, and aged for 2 h. The solids were collected by filtration, washed with H_2O, and dried at 50-60 °C to constant weight. Yield: 2.1g, 71.3%; ES LC-MS *m/z* = 755.4 ($M-H^+$);

(2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate)

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-O'2,O2-((9H-fluorene-2,7-diyl)bis(2-oxoethane-2,1-diyl)) 1-di-tert-butyl bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate) (2 g, 1.850 mmol) in dry 1,4-dioxane (18.50 mL) was added ammonium acetate (3.56 g, 46.2 mmol) (25 equiv.). The reaction was refluxed for 6 h. The reaction was cooled slightly then hot filtered and concentrated. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol in DCM. Fractions were concentrated to give the title compound a brown solid.

Yield: 900 mg, 59%; ES LC-MS *m/z* = 715.4($M-H^+$);

2,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9H-fluorene, 4 Hydrochloride

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate) (900 mg, 1.092 mmol) in dry 1,4-dioxane (10mL) and methanol (2 mL) was added HCl (4M in 1,4-dioxane, 7.59 mL, 30.4 mmol). The reaction was stirred for 1 h, and then the solid was collected by filtration. The solid was washed twice with 1, 4-dioxane and twice with ether. The solid was dried to give a brown solid.

Yield: 600 mg, 83%; ES LC-MS *m/z* = 517.4 ($M+H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 10.60 (br. s., 2H), 10.01 (br. s., 2H), 7.93 - 8.33 (m, 8H), 4.97 (br. s., 2H), 4.21 (br. s.2H), 4.10 (s, 2H), 2.91 - 3.09 (m, 2H), 2.62 - 2.79 (m, 2H), 1.91 - 2.22 (m, 6H), 1.73 - 1.84 (m, 2H), 1.61 - 1.72 (m, 6H)

Example 4: dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate:

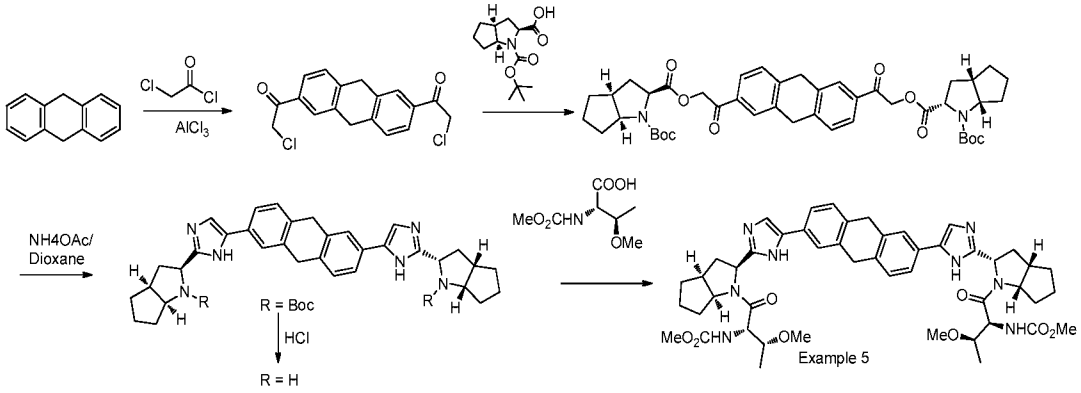
To a stirred solution of (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid (177 mg, 0.928 mmol) in ethanol (5.5 mL) was added DIPEA (0.791 mL, 4.53 mmol) and 2,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9H-fluorene, 4 hydrochloride (300 mg, 0.453 mmol). This was placed in an ice bath and T3P 50% in ethyl acetate (1.078 mL, 1.811 mmol) was added slowly maintaining the reaction temp below 10 °C. The reaction was stirred at 0 °C for 1 h. The reaction was filtered and the ethanol removed from the filtrate by rotary evaporation. The residue was dissolved in EtOAc (20mL) and washed twice with 1M sodium carbonate, twice with sat ammonium chloride and then brine. The organics were dried over Mg_2SO_4 and concentrated to give a brown solid. This crude material was purified on silica gel

eluted with 0-7% 2M ammonia in methanol to DCM. The desired fractions were combined and concentrated to give a brown solid.

Yield: 65 mg, 15.8%; ES LC-MS *m/z* = 861.6 ($M-H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 11.30 - 12.49 (m, 2H), 6.93 - 8.00 (m, 10H), 5.10 (t, J = 7.5 Hz, 2H), 4.80 (q, J = 7.6Hz, 2H), 4.33 - 4.49 (m, 1H), 4.15 - 4.33 (m, 2H), 3.83 - 4.03 (m, 2H), 3.50 - 3.59 (m, 8H), 3.12 - 3.27 (m, 6H), 2.58 - 2.82 (m, 2H), 2.30 - 2.45 (m, 2H), 1.97 - 2.21 (m, 4H), 1.69 - 1.95 (m, 4H), 1.43 - 1.65 (m, 4H), 0.95 - 1.28 (m, 7H).

Preparation of Example 5



1,1'-(9,10-dihydroanthracene-2,6-diyl)bis(2-chloroethanone)

To a stirred solution of 2-chloroacetyl chloride (3.53 mL, 44.4 mmol) and aluminum trichloride (5.92 g, 44.4 mmol) in dichloromethane (DCM) (50 mL), 9,10-dihydroanthracene (2g, 11.10 mmol) in dichloromethane (DCM) (50 mL) was added dropwise over 5 min at r.t. and left stirring for 1 h. The reaction mixture was then added to a mixture of methanol (100mL) and H_2O (100mL) chilled to -5°C. The slurry was warmed to ambient temperature, stirred for 30-60 min. and the solids were collected and were washed well with H_2O and dried at 50-60°C to constant weight.

Yield: 2.2g, 58.9%; ES LC-MS *m/z* = 334.9 ($M+H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 7.95 (s, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.52 (d, 2H), 5.17 (s, 4H), 4.08 (s, 4H)

(2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((9,10-dihydroanthracene-2,6-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate)

1,1'-(9,10-dihydroanthracene-2,6-diyl)bis(2-chloroethanone) (2g, 6.00 mmol), (2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (3.22 g, 12.60 mmol), and DIPEA (6.29 mL, 36.0 mmol) were mixed in acetonitrile (90 mL)and stirred 6 h at 70 °C. The reaction mixture was then filtered to remove the insoluble solids, which were washed

with additional acetonitrile (2 x10 mL). The organic mixture was reduced to ~40 mL and added to H_2O (200 mL). The resulting slurry was cooled to 0-5 °C, and aged for 2 h. The solids were collected by filtration, washed with H_2O, and dried at 50-60 °C to constant weight.
Yield: 2.5 g, 49.2 %; ES LC-MS *m/z* = 769.3 ($M-H^+$);

(2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9,10-dihydroanthracene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate)

To a stirred solution of (2S,3aS,6aS)-2-(2-(6-(2-(((2R,3aS,6aS)-1-(tert-butoxycarbonyl)octahydropentalene-2-carbonyl)oxy)acetyl)-9,10-dihydroanthracen-2-yl)-2-oxoethyl) 1-tert-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate (2.5g, 2.95 mmol) in dry 1,4-dioxane (29.5 mL) was added ammonium acetate (5.69 g, 73.9 mmol). The reaction was refluxed for 6 h. The reaction was cooled slightly then hot filtered and concentrated. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol in DCM. The fractions that were clean were combined and concentrated to give a brown solid.
Yield: 400 mg, 17.78%; ES LC-MS *m/z* = 731.4($M+H^+$);

2,6-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9,10-dihydroanthracene, 4 Hydrochloride

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9,10-dihydroanthracene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate) (400mg, 0.547 mmol) in dry 1,4-dioxane (5mL) and methanol (1 mL) was added HCl (4M in 1,4-dioxane, 3.80 mL, 15.21 mmol). The reaction was stirred for 1 h then the solid was collected by filtration. The solid was washed twice with 1, 4-dioxane and twice with ether. The solid was dried to give a yellow solid.
Yield: 250 mg, 66.8%; ES LC-MS *m/z* = 531.4 ($M+H^+$);
1H NMR (400 MHz, *DMSO-d6*) δppm 10.53 (br. s., 2H), 9.81 (br. s., 2H), 8.12 (s, 2H), 7.90 (s, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.45 - 7.58 (m, 2H), 4.90 (br. s., 2H), 4.19 (br. s., 2H), 4.02 (s, 4H), 2.90 - 3.04 (m, 2H), 2.61 - 2.75 (m, 2H), 1.93 - 2.17 (m, 6H), 1.73 - 1.84 (m, 2H), 1.61 - 1.71 (m, 6H)

Example 5: dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(9,10-dihydroanthracene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate:

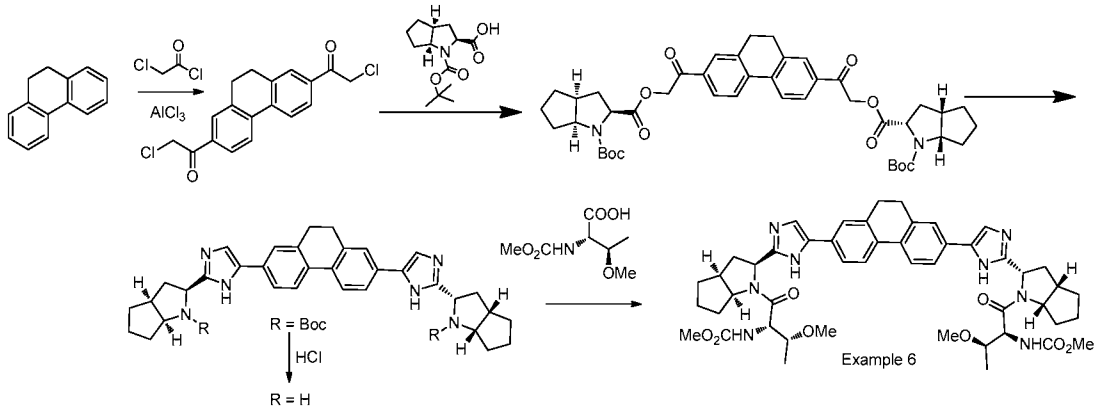
To a stirred solution of (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid (130 mg, 0.682 mmol) in Ethanol (5 mL) was added DIPEA (0.581 mL, 3.33 mmol) and 2,6-

bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9,10-dihydroanthracene, 4 Hydrochloride (225 mg, 0.333 mmol). This was placed in an ice bath and T3P 50% in ethyl acetate (0.792 mL, 1.330 mmol) was added slowly maintaining the reaction temp below 10 °C. The reaction was stirred at 0 °C for 1h. The reaction was filtered and the ethanol was removed from the filtrate by rotary evaporation. The residue was dissolved in EtOAc(20mL) and washed twice with 1M sodium carbonate, twice with sat ammonium chloride and then brine. The organics were dried over Mg_2SO_4 and concentrated to give a pale yellow solid. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol to DCM. The desired fractions were combined and concentrated to give a pale yellow solid.

Yield: 29 mg - 9.45%; ES LC-MS *m/z* = 875.4 ($M-H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 11.96 - 12.21 (m, 1H), 11.66 (br. s., 1H), 6.93 - 7.75 (m, 10H), 5.06 - 5.18 (m, 2H), 4.71 - 4.89 (m, 2H), 4.16 - 4.34 (m, 2H), 3.84 - 3.95 (m, 4H), 3.65 (s, 1H), 3.52 - 3.60 (m, 9H), 3.24 - 3.27 (m, 1H), 3.18 - 3.22 (m, 4H), 2.75 (br. s., 2H), 2.31 - 2.43 (m, 2H), 1.97 - 2.20 (m, 4H), 1.70 - 1.95 (m, 4H), 1.41 - 1.68 (m, 4H), 0.97 - 1.27 (m, 7H).

Preparation of Example 6



1,1'-(9,10-dihydrophenanthrene-2,7-diyl)bis(2-chloroethanone)

To a stirred solution of 2-chloroacetyl chloride (1.765 mL, 22.19 mmol) and aluminum trichloride (2.96 g, 22.19 mmol) in 1,2-dichloroethane (DCE) (20 mL), 9,10-dihydrophenanthrene (1 g, 5.55 mmol) in 1,2-dichloroethane (DCE) (20 mL) was added dropwise over 5 min at r.t. and the reaction mixture was stirred for 1 h at r.t. and 1 h at 60 °C. The reaction mixture was cooled to r.t. then added to a mixture of methanol (50 mL) and H_2O (50 mL) and chilled to -5 °C. The slurry was warmed to ambient, stirred for 30-60 min and the solids collected. The solids were washed well with H_2O and dried at 50-60 °C to constant weight.

Yield: 500 mg, 26.5%; ES LC-MS *m/z* = 333.2 ($M+H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 8.09 - 8.14 (m, 2H), 7.92 - 7.99 (m, 4H), 5.24 (s, 4H), 2.95 (s, 4H).

(2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((9,10-dihydrophenanthrene-2,7-diyl)bis (2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate)

1,1'-(9,10-dihydrophenanthrene-2,7-diyl)bis(2-chloroethanone) (500mg, 1.501 mmol),(2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (805 mg, 3.15 mmol) and DIPEA (1.572 mL, 9.00 mmol) were mixed in acetonitrile (22 mL), and stirred 6 h at 70 °C. The reaction mixture was then filtered to remove the insoluble solids, which were washed with additional acetonitrile (2 x5 mL). The organic mixture was reduced to ~10 mL. and added to H_2O (50 mL). The resulting slurry was cooled to 0-5 °C, and aged for 2 h. The solids were collected by filtration, washed with H_2O, and dried at 50 - 60 °C to constant weight.

Yield: 1g, 86 %; ES LC-MS *m/z* = 771.3 ($M+H^+$);

(2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9,10-dihydrophenanthrene-2,7-diyl)bis (1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate)

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((9,10-dihydrophenanthrene-2,7-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b] pyrrole-1,2(2H)-dicarboxylate) (1.0 g, 1.297 mmol) in dry1,4-dioxane (12.97 mL) was added ammonium acetate (2.500 g, 32.4 mmol) (25 equiv.). The reaction was refluxed for 6 h. The reaction was cooled slightly then hot filtered and concentrated to give a brown solid. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol to DCM. The fractions that were clean were combined and concentrated to give a brown solid.

Yield: 800 mg - 81%; ES LC-MS *m/z* = 731.4($M+H^+$);

2,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9,10-dihydrophenanthrene, 4 Hydrochloride

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9,10-dihydrophenanthrene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b] pyrrole-1(2H)-carboxylate) (800 mg, 1.094 mmol) in dry 1,4-dioxane (10 mL) and methanol (2.000 mL) was added HCl (4M in 1,4-dioxane, 7.61 mL, 30.4 mmol). The reaction was stirred for 1 h, and then the solid was collected by filtration. The solid was washed twice with 1,4-dioxane and twice with ether and the solid was dried to give a brown solid.

Yield: 600 mg - 67.3%; ES LC-MS *m/z* = 529.3 ($M+H^+$);

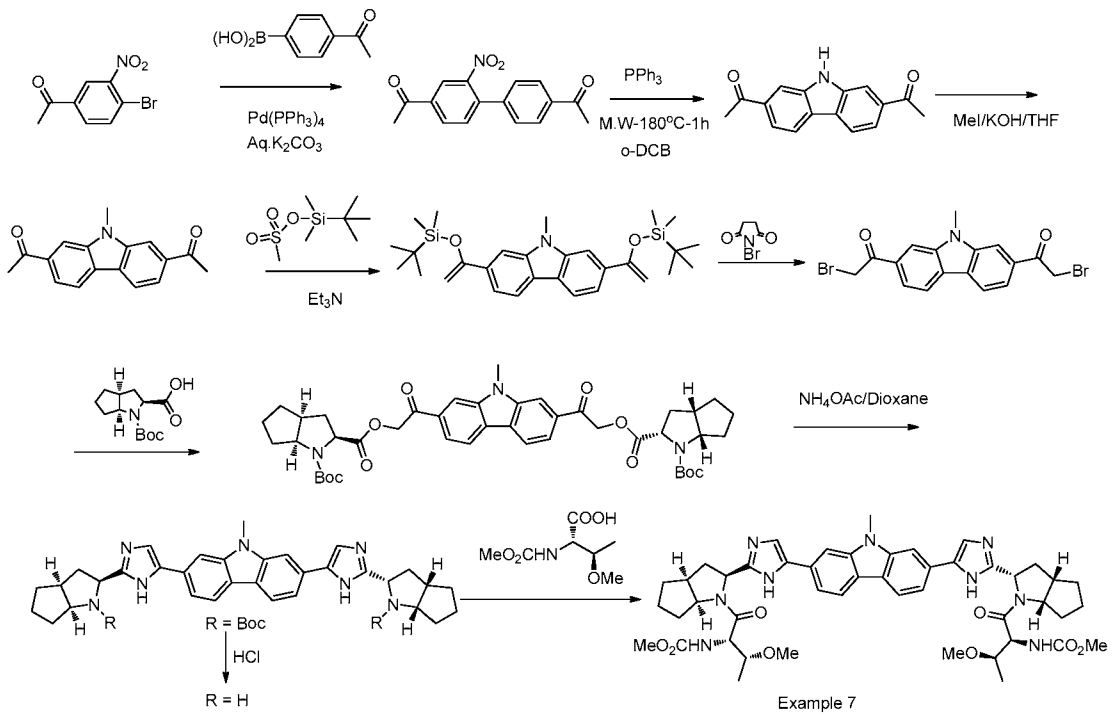
1H NMR (400 MHz, *DMSO-d6*) δppm 10.36 (br. s., 1H), 9.49 (br. s., 1H), 8.05 (br. s., 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.79 - 7.87 (m, 4H), 4.83 (br. s., 2H), 4.16 (br. s., 4H), 2.96 (br. s., 2H), 2.91 (s, 4H), 2.62 - 2.74 (m, 2H), 1.87 - 2.16 (m, 6H), 1.75 (br. s., 2H), 1.57 - 1.70 (m, 6H).

Example 6: Dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(9,10-dihydrophenanthrene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate

To a stirred solution of (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid (174 mg, 0.909 mmol) in ethanol (6 mL) was added DIPEA (0.774 mL, 4.43 mmol) and 2,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9,10-dihydrophenanthrene, 4 hydrochloride (300 mg, 0.443 mmol). This was placed in an ice bath and T3P 50% in ethyl acetate (1.056 mL, 1.774 mmol) was added slowly maintaining the reaction temp below 10 °C. The reaction was stirred at 0 °C for 1 h. The reaction was filtered and the ethanol removed from the filtrate by rotary evaporation. The residue was dissolved in EtOAc (20 mL) and washed twice with 1M sodium carbonate, twice with sat ammonium chloride and then brine. The organics were dried over Mg_2SO_4 and concentrated to give a pale yellow solid. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol to DCM. The desired fractions were combined and concentrated to give a pale yellow solid.

Yield: 39 mg, 11.96%; ES LC-MS *m/z* = 875.6 ($M-H^+$);
1H NMR (400 MHz, *DMSO-d6*) δppm 11.99 - 12.24 (m, 1H), 11.70 (br. s., 1H), 7.43 - 7.83 (m, 10H), 5.03 - 5.17 (m, 2H), 4.80 (d, J = 7.6 Hz, 2H), 4.33 - 4.49 (m, 1H), 4.16 - 4.33 (m, 2H), 3.49 - 3.58 (m, 9H), 3.17 - 3.25 (m, 6H), 2.71 - 2.85 (m, 5H), 2.29 - 2.43 (m, 2H), 1.97 - 2.13 (m, 4H), 1.67 - 1.93 (m, 4H), 1.38 - 1.66 (m, 4H), 0.95 -1.15 (m, 7H).

Preparation of Example 7



1,1'-(2-nitro-[1,1'-biphenyl]-4,4'-diyl)diethanone

1-(4-bromo-3-nitrophenyl)ethanone (2 g, 8.20 mmol) and (4-acetylphenyl)boronic acid (2.016 g, 12.29 mmol), aq.K_2CO_3 (2M, 12.08 mL, 24.17 mmol) and $Pd(PPh_3)_4$ (0.33 g, 0.286 mmol) were dissolved in toluene (40 mL) and heated at 110 °C for 2 days. The crude product was extracted with DCM and purified on silica gel (0-100% EtOAc/Hexane). Fractions were concentrated to give the title compound as a white solid.

Yield: 1.5g, 64%; ES LC-MS *m/z* = 284.1 ($M+H^+$);

^{1}H NMR (CHLOROFORM-d) δppm 8.45 (d, J = 1.8 Hz, 1H), 8.20 (dd, J = 8.0, 1.8 Hz, 1H), 8.00 - 8.05 (m, 2H), 7.54 - 7.58 (m, 1H), 7.39 - 7.44 (m, 2H), 2.68 (s, 3H), 2.63 (s, 3H).

1,1'-(9H-carbazole-2,7-diyl)diethanone

The mixture of triphenylphosphine (3.47 g, 13.24 mmol) and 1,1'-(2-nitro-[1,1'-biphenyl]-4,4'-diyl)diethanone (1.5g, 5.30 mmol) in 1,2-dichlorobenzene (o-DCB) (15.90 mL) was heated at 180 °C under microwave irradiation for 1 h. The reaction mixture was cooled and poured in to the hexane (50 mL). Most of the impurities were removed by precipitation from hexane. The compound was further purified on silica gel ((0-100% EtOAc/Hexane). Fractions were concentrated to give the title compound as a yellow solid.

Yield: 1g, 74.4%; ES LC-MS *m/z* = 252.1($M+H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 11.79 (s, 1H), 8.31 (d, J = 8.2 Hz, 2H), 8.10 - 8.18 (m, 2H), 7.81 (dd, J = 8.2, 1.4 Hz, 2H), 2.68 (s, 6H).

1,1'-(9-methyl-9H-carbazole-2,7-diyl)diethanone

Iodomethane (0.747 mL, 11.94 mmol) was added to the mixture of 1,1'-(9H-carbazole-2,7-diyl)diethanone (1 g, 3.98 mmol) and potassium hydroxide (0.223 g, 3.98 mmol) in THF (20 mL) and stirred for overnight at room temperature. The solvent was then removed under reduced pressure and the crude was extracted with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated to get the pure product as yellow solid.

Yield: 1g , 93%; ES LC-MS *m/z* = 266.1($M+H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 8.33 (d, J = 8.2 Hz, 2H), 8.25 (s, 2H), 7.79 - 7.87 (m, 2H), 4.03 (s, 3H), 2.71 (s, 6H).

2,7-bis(1-((tert-butyldimethylsilyl)oxy)vinyl)-9-methyl-9H-carbazole

To a mixture of 1,1'-(9-methyl-9H-carbazole-2,7-diyl)diethanone (400mg, 1.508 mmol) and triethylamine (848 mL, 6034 mmol) in toluene (12 mL), tert-butyldimethylsilyl trifluoromethanesulfonate (1.040 mL, 4.52 mmol) was added at 0 °C. The reaction mixture was stirred for 10 min at the same temperature and then stirred for 3 h at room temperature. The reaction mixture was then extracted with ethyl acetate, the organic layer was dried over Na_2SO_4 and it was concentrated to dryness to give the desired product.

Yield: 700 mg - 94%;

1H NMR (CHLOROFORM-d)) δppm 7.95 - 8.00 (m, 2H), 7.66 (d, J = 1.0 Hz, 2H), 7.47 - 7.51 (m, 2H), 5.03 (d, J = 1.6 Hz, 2H), 4.50 (d, J = 1.6 Hz, 2H), 3.84 (s, 3H), 1.05 (s, 18H), 0.24 (s, 12H).

1,1'-(9-methyl-9H-carbazole-2,7-diyl)bis(2-bromoethanone)

NBS (505 mg, 2.83 mmol) was added to 2,7-bis(1-((tert-butyldimethylsilyl)oxy)vinyl)-9-methyl-9H-carbazole (700mg, 1.417 mmol) in THF (20 mL) at 0

°C and the reaction mixture was stirred at same temperature for 30 min. The yellow suspension was filtered and dried to give the desired product.

Yield: 500 mg, 83%;

1H NMR (400 MHz, *DMSO-d6*) δppm 8.34 - 8.44 (m, 4H), 7.89 (dd, J = 8.3, 1.3 Hz, 2H), 5.10 (s, 4H), 4.06 (s, 4H).

(2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((9-methyl-9H-carbazole-2,7-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate)

1,1'-(9-methyl-9H-carbazole-2,7-diyl)bis(2-bromoethanone) (500 mg, 1.182 mmol), (2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (634 mg, 2.482 mmol) and DIPEA (1.238 mL, 7.09 mmol) was taken in acetonitrile (20 mL), and was stirred for 3 h at 70 °C. The reaction mixture was filtered to remove the insoluble solids, which were washed with additional acetonitrile (2 x 5 mL). The organic mixture is reduced to ~10 mL and added to H_2O (50 mL). The resulting slurry is cooled to 0-5 °C, and aged for 2 h. The solids were collected by filtration, washed with H_2O, and dried at 50-60 °C to constant weight.

Yield: 800 mg, 83%; ES LC-MS *m/z* = 772.6 ($M+H^+$);

(2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9-methyl-9H-carbazole-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate)

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((9-methyl-9H-carbazole-2,7-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate) (800mg, 0.985 mmol) in dry 1,4-dioxane (10 mL) was added ammonium acetate (1897 mg, 24.61 mmol) (25 equiv.). The reaction was refluxed for 6 h. The reaction was cooled slightly, filtered and concentrated. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol in DCM. The fractions that were clean were combined and concentrated to give a brown solid.

Yield: 250 mg, 26.4%; ES LC-MS *m/z* = 732.7 ($M+H^+$);

9-methyl-2,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9H-carbazole, 4 Hydrochloride

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9-methyl-9H-carbazole-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate) (250 mg, 0.260 mmol) in dry 1,4-dioxane (3mL) and methanol (0.600 mL) was added HCl (4M in 1,4-dioxane, 1.804 mL, 7.22 mmol). The reaction was stirred for 1h then the solid was collected by filtration. The solid was washed twice with 1,4-dioxane and twice with ether. The solid was dried to give a brown solid.

Yield: 150 mg, 69.9%; ES LC-MS *m/z* = 532.3 ($M+H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 10.39 (br. s., 2H), 9.60 (br. s., 2H), 8.20 - 8.29 (m, 4H), 8.17 (br. s., 2H), 7.71 - 7.76 (m, 2H), 4.88 (br. s., 2H), 4.18 (br. s., 2H), 3.94 - 4.00 (m, 3H), 2.98 (br. s., 2H), 2.63 - 2.77 (m, 2H), 1.89 - 2.21 (m, 6H), 1.75 (br. s., 2H), 1.58 - 1.70 (m, 6H).

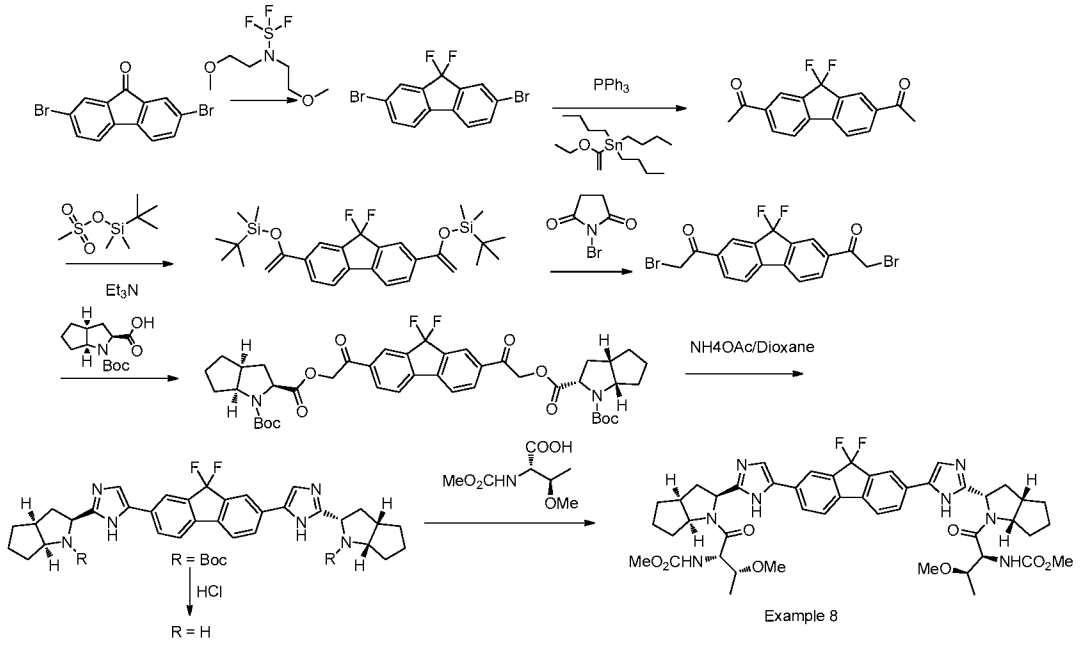
Example 7: dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(9-methyl-9H-carbazole-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate

To a stirred solution of (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid (87 mg, 0.454 mmol) in ethanol (3 mL) was added DIPEA (0.387 mL, 2.214 mmol) and 9-methyl-2,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)-9H-carbazole, 4 Hydrochloride (150mg, 0.221 mmol). This was placed in an ice bath and T3P 50% in ethyl acetate (0.527 mL, 0.886 mmol) was added slowly maintaining the reaction temperature below 10 °C. The reaction was stirred at 0 °C for 1 h. The reaction was filtered and the ethanol removed from the filtrate by rotary evaporation. The residue was dissolved in EtOAc(10 mL) and washed twice with 1M sodium carbonate, twice with sat ammonium chloride and then brine. The organics were dried over Mg_2SO_4 and concentrated to give a brown solid. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol to DCM. The desired fractions were combined and concentrated to give a pale yellow solid.

Yield: 25mg – 15.53%; ES LC-MS *m/z* = 876.5 ($M-H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 11.89 - 12.51 (m, 1H), 11.68 (br. s., 1H), 7.25 - 8.19 (m, 10H), 4.98 - 5.22 (m, 2H), 4.70 - 4.88 (m, 2H), 4.34 - 4.45 (m, 1H), 4.16 - 4.33 (m, 2H), 3.77 - 3.93 (m, 3H), 3.49 - 3.55 (m, 8H), 3.13 - 3.24 (m, 6H), 2.62 - 2.83 (m, 2H), 2.28 - 2.42 (m, 2H), 1.95 - 2.21 (m, 4H), 1.66 - 1.93 (m, 4H), 1.36 - 1.65 (m, 4H), 0.94 - 1.19 (m, 7H).

Preparation of Example 8



2,7-dibromo-9,9-difluoro-9H-fluorene

Deoxofluor (8 mL, 43.4 mmol) was added to 2, 7-dibromo-9H-fluoren-9-one (1g, 2.96 mmol) followed by two drops of ethanol. The reaction mixture was heated at 90 ^{O}C for 2 days. The mixture was cooled and poured in to ice water then neutralized with saturated sodium bicarbonate solution. The reaction mixture was extracted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (Na_2SO_4) and concentrated. The crude was purified on silica gel eluted with 0-20 % ethyl acetate in hexane. The desired fractions were concentrated to give a white solid.

Yield: 900 mg, 84%;

^{1}H NMR (400 MHz,CHLOROFORM-d) δppm 7.74 (d, J = 1.6 Hz, 2H), 7.60 (dd, J = 7.7, 1.3 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H).

1,1'-(9,9-difluoro-9H-fluorene-2,7-diyl)diethanone

A mixture of 2,7-dibromo-9,9-difluoro-9H-fluorene (900mg, 2.500 mmol), Tributyl(1-ethoxyvinyl)tin (3.38 mL, 10.00 mmol) and $Pd(Ph_3P)_4$ (289 mg, 0.250 mmol) in 1,4-dioxane (25mL) were degassed with nitrogen for 10 min then it was heated at 90 ^{o}C for overnight under nitrogen. The reaction mixture was cooled to room temperature and 15 mL of 10 % HCl was added then stirred for 1 h. The mixture was extracted with ethyl acetate and the organic layer was washed with water and brine. The organics were dried (Na_2SO_4) and concentrated. The crude material was purified on silica gel using 0-100 % ethyl acetate in hexane. The desired fractions were concentrated to give a white solid.

Yield: 600mg, 84%; ES LC-MS *m/z* = 287.1($M+H^+$);

^{1}H NMR (CHLOROFORM-d) δppm 8.22 (d, J = 1.0 Hz, 2H), 8.14 (d, J = 8.0 Hz, 2H), 7.73 (d, 2H), 2.65 (s, 6H).

(((9,9-difluoro-9H-fluorene-2,7-diyl)bis(ethene-1,1-diyl))bis(oxy))bis(tert-butyldimethyl silane)

To a mixture of 1,1'-(9,9-difluoro-9H-fluorene-2,7-diyl)diethanone (600mg, 2.096 mmol) and triethylamine (1.178 mL, 8.38 mmol) in toluene (20 mL) tert-butyldimethylsilyltrifluoromethanesulfonate (1.358 mL, 6.29 mmol) was added at 0 ^{O}C. The reaction mixture was stirred for 10 min at the same temperature and then stirred for 3 h at room temperature. The reaction mixture was then extracted with ethyl acetate, the organic layer was dried over Na_2SO_4 and it was concentrated to dryness to give the desired product.

Yield: 960 mg, 89%;

^{1}H NMR (400 MHz,CHLOROFORM-d) δppm 7.83 (d, J = 1.2 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 4.95 (d, J = 2.0 Hz, 2H), 4.47 (d, J = 2.1 Hz, 2H), 1.00 (s, 18H), 0.21 (s, 12H).

1,1'-(9,9-difluoro-9H-fluorene-2,7-diyl)bis(2-bromoethanone)

NBS (680 mg, 3.82 mmol) was added to (((9,9-difluoro-9H-fluorene-2,7-diyl)bis(ethene-1,1-diyl))bis(oxy))bis(tert-butyldimethylsilane) (0.800 mL, 1.865 mmol) in THF (20 mL) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The organic mixture is reduced to 10 mL then the white suspension was filtered and dried to give the desired product.

Yield: 500 mg, 60.4%;

^{1}H NMR (400 MHz, CHLOROFORM-d) δppm 7.95 - 8.00 (m, 2H), 7.66 (d, J = 1.0 Hz, 2H), 7.47 - 7.51 (m, 2H), 5.03 (d, J = 1.6 Hz, 2H), 4.50 (d, J = 1.6 Hz, 2H), 3.84 (s, 3H), 1.05 (s, 18H), 0.24 (s, 12H).

(2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((9,9-difluoro-9H-fluorene-2,7-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate)

1,1'-(9,9-difluoro-9H-fluorene-2,7-diyl)bis(2-bromoethanone) (500mg, 1.126 mmol),(2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (604 mg, 2.365 mmol) in acetonitrile (20 mL), and DIPEA (1.180 mL, 6.76 mmol) were mixed and stirred for 3 h at 70 °C. The reaction mixture was then filtered to remove the insoluble solids, which were washed with additional acetonitrile (2 x 5 mL). The organic mixture was reduced to ~10 mL. and added to briskly stirring H_2O (50 mL). The resulting slurry was cooled to 0-5 °C, and aged for 2 h. The solids are collected by filtration, washed with H_2O, and dried at 50-60 °C to constant weight.

Yield: 800 mg, 89%; ES LC-MS *m/z* = 791.4 ($M-H^+$);

(2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9,9-difluoro-9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate)

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((9,9-difluoro-9H-fluorene-2,7-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate) (800 mg, 1.009 mmol) in dry 1,4-dioxane (10 mL) was added ammonium acetate (1.944 g, 25.2 mmol) (25 equiv.). The reaction was refluxed for 6 h. The reaction was cooled slightly then hot filtered and concentrated. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol in DCM. The fractions that were clean were combined and concentrated to give a brown solid.

Yield: 350 mg, 41.5%; ES LC-MS *m/z* = 753.4 ($M+H^+$);

(2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(9,9-difluoro-9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(octahydrocyclopenta[b]pyrrole), 4 Hydrochloride

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(9,9-difluoro-9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole1 (2H)-carboxylate) (350mg, 0.465 mmol) in dry 1,4-dioxane (3mL) and methanol (0.600 mL) was added HCl (4M in 1,4-dioxane, 3.23 mL, 12.92 mmol). The reaction was stirred for 1 h then the solid was collected by filtration. The solid was washed twice with 1,4-dioxane and twice with ether. The solid was dried to give a brown solid.

Yield: 150 mg, 44.8 %; ES LC-MS *m/z* = 551.2 ($M-H^+$);

Example 8: Dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(9,9-

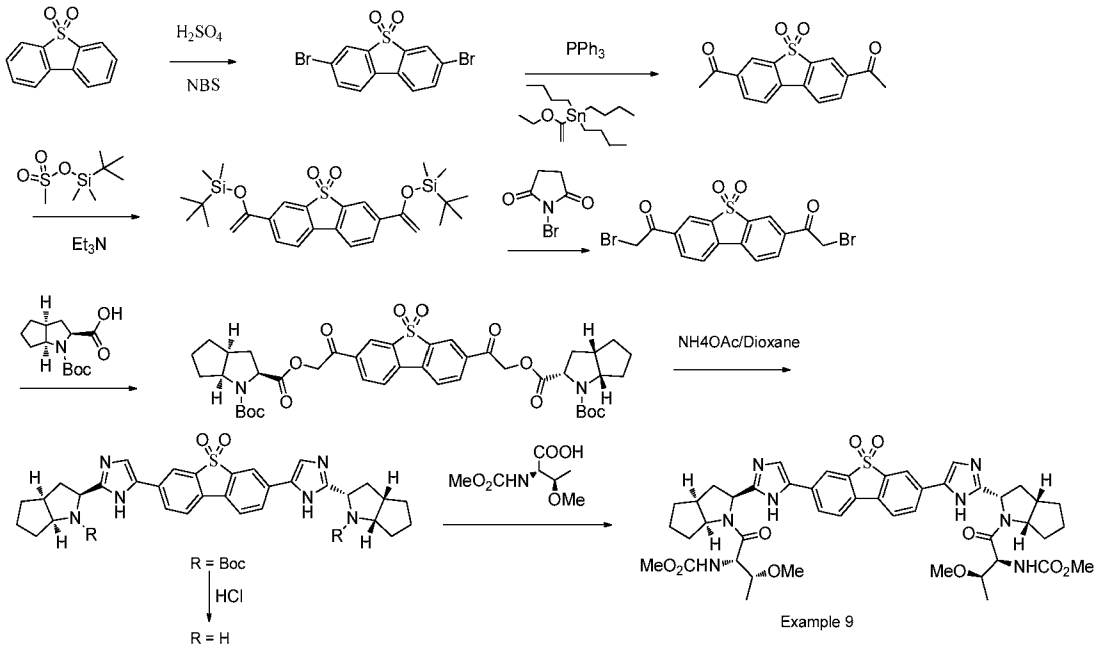
difluoro-9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate

To a stirred solution of (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid (46.0 mg, 0.241 mmol) in ethanol (3 mL) was added DIPEA (0.205 mL, 1.174 mmol) and (2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(9,9-difluoro-9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(octahydrocyclopenta[b]pyrrole), 4 Hydrochloride (100 mg, 0.117 mmol). This was placed in an ice bath and T3P 50% in ethyl acetate (0.279 mL, 0.470 mmol) was added slowly maintaining the reaction temp below 10 °C. The reaction was stirred at 0 °C for 1 h. The reaction was filtered and the ethanol removed from the filtrate by rotary evaporation. The residue was dissolved in EtOAc(10 mL) and washed twice with 1M sodium carbonate, twice with sat ammonium chloride and then brine. The organics were dried over Mg_2SO_4 and concentrated to give a brown solid. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol in DCM. The desired fractions that were clean were combined and concentrated to give a pale yellow solid.

Yield: 8 mg, 6.97%; ES LC-MS *m/z* = 897.4 ($M-H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 11.73 - 12.46 (m, 2H), 7.36 - 8.04 (m, 10H), 5.07 (t, J = 7.5 Hz, 2H), 4.78 (q, J = 7.6 Hz, 2H), 4.14 - 4.45 (m, 2H), 3.46 - 3.54 (m, 7H), 3.14 - 3.22 (m, 6H), 2.60 - 2.83 (m, 2H), 2.28 - 2.39 (m, 2H), 2.01 - 2.19 (m, 3H), 1.90 - 2.01 (m, 2H), 1.66 - 1.90 (m, 4H), 1.54 (br. s., 3H), 1.38 - 1.47 (m, 2H), 0.93 - 1.13 (m, 7H).

Preparation of Example 9



3,7-dibromodibenzo[b,d]thiophene 5,5-dioxide

To a solution of dibenzo[b,d]thiophene 5,5-dioxide (2g, 9.25 mmol) in conc. H_2SO_4 (60 mL) was added NBS (3.29 g, 18.50 mmol) at room temperature. After 24 h, the solution was poured into ice water carefully. Colorless solids were filtrated and washed with water and methanol. The obtained solids were recrystallized from chlorobenzene to afford colorless needles. Yield: 1.6 g, 44.9%;

1H NMR (400 MHz, *DMSO-d6*) δppm 8.33 (d, J = 1.8 Hz, 2H), 8.11 - 8.16 (m, 2H), 7.99 (dd, J = 8.2, 1.8 Hz, 2H).

1,1'-(5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)diethanone

A mixture of 3,7-dibromodibenzo[b,d]thiophene 5,5-dioxide (600mg, 1.604 mmol), Tributyl(1-ethoxyvinyl)tin (2.251 mL, 6.67 mmol) and $Pd(Ph_3P)_4$ (185 mg, 0.160 mmol) in 1,4-dioxane (15 mL) were degassed with nitrogen for 10 min then it was heated at 90 °C for overnight under nitrogen. The reaction mixture was cooled to room temperature and 15 mL of 10 % HCl was added then stirred for 1 h. The mixture was extracted with ethyl acetate and the organic layer was washed with water and brine. The organics were dried (Na_2SO_4) and concentrated. The crude material was purified on silica gel using 0-100 % ethyl acetate in hexane. The desired fractions were concentrated to give a white solid..

.Yield: 400mg, 81%;

^{1}H NMR (CHLOROFORM-d) δppm 8.39 (d, J = 1.2 Hz, 2H), 8.28 (dd, J = 8.0, 1.6 Hz, 2H), 7.96 (d, 2H), 2.68 (s, 6H).

3,7-bis(1-((tert-butyldimethylsilyl)oxy)vinyl)dibenzo[b,d]thiophene 5,5-dioxide

To a mixture of 1,1'-(5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)diethanone (350mg, 1.165 mmol) and triethylamine (0.655 mL, 4.66 mmol) in toluene (12 mL), tert-butyldimethylsilyl trifluoromethanesulfonate (0.804 mL, 3.50 mmol) was added at 0 ^{o}C. The reaction mixture was stirred for 10 min at the same temperature and then stirred for 3 h at room temperature. The reaction mixture was then extracted with ethyl acetate, the organic layer was dried over Na_2SO_4 and it was concentrated to dryness to give the desired product.

Yield: 600 mg, 95%; ES LC-MS *m/z* = 529.2($M+H^+$);

^{1}H NMR (400 MHz, CHLOROFORM-d) δppm 8.02 (d, J = 1.2 Hz, 2H), 7.86 (dd, J = 8.1, 1.7 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 5.01 (d, J = 2.3 Hz, 2H), 4.56 (d, J = 2.3 Hz, 2H), 1.01 (s, 18H), 0.23 (s, 12H).

1,1'-(5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)bis(2-bromoethanone):

NBS (404 mg, 2.269 mmol) was added to 3,7-bis(1-((tert-butyldimethylsilyl)oxy)vinyl)dibenzo[b,d]thiophene 5,5-dioxide (600 mg, 1.135 mmol) in THF (15 mL) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The white suspension was filtered and dried to give the desired product. The product was not purified further.

Yield: 350 mg, 68.7%;

1H NMR (400 MHz, *DMSO-d6*) δppm 8.34 - 8.44 (m, 4H), 7.89 (dd, J = 8.3, 1.3 Hz, 2H), 5.10 (s, 4H), 4.06 (s, 4H).

(2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate)

1,1'-(5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)bis(2-bromoethanone) (350 mg, 0.764 mmol), (2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (410 mg, 1.604 mmol) in acetonitrile (15 mL), and DIPEA (0.801 mL, 4.58 mmol) were mixed and stirred for 3 h at 70 °C. The reaction mixture was then filtered to remove the insoluble solids, which were washed with additional acetonitrile (2 x 5 mL). The organic mixture was reduced to ~10 mL and added to briskly stirring H_2O (50 mL). The resulting slurry was cooled to 0 - 5 °C, and aged for 2 h. The solids were collected by filtration, washed with H_2O, and dried at 50 - 60 °C to constant weight.

Yield: 600 mg, 92%; ES LC-MS *m/z* = 805.3 ($M-H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 8.62 (d, J = 19.0 Hz, 2H), 8.48 (d, J = 8.0 Hz, 2H), 8.36 (d, J = 8.2 Hz, 2H), 5.42 - 5.79 (m, 4H), 4.31 - 4.46 (m, 2H), 3.98 - 4.14 (m, 2H), 2.66 (br. s., 2H), 1.53 - 1.97 (m, 12H), 1.34 (d, J = 9.6 Hz, 22H).

(2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate)

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-1-di-tert-butyl O'2,O2-((5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)bis(2-oxoethane-2,1-diyl)) bis(hexahydrocyclo penta[b]pyrrole-1,2(2H)-dicarboxylate) (600 mg, 0.706 mmol) in dry 1,4-dioxane (10 mL) was added ammonium acetate (1361 mg, 17.66 mmol) (25 equiv.). The reaction was refluxed for 6 h. The reaction was cooled slightly then hot filtered and concentrated. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol in DCM. The fractions that were clean were combined and concentrated to give a pale yellow solid.

Yield: 250 mg, 40.6%; ES LC-MS *m/z* = 765.3($M-H^+$);

3,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)dibenzo[b,d] thiophene 5,5-dioxide, 4 Hydrochloride

To a stirred solution of (2S,2'S,3aS,3a'S,6aS,6a'S)-di-tert-butyl 2,2'-(5,5'-(5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclo penta[b]pyrrole-1(2H)-carboxylate) (250mg, 0.326 mmol) in dry 1,4-dioxane (3mL) and methanol (0.600 mL) was added HCl (4M in 1,4-dioxane, 2.265 mL, 9.06 mmol). The reaction was stirred for 1 h then the solid was collected by filtration. The solid was washed twice with 1,4-dioxane and twice with ether. The solid was dried to give a pale yellow solid.

Yield: 100 mg, 32.3%; ES LC-MS *m/z* = 565.2 ($M-H^+$);

Example 9: dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(5,5-dioxidodibenzo[b,d]thiophene-3,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate

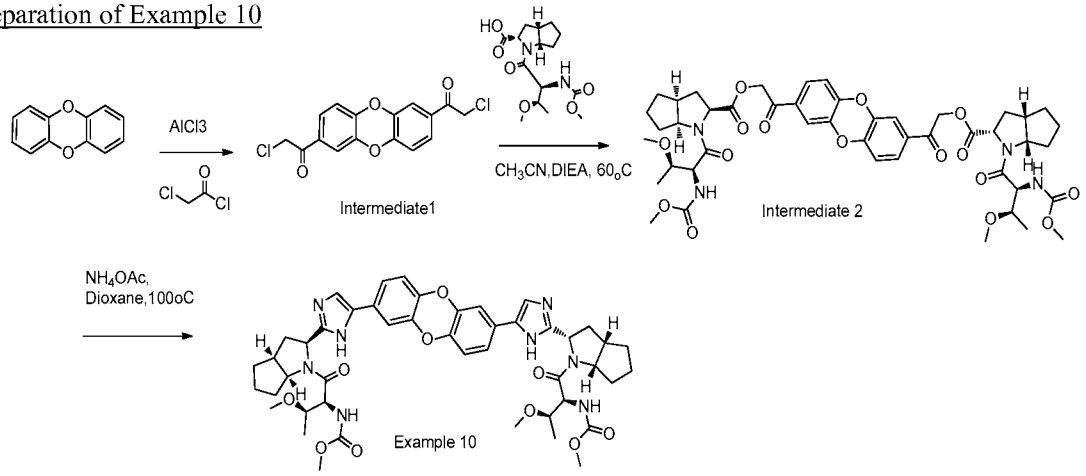
To a stirred solution of (2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid (55.0 mg, 0.288 mmol) in Ethanol (3 mL) was added DIPEA (0.245 mL, 1.403 mmol) and 3,7-bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-5-yl)dibenzo[b,d]thiophene 5,5-dioxide, 4 Hydrochloride (100 mg, 0.140 mmol). This was placed in an ice bath and T3P 50% in ethyl acetate (0.334 mL, 0.561 mmol) was added slowly maintaining the reaction temp below 10 °C. The reaction was stirred at 0 °C for 1 h. The reaction was filtered and the ethanol removed from the filtrate by rotary evaporation. The residue was dissolved in EtOAc(10mL) and washed twice with 1M sodium carbonate, twice with sat ammonium chloride and then brine. The organics were dried over Mg_2SO_4 and concentrated to give a brown solid. This crude material was purified on silica gel eluted with 0-7% 2M ammonia in methanol to DCM. The

desired fractions were combined and concentrated to give a pale yellow solid.

Yield: 9mg ,10.43%; ES LC-MS *m/z* = 911.2 ($M-H^+$);

1H NMR (400 MHz, *DMSO-d6*) δppm 11.60 - 12.73 (m, 2H), 7.46 - 8.38 (m, 10H), 4.99 - 5.16 (m, 2H), 4.72 - 4.84 (m, 2H), 4.22 - 4.47 (m, 2H), 3.49 - 3.54 (m, 6H), 3.38 - 3.48 (m, 2H), 3.14 - 3.24 (m, 6H), 2.59 - 2.83 (m, 2H), 2.31 - 2.42 (m, 2H), 2.10 (br. s., 3H), 1.90 - 2.00 (m, 1H), 1.67 - 1.89 (m, 4H), 1.35 - 1.66 (m, 5H), 0.88 - 1.10 (m, 7H).

Preparation of Example 10



Intermediate 1: 1,1'-(dibenzo[b,e][1,4]dioxine-2,7-diyl)bis(2-chloroethanone)

Dibenzo[b,e][1,4]dioxine (2g, 10.86 mmol), was taken in dichloromethane (10ml), 2-chloroacetyl chloride (2.0 ml, 24.97 mmol) was added and the reaction was cooled to -78°C. Aluminium chloride (5.79 g, 43.4 mmol) was added carefully and was stirred for additinoal 2h at -78°C, then slolwy allowed to reach rt and stirred for additional 2h. Cooled to 0°C and ice was added, stirred for few min, white precipitation noticed, MeOH (5mL) was added and stirred for 1h.The precipitate was filtered and washed with water and used in the next step. Yield: 1.8 ,50%; ES LC-MS *m/z* = 337 ($M-H^+$);

Intermediate 2: (S,R,2S,2'S,3aS,3a'S,6aS,6a'S)-dibenzo[b,e][1,4]dioxine-2,7-diylbis(2-oxoethane-2,1-diyl) bis(1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)octahydrocyclopenta[b]pyrrole-2-carboxylate)

Under N_2 atmosphere, to a stirred suspension of1,1'-(dibenzo[b,e][1,4]dioxine-2,7-diyl)bis(2-chloroethanone) (130 mg, 0.270 mmol) in acetonitrile (5.00 mL) was added (2S,3aS,6aS)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (177 mg, 0.540 mmol) followed by addition of DIEA (0.094 mL, 0.540 mmol). The mixture was stirred at 60°c for 12h. After evaporation of solvent the material was used in the next step. Small amount

was subjected to HPLC purification to provide two product in ~4: 1 ratio as a mixture of intermediate 2 and other regiomer.

Yield: 130mg ,52%; ES LC-MS *m/z* = 921.3 ($M-H^+$);

^{1}H NMR (400 MHz, DMSO-d6) δ: 7.65 - 7.76 (m, 3 H), 7.52 - 7.63 (m, 2 H), 7.07 - 7.29 (m, 2 H), 5.49 - 5.61 (m, 2 H), 5.39 (d, *J*=16.9 Hz, 2 H), 4.77 (d, *J*=6.1 Hz, 2 H), 4.59 (t, *J*=8.3 Hz, 2 H), 4.23 (t, *J*=8.5 Hz, 2H), 3.33 (s, 12 H), 3.23 (s, 6 H), 2.80 (br. s., 2 H), 2.09 (br. s., 2 H), 1.85 - 1.94 (m, 2 H), 1.79 (br. s., 5 H), 1.55 (br. s., 4 H), 1.05 (d, *J*=5.9 Hz, 6 H).

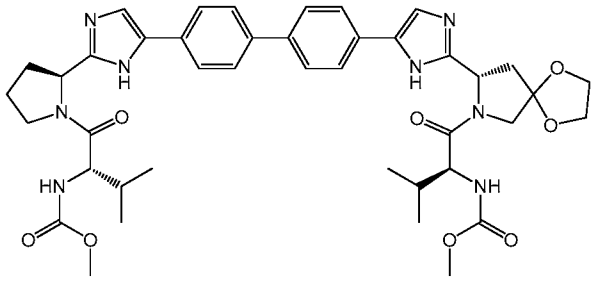
Example 10: Dimethyl ((2S,2'S,3R,3'R)-((2S,2'S,3aS,3a'S,6aS,6a'S)-2,2'-(5,5'-(dibenzo[b,e][1,4]dioxine-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(hexahydrocyclopenta[b]pyrrole-2,1(2H)-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate

To a stirred solution of (S,R,2S,2'S,3aS,3a'S,6aS,6a'S)-dibenzo[b,e][1,4]dioxine-2,7-diylbis(2-oxoethane-2,1-diyl) bis(1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)octahydrocyclopenta[b]pyrrole-2-carboxylate) (130 mg, 0.141 mmol) in 1,4-Dioxane (5 mL) in a sealed tube was addedammonium acetate (416 mg, 5.40 mmol) . The reaction mixture was refluxed at 100°C for 10h. Cooled down to rt, filtered off excess of ammonium acetate. The filtrate was evaporated and the residue was purified by column (ISCO-silica gel, 0-15% methanol in ethyl acetate) and then by HPLC (ACN:H_2O- 0.1% NH_4OH) to give the product as a solid.

Yield: 30mg ,25%; ES LC-MS *m/z* = 881.4 ($M-H^+$);

^{1}H NMR (400 MHz, DMSO-d6) δ: 11.61 - 12.20 (m, 2 H), 7.52 - 7.65 (m, 2 H), 7.45 (d, *J*=1.8 Hz, 2 H), 7.32 - 7.36 (m, 2 H), 7.27 - 7.31 (m, 2 H), 6.97 (d, *J*=8.3 Hz, 2 H), 5.10 (t, *J*=7.5 Hz, 2 H), 4.82 (d, *J*=7.7 Hz, 2 H), 4.28 (t, *J*=8.4 Hz, 2 H), 3.56 (s, 5 H), 3.43 - 3.50 (m, 2 H), 3.41 (s, 1 H), 3.31 (s, 1 H), 3.25 - 3.28 (m, 2 H), 3.22 (s, 4 H), 2.67 - 2.83 (m, 2 H), 2.39 (dt, *J*=13.1, 8.8 Hz, 2 H), 2.14 (br. s., 3 H), 1.91 - 2.03 (m, 2 H), 1.86 (d, *J*=12.2 Hz, 2H), 1.69 - 1.81 (m, 2 H), 1.45 - 1.67 (m, 3 H), 1.20 - 1.32 (m, 1 H), 1.08 (d, *J*=6.1 Hz, 6 H).

Example 11: methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate



Methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl] amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate may be prepared according to the procedures described in International Patent Application Publication No. WO 2011/028596.

Example 12: Pharmaceutical Composition

Table 2

Component	Quantity (mg/tablet)
Compound of Example 11, Spray Dried Dispersion	14.00
Microcrystalline Cellulose (~100 µm)	5.50
Microcrystalline Cellulose (~20 µm)	4.31
Croscarmellose Sodium	0.752
Colloidal Silicone Dioxide	0.25
Magnesium Stearate	0.188
Total Tablet Weight (mg/tablet)	25.0

A solution of methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate and hypromellose acetate succinate is prepared in acetone for spray drying. The solution is spray dired and then the resulting powder dried to provide an amorphous spray dried dispersion. The spray dried dispersion is blended with microcrystalline cellulose (~20 µm particle size). Croscarmellose Sodium, Colloidal Silicon Dioxide and microcrystalline

cellulose (~100 µm particle size) are then added and blended. Magnesium stearate is added and blended further. The blend is compressed into tablets.

Example 13: Pharmaceutical Composition

Table 3

Component	Quantity (mg/tablet)
Compound of Example 11, Spray Dried Dispersion	420
Microcrystalline Cellulose (~100 µm)	165
Microcrystalline Cellulose (~20 µm)	129.3
Croscarmellose Sodium	22.56
Colloidal Silicone Dioxide	7.5
Magnesium Stearate	5.64
Total Tablet Weight (mg/tablet)	750

A tablet may be prepared according to the procedure of Example 2 using the quantities from the table above.

Example 14: Pharmaceutical Composition

Table 4

Component	Quantity (mg/tablet)
Compound of Example 11, Spray Dried Dispersion	420
Ribavirin	400
Microcrystalline Cellulose (~100 µm)	165
Microcrystalline Cellulose (~20 µm)	129.3
Croscarmellose Sodium	22.56

Colloidal Silicone Dioxide	7.5
Magnesium Stearate	5.64
Total Tablet Weight (mg/tablet)	1150

A tablet, further comprising ribavirin, may be prepared according to the procedure of Example 12 using the quantities from the table above.

Example 15: Pharmaceutical Composition

Table 5

Component	Quantity (mg/tablet)
Compound of Example 11, Spray Dried Dispersion	420
Ritonavir	100
Microcrystalline Cellulose (~100 µm)	165
Microcrystalline Cellulose (~20 µm)	129.3
Croscarmellose Sodium	22.56
Colloidal Silicone Dioxide	7.5
Magnesium Stearate	5.64
Total Tablet Weight (mg/tablet)	850

A tablet, further comprising ritonavir, may be prepared according to the procedure of Example 12 using the quantities from the table above.

Example 16: Biological Activity

Genotype 1b replicon cells, henceforth referred to as ET cells, were licensed from ReBLikon GmbH (Mainz, Germany). The cells carry the adapted con-1 NS3-5B bicistronic subgenomic replicon. Fresh cells were maintained in DMEM containing 10% FBS, supplemented with GlutaMAX™-1, penicillin-streptomycin, geneticin, and non-essential amino acids (complete media) as subconfluent cultures and were split 1:4-1:6 twice a week.

Fresh ET cells were maintained subconfluent in T225 flasks prior to the assay. Media was aspirated from the flasks and two PBS washes were performed. Cells were trypsinized and resuspended in media containing 5% FBS, supplemented with GlutaMAX™-1, penicillin-streptomycin, and non-essential amino acids (assay media). The cells were then pooled, counted on a hemacytometer, and diluted to 1.5×10^5 cells/mL. 92 μL of assay medium was added to all wells of three 96-well white assay plates and three 96-well black assay plates. 4 μL from both the first and second compound plates were added to each of the assay plates using the Biomek FX (Beckman Coulter). Assay plates were then centrifuged briefly for 10 seconds at 3K rpm. 100 ul of cell suspension was added to all wells of the assay plates except 8 background wells, which received assay medium. Plates were covered with breathable sealing tape and incubated at 37°C, 5% CO_2, for approximately 48 hours.

Media was aspirated from the assay plates and 100 μL room temperature assay medium was added to each well. 100 μL Steady-Glo® reagent was then added to each well of the assay plates. The plates were sealed and shaken at 600-700 rpm for 1 minute and incubated for 30 minutes in the dark prior to reading the luminescence in the Envision Multilabel Reader (PerkinElmer).

Interferon α (IFNα) and ribavirin were purchased from Sigma. Solid compounds, with the exception of IFNα, were dissolved in DMSO. IFNα was dissolved in PBS supplemented with BSA, aliquoted, stored at -80°C, then diluted on the day of the experiment.

The EC_{50}, the concentration of compound required to inhibit 50% of the assay response, was defined here as the concentration that gives a response halfway between the mean of wells containing cells with no compound and wells containing no cells. To estimate the EC_{50} all data analyses were performed on square-root (sqrt) transformed data values. The mean sqrt-values of untreated controls and no cells controls were used to calculate inhibition on each of three replicate plates for the sqrt transformed response for each combination. Curve fitting and EC_{50} estimation was performed for the horizontally-diluted compound at each experimental level of the vertically-diluted compound and vice versa. In each case, a four parameter Hill curve (see equation below) was fit to the inhibition data of the three replicate plates using XLfit5.1 (IDBS), and the EC_{50} was estimated from the fitted curve.

$$y = a + [(b-a) / (1 + (x/c)^d)]$$

Where y = response, i.e. inhibition of sqrt-transformed data, a = lower asymptote, i.e. minimum response (i.e. no inhibition), b = upper asymptote, i.e. maximum response, x =

compound concentration, $c = EC_{50}$, i.e. concentration that gives a response half way between upper and lower asymptote *b* and *a*, and *d* = Hill coefficient. In some instances, data points that looked like outliers were manually excluded and curves were refit.

The combination index *CI* is based on the dosewise-additivity model. At 50% inhibition it is calculated as $CI = (d_A/EC_{50A}) + (d_B/EC_{50B})$ where EC_{50A} and EC_{50B} are the concentrations of compounds *A* and *B* that result in 50% inhibition for each respective compound alone, and (d_A, d_B) are concentrations of each compound in the mixture that yield 50% inhibition. *CI* measures the type and amount of interaction between two compounds, *A* and *B*. $CI < 1$ implies dosewise synergism between compounds *A* and *B*, $CI = 1$ implies dose-wise additivity, and $CI > 1$ implies dosewise antagonism between compounds *A* and *B*. For each fixed concentration of compound A in the plate layout, the concentration of compound B required to give 50% inhibition, and the combination index *CI* for these component concentrations was calculated. A similar calculation was repeated for each fixed concentration of compound B. The reported *CI* is the average across all individual *CI*s.

Table 6

CI	Dosewise-Additivity Result (CalcuSyn Recommended)
< 0.1	Very strong synergism
0.1-0.3	Strong synergism
0.3-0.7	Synergism
0.7-0.85	Moderate synergism
0.85-0.9	Slight synergism
0.9-1.1	Nearly additive
1.1-1.2	Slight antagonism
1.2-1.45	Moderate antagonism
1.45-3.3	Antagonism
3.3-10	Strong antagonism
>10	Very strong antagonism

Data reported in Table 1 are for three independent studies preformed in triplicate evaluating the combination of the compound of Example 11 with IFNα and two independent studies preformed in triplicate evaluating the combination of the compound of Example 11 with ribavirin.

Table 7

Compound combined with the compound from Example 11	***CI***	**Dosewise-additivity Result**
IFNα	0.98	Nearly additive
	1.09	Nearly additive
Ribavirin	1.11	Slight antagonism
	1.11	Slight antagonism
	1.23	Moderate antagonism

Synergy and antagonism volumes are based on the Bliss independence model, which assumes that both compounds act independently on different targets. A set of predicted fractional responses fa_{AB} under the Bliss independence model was calculated as $fa_{AB} = fa_A + fa_B - fa_A \bullet fa_B$ with fa_A and fa_B being the fraction of possible responses, e.g. % inhibition, of compounds *A* and *B* at amounts d_A and d_B respectively, and fa_{AB} being the % inhibition of a combination of compounds *A* and *B* at amount (d_A+d_B). If $fa_{AB} > fa_A + fa_B - fa_A \bullet fa_B$ then there is Bliss synergy; if $fa_{AB} < fa_A + fa_B - fa_A \bullet fa_B$ then there is Bliss antagonism. The 95% synergy/antagonism volumes are the summation of the differences between the observed inhibition and the 95% confidence limit on the prediction of fa_{AB} under the Bliss independence model. MacSynergy II was used for data analysis.

Table 8

MacSynergy II Synergy/Antagonism Volumes Description @ 95% Confidence

Volume	Volume Description
<25	Insignificant synergism/antagonism
25-50	Minor but significant synergism/antagonism
50-100	Moderate synergism/antagonism - maybe important *in vivo*

>100	Strong synergism/antagonism - probably important *in vivo*
>1000	Probable Errors

Data reported in Table 2 are for three independent studies preformed in triplicate evaluating the combination of the compound of Example 11 with IFNα and two independent studies preformed in triplicate evaluating the combination of the compound of Example 11 with ribavirin.

Table 9

Compound combined with the compound from Example 11	**Synergy Volume**	**Antagonism Volume**	**Bliss Independence Analysis Result Synergism**	**Bliss Independence Analysis Result Antagonism**
IFNα	21.72	-9.11	Insignificant	Insignificant
	54.6	-4.14	Moderate	Insignificant
Ribavirin	55.1	-2.8	Moderate	Insignificant
	17.63	-0.17	Insignificant	Insignificant
	77.24	0	Moderate	Insignificant

Example 17: Activity with combinations of the Compound of Example 11 and Alternative HCV Therapeutic Agents

The compound of Example 11 is a potent inhibitor of HCV replicons and virus. It has picomolar activity in genotype 1a, 1b and 2a (JFH-1) replicons as well as in a genotype 2a virus. The ability of the compound of Example 1 to work in combination with an inhibitor of site II of the HCV polymerase and with a cyclophilin inhibitor was assessed. Cytotoxicity was also evaluated in parallel.

In this study, Example 11 was tested in combination with an inhibitor of site II of HCV polymerase and with a cyclophilin inhibitor, using the HCV replicon system. The data were analyzed via two models – dosewise-additivity and the Bliss Independence model. Although the dose-wise additivity model found slight antagonism with the Example 11/cyclophilin inhibitor combinations, the analysis showed that the Example 11/site II HCV

polymerase inhibitor combinations were nearly additive. The Bliss Independence model found insignificant synergism and insignificant antagonism for both combinations tested. The conclusion from this data set is that Example 11 is not antagonistic with the tested compounds. Cytotoxicity was assessed in parallel with the combination studies. No appreciable toxicity was seen in this study with either of the combinations tested.

Compound plate preparation:

The starting concentration for each compound is ≅ 4X the EC_{50} determined in the ET replicon assay. Compound stocks were prepared at 400X the final desired concentration. 40 μL of the 400X stock of the first compound were plated in all 8 wells of column 2 of a 96-well V- bottom plate. A separate plate was prepared in the same manner for the second compound being tested in the combination assay. Compounds were serially diluted 1:2 in DMSO using a Biomek 2000 (Beckman Coulter) to create a 7-point dose response plate. DMSO was added to the appropriate control wells, and 140 μL assay medium were added to all wells containing compound or DMSO. For the second compound, the material in all wells was moved with a manual multichannel pipetter to a new 96-well V-bottom plate and transposed to create a 7-point dose response curve vertically.

Cell preparation and Combination Study set up:

Fresh ET cells were maintained subconfluent in T225 flasks prior to the assay. Medium was aspirated from the flasks and two PBS washes were performed. Cells were detached using a solution of versene plus 10% trypsin (0.25%) and resuspended in DMEM supplemented with 5% FBS, GlutaMAX™-1, penicillin-streptomycin, and non-essential amino acids (assay medium). The cells were pooled, counted on a hemacytometer, and diluted to 1.5 x 10^4 cells/mL. 92 μL of assay medium were added to all wells of three 96-well white assay plates and three 96-well black assay plates. 4 μL from both the first and second compound plates were added to each of the assay plates using the Biomek FX (Beckman Coulter). Assay plates were then centrifuged briefly for 10 sec at 3K rpm. 100 μl of cell suspension were added to all wells of the assay plates except 8 background wells, which received assay medium. Plates were covered with breathable sealing tape and incubated at 37°C, 5% CO_2, for approximately 48 hr.

Luciferase and cytotoxicity assays

Medium was aspirated from the assay plates and 100 μL room-temperature assay medium were added to each well. 100 μL Steady-Glo™ reagent were then added to each well of the three white assay plates. For the cytotoxicity assessment, 100 μL CellTiter-Glo™ reagent were added to each well of the three black assay plates. The plates were sealed and shaken at 600-700 rpm for 1 min and incubated for 30 min in the dark prior to reading the luminescence in the Envision Multilabel Reader (PerkinElmer).

Drugs and Materials:

The compound of Example 11 and a (site II HCV polymerase inhibitor), and a (cyclophilin inhibitor) were obtained from an internal compound collection in powder form. Solid compounds were dissolved in DMSO and diluted as described in the Methods section.

Materials:

DMEM (Invitrogen #11965-092)
Fetal Bovine Serum (FBS) (SAFC #12176C)
MEM non-essential amino acids (Invitrogen #1140-035)
Geneticin (Invitrogen #10131-027)
Penicillin-streptomycin (Invitrogen #25030-024)
GlutaMAX™-1 (Invitrogen #35035-061)
Phosphate buffered saline (Invitrogen #14190)
Trypsin 0.25% (Invitrogen #25200-056)
Versene (Invitrogen #15040-066)
Steady-Glo™ Luciferase Assay System (Promega #E2550)
CellTiter-Glo™ Luminescent Cell Viability Assay (Promega #G7573)
96-well white assay plate (PerkinElmer #6005680)
96-well black assay plate (Corning #3904)
96-well V-bottom plate (Corning #3357)
Breathable sealing tape (Corning #3345)
TopSeal™-A sealing film (PerkinElmer #6005185)

Calculation of EC_{50} values

The dose-wise additivity model requires estimates of the replicon EC_{50} values for each compound in combination or alone. The EC_{50}, the concentration of compound required to inhibit 50% of the assay response, was defined here as the concentration that gives a response half way between the mean of wells containing cells with no compound and wells containing no cells. To estimate the EC_{50} all data analyses were performed on square-root (sqrt) transformed data values. The mean sqrt values of untreated controls and no cells controls were used to calculate inhibition on each of three replicate plates for the sqrt-transformed response for each combination. Curve fitting and EC_{50} estimation was performed for the horizontally diluted compound at each experimental level of the

vertically diluted compound and vice versa. In each case, a four-parameter Hill curve (see equation below) was fit to the inhibition data of the three replicate plates using XLfit5.1 (IDBS), and the EC_{50} was estimated from the fitted curve.

$y = a + [(b-a) / (1 + (x/c)^d)$:

where y = response, i.e. inhibition of sqrt-transformed data, a = lower asymptote, i.e. minimum response (i.e. no inhibition), b = upper asymptote, i.e. maximum response, x = compound concentration, $c = EC_{50}$, i.e. concentration that gives a response half way between upper and lower asymptote b and a, and d = Hill coefficient. In some instances, data points that looked like outliers were manually excluded and curves were refit.

Combination Index Calculations:

The combination index *CI* is based on the dosewise-additivity model. At 50% inhibition it is calculated as $CI = (d_A/EC_{50A}) + (d_B/EC_{50B})$ where EC_{50A} and EC_{50B} are the concentrations of compounds *A* and *B* that result in 50% inhibition for each respective compound alone, and (d_A, d_B) are concentrations of each compound in the mixture that yield 50% inhibition. Calculations of EC_{50} values are described in Section 0. *CI* measures the type and amount of interaction between two compounds, *A* and *B*. $CI < 1$ implies dosewise synergism between compounds *A* and *B*, $CI = 1$ implies dose-wise additivity, and $CI > 1$ implies dosewise antagonism between compounds *A* and *B*. For each fixed concentration of compound A in the plate layout, we calculate the concentration of compound B required to give 50% inhibition, and calculate the combination index *CI* for these component concentrations. A similar calculation is repeated for each fixed concentration of compound B. The number *CI* that is being reported here is the average across all individual *CI*s. Below is a table showing the additivity result for the calculated *CI*.

CI	Dosewise-Additivity Result (CalcuSyn Recommended)
< 0.1	Very strong synergism
0.1-0.3	Strong synergism
0.3-0.7	Synergism
0.7-0.85	Moderate synergism
0.85-0.9	Slight synergism
0.9-1.1	Nearly additive

CI	Dosewise-Additivity Result (CalcuSyn Recommended)
1.1-1.2	Slightly antagonistic
1.2-1.45	Moderate antagonistic
1.45-3.3	Antagonism
3.3-10	Strong antagonism
>10	Very strong antagonism

Calculations for Synergy/Antagonism Volume (Bliss Independence Model):

Synergy and antagonism volumes are based on the Bliss independence model, which assumes that both compounds act independently on different targets. A set of predicted fractional responses fa_{AB} under the Bliss independence model is being calculated as $fa_{AB} = fa_A + fa_B - fa_A \bullet fa_B$ with fa_A and fa_B being the fraction of possible responses, e.g. % inhibition, of compounds *A* and *B* at amounts d_A and d_B respectively, and fa_{AB} being the % inhibition of a combination of compounds *A* and *B* at amount (d_A+d_B). If $fa_{AB} > fa_A + fa_B - fa_A \bullet fa_B$ then we have Bliss synergy; if $fa_{AB} < fa_A + fa_B - fa_A \bullet fa_B$ then we have Bliss antagonism. The 95% synergy/antagonism volumes are the summation of the differences between the observed inhibition and the 95% confidence limit on the prediction of fa_{AB} under the Bliss independence model. The table below shows the volumes and corresponding volume descriptions for the results of the Bliss Independence Analysis. MacSynergy II was used for data analysis.

MacSynergy II Synergy/Antagonism Volumes Description @ 95% Confidence	
Volume	Volume Description
<25	Insignificant synergism/antagonism
25-50	Minor but significant synergism/antagonism
50-100	Moderate synergism/antagonism – maybe important *in vivo*
>100	Strong synergism/antagonism – probably important *in vivo*
>1000	Probable Errors

Calculations for Combination Toxicity:

For the combination toxicity studies, the identical checkerboard pattern layout was used for the dose responses of each compound alone and in combination at various concentrations. At every concentration of each compound in the combination, the average percent inhibition was calculated and graphed relative to the appropriate concentration of the second compound.

Combination of Example 11 with a site II HCV polymerase inhibitor or with a cyclophilin inhibitor analyzed using the dosewise-additivity model

The results of the dosewise-additivity analysis of Example 11 combined with a site II HCV polymerase inhibitor or with a cyclophilin inhibitor are listed in Table 11.

Combination of Example 11 with a site II HCV polymerase inhibitor or with a cyclophilin inhibitor analyzed by the Bliss Independence Model

The results of the Bliss Independence analysis of Example 11 combined with a site II HCV polymerase inhibitor or with a cyclophilin inhibitor are listed in Table 12Table. MacSynergy II was used to perform the Bliss Independence analysis.

Combination toxicity of Example 11 with a site II HCV polymerase inhibitor

The results of the combination toxicity assay of Example 11 with a site II HCV polymerase inhibitor are shown in Figure 1 and Figure 2.

Combination toxicity of Example 11 with a cyclophilin inhibitor

The results of the combination toxicity assay of Example 11 with a cyclophilin inhibitor are shown in Figure 3**Error! Reference source not found.** and Figure 4.

The *in vitro* combination studies performed demonstrate that Example 11 is a good candidate for HCV combination therapy either with an inhibitor of site II of the HCV polymerase or with a cyclophilin inhibitor.

Analysis using the dosewise-additivity model showed that Example 11 was nearly additive when combined with the site II HCV polymerase inhibitor. Data analysis was also performed using the Bliss Independence model via the MacSynergy II program, and the combinations of Example 11 with the site II HCV polymerase inhibitor resulted in insignificant synergism and insignificant antagonism. The two analysis methods were in agreement that there was no antagonism between Example 11 and the site II HCV polymerase inhibitor.

For the Example 11 combination with the cyclophilin inhibitor, analysis using the dosewise-additivity model resulted in slight antagonism. However, the Bliss Independence model, via the MacSynergy II program, concluded that Example 11 and cyclophilin inhibitor combinations showed insignificant synergism and insignificant antagonism. The methods of data analysis are different, and they did not reach the same conclusion.

There is no general agreement over which model best predicts *in vivo* outcome, but we believe both models are in general agreement that there is no significant antagonism between the tested compounds and Example 11. Although antagonism was detected with the dosewise-additivity analysis for the cyclophilin combinations, it was classified as 'slight,' and this interpretation was not supported by the Bliss Independence analysis on the same set of data. In a previous study, when we dosed an HCV nucleoside inhibitor in combination with ribavirin, both methods of analysis detected antagonism or strong antagonism, demonstrating that antagonism can be detected with our methods

The combination toxicity studies demonstrate that Example 11 is not cytotoxic when dosed with either of the two compounds tested in this study. For both combinations, the maximum toxicity was 5-10% at the highest concentrations tested. This is comparable to the toxicity seen when Example 11 is combined with itself. We hypothesized that this small amount of apparent toxicity could be an artifact of the plate layout. After conducting a number of experiments to address this question, we concluded that we were indeed observing a plate effect and that the small amount of toxicity observed in most combinations was an artifact of the experimental system.

We conclude from these and previous studies that Example 11 is a good candidate for HCV combination therapy and that the observed effect of this agent is not due to toxicity.

Table 11 **Combination of Example 11 with a site II inhibitor of HCV polymerase or with a cyclophilin inhibitor analyzed using the dosewise-additivity model**

Compound in combination with Eaxmple 11	CI	Dosewise-additivity Result
NS5B polymerase site II inhibitor	1.08	Nearly additive
	1.06	Nearly additive
Cyclophilin inhibitor	1.16	Slight antagonism
	1.13	Slight antagonism

Table 12 Combination of Example 11 with a site II inhibitor of HCV polymerase or with a cyclophilin inhibitor analyzed using the Bliss Independence Model

Compound in combination with Example 11	Synergy Volume	Antagonism Volume	Bliss Independence Analysis Result Synergism	Bliss Independence Analysis Result Antagonism
NS5B polymerase site II inhibitor	5.27 18.11	0 -8.08	Insignificant Insignificant	Insignificant Insignificant
Cyclophilin inhibitor	24.81 17.1	-5.78 -2.63	Insignificant Insignificant	Insignificant Insignificant

Example 18: Combination Activity

Example 11 is a potent inhibitor of HCV replicon and virus. It has picomolar activity in genotype 1a, 1b and 2a (JFH-1) replicons as well as a genotype 2a virus. Although it has impressive activity, the high mutation rate of HCV results in the rapid emergence of viral resistance during monotherapy [**Error! Reference source not found.**, **Error! Reference source not found.**] . Thus, Example 11 will be used in combination either with interferon α and ribavirin (SOC), with other direct acting antivirals (DDAs) or with a combination of other DAAs and SOC.

Example 11 was tested in combination using the HCV replicon system with representative protease, polymerase, replicase, and NS4B inhibitors as well as cyclosporine A, interferon α, and ribavirin. Data was analyzed via two models – dosewise-additivity and the Bliss Independence model. Although the dose-wise additivity model found slight antagonism with one Example 11/ ribavirin combination and both Example 11/NS4B inhibitor combinations, the analysis showed all of the other tested combinations were nearly additive or moderately synergistic. The Bliss-independence model found all of the combinations to be strongly synergistic. The antagonism identified by dose-wise additivity was not supported by the Bliss Independence analysis and was classified as 'slight antagonism'. A control experiment was performed to demonstrate that antagonism could be detected. Ribavirin was combined with an HCV nucleoside inhibitor and data

analysis using the dose-wise additivity model showed the combination was antagonistic while the Bliss independence model found strong antagonism, demonstrating that antagonism can be detected using this assay. The conclusion from this data set is that Example 11 is not antagonistic with any of the compounds tested.

Genotype 1b replicon cells – ET cells

Genotype 1b replicon cells, henceforth referred to as ET cells, were licensed from ReBLikon GmbH (Mainz, Germany).[**Error! Reference source not found.**, **Error! Reference source not found.**] The cells carry the adapted con -1 NS3-5B bicistronic subgenomic replicon. Fresh cells were maintained in DMEM containing 10% FBS, supplemented with gluta-max, penicillin-streptomycin and non-essential amino acids (complete media) as subconfluent cultures and were split 1:4-1:6 twice a week.

Experimental Protocol(s)

Compound plate preparation

The starting concentration for each compound is ≅ 4X the EC_{50} determined in the ET replicon assay. Compound stocks were prepared at 400X the final desired concentration. 40 μL of the 400X stock of the first compound was plated in all 8 wells of column 2 of a 96-well V- bottom plate. A separate plate was prepared in the same manner for the second compound being tested in the combination assay. Compounds were serially diluted 1:2 in DMSO using a Biomek 2000 to create a 7-point dose response plate. DMSO was added to the appropriate control wells, and 140 μL assay medium was added to all wells containing compound or DMSO. For the second compound, the material in all wells was moved with a manual multichannel pipetter to a new 96-well V-bottom plate and transposed to create a 7-point dose response curve vertically.

Cell preparation and Combination Study set up

Fresh ET cells were maintained subconfluent in T225 flasks prior to the assay. Media was aspirated from the flasks and two PBS washes were performed. Cells were trypsinized and resuspended in media containing 5% FBS, supplemented with gluta-max, penicillin-streptomycin and non-essential amino acids (assay media). The cells were then pooled, counted on a hemacytometer then diluted to 2 x 10^5 cells/mL. 92 μL of resuspended cells was added to all wells of three 96-well assay plates then 4 μL from both the first and second compound plates to each of the assay plates using the Biomek

FX. Assay plates were then centrifuged briefly for 10 seconds at 3K rpm. Plates were then incubated at 37°C, 5% CO_2, for approximately 48 hours.

Luciferase assay

Media was aspirated from the assay plates and 100 μL room-temperature cell culture medium was added to each well. 100 μL Steady-Glo reagent was then added to each well, the plates were sealed and shaken at 600-700 rpm for 1 minute then incubated for 15 minutes in the dark prior to reading the luminescence in the Envision Multilabel Reader.

Drugs and Materials

Drugs

Example 11 was obtained from an internal compound collection in powder form. Interferon α (IFN α), ribavirin, and cyclosporin A were purchased from Sigma. All other inhibitors were obtained from an internal compound collection as solids. Solid compounds, with the exception of IFNα, were dissolved in DMSO and diluted as described in the methods section. IFNα was dissolved in PBS supplemented with BSA, aliquoted, stored at -80°C, then diluted as described in the methods section on the day of the experiment.

Materials

DMEM (Gibco #12430; Invitrogen 31053-028)
Fetal Bovine Serum, (SAFC #12176C)
MEM non-essential amino acids (Invitrogen #1140-035)
Penicillin-Streptomycin (Invitrogen #25030-024)
Glutamax (Invitrogen #35035-061)
Phosphate buffered saline (Invitrogen #14190)
Trypsin 0.25% (Gibco #25200-056)
Versene (Invitrogen #15040-066)
Steady Glo reagent (Promega #E2548)
Perkin Elmer 96 well assay plate (Perkin Elmer #6005680)
96 well V bottom trays (Costar #3357)
Interferon α human A/D (Sigma #I4401)
Ribavirin (Sigma #R9644)
Cyclosporin A (Sigma #C3662)
Bovine Serum Albumin (Sigma #A7906)

Data Analysis

Calculation of EC_{50} values

The dose-wise additivity model requires estimates of the replicon EC_{50} values for each compound in combination or alone. The EC_{50}, the concentration of compound required to inhibit 50% of the assay response, was defined here as the concentration that gives a response half way between the mean of wells containing cells with no compound and wells containing no cells. To estimate the EC_{50} all data analyses were performed on square-root (sqrt) transformed data values. The mean sqrt-values of untreated controls and no cells controls were used to calculate inhibition on each of three replicate plates for the sqrt transformed response for each combination. Curve fitting and EC_{50} estimation was performed for the horizontally-diluted compound at each experimental level of the vertically-diluted compound and vice versa. In each case, a four parameter Hill curve (see equation below) was fit to the inhibition data of the three replicate plates using XLfit5.1 (IDBS), and the EC_{50} was estimated from the fitted curve.

$y = a + [(b-a) / (1 + (x/c)^d)]$

Where y = response, i.e. inhibition of sqrt-transformed data, a = lower asymptote, i.e. minimum response (i.e. no inhibition), b = upper asymptote, i.e. maximum response, x = compound concentration, $c = EC_{50}$, i.e. concentration that gives a response half way between upper and lower asymptote b and a, and d = Hill coefficient. In some instances, data points that looked like outliers were manually excluded and curves were refit.

Combination Index Calculations

The combination index *CI* is based on the dose-wise additivity model. At 50% inhibition it is calculated as $CI = (d_A/EC_{50A}) + (d_B/EC_{50B})$ where EC_{50A} and EC_{50B} are the concentrations of compounds *A* and *B* that result in 50% inhibition for each respective compound alone, and (d_A, d_B) are concentrations of each compound in the mixture that yield 50% inhibition. Calculations of EC_{50} values are described in section 3.4.2. *CI* measures the type and amount of interaction between two compounds, *A* and *B*. $CI < 1$ implies dose-wise synergism between compounds *A* and *B*, $CI = 1$ implies dose-wise additivity, and $CI > 1$ implies dose-wise antagonism between compounds *A* and *B*. For each fixed concentration of compound A in the plate layout, we calculate the concentration of compound B required to give 50% inhibition, and calculate the combination index *CI* for these component concentrations. A similar calculation is repeated for each fixed concentration of compound B. The number *CI* that is being reported here is the average

across all individual *CI*s. Below is a table showing the additivity result for the calculated *CI*.

CI	Dose-wise Additivity Result (CalcuSyn Recommended)
< 0.1	Very strong synergism
0.1-0.3	Strong synergism
0.3-0.7	Synergism
0.7-0.85	Moderate synergism
0.85-0.9	Slight synergism
0.9-1.1	Nearly additive
1.1-1.2	Slightly antagonistic
1.2-1.45	Moderate antagonistic
1.45-3.3	Antagonism
3.3-10	Strong antagonism
>10	Very strong antagonism

Calculations for Synergy/Antagonism Volume (Bliss Independence Model)

Synergy and antagonism volumes are based on the Bliss independence model, which assumes that both compounds act independently on different targets. A set of predicted fractional responses fa_{AB} under the Bliss independence model is being calculated as $fa_{AB} = fa_A + fa_B - fa_A \bullet fa_B$ with fa_A and fa_B being the fraction of possible responses, e.g. % inhibition, of compounds *A* and *B* at amounts d_A and d_B respectively, and fa_{AB} being the % inhibition of a combination of compounds *A* and *B* at amount (d_A+d_B). If $fa_{AB} > fa_A + fa_B - fa_A \bullet fa_B$ then we have Bliss synergy; if $fa_{AB} < fa_A + fa_B - fa_A \bullet fa_B$ then we have Bliss antagonism. The 95% synergy/antagonism volumes are the summation of the differences between the observed inhibition and the 95% confidence limit on the prediction of fa_{AB} under the Bliss independence model. The table below shows the volumes and corresponding volume descriptions for the results of the Bliss Independence Analysis. MacSynergy II was used for data analysis.

MacSynergy II Synergy/Antagonism Volumes Description @ 95% Confidence	
Volume	Volume Description
<25	Insignificant synergism/antagonism
25-50	Minor but significant synergism/antagonism
50-100	Moderate synergism/antagonism – maybe important *in vivo*
>100	Strong synergism/antagonism – probably important *in vivo*
>1000	Probable Errors

RESULTS

Combination of Example 11 with IFNα or ribavirin (SOC) analyzed using the dosewise-additivity model

The results of the dosewise-additivity analysis of Example 11 combined with IFNα or ribavirin is listed in Table 13.

Combination of Example 11 with other DAAs analyzed using dosewise-additivity model

The results of the dosewise-additivity analysis of Example 11 combined with itself or other DAAs are listed in Table 14.

Combination of Example 11 with IFNα or ribavirin (SOC) analyzed by the Bliss Independence Model

The results of the Bliss Independence analysis of Example 11 combined with IFNα or ribavirin are listed in Table 15. MacSynergy II was used to perform the Bliss Independence analysis.

Combination of Example 11 with other DAAs analyzed by the Bliss Independence Model

The results of the Bliss Independence analysis of Example 11 combined with itself or with other DAAs are listed in Table 16. MacSynergy II was used to perform the Bliss Independence analysis.

Antagonism control analyzed by the dosewise-additivity Model

The result of the dosewise-additivity analysis of an HCV nucleoside inhibitor combined with ribavirin is listed in Table 17.

Antagonism control analyzed by the Bliss Independence Model

The result of the Bliss Independence analysis of an HCV nucleoside inhibitor combined with ribavirin is listed in Table 18. MacSynergy II was used to perform the Bliss Independence analysis.

The *in vitro* combination studies performed demonstrate that Example 11 is a good candidate for HCV combination therapy either with SOC, other classes of DAAs or a combination with both SOC and other DAAs.

Analysis using the dose-wise additivity model showed that Example 11 is nearly additive or moderately synergistic when combined with IFNα, cyclosporin A, an NS3 protease inhibitor, a replicase inhibitor, two HCV nucleoside inhibitors, and inhibitors targeting allosteric sites 1, 3, and 4 of the NS5B polymerase as well as with itself. The combination of Example 11 with ribavirin was performed two independent times in triplicate – once leading to analysis of slight antagonism and once leading to a nearly additive result. The combination of Example 11 with the NS4B inhibitor was also performed on two independent occasions and gave a result of slightly antagonistic. Data analysis was also performed using the Bliss Independence model via the MacSynergy II program. In all combinations tested, the combinations produced strong synergism and insignificant antagonism.

The methods of data analysis are different and they did not reach the same conclusions. The Bliss Independence Model shows strong synergism for every combination tested while the dosewide additivity found near additivity or moderate synergism from the same data set when Example 11 was combined with IFNα, cyclosporin A, a protease inhibitor, two nucleoside inhibitors and NS5B allosteric inhibitors as well as with itself. The dosewise additivity model also found slight antagonism once when ribavirin was dosed and twice when NS4B inhibitors were used in combination with Example 11.

There is no general agreement over which model best predicts *in vivo* outcome but we believe both models are in general agreement that there is no antagonism between the tested compounds and Example 11. Although slight antagonism was detected with the dose-wise-additivity analysis for the NS4B combinations and one ribavirin combination, it was classified as 'slight' and this interpretation was not supported by the Bliss-

Independence analysis on the same set of data. When we dosed an HCV nucleoside inhibitor in combination with ribavirin, both methods of analysis detected antagonism or strong antagonism, demonstrating that antagonism can be detected with our methods. We conclude from these studies that Example 11 is a good candidate for HCV combination therapy.

Table 13 Combination of Example 11 with IFNα or Ribavirin (SOC) analyzed using the dosewise-additivity model

Compound in combination with Example 11	CI	dosewise-additivity result
IFNα	0.99	Nearly additive
Ribavirin	1.12 1.01	Slightly antagonistic Nearly Additive

Table 14 Combination of Example 11 with other DAAs analyzed using the dosewise-additivity model

DAA combined with Example 11	CI	dosewise-additivity result
Protease	1.02	Nearly additive
NS4B	1.11 1.16	Slightly antagonistic Slightly antagonistic
Example 11	0.9	Nearly additive
HCV Nucleoside – 1	1.01	Nearly additive
HCV Nucleoside – 2	0.98	Nearly additive
NS5B Polymerase site I	0.92	Nearly additive
NS5B Polymerase site III	0.81	Moderate Synergism
NS5B Polymerase site IV	1.01	Nearly additive
Replicase	0.94 0.94	Nearly additive Nearly additive
Cyclosporin A	1.01	Nearly additive

Table 15 **Combination of Example 11 with IFNα or Ribavirin (SOC) analyzed by the Bliss Independence Model**

Compound in combination with Example 11	Synergy Volume	Antagonism Volume	Bliss Independence Analysis Result Synergism	Bliss Independence Analysis Result Antagonism
IFNα	172.88	-3.03	Strong Synergism	Insignificant Antagonism
Ribavirin	102.28	0	Strong Synergism	Insignificant Antagonism
	256.71	0	Strong Synergism	Insignificant Antagonism

Table 16 Combination of Example 11 with other DAAs analyzed by the Bliss Independence Model

DAA combined with Example 11	Synergy Volume	Antagonism Volume	Bliss Independence Analysis Result Synergism	Bliss Independence Analysis Result Antagonism
Protease	110.6	-14.68	Strong Synergism	Insignificant Antagonism
NS4B	121.49 196.46	-1.49 -0.5	Strong Synergism Strong Synergism	Insignificant Antagonism Insignificant Antagonism
GSK2335805A	289.03	-4.36	Strong Synergism	Insignificant Antagonism
Nucleoside – 1	151.59	-6.03	Strong Synergism	Insignificant Antagonism
Nucleoside – 2	219.71	-2.01	Strong Synergism	Insignificant Antagonism
NS5B Polymerase site I	273.73	0	Strong Synergism	Insignificant Antagonism
NS5B Polymerase site III	214.65	-0.5	Strong Synergism	Insignificant Antagonism
NS5B Polymerase site IV	103.92	-3.57	Strong Synergism	Insignificant Antagonism
Replicase	443.54 245.05	0 0	Strong Synergism Strong Synergism	Insignificant Antagonism Insignificant Antagonism
Cyclosporin A	233.68	-1.34	Strong Synergism	Insignificant Antagonism

5 **Table 17 Antagonism Control analyzed by dose-wise additivity model**

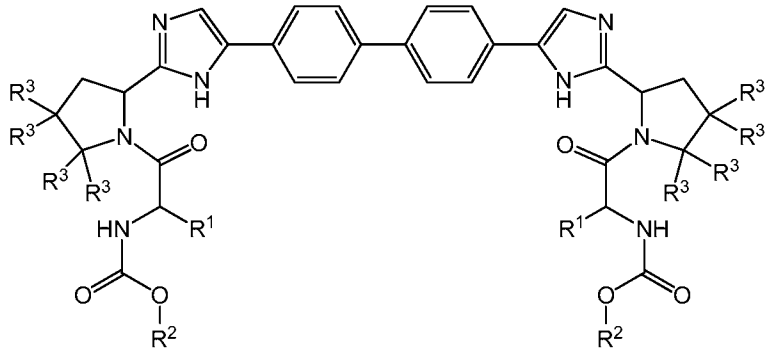
Compounds in combination	CI	dosewise-additivity result
HCV Nucleoside inhibitor + ribavirin	2.77	Antagonism

Table 18 Antagonism Control analyzed by the Bliss Independence Model

Compounds in combination	Synergy Volume	Antagonism Volume	Bliss Independence Analysis Result Synergism	Bliss Independence Analysis Result Antagonism
HCV Nucleoside inhibitor + ribavirin	0	-394.2	Insignificant synergism	Strong antagonism

Claims

1. A method of treating Hepatitis C in a human in need thereof comprising administering to the human a therapeutically effective amount of a compound of Formula (III):



(III)

wherein:

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

on each carbon to which there are R^3 groups attached, either both R^3s are H or the R^3 groups together with the carbon to which they are bonded form a 4-, 5-, or 6-membered saturated spiro ring with the proviso that there is no more than 1 spiro ring on each saturated nitrogen-containing ring;

each saturated spiro formed from R^3 groups is independently cycloalkyl, or may contain 1 or 2 oxygen atoms, or 1 or 2 sulfur atoms, or 1 SO_2, or 1 NR^4;

each R^4 is independently H, $C(O)OC_{1-4}$alkyl, $C(O)C_{1-4}$alkyl, $C(O)NC_{1-4}$alkyl, or SO_2C_{1-4}alkyl; and

each spiro ring may optionally be substituted with deuterium, fluorine, or 1 or 2 methyl groups;

or a pharmaceutically acceptable salt thereof,

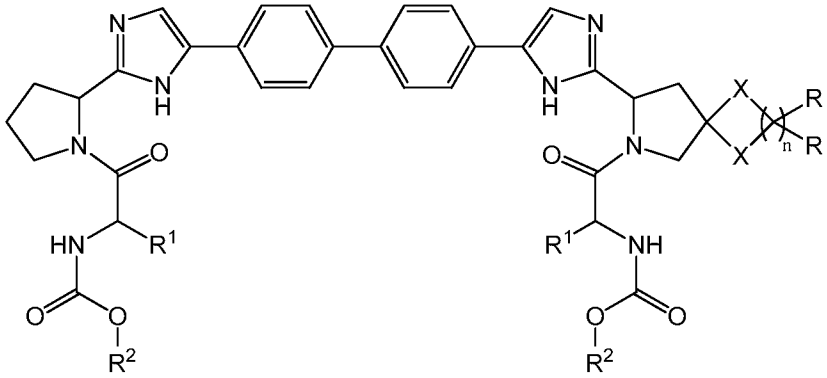
in combination with a one or more additional therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

2. The method according to claim 1 wherein the R^3 groups form a spiro ring on each of the two depicted saturated nitrogen-containing rings.

3. The method according to claim 2 wherein each of said spiro rings is bonded to the same relative carbon atom in each saturated nitrogen-containing ring.

4. The method according to claim 1 wherein the R^3 groups form a spiro ring on only one of the two depicted saturated nitrogen-containing rings.

5. A method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I):



(I)

wherein:

n is 2 or 3;

each R^1 is independently H or $C_{1\text{-}3}$alkyl;

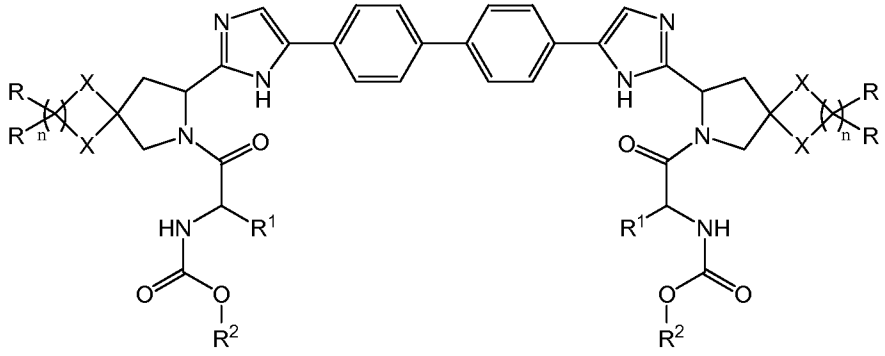
each R^2 is independently $C_{1\text{-}3}$alkyl;

each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

6. A method of treatment of Hepatitis C Virus in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula (II):



(II)

wherein:

n is 2 or 3;

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

7. The method according to claim 5 or claim 6 wherein each X is identical.

8. The method according to any one of claims 5-7, wherein X is S or O.

9. The method according to any one of claims 5-8, wherein every CRR is CH_2.

10. The method according to any one of claims 5-8, wherein no more than two Rs in each spiro are methyl.

11. The method according to any one of claims 1-10, wherein each R^1 is isopropyl.

12. The method according to any one of claims 1-11, wherein each R^2 is methyl.

13. The method according to claim 1 wherein the compound of Formula (III) is selected from the group consisting of:

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(3*S*,7*S*,9*S*)-7,9-dimethyl-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

dimethyl (4,4'-biphenyldiylbis{1*H*-imidazole-4,2-diyl[(3*S*,7*S*,9*S*)-7,9-dimethyl-6,10-dioxa-2-azaspiro[4.5]decane-3,2-diyl][(2*S*)-3-methyl-1-oxo-1,2-butanediyl]})biscarbamate;

dimethyl (4,4'-biphenyldiylbis{1*H*-imidazole-4,2-diyl(8*S*)-1,4-dioxa-7-azaspiro[4.4]nonane-8,7-diyl[(2*S*)-3-methyl-1-oxo-1,2-butanediyl]})biscarbamate;

methyl ((1*S*)-1-methyl-2-{(3*S*)-3-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-6,10-dioxa-2-azaspiro[4.5]dec-2-yl}-2-oxoethyl)carbamate;

methyl [(1S)-2-methyl-1-({(2S)-2-[4-(4'-{2-[(3S)-2-((2S)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(3*S*)-8,8-dimethyl-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(3*S*)-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6,10-dioxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate-d_6;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate-d_4;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(2*R*,3*R*,8*S*)-2,3-dimethyl-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-5-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(2*S*,3*S*,8*S*)-2,3-dimethyl-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-5-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dithia-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl[(1S)-2-methyl-1-({(2S)-2-[4-(4'-{2-[(8S)-7-((2S)-2-{[(methyloxy) carbonyl]amino}butanoyl)-1,4-dithia-7-azaspiro[4.4]non-8-yl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-({[(methyloxy)carbonyl] amino}acetyl)-1,4-dithia-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-8-oxa-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-8,8-dioxido-8-thia-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[8,8-difluoro-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-azaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

dimethyl (4,4'-biphenyldiylbis{1*H*-imidazole-4,2-diyl(3*S*)-8-oxa-2-azaspiro[4.5]decane-3,2-diyl[(2*S*)-3-methyl-1-oxo-1,2-butanediyl]})biscarbamate;

1,1-dimethylethyl 2-{*N*-[(methyloxy)carbonyl]-L-valyl}-3-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,8-diazaspiro[4.5]decane-8-carboxylate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,8-diazaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate.;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[8-acetyl-2-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,8-diazaspiro[4.5]dec-3-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl 2-{*N*-[(methyloxy)carbonyl]-L-valyl}-3-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,8-diazaspiro[4.5]decane-8-carboxylate;

1,1-dimethylethyl 6-{*N*-[(methyloxy)carbonyl]-L-valyl}-7-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[2-acetyl-6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl 6-{*N*-[(methyloxy)carbonyl]-L-valyl}-7-(4-{4'-[2-((2*S*)-1-{*N*-[(methyloxy)carbonyl]-L-valyl}-2-pyrrolidinyl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[2-[(methylamino)carbonyl]-6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-(methylsulfonyl)-2,6-diazaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[(7*S*)-2,2-difluoro-6-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-6-azaspiro[3.4]oct-7-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-8-oxa-1-azaspiro[4.5]dec-2-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

methyl ((1*S*)-1-{[(2*S*)-2-(4-{4'-[2-(1-acetyl-8-oxa-1-azaspiro[4.5]dec-2-yl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-1-pyrrolidinyl]carbonyl}-2-methylpropyl)carbamate;

methyl [(1*S*)-1-({(2*S*)-2-[4-(4'-{2-[8,8-difluoro-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1-azaspiro[4.5]dec-2-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)-2-methylpropyl]carbamate;

methyl [(1*S*)-1-({8,8-difluoro-2-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-azaspiro[4.5]dec-1-yl}carbonyl)propyl]carbamate;

methyl ((1*S*)-2-{8,8-difluoro-2-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-azaspiro[4.5]dec-1-yl}-1-methyl-2-oxoethyl)carbamate;

methyl [(1*S*)-1-({8,8-difluoro-2-[4-(4'-{2-[(2*S*)-1-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-azaspiro[4.5]dec-1-yl}carbonyl)-3-methylbutyl]carbamate;

methyl ((1*S*)-1-{[(2*S*)-2-(4-{4'-[2-(1-acetyl-8,8-difluoro-1-azaspiro[4.5]dec-2-yl)-1*H*-imidazol-4-yl]-4-biphenylyl}-1*H*-imidazol-2-yl)-1-pyrrolidinyl]carbonyl}-2-methylpropyl)carbamate; and

methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[1-((2*S*)-3-methyl-2-{[(methyloxy) carbonyl]amino}butanoyl)-8,8-dioxido-8-thia-1-azaspiro[4.5]dec-2-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate;

or a pharmaceutically acceptable salt thereof.

14. The method according to claim 1 wherein the compound of Formula (III) is methyl [(1*S*)-2-methyl-1-({(2*S*)-2-[4-(4'-{2-[(8*S*)-7-((2*S*)-3-methyl-2-{[(methyloxy)carbonyl]amino}butanoyl)-1,4-dioxa-7-azaspiro[4.4]non-8-yl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}carbonyl)propyl]carbamate or a pharmaceutically acceptable salt thereof.

15. The method according to any one of claims 1-14, wherein the second therapeutic agent is an interferon.

16. The method according to claim 15 wherein the interferon is selected from the group consisting of interferon alfa-2a, peginterferon alfa-2a, interferon alfa-2b, peginterferon alfa-2b, an interferon alfa-2b analogue, interferon alpha-2b XL, interferon alfacon-1, interferon alfa-n1, interferon omega, HDV-interferon, peginterferon beta, peginterferon lambda, and interferon-alpha5.

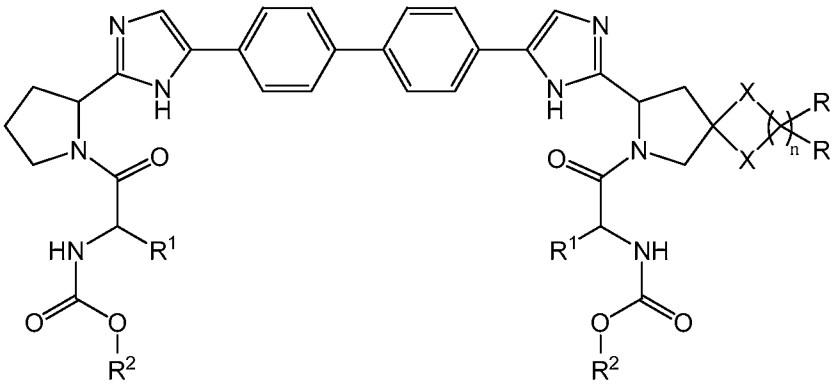
17. The method according to claim 15 wherein the interferon is selected from the group consisting of interferon alfa-2a, peginterferon alfa-2a, interferon alfa-2b, peginterferon alfa-2b, an interferon alfa-2b analogue, interferon alfacon-1, and interferon alfa-n1.

18. The method according to any one of claims 15-17 further comprising administering a nucleoside analogue.

19. The method according to claim 18 wherein the nucleoside analogue is ribavirin.

20. The method according to claim 1, wherein the one or more additional therapeutic agents are selected from those agents listed in Table 1.

21. A pharmaceutical composition comprising a compound of Formula (I):



(I)

wherein:

n is 2 or 3;

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

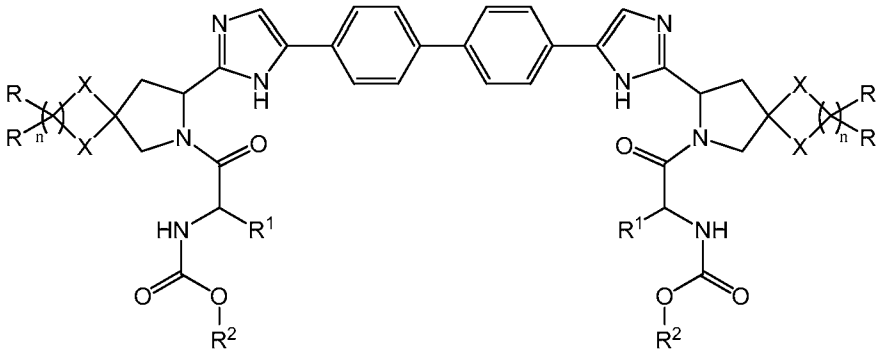
each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, and one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue;

and a pharmaceutically acceptable excipient.

22. A pharmaceutical composition comprising a compound of Formula (II):



(II)

wherein:

n is 2 or 3;

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

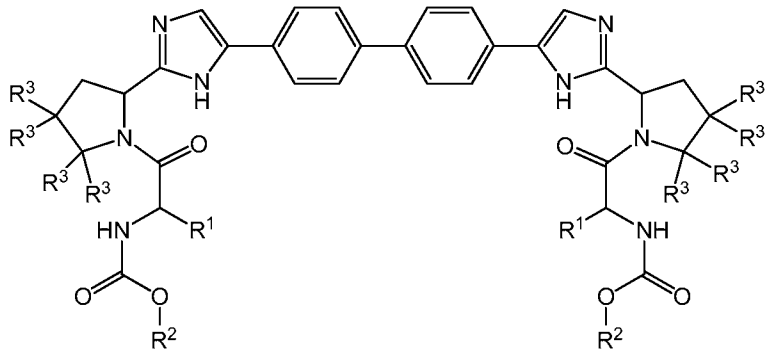
each X is independently CRR, O, or S; and

each R is independently methyl, hydrogen, or deuterium;

or a pharmaceutically acceptable salt thereof, and one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue;

and a pharmaceutically acceptable excipient.

23. A pharmaceutical composition comprising a compound of Formula (III):



(III)

wherein:

each R^1 is independently H or C_{1-3}alkyl;

each R^2 is independently C_{1-3}alkyl;

on each carbon to which there are R^3 groups attached, either both R^3s are H or the R^3 groups together with the carbon to which they are bonded form a 4-, 5-, or 6-membered saturated spiro ring with the proviso that there is no more than 1 spiro ring on each saturated nitrogen-containing ring;

each saturated spiro formed from R^3 groups is independently cycloalkyl, or may contain 1 or 2 oxygen atoms, or 1 or 2 sulfur atoms, or 1 SO_2, or 1 NR^4;

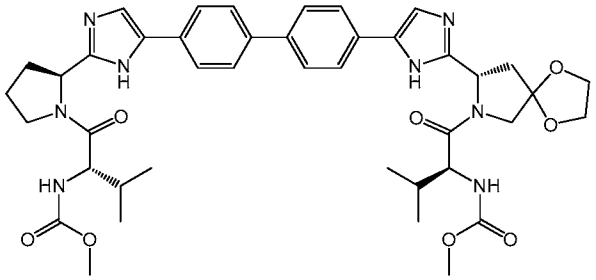
each R^4 is independently H, $C(O)OC_{1-4}$alkyl, $C(O)C_{1-4}$alkyl, $C(O)NC_{1-4}$alkyl, or SO_2C_{1-4}alkyl; and

each spiro ring may optionally be substituted with deuterium, fluorine, or 1 or 2 methyl groups;

or a pharmaceutically acceptable salt thereof, and one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue;

and a pharmaceutically acceptable excipient.

24. A pharmaceutical composition comprising a compound having the structure:

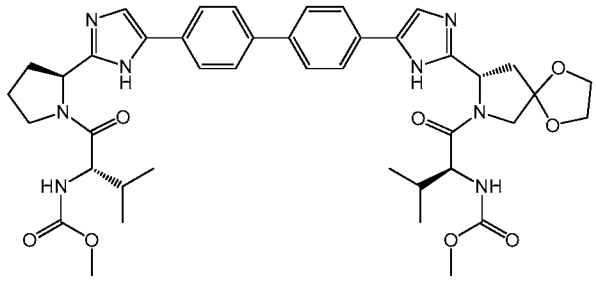


or a pharmaceutically acceptable salt thereof,

in combination with a one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue;

and a pharmaceutically acceptable excipient.

25. A pharmaceutical composition comprising a compound having the structure:

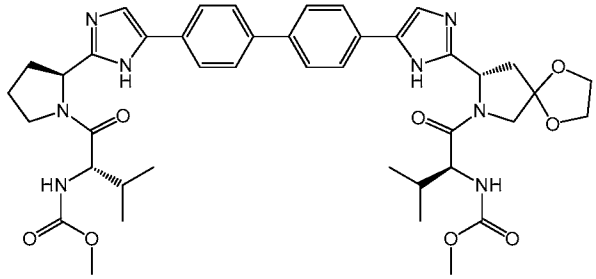


or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds listed in Table 1;

and a pharmaceutically acceptable excipient.

26. A pharmaceutical composition comprising a compound having the structure:



or a pharmaceutically acceptable salt thereof,

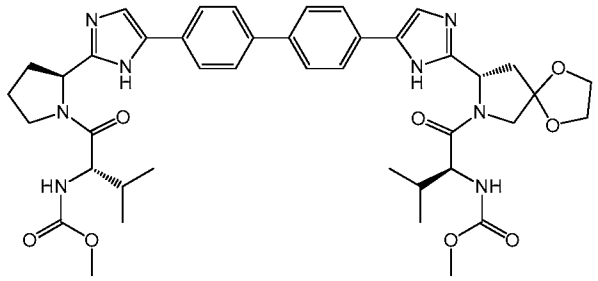
in combination with one or more compounds selected from the group of:

Telaprevir	Vertex
Boceprevir	Merck
Vaniprevir (MK-7009)	Merck
MK-5172	Merck
Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
IDX-077	Idenix
IDX-791	Idenix
ACH-1625	Achillion
ACH-2684	Achillion
ABT-450	Abbott
VX-222	Vertex
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
IDX-375	Idenix
ALS-2200	Vertex
ALS-2158	Vertex

Mericitabine (RG-7128)	Roche
IDX-184	Idenix
MK-4882	Merck
IDX-719	Idenix
IDX-19370	Idenix
IDX-19368	Idenix
ACH-2928	Achillion
ACH-3102	Achillion
PPI-461	Presidio
PPI-668	Presidio
PPI-437	Presidio
EDP-239	Novartis
MK-4882	Merck
GS-5885	Gilead
Daclatasvir (BMS-790052)	BMS
BMS-824393	BMS
ABT-267	Abbott
BI-201335	BI
BI-207127	BI
Filibuvir (PF-868554)	Pfizer
BMS-791325	BMS
INX-189	BMS
ABT-333	Abbott
ABT-072	Abbott
Debio-025	Novartis
SCY-635	Scynexis
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead;

and a pharmaceutically acceptable excipient.

27. A pharmaceutical composition comprising a compound having the structure:



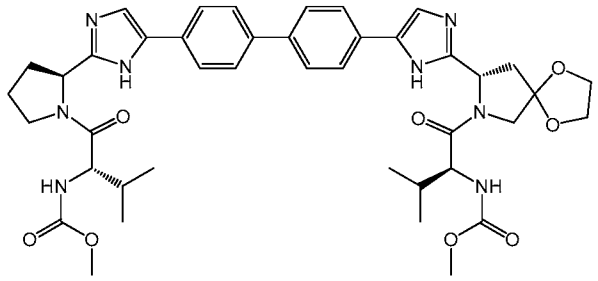
or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055	J&J
Mericitabine (RG-7128)	Roche
GS-5885	Gilead
Tegobuvir (GS-9190)	Gilead
GS-9669, and	Gilead
GS-7977	Gilead;

and a pharmaceutically acceptable excipient.

28. A pharmaceutical composition comprising a compound having the structure:



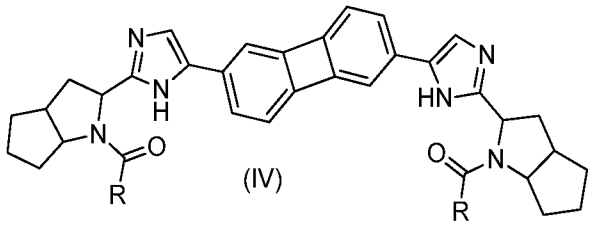
or a pharmaceutically acceptable salt thereof,

in combination with one or more compounds selected from the group of:

Danoprevir (RG7227) (ITMN-191)	Roche
Simeprevir (TMC-435)	JNJ Tibotec
Setrobuvir (RG-7790) (ANA-598)	Roche
TMC-647055, and	J&J
Mericitabine (RG-7128)	Roche;

and a pharmaceutically acceptable excipient.

29. A composition comprising a compound of Formula (IV):



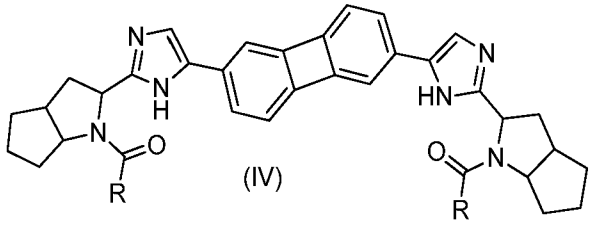
wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

30. A method of preventing or treating Hepatitis C in a human in need thereof comprising administering to the human a compound of Formula (IV):



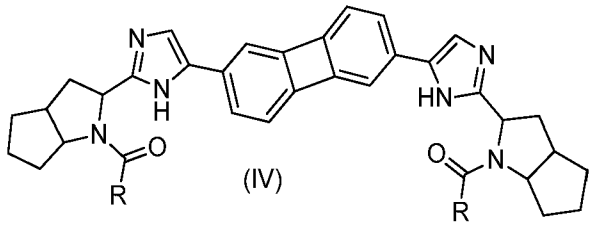
wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue.

31. A pharmaceutical composition comprising a compound of Formula (IV):



(IV)

wherein each R is independently -CH(R^1)-NH-C(O)-OR^2;

wherein each R^1 is independently –CH(OH)-CH_3 or –CH(OCH_3)-CH_3; and

each R^2 is independently C_{1-3}alkyl;

or a pharmaceutically acceptable salt thereof, in combination with one or more additional Hepatitis C therapeutic agents selected from the group consisting of an HCV NS2 protease inhibitor, an HCV NS3/4A protease inhibitor, an HCV NS3 helicase inhibitor, an HCV NS4B replication factor inhibitor, an HCV NS5B polymerase inhibitor, an HCV entry inhibitor, an HCV internal ribosome entry site inhibitor, a microsomal triglyceride transfer protein inhibitor, an α-glucosidase inhibitor, a caspase inhibitor, a cyclophilin inhibitor, an immunomodulator, a metabolic pathway inhibitor, an interferon, and a nucleoside analogue,

and a pharmaceutically acceptable carrier.

Figure 1

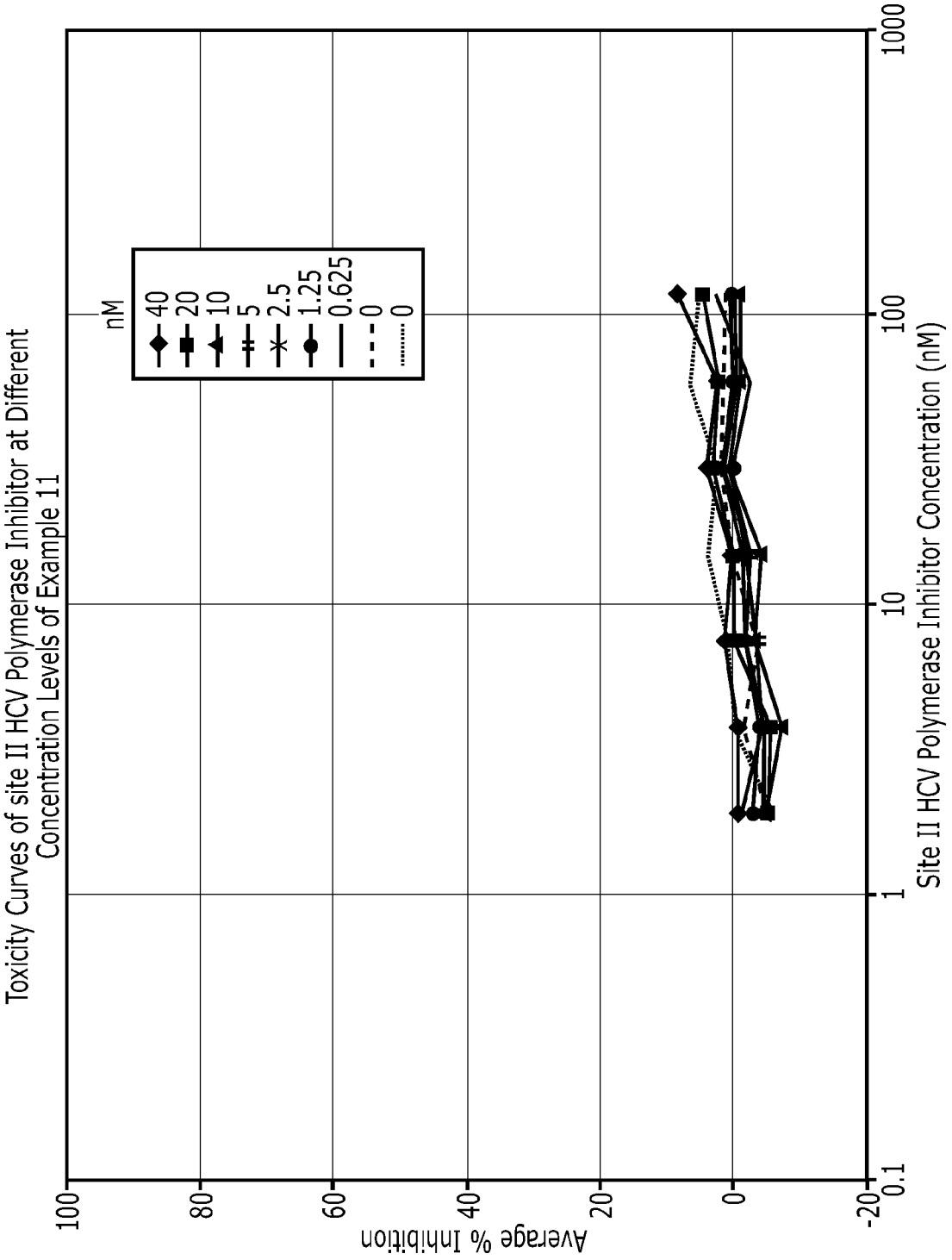
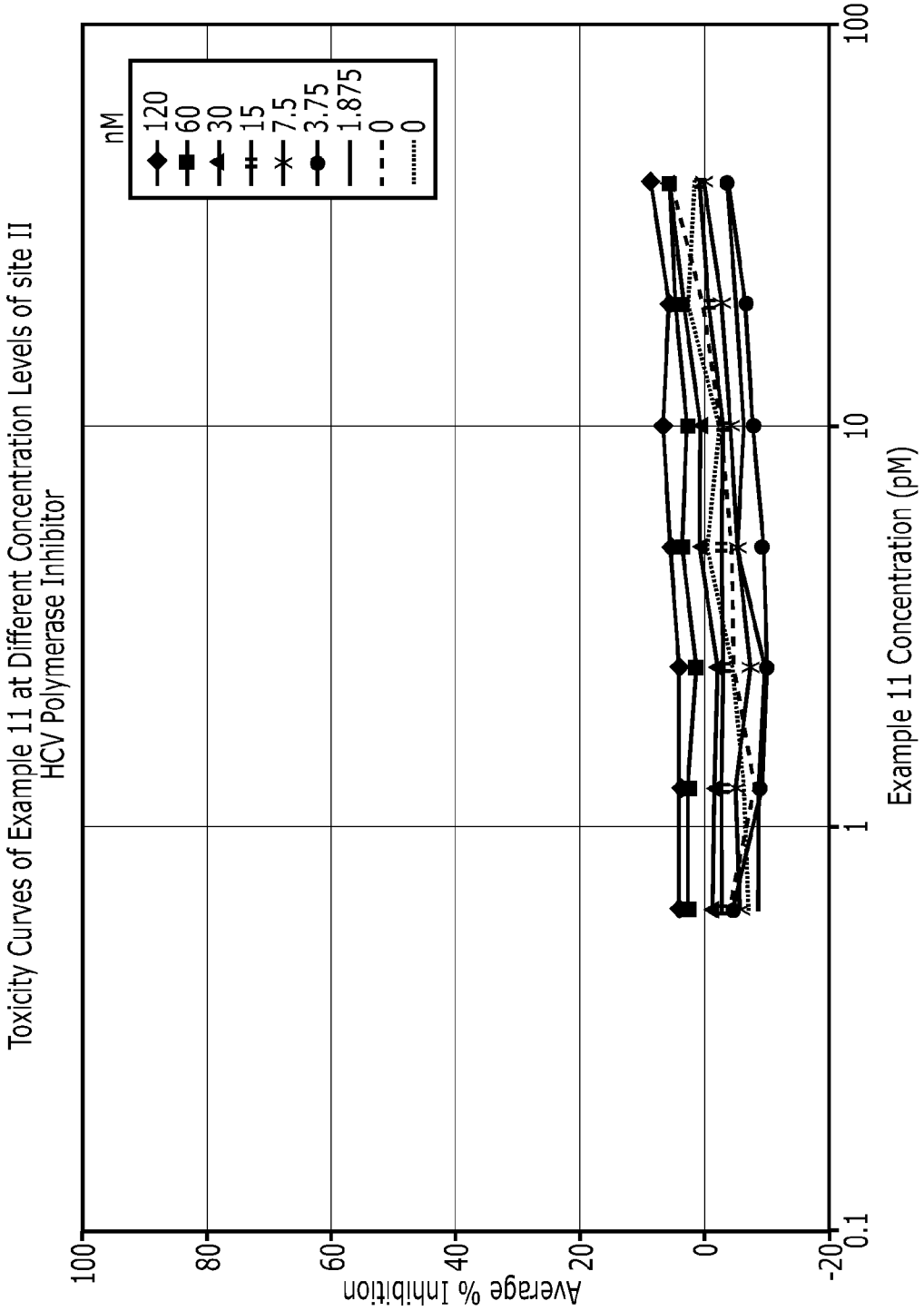

Toxicity Curves of site II HCV Polymerase Inhibitor at Different Concentration Levels of Example 11
nM
40
20
10
5
2.5
1.25
0.625
0
0
Average % Inhibition
100
80
60
40
20
0
-20
0.1
1
10
100
1000
Site II HCV Polymerase Inhibitor Concentration (nM)

Figure 2A


Toxicity Curves of Example 11 at Different Concentration Levels of site II
HCV Polymerase Inhibitor
nM
120
60
30
15
7.5
3.75
1.875
0
0
Average % Inhibition
100
80
60
40
20
0
-20
0.1
1
10
100
Example 11 Concentration (pM)

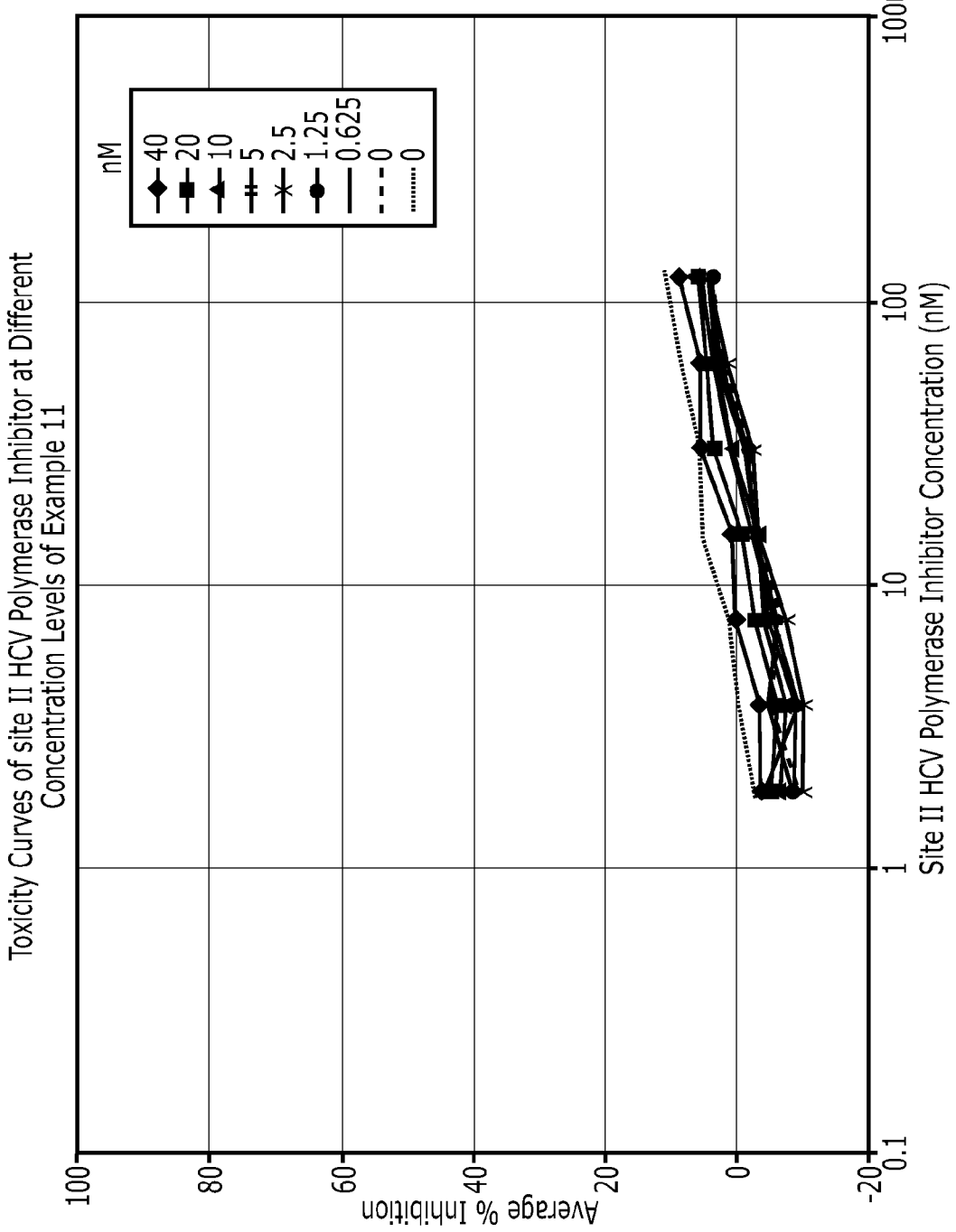

Toxicity Curves of site II HCV Polymerase Inhibitor at Different Concentration Levels of Example 11
nM
40
20
10
5
2.5
1.25
0.625
0
0
Average % Inhibition
100
80
60
40
20
0
-20
0.1
1
10
100
1000
Site II HCV Polymerase Inhibitor Concentration (nM)

Figure 2B

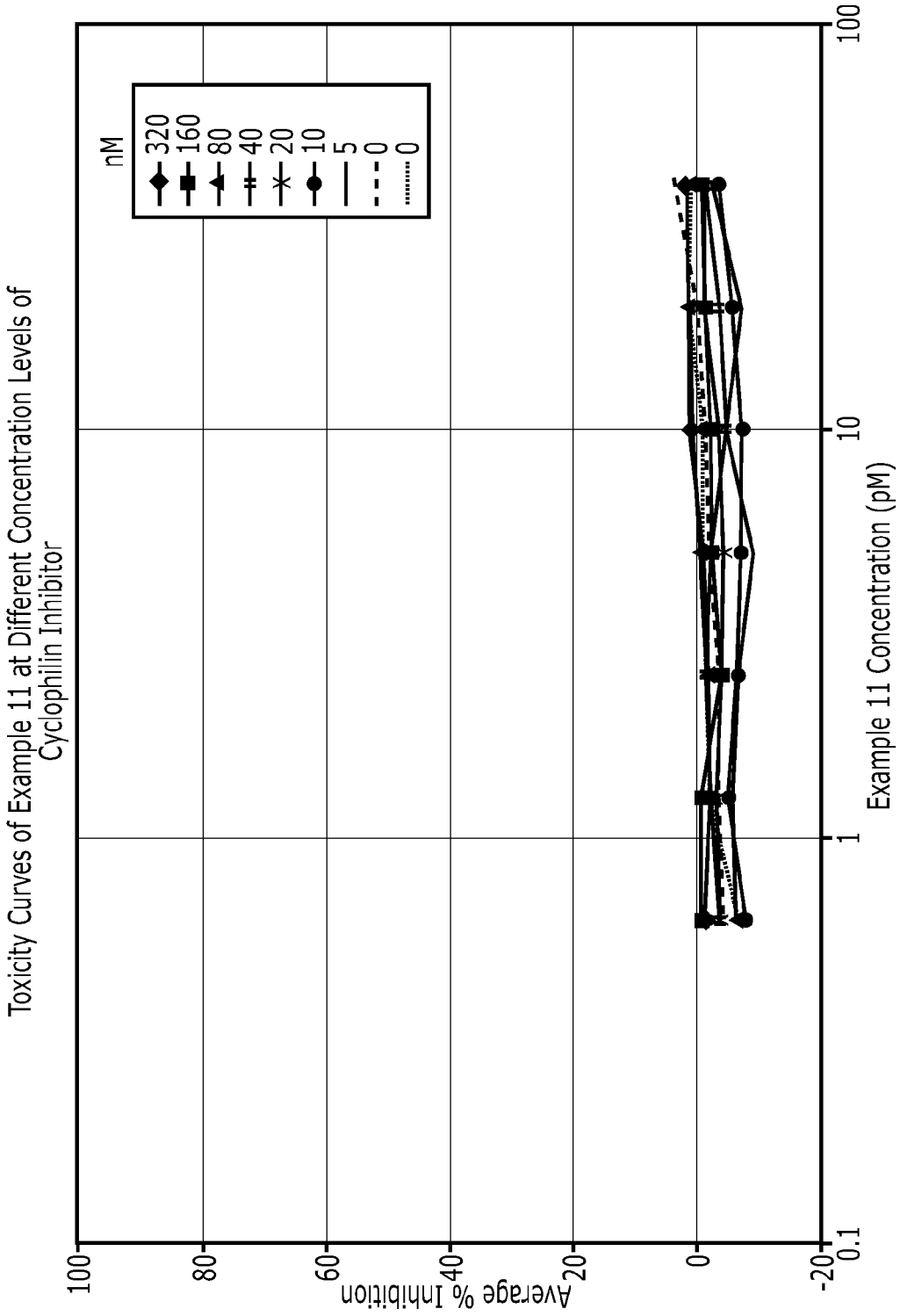

Toxicity Curves of Example 11 at Different Concentration Levels of Cyclophilin Inhibitor
nM
320
160
80
40
20
10
5
0
0
Average % Inhibition
100
80
60
40
20
0
-20
0.1
1
10
100
Example 11 Concentration (pM)

Figure 3A

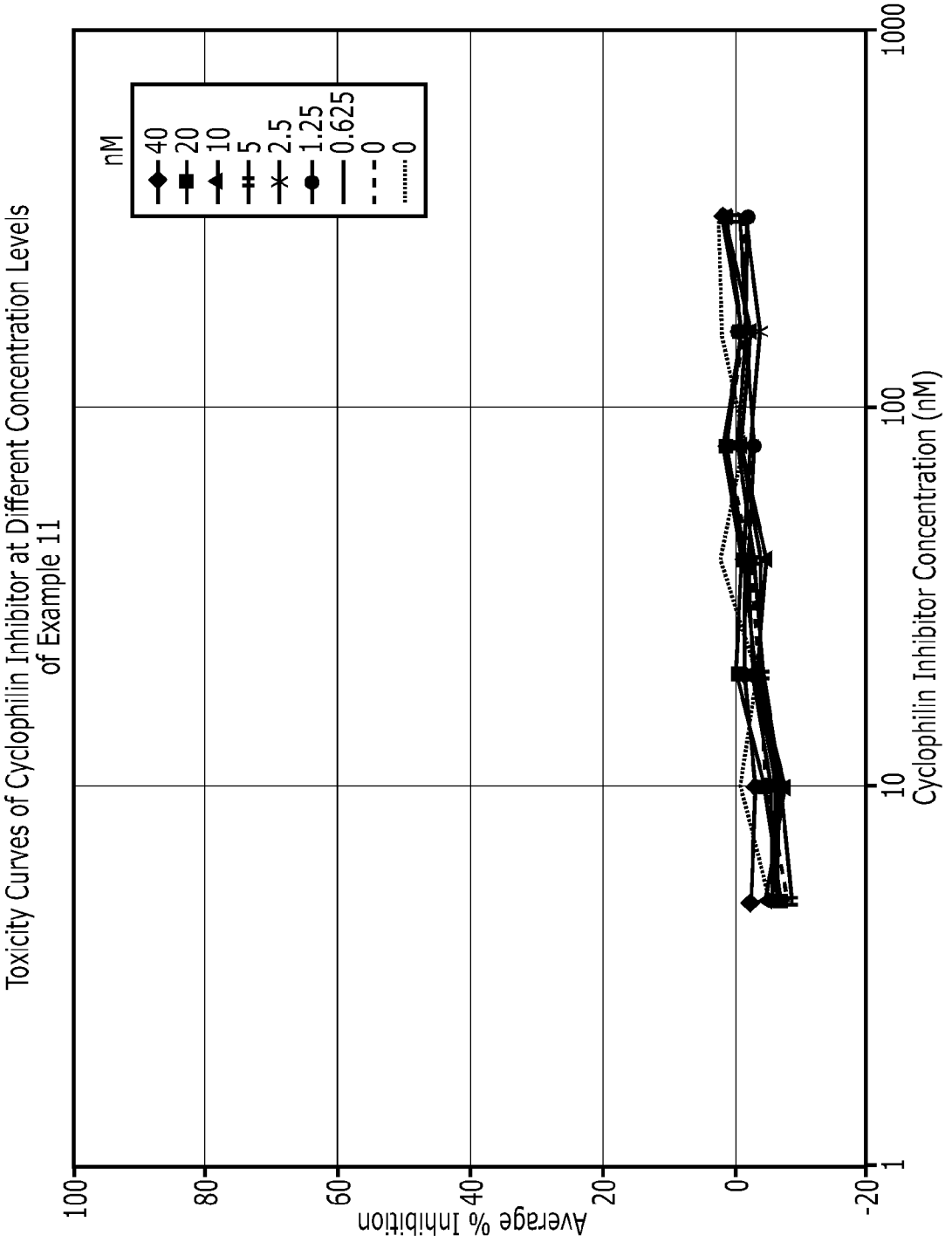
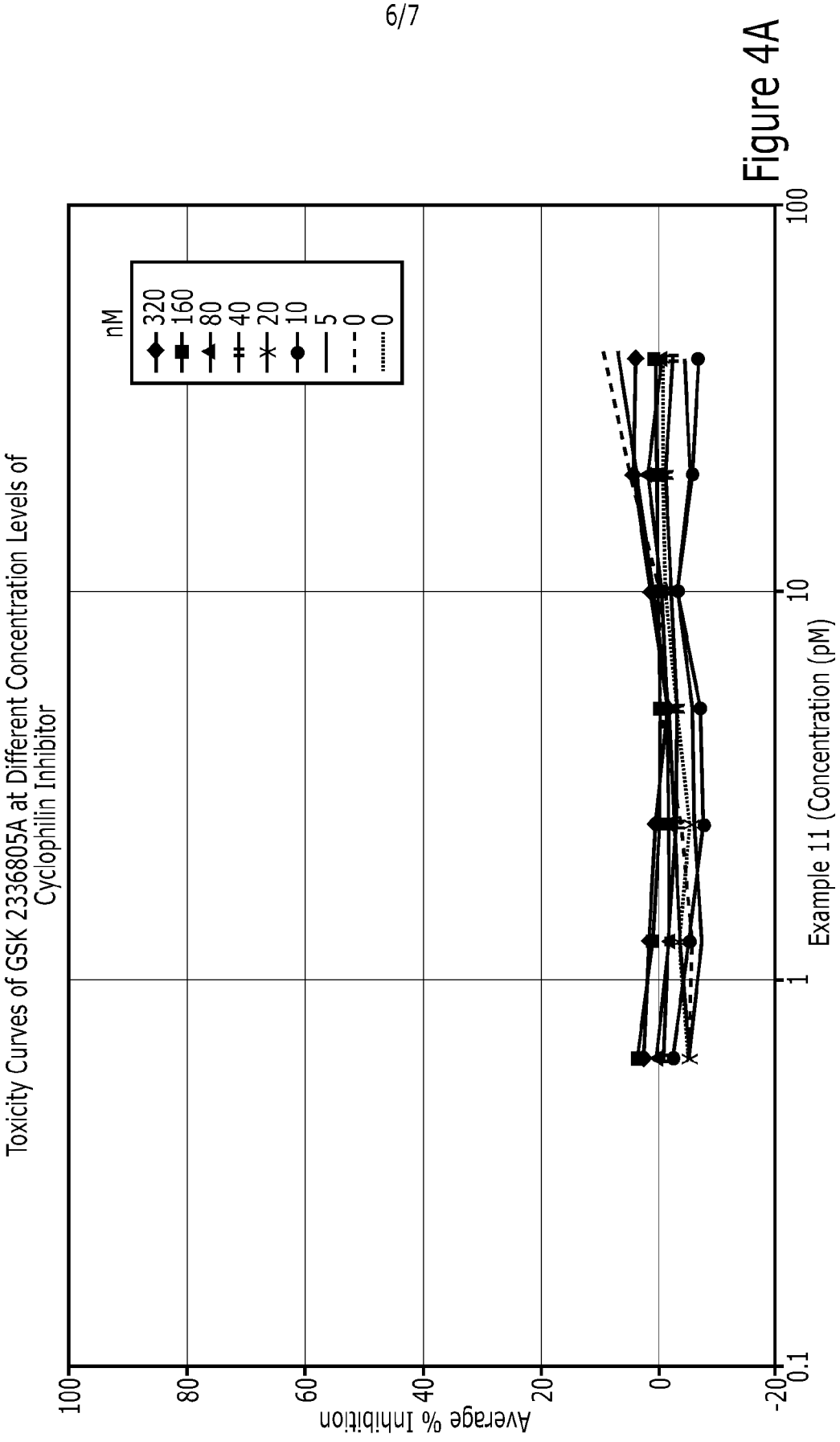

Toxicity Curves of Cyclophilin Inhibitor at Different Concentration Levels of Example 11
nM
40
20
10
5
2.5
1.25
0.625
0
0
Average % Inhibition
100
80
60
40
20
0
-20
1
10
100
1000
Cyclophilin Inhibitor Concentration (nM)

Figure 3B

Figure 4A


Toxicity Curves of GSK 2336805A at Different Concentration Levels of Cyclophilin Inhibitor
nM
320
160
80
40
20
10
5
0
0
Average % Inhibition
100
80
60
40
20
0
-20
0.1
1
10
100
Example 11 (Concentration (pM)

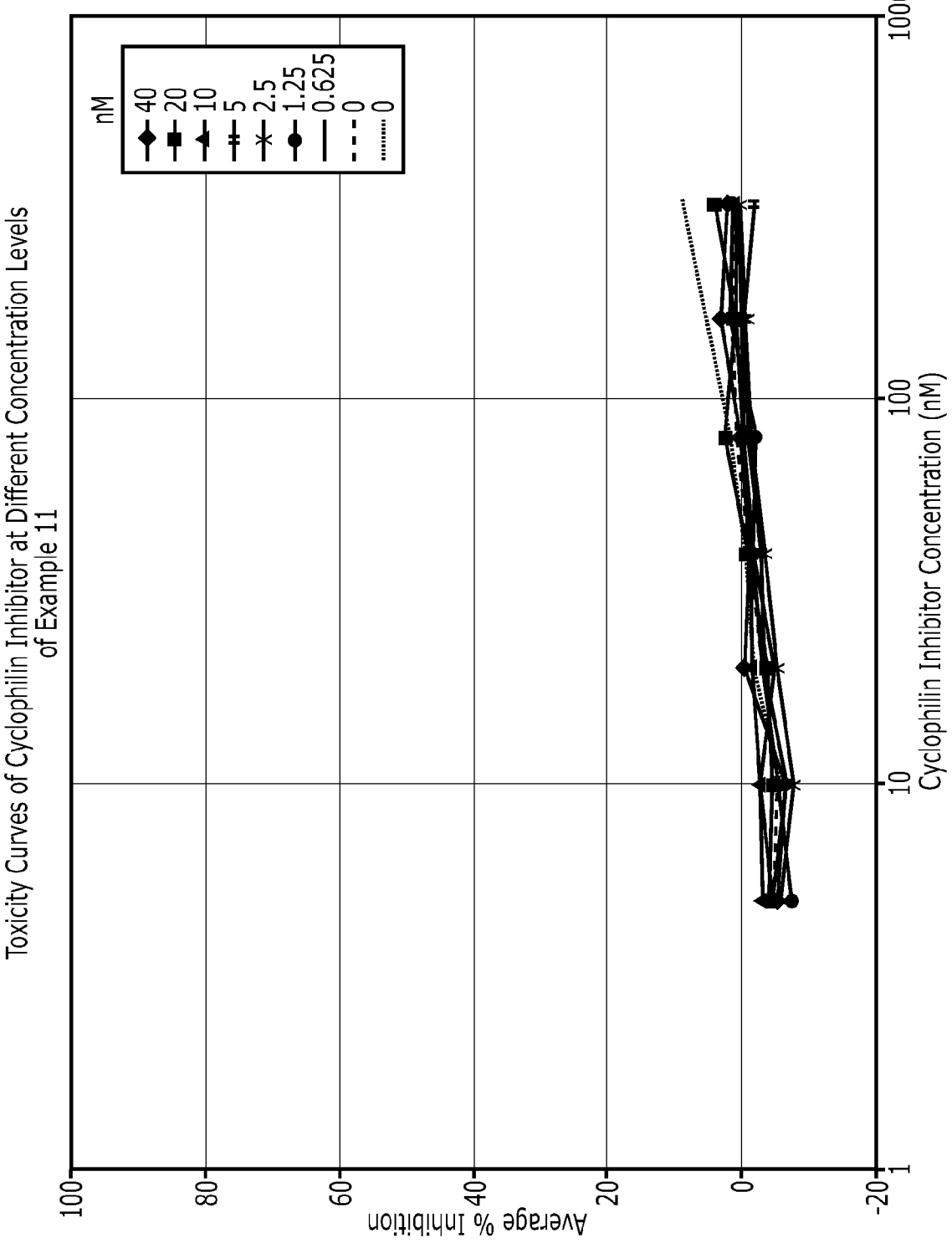

Toxicity Curves of Cyclophilin Inhibitor at Different Concentration Levels of Example 11
nM
40
20
10
5
2.5
1.25
0.625
0
0
Average % Inhibition
100
80
60
40
20
0
-20
1
10
100
1000
Cyclophilin Inhibitor Concentration (nM)

Figure 4B